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In the fixation of adult femoral neck fractures, does percutaneous hematoma drainage have an effect on bone union?

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Ethics Committee Approval
The study was approved by Suleyman Demirel University, Faculty of Medicine Clinical Research Ethics Committee Chair, Number: 33429/13.02.2021.
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Major blood circulation of the femur head is provided by retrograde flow from the medial femoral circumflex artery. The biggest problem here is uncertainty that the fracture hematoma disrupts the feeding of the femoral head. The aim of this study was to evaluate the effect on bone union of percutaneous hematoma punction in femoral neck fractures in patients aged <60 years and in patients with similar fracture types operated on in similar periods and to compare the outcomes in respect of complications.

Methods: In this retrospective cohort study, from a total of 58 patients who presented at the Orthopedics and Traumatology Clinic of a tertiary level training and research hospital between January 2014 and December 2018 and were diagnosed with intracapsular femoral neck fracture, the study included 49 patients who met the inclusion criteria and had follow-up of at least 1 year. In the treatment of all the fractures, 3 cannulated spongious screws were used. Percutaneous hematoma drainage was applied to 25 patients [Hem (+)=Group 1], and was not applied to 24 patients [Hem (-)=Group 2]. The patients were separated into two groups as those with and without fracture hematoma. The demographic data, time to union and femoral neck anatomic parameters were statistically compared between the two groups. Clinical and radiographic evaluations were made at the end of postoperative 1 month, 3 months, 6 months and 1 year. The Harris Hip Score was used in the clinical evaluation.

Results: The mean follow-up period was 21 months (range, 12-36 months). Group 1 comprised 18 (72%) females and 7 (28%) males with a mean age of 38 years (range, 19-53 years), and Group 2 comprised 16 (66%) females and 8 (34%) males with a mean age of 40 years (range, 19-58 years) (age: P=0.483). In Group 1, the right side was affected in 14 patients (56%) and the left side in 11 (44%). In Group 2, the right side was affected in 14 patients (58%) and the left side in 10 (42%) (P=0.869). A mean of 28 cc hematoma was drained from Group 1. In 47 patients, the operation was performed within the first 24 hours. The fractures were determined as Garden type 3 in 52% (n=13) of Group 1 and in 54% (n=13) of Group 2 (P=0.940). Full bone union was obtained in 80% (n=20) of Group 1 and in 79% (n=19) of Group 2 (P=0.728). Revision surgery was required in 7 patients in Group 1 and in 3 patients in Group 2. At the final follow-up examination, the difference between the healthy side and the fractured side femoral neck offset values were calculated. The difference in femoral offset compared with the healthy non-operated side was -3.48 (9.44) mm in Group 1, and -2.25 (7.97) mm in Group 2 (P=0.625). No significant difference was determined between the groups in respect of the anatomic parameters after union. The Harris Hip Scores were determined as mean 89 (range, 63-98) in Group 1 and 91 (range, 64-98) in Group 2 (P=0.616). No statistically significant difference was determined between the groups in respect of the clinical evaluation. Avascular necrosis developed in the femoral head in 4 (16%) patients in Group 1 and in 1 (4.17%) in Group 2 (P=0.349).

Conclusion: From the results of this study it was seen that unlike hematoma formed in extremity fractures, hematoma in femoral neck fractures has an effect that makes union difficult rather than facilitating callus formation. Hematoma punction led to an increased risk of avascular necrosis with impaired intraosseous circulation flowing in reverse to the femoral head due to negative pressure formed in the fracture line.

Keywords: Femoral neck fracture, Intracapsular fracture, Cannulated screw, Fracture hematoma, Hematoma punction

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Introduction

Intracapsular femoral neck fractures in young adults account for approximately 3% of the total hip fracture population [1, 2]. Major blood circulation of the femur head is provided by retrograde flow from the medial femoral circumflex artery (MFCA). Unlike intracapsular femoral neck fractures in the elderly, these fractures in the younger population result from high-energy trauma and vascular damage associated with the fracture has a significant effect on femoral head perfusion [3]. Therefore, the treatment of femoral neck fractures continues to be a significant clinical challenge.

The selection of the options of arthroplasty or internal fixation in treatment must be decided taking into consideration the age, bone quality, activity level, and general condition of the patient [4]. If open reduction and internal fixation is selected in respect of a good anatomic and clinical outcome, the vascular pathology should be well understood. Internal fixation is the recommended surgical treatment for non-displaced fractures in patients aged <60 years [3]. The most commonly used fixation material in non-displaced femoral neck fractures is multiple cannulated spongious screws. The most accepted procedure is 3 cannulated screws placed parallel or cranial based in a triangular shape to provide controlled compression of the fracture ends [5].

Major complications in these fractures are implant failure, non-union, and femoral head avascular necrosis (AVN). Direct damage to the retinacular vessels at the time of fracture or the possible tamponade effect of intracapsular hematoma can lead to AVN [6]. There are studies in literature that have determined intracapsular pressure as this tamponade effect [4, 6]. In the general trauma approach, it is aimed to protect the fracture hematoma as much as possible, as one of the factors facilitating fracture union. However, it has been stated that unlike in femoral neck fractures, by increasing intracapsular pressure, femoral neck fracure hematoma impairs vascular support and is one of the factors leading to AVN.

The aim of this study was to evaluate the effect on union of percutaneous hematoma punction in femoral neck fractures in patients aged <60 years and in patients with similar fracture types operated on in similar periods and to compare the outcomes in respect of non-union and avascular necrosis.

Materials and methods

Approval for this study was granted by the Suleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (decision no: 72867572-050.01.04-33429, dated: 12.02.2021).

In the period between January 2014 and December 2018, a total of 58 patients presented at the Orthopedics and Traumatology Clinic of a tertiary level training and research hospital and were diagnosed with femoral neck fracture.

The study exclusion criteria were defined as age <18 years or >65 years, pathological fracture, fractures of a bone with incomplete maturation, operations performed following a period in the intensive care unit because of multiple organ damage, open reduction, the use of implants other than cannulated screw, and hemodynamic instability. A total of 9 patients were excluded from the study; 5 who were aged <18 years and 4 who could not be contacted.

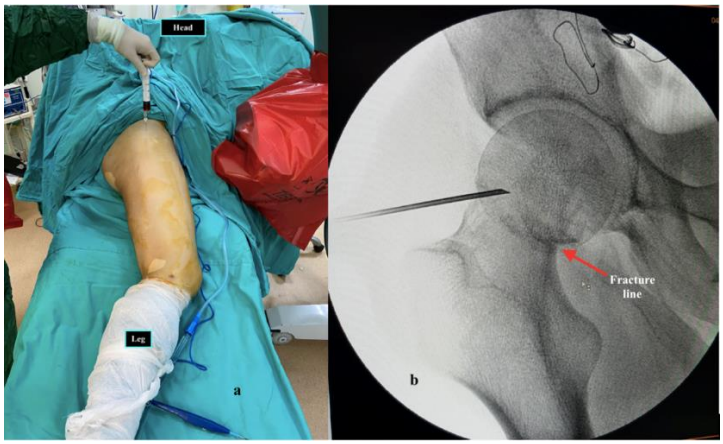
Thus, 49 patients, who met the inclusion criteria and had follow-up of at least 1 year, were included in the study for comparisons of the clinical and radiological data.

On first presentation, standard anterior-posterior (AP) pelvis radiographs and hip-femur radiographs were taken of all patients. Computed tomography (CT) was used to determine the status of fragments in displaced fractures. Classification of the fractures was made according to the Garden and Pauwel classifications [8, 9].

All the patients were examined in respect of demographic data such as age and gender (Table 1), union status, follow-up period, and whether or not percutaneous punction was performed in the fracture field. All the preoperative, intraoperative, and postoperative records of the patients were examined.

With the exception of two patients, the operations were performed within the first 24 hours. All the patients were operated on in the lateral decubitus position. The patients were separated into two groups as those who were applied with percutaneous hematoma punction with a spinal needle under intraoperative fluoroscopy guidance, and those who did not undergo hematoma punction (Figure 1).

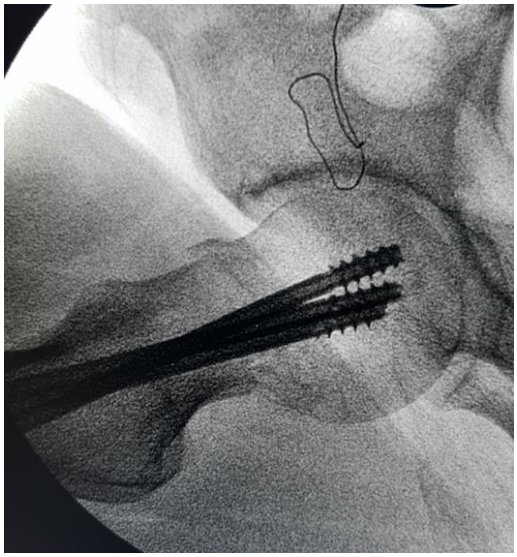
Figure 1: Intraoperative fluoroscopic view of hematoma drainage from the fracture line.



Application of percutaneous hematoma drainage from the anterolateral region with a spinal needle in the lateral decubitus position (a) under the guidance of intraoperative fluoroscopy (b).

At 30 mins before the operation all the patients were administered 1 gr cefazoline intravenously as prophylaxis. As the surgical method, closed reduction and fixation with cannulated screws was applied to all patients (Figure 2). Standard fixation was applied with 3 cannulated screws. Postoperatively, thromboembolism prophylaxis of low-molecular weight heparin (enoxaparin) was started for all patients at a weight-adjusted dose. Immediately postoperatively, anti-embolic stockings were applied to both lower extremities. Within the standard protocol, AP pelvis digital radiographs were taken on the first postoperative day. Pelvis AP radiographs were taken with the patient supine, the extremities in 10°-15° internal rotation and centered on the symphysis pubis. Patients were mobilized on the postoperative first day with no weight-bearing on the operated side.

Figure 2: Intraoperative fluoroscopic lateral view



Standard fixation was applied with 3 cannulated screws. The lateral fluoroscopic view shows ideal reduction.

Clinical and radiographic evaluations were made at the end of postoperative 1 month, 3 months, 6 months, and 1 year. Radiological bone union was checked on the full pelvis AP radiographs. In cases of delayed union or when there was thought to be impaction on the radiograph, the hip joint was evaluated with CT. The following measurements were compared with the healthy non-operated side:

1. Femoral lateral offset, stated as the horizontal distance between the femur shaft anatomic axis and the center of hip rotation
2. Head-neck angle, stated as the angle between the femur shaft and the line drawn from the center of the proximal of the femoral neck fracture
3. Femoral head-intertrochanteric distance, stated as the distance between the intertrochanteric line and the center of the femoral head.

Statistical analysis

Data obtained in the study were analyzed statistically using IBM SPSS v. 23.00 software. Conformity of quantitative data to normal distribution was assessed with the Kolmogorov-Smirnov test. Variables with normal distribution were compared using the Student's t-test and data not showing normal distribution with the Mann Whitney U-test and the Kruskal Wallis test. Categorical variables were statistically compared with Chi-square analysis and descriptive statistics were shown as number (n) and percentage (%). Correlations between variables were examined with the Pearson correlation test and linear regression analyses. A value of $P<0.05$ was accepted as statistically significant.

Results

In this retrospective cohort study, evaluation was made of 49 patients with intracapsular femoral neck fracture. The mean follow-up period was 21 months (range, 12-36 months). Percutaneous hematoma drainage (mean 28cc) was applied to 25 patients (Group 1), and was not applied to 24 patients (Group 2). The mean age of the patients was 38 years (range, 19-53 years) in Group 1 and 40 years (range, 19-58 years) in Group 2. In 47 patients, the operation was performed within the first 24 hours. Spinal anesthesia was applied to all the patients. The mean operating time was 63 mins (range, 45-110 mins). The mean length of hospital stay was 3 days. All the patients were mobilized on postoperative day 1.

The fractures were determined as Garden type 3 in 52% (n=13) of Group 1 and in 54% (n=13) of Group 2 (Table 1). Full bone union was obtained in 80% (n=20) of Group 1 and in 79% (n=19) of Group 2. Comorbid diseases were present in 96% of the patients in Group 1, and in 87.5% of Group 2. Revision surgery was required in 7 patients in Group 1 and in 3 patients in Group 2. Compared with the non-operated side, the difference in femoral head intertrochanteric distance was determined as -6.12 (6.59) mm in Group 1, and -5.83 (5.06) mm in Group 2 ($P=0.866$). The difference in femoral offset compared with the healthy non-operated side was -3.48 (9.44) mm in Group 1, and -2.25 (7.97) mm in Group 2 ($P=0.625$). The difference in head-neck angle between the operated and healthy sides was -2.6° (7.69°) in Group 1 and -3.5° (9.22°) in Group 2 ($P=0.712$). No significant difference was determined between the groups in respect of the anatomic parameters after union.

Table 1: Demographic data of the patients

	Group 1	Group 2	*P*-value
Age	38 (19-53)	40 (19-58)	0.483
Side			0.869
Right	14 (56%)	14 (58%)	
Left	11 (44%)	10 (42%)	
Sex			0.686
Female	18 (72%)	16 (66%)	
Male	7 (28%)	8 (34%)	
Garden Type			0.940
2	4 (16%)	3 (13.5 %)	
3	13 (52%)	13 (54.1%)	
4	8 (32%)	8 (32.4%)	
Union			0.728
+	20 (80%)	19 (79%)	
-	5 (20%)	5 (21%)	
Union Time (week)	17 (8-32)	16 (9-20)	0.762

Group 1: Percutaneous Hematoma Drainage was applied, Group 2: Percutaneous Hematoma Drainage was not applied. *$P<0.05$ statistically significant

The Harris Hip Score (HHS) was used in the postoperative evaluations. The mean HHS was determined as 89 (range, 63-98) in Group 1 and 91 (range, 64-98) in Group 2 ($P=0.616$). No statistically significant difference was determined between the groups in respect of the clinical evaluation. Avascular necrosis developed in the femoral head in 4 (16%) patients in Group 1 and in 1 (4.17%) in Group 2 ($P=0.349$) (Table 2).

Table 2: Results of anatomical and clinical parameters

	Mean (SD)	Med (min - max)	Mean (SD)	Med (min - max)	*P*-value
	Group 1		Group 2		
Garden	3.16 (0.69)	3 (2 - 4)	3.21 (0.66)	3 (2 - 4)	0.816
Pauwal	2.84 (0.37)	3 (2 - 3)	2.83 (0.38)	3 (2 - 3)	0.95
FH-ID	-6.12 (6.59)	-6 (-17 - 4)	-5.83 (5.06)	-5 (-16 - 2)	0.866
femoral offset	-3.48 (9.44)	-2 (-24 - 12)	-2.25 (7.97)	-2.5 (-22 - 12)	0.625
FH-NA	-2.6 (7.69)	-2 (-22 - 9)	-3.5 (9.22)	-3 (-22 - 11)	0.712
Harris HS	86.88 (9.46)	89 (63 - 98)	87.96 (8.96)	91 (64 - 98)	0.616

FH-ID: Distance between femoral head and intertrochanteric line, fem. offset: femoral offset, FH-NA: angle between femoral head and femoral neck, HHS: Harris hip score. *$P<0.05$ statistically significant; t: Independent Samples t test; SD: Standard Deviation; Med (min – max): Median (minimum – maximum values).

Discussion

In this study, the effect of fracture hematoma was examined on bone union and anatomic parameters in patients with a diagnosis of intracapsular femoral neck fracture who were operated on within the first 24 hours. The results of the study demonstrated that in the comparison of the two groups, in which mean age and fracture type were very similar, the anatomic parameters (femoral offset, femur neck angle, femoral head-intertrochanteric line distance) were increased in Group 1

compared to Group 2. The time to union was longer in Group 1 than in Group 2, but not to a statistically significant level. It was concluded that fracture hematoma drainage led to an amount of impairment in the anatomy and to a slight delay in bone union.

The general approach in non-displaced intracapsular femoral neck fractures is closed reduction and in situ fixation. Cannulated screws and dynamic hip screws (DHS) are the fixation materials usually selected. The most accepted procedure is the placement of 3 cannulated screws parallel or in a triangle shape proximal of the base [11]. In displaced fractures, the most preferred fixation methods are multiple cannulated spongious screws (46%) and DHS (49%). Most orthopedists prefer closed reduction and to perform the operation within the first 8-24 hours [12].

Tükenmez et al. [13] applied multiple cannulated screws to 22 patients and DHS to 19, and there was reported to be no significant difference in respect of the outcomes. Fixation with multiple cancellous screws is a method which can still be used, especially in non-displaced fractures, and when used together with hematoma drainage, reduction as early as possible, first fully applied closed, it has been concluded that the fixation should be rigid [14]. In the current series of 49 patients, closed reduction was applied to all the patients and fixation with 3 cannulated spongious screws.

At the time of fracture, the capsule may be torn as a result of severe trauma. This mechanism will reduce intracapsular pressure and prevent venous stasis without open reduction, thereby increasing the chance of union. When the capsule is intact, capsular distension together with increased intracapsular pressure is thought to be a cause of potential post-traumatic osteonecrosis, and it can therefore be debated that hematoma aspiration during fixation or decompression with capsulotomy is useful. It has been shown that needle aspiration or hematoma decompression with capsulotomy reduces intracapsular pressure and improves blood flow in the femoral head, but it has also been reported that there is insufficient evidence to justify capsulotomy from a practical perspective [11]. After ultraound examination of intracapsular fractures, therapeutic punction of the joint and hemarthrosis drainage will reduce intracapsular pressure and it has been recommended that this is performed within 6 hours of the injury to patients who cannot be treated with osteosynthesis or that capsulotomy is performed intraoperatively before osteosynthesis [15]. Harper et al. [16] measured intracapsular and intra-articular pressure. It was determined that intraosseous pressure fell after aspiration of intracapsular fractures and it was concluded that elimination of the initial venous obstruction was associated with the removal of the intracapsular hematoma. Rawall et al. [17] stated that a greater increase in intracapsular pressure could be a strong determinant of AVN, and could therefore be an important prognostic factor. In these types of cases with a significant intracapsular pressure difference, early capsulotomy was recommended to reduce the incidence of AVN. Jain et al. [18] suggested that the rate of avascular necrosis might be higher when reduction and fixation is delayed for more than 12 hrs after a subcapital hip fracture in young adults. In a series with 7 years of clinical follow-up, Maruenda et al. [19] concluded that the vascular damage at the time of the fracture, and not the tamponade effect from the intracapsular hematoma, was associated with avascular necrosis. Dedrick et al. [20] reported that open reduction with formal capsulotomy was not related to the outcome. In the current study of 49 patients, punction (mean 28cc) was performed under preoperative aseptic conditions to 25 patients. Reduction was seen to be obtained more easily after punction. The femoral offset values were found to be lower in the group where hematoma was protected but the difference was not statistically significant. Non-union developed in 5 patients in each group, with no difference determined.

In a study by Kinik et al. [21], open capsulotomy was applied from the anterior to all 22 patients in the series, and it was reported that AVN developed in 3 patients, non-union in 2 patients, and 17 patients recovered without complications. Bulut et al. [14] reported that of 42 patients, AVN was determined in 7 (16.7%) and non-union in 3 (7.1%) in the late-term. It was stated that displacement in the initial status of the fracture had a significant effect on complications. Rawall et al. [17] measured intraoperative intracapsular pressure and reported that of 16 cases with pressure difference <30 mmHg, AVN developed in only 1 (6%) and non-union developed in 4 (25%), whereas of the 11 cases with pressure difference >30 mmHg, AVN developed in 5 (45%) and non-union developed in 4 (36%).

Some authors have determined a statistically higher incidence of non-union in fractures applied with open reduction compared to fractures stabilized with closed reduction. A higher incidence of AVN has been determined in fractures applied with closed reduction compared to those applied with open reduction, which suggests that open reduction may be better than closed reduction for decreasing the incidence of AVN [3, 22]. In the current study, AVN developed in 4 (16%) patients in Group 1 and in 1 (4.17%) patient in Group 2. Revision surgery due to other complications was applied to 7 (28%) patients in Group 1.

There were some limitations to this study, primarily the low number of patients in the groups. This study was retrospective in design. Each fracture should be evaluated individually and patient comorbidities may have affected bone union and the other parameters. Therefore, there is a need for further studies of more extensive patient series to evaluate microvascular circulation to be able to make patient-based evaluations.

Conclusion

From the results of this study, it was seen that unlike hematoma formed in extremity fractures, hematoma in femoral neck fractures has an effect that makes union difficult rather than facilitating callus formation.

Hematoma punction led to an increased risk of avascular necrosis with impaired intraosseous circulation flowing in reverse to the femoral head due to negative pressure formed in the fracture line.

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The efficacy of kinesio taping versus forearm-band therapy in treating lateral epicondylitis: A prospective, single-blind, randomized, controlled clinical trial

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Ethics Committee Approval
Ethical approvement was obtained from University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital Ethics Committe (2011-KAEK-25 2019/10-12). 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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The treatment of lateral epicondylitis (LE) is generally conservative, but evidence for its effects is insufficient. Although Kinesio Tape (KT) and forearm bandages (FB) are applied in the treatment of LE, the results regarding the effectiveness of these two treatment methods are controversial. Moreover, to our knowledge, no study compared these two methods with each other. Our aim was to investigate the effects of Kinesio Tape (KT) and forearm bandages (FB) on pain, tenderness, grip strength, function and quality of life and to compare these two methods.

Methods: This study included 62 patients with LE diagnosis, between ages of 20 and 65. Patients were randomly assigned to one of two groups, representing KT (Group 1 = 31) and FB (Group 2 = 31), respectively. LE exercises were assigned as home programmes to both groups. Pain (VAS), the pressure pain thresholds (PPT), handgrip strength (HGS), the patient-rated tennis elbow evaluation (PRTEE), and the 'Short Form-12' evaluation parameters were used. Patients were evaluated at the beginning, third and sixth weeks.

Results: Significant difference was not observed between two groups in terms of demographic data and baseline evaluation parameters ($P>0.05$). In group 1, a significant improvement was observed across all evaluation parameters at both the third and sixth weeks, except the PPT at the sixth week ($P<0.05$). Meanwhile, in group 2, a significant improvement was observed across all evaluation parameters except the PPT at the third week and the SF-12 mental component at the third and sixth weeks ($P<0.05$). No significant difference in evaluation-parameter scores was observed between the two groups at the third and sixth weeks ($P>0.05$)

Conclusion: The KT and FB treatments significantly improve LE patients' pain, handgrip strength, functions and quality of life. Moreover, neither method is superior to the other in this regard.

Keywords: Forearm band, Kinesio tape, Lateral epicondylitis, Tennis elbow, Treatment

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Introduction

Lateral epicondylitis (LE) is the most common cause of elbow pain, and called as *tennis elbow* [1]. LE's prevalence is reported at 3% among the general population, and this rate is expected to increase among factory workers and paddle athletes [2-4]. LE commonly affects the middle age (40-54 years) population, and affects women and men in equal proportion. The dominant upper limb is more frequently affected [5]. Difficult or repetitive movements of the wrist or forearm and firm hand grips at a ≥ 45° forearm pronation have been reported as risk factors for LE [6]. The condition clinically presents as pain around the lateral epicondyle, which manifests in a strong wrist extension. Degenerative angiofibroblastic hyperplasia of the wrist extensor tendons due to recurrent microtraumas is considered to be responsible for LE etiopathogenesis [7]. Patients with LE have also been reported to exhibit sensorial system alterations and neuromuscular insufficiency [8, 9]. Although LE treatment is generally conservative (e.g., oral drugs, steroid injections, physiotherapy and orthosis), insufficient evidence has been found for the effects of many treatments [10, 11].

Kinesio Taping (KT) has been widely used to manage various musculoskeletal problems. Invented by the Japanese chiropractor Kenzo Kase in the 1970s, the tape is composed of a heat-sensitive acrylic adhesive and an elastic woven cotton with a maximum usable tension of about 40–60% of its overall length. KT is assumed to have many physiological effects, including pain relief, normalized muscle functions, improved proprioceptive feedback, corrected joint incompatibility, and increased subcutaneous blood and lymphatic circulation [12]. There is no consensus regarding the optimal tape type and its application technique [13]. Moreover, the evidence regarding KT's both immediate and short-term follow-up effects is contradictory, and few studies have investigated its effects as a short-term therapy [5]. Dilek et al. [12] reported that, patients with LE experienced decreased pain and significantly increased grip strength after applying KT. In a placebo-controlled study, KT seemed to have additional effects in controlling the pain associated with elbow wrist extensions while tactual pain relief and painless grip strength had equivalent effect to a placebo [7].

Forearm bandages (FB) are a commonly used orthosis to treat LE. They are worn under the elbow. FB's main purpose is to target the cause of a lesion by reducing overload on the wrist extensors' common origin [14, 15]. Studies have shown that the use of orthoses provides immediate relief and is more effective for patients' daily activities than other methods, such as steroids, ultrasound, laser, massage, and exercise therapy [16]. In some studies of patients with LE, FB's effect on handgrip strength and pain was not observed, meanwhile, some studies' results showed that FB increases handgrip strength and reduces pain [17, 18].

Extensive literature has offered many controversial positive and negative findings regarding the effectiveness of these two treatment approaches (KT and FB). However, we did not find sufficient data comparing the effectiveness of these approaches. Therefore, the current study is aimed to investigate the effects of kinesiological banding versus orthosis applications (ACL) on pain, sensitivity, handgrip strength, functions, and quality of life in treating LE.

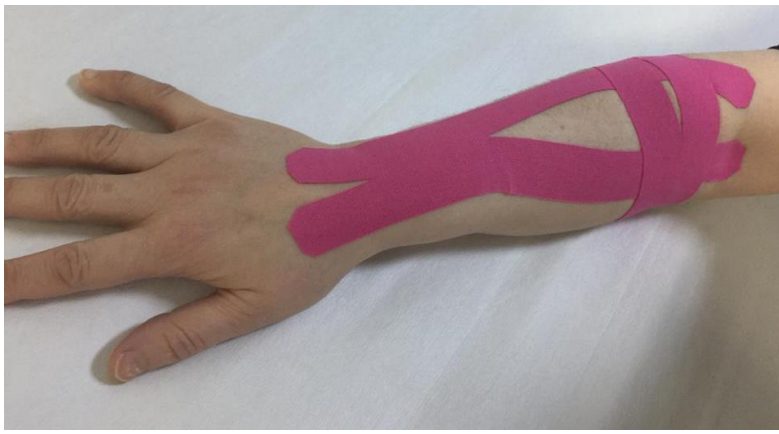
Materials and methods

This single-blind, randomized and controlled clinical study was conducted at the University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Physical Medicine and Rehabilitation outpatient clinic. The study was planned in accordance with the rules of the Declaration of Helsinki, and local ethics committee approval was received (2011-KAEK-25 2019/10-12). All participants were informed about the study, and their written consent was obtained.

Sixty-two patients were included in this study. All participants included in the study had been diagnosed with chronic LE, were 20–65 years old, had pain of the lateral epicondyle for at least three months, sensitivity of the lateral epicondyle during their examinations and pain triggered by a resistant extension of the wrist. Patients with cervical radiculopathy, peripheral neuropathy, pregnancy, elbow arthritis, acute trauma to the elbow, skin lesions on the forearm, allergies, a history of surgical intervention in the upper extremities, inflammatory, autoimmune, endocrine or renal diseases, previous KT and FB treatment, previous physiotherapy, or steroid injections in the last three months for LE were excluded from the study.

Patients' demographic data were recorded. Additionally, patients were asked whether they had a job or hobby that required repetitive arm movements or upper limb strength. According to their responses, occupational disease was recorded as either *present* or *absent*. Patients were randomly assigned to one of two groups via a computer, using a random number table (http://www.random.org/). Patients in the first group received KT treatment (Group 1 = 31), and patients in the second group received FB treatment (Group 2 = 31). KT was applied by a certified researcher from the forearm extensor muscles' origin to their insertion, using a muscle technique for a longitudinal KT strip, additionally, a transverse elbow band was applied using the 'fascial correction' technique (twice per week for three weeks; Figure 1).

Figure 1: KT application was applied from the origin of the forearm extensor muscles to the insertion using a muscle technique as a longitudinal kinesiotape strip and additionally a transverse elbow band was applied using the 'facial correction' technique.



The FB used in this study was a brace made of neoprene with triangular padding that was approximately 5 cm wide. This FB was placed on the extensor muscle mass, distally to the lateral epicondyle. FB patients were informed of their treatment according to a standard protocol about the use and application of

FB, and they were instructed to wear their FB continuously for three weeks. In the event of any discomfort, they were told to remove their bandages for no longer than an hour. Moreover, they were allowed to continue their daily activities to the extent FB enabled. LE exercises – including stretching and strengthening exercises – were assigned as a home programme to both groups (three sets and 10 repetitions). Patients were instructed to continue these exercises even if they experienced mild pain. However, they were instructed to stop these exercises if their pain became disabling.

All patients were warned to avoid rigorous activities, NSAIDs and analgesics. Patients were evaluated by the same investigator, who was kept uninformed of patients' respective therapies before treatment, at the end of their three-week treatment (at the third week after the beginning of their treatment) and at the end of the following three-week, treatment-free period (at the sixth week after the beginning of their treatment).

Evaluation parameters

Pain: Pain was assessed with a visual analogue scale (VAS) during four different activities (resting VAS, night VAS, handgrip VAS and VAS during daily-life activities).

Pain pressure threshold (PPT): Patients' PPT was evaluated with a pressure algometer (Baseline® Dolorimeters, New York, USA, 2015). Measurements were obtained from the lateral epicondyle by the same investigator under the same test conditions, at the same room temperature and test equipment. For evaluations, a 1 cm^2 circular probe connected to a pressure device was calibrated to Newton/cm^2 and used as the power unit. The pressure was increased at a rate of 1 N/sec until subjects detected pain. The test was stopped upon subjects' 'stop' command, and the onscreen values were recorded. Each measurement was conducted three times, and the average of each patient's three measurements was recorded as their PPT.

Hand grip strength (HGS): A standard hand dynamometer (Jamar® Plus + Digital Hand Dynamometer from Patterson Medical by Sammons Preston, Bolingbrook, USA) was used to measure grip strength. The reliability and validity of the Jamar dynamometer are high; therefore, the device has been considered the gold standard in assessing grip strength [19]. Hand grip strength was evaluated while patients were seated in a chair. Their shoulders were adducted and neutrally rotated. Patients' elbows were flexed to 90°, and their forearms and wrists were in a neutral position. Grip strength tests were performed three times with one-minute intervals, and the mean of these three measurements was calculated. Patients' grip strength was measured in kilogram force.

Patient-rated tennis elbow evaluation (PRTEE): A questionnaire comprising 15 questions to measure pain severity and disability levels, including pain and subdivision, was used for this study's PRTEE. The pain component consisted of five questions: pain while at rest, pain during repetitive arm movements, pain when carrying a shopping bag, and the lowest and highest amounts of pain. Meanwhile, the function component comprised six questions about specific activities and four questions about daily activities. Each response was scored on a scale of 0–10 (0 = no pain/no strain, 10 = the most pain felt/no action). Total scores were calculated out of 100. The higher the score, the greater a respondent's disability. The questionnaire's validity and reliability in Turkish had been confirmed previously by Altan et al. [20].

Short Form-12: The 12-item 'Short Form (SF-12)' was obtained by shortening the 'SF-36 Health Research' form. It comprised 12 questions that aimed to measure respondents' state of health and well-being from a patient perspective. The SF-12 determined a physical component score (PCS) and mental component score (MCS) for patients [21].

Statistical analysis

The Power Analysis**:** A G*Power 3.0.10 statistical power analysis programme was used for this study's power analysis. The study power (1-β) was found to be 0.79 with a post hoc analysis of $n1 = 29$, $n2 = 31$, $\alpha = 0.05$ and effect size $d = 0.98$

IBM SPSS 23.0 statistical software was used to analyze this study's data. Continuous variables were expressed as mean (standard deviation) if the data conformed to a normal distribution and 'median (minimum-maximum)' if the data did not conform to normal distribution. A chi-square (χ^2) test was used to compare categorical data. The data's suitability for normal distribution was evaluated with a Shapiro-Wilk test. In cases where the data showed a normal distribution, Student's *t*-test was used. In cases where the data did not show a normal distribution, a Wilcoxon signed-rank test was used for intra-group comparisons, and a Mann-Whitney U test was used to compare between groups. Values of $P \leq 0.05$ were considered significant, confirming that 'there is a difference between the groups'.

Results

Two patients from group 1 did not respond to our follow-up attempts. Therefore, this study was completed with 60 patients (Group 1: n=29; Group 2: n=31) (Figure 2). No statistically significant difference was observed between two groups in terms of demographic data and baseline evaluation parameters ($P>0.05$; Table 1).

In group 1, a statistically significant improvement was observed across all evaluation parameters at both the third and sixth weeks, except PPT at the sixth week ($P<0.05$) (Table 2). In group 2, a significant improvement was observed across all evaluation parameters, except PPT at the third week and the SF-12 mental component at the third and sixth weeks ($P<0.05$; Table 2).

A comparison of the groups' difference scores revealed no significant difference in evaluation parameters between the two groups at the third and sixth weeks ($P>0.05$; Table 3). During treatment, side effects were not observed in either group.

Figure 2: Flow diagram of the study

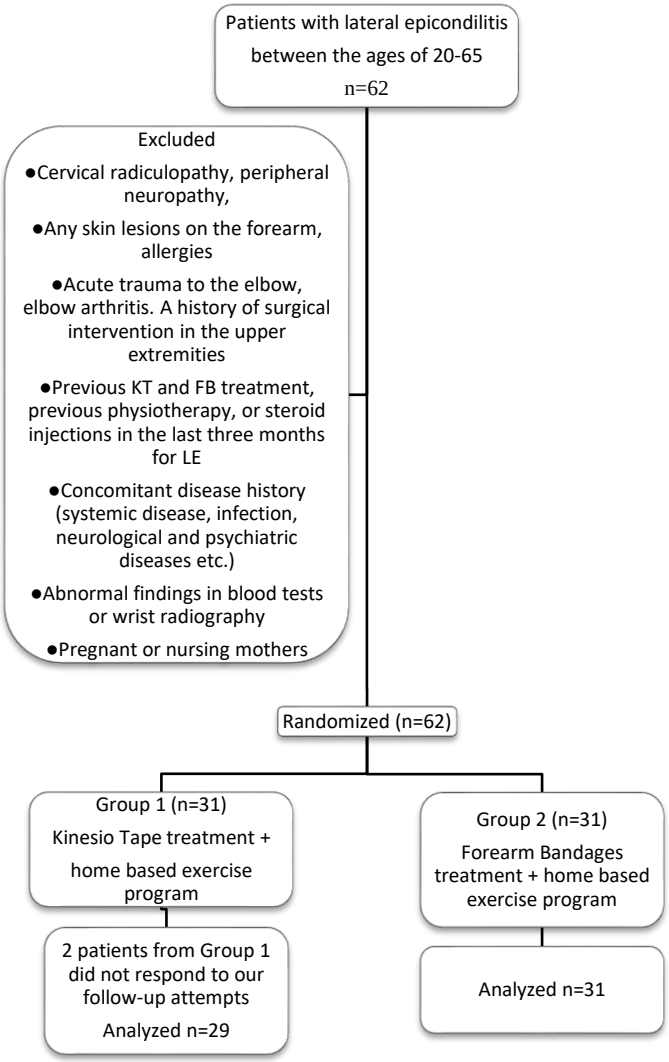


Table 1: Comparison of the demographic characteristics of the patients and pre-treatment evaluation parameters

		Group 1 (n=29)	Group 2 (n=31)	*P*-value
Age (year)		43.31 (9.06)	43.94 (9.28)	0.473
BMI Kg/cm^2		26.20 (21.6-38.6)	26.90 (21.8-41.4)	0.610
Gender	Female n (%)	19 (65.5%)	18 (58.1%)	0.556
	Male n (%)	10 (35.5%)	13 (41.9%)	
Occupational disease	Yes n (%)	16 (55.2%)	19 (61.3%)	0.634
	No n (%)	13 (44.8%)	12 (38.7%)	
Dominant side	Right n (%)	25 (86.2%)	30 (96.8%)	0.142
	Left n (%)	4 (13.8%)	1 (3.2%)	
Affected side	Right n (%)	13 (44.8%)	20 (64.5%)	0.129
	Left n (%)	16 (55.2%)	11 (35.5%)	
Duration of symptoms (month)		3 (3-12)	4 (3-12)	0.737
Resting VAS		4 (0-10)	3 (0-8)	0.290
Night VAS		3 (0-10)	2 (0-10)	0.378
Hand grip VAS		8 (5-10)	8 (5-10)	0.396
ADL VAS		8 (5-10)	8 (5-10)	0.507
PPT Newton/cm^2		8.5 (5.5-14)	9 (5.5-13)	0.824
Hand Grip Strength		25.46 (6.36)	28.17 (4.86)	0.072
PRTEE Pain		23 (15-41)	23 (16-45)	0.689
PRTEE function		30 (9.5-42)	25.50 (17-40)	0.200
PRTEE total		57 (24.50-81)	47.5 (36-85)	0.239
Sf 12 Physical		36.42 (4.85)	35.52 (5.72)	0.511
Sf 12 Mental		45.57 (6.76)	48.00 (7.90)	0.205

Mean (SD), Median (minimum-maximum), ADL: Activities of daily life, PPT: Pain pressure threshold, PRTEE: Patient rated tennis elbow evaluation, Sf 12: Short Form-12, *P*<0.05: Significant

Table 2: Intra-group comparison of 3rd week (post-treatment) and 6th week values

		3rd week (post-treatment)	6th week	*P*-value (0-3rd week)	*P*-value (0-6th week)
Resting VAS	Group1 (n=29)	0 (0-9)	0 (0-8)	<0.001	<0.001
	Group2 (n=31)	0 (0-5)	0 (0-5)	0.001	<0.001
Night VAS	Group1 (n=29)	0 (0-9)	0 (0-9)	<0.001	<0.001
	Group2 (n=31)	0 (0-5)	0 (0-4)	0.002	0.001
Hand grip VAS	Group1 (n=29)	4 (0-10)	4 (0-10)	<0.001	<0.001
	Group2 (n=31)	4 (0-10)	3 (0-9)	<0.001	<0.001
ADL VAS	Group1 (n=29)	4 (0-10)	4 (0-10)	<0.001	<0.001
	Group2 (n=31)	3 (0-10)	3 (0-10)	<0.001	<0.001
PPT Newton/cm2	Group1 (n=29)	9 (6-15)	8.5 (5-15)	0.024	0.087
	Group2 (n=31)	9 (6-14)	9 (7-14)	0.121	0.015
Hand Grip Strength	Group1 (n=29)	28.26 (6.73)	30.82 (7.39)	<0.001	<0.001
	Group2 (n=31)	30.79 (4.64)	32.49 (4.78)	<0.001	<0.001
PRTEE Pain	Group1 (n=29)	13 (0-34)	13 (0-30)	<0.001	<0.001
	Group2 (n=31)	12 (0-36)	12 (0-39)	<0.001	<0.001
PRTEE Function	Group1 (n=29)	15.50 (0-22.50)	14 (0-22)	<0.001	<0.001
	Group2 (n=31)	15 (4.50-23)	14 (0-23)	<0.001	<0.001
PRTEE Total	Group1 (n=29)	28.5 (0-54)	27 (0-54)	<0.001	<0.001
	Group2 (n=31)	27 (4.50-56)	27 (0-59.50)	<0.001	<0.001
Sf 12 Physical	Group1 (n=29)	42.17 (6.61)	42.32(6.24)	<0.001	<0.001
	Group2 (n=31)	42.93 (7.79)	43.44 (8.09)	<0.001	<0.001
Sf 12 Mental	Group1 (n=29)	47.90 (5.23)	46.74 (5.04)	0.006	0.017
	Group2 (n=31)	49.48 (5.24)	48.36 (7.70)	0.138	0.775

Mean (SD), Median (minimum-maximum), ADL: Activities of daily life, PPT: Pain pressure threshold, PRTEE: Patient rated tennis elbow evaluation, Sf 12: Short Form-12, *P*<0.05: Significant

Table 3: Comparison of the difference scores between the groups

	0-3rd week			0-6th week		
	Group 1	Group 2	*P*-value	Group1	Group 2	*P*-value
Resting VAS	-3 (-6-0)	0 (-6-0)	0.202	-3 (-6-0)	-1 (-6-2)	0.187
Night VAS	-2 (-10-0)	0 (-10-3)	0.266	-3 (-10-0)	-1 (-10-3)	0.378
Hand grip VAS	-4 (-9-4)	-4 (-8-0)	0.544	-4 (-9-0)	-5 (-8-0)	0.610
ADL VAS	-4 (-9-4)	-5 (-8-0)	0.611	-4 (-9-0)	-5 (-8-1)	0.606
PPT Newton/cm2	0.5 (-3-2)	0.5 (-3-4)	0.765	0.5 (-7-3)	0.5 (-3-2.5)	1.000
Hand Grip Strength	2 (-1-10)	1.9 (-0.3-16.4)	0.706	5.5 (-0.4-13.4)	4 (-1-13.4)	0.344
PRTEE Pain	-14.03 (7.21)	-13.32 (7.73)	0.923	-14.93 (6.81)	-13.16 (8.03)	0.535
PRTEE Function	-15.06 (7.49)	-11.95 (7.60)	0.728	-15.29 (7.75)	-12.32 (7.47)	0.774
PRTEE Total	-29.06 (13.67)	-25.17 (13.81)	0.559	-30.12 (13.98)	-25.38 (14.35)	0.956
Sf 12 Physical	6.15 (-0.78-20.43)	7.39 (-2.53-23.39)	0.684	5.68 (0-20.43)	7.39 (-2.88-23.39)	0.559
Sf 12 Mental	2.42 (-6.63-19.33)	-0.07 (-7.63-19.1)	0.231	2.42 (-9.77-15.73)	-0.28 (-22.35-20.21)	0.107

Mean (SD), Median (minimum-maximum), ADL: Activities of daily life, PPT: Pain pressure threshold, PRTEE: Patient rated tennis elbow evaluation, Sf 12: Short Form-12, *P*<0.05: Significant

Discussion

Our study's results showed that both KT and FB treatments achieved significant improvements in patients' pain, handgrip strength, functions, and quality of life. We also found that neither method is superior to the other method in treating LE.

LE treatment typically aims to reduce pain, alter the muscle-joint load, and improve neuromuscular strength and control [13]. KT has been recently accepted as a popular treatment method [22]. KT is thought to decrease the pressure on muscles, which affects the cutaneous mechanoreceptors (an

effect of neurophysiology), thereby reducing the force applied to soft tissue. KT's other mechanisms of action are as follows: normalizing muscle function through the inhibition of the hyperactive muscles and stimulation of the weak muscles, increasing vascular and lymphatic flow, fixing abnormal muscle, correcting joint function impairment with tension and elevating the skin under the KT, providing more space [23, 5]. Studies examining KT's acute effects emphasized improvements in resting pain intensity and function [24, 25]. These improvements could be explained by a neurophysiological effect, whereby tactile stimulation of the skin and subcutaneous tissue can alter nociceptive input, reduce pain and improve muscle activity [5]. While Goel et al. [24] showed improvements in pain and grip strength, Au et al. [26] did not report any change in grip strength, pain or muscle activity following KT administration. In both these studies, inconsistency has been associated with the taping technique [24, 26]. Goel et al. [24] applied a 'fascial correction' strip tape in addition to a longitudinal KT strip applied to the forearm extensor muscles. This transverse tape has been claimed to reduce pain more effectively when used to reinforce longitudinal tape [27]. Transverse tape application has been reported to improve joint position senses and force reproduction. A reduction in pain has also been reported to enhance proprioceptive functions. Changes in pain are likely to affect changes in function, or otherwise [5]. In our study, we added a 'fascial correction' strip tape to the forearm extensor muscles and a longitudinal KT strip, applying them for three weeks. Two studies evaluating short-term effects have applied two different techniques. A study by Dilek et al. [12] observed improvements in five different pain measurements after facilitator KT was applied twice per week for two weeks for patients with LE. Dilek et al. stated that this recovery increased even more in the sixth week. Similarly, Shakeri et al. [28] reported greater improvement in pain during daily life activities compared to a placebo control group, following the application of three diamond KT in a week. In contrast, neither group demonstrated significant improvements in PPTs or pain intensity during the palpation of a myofascial trigger point in the forearm extensor muscles. Patient-rated pain and disability were improved in both studies [12, 28] when evaluating short-term treatment outcomes.

The previous results regarding KT's effects on grip strength are contradictory. Dilek et al. [12] demonstrated a 29% increase in maximum grip strength after two weeks of facilitating KT treatment. On the contrary, Shakeri et al. [28] found no significant difference in maximum grip strength compared to diamond KT and placebo KT. Another study found a reduction in grip strength [29]. Additionally, studies have reported that therapeutic tape may offer a valuable contribution to multimodal therapy in treating LE [30]. Our results showed a significant improvement in pain, grip strength and function when used with exercise. In the PPT, a significant improvement was noted at the end of patients' three-weeks treatment, but during the sixth week, this improvement did not continue. Studies have reported a correlation between pain severity and PPT. KT causes dimensional force and mechanical pressure on the skin, thereby changing the skin's tension and, consequently, affecting the PPT [23]. Indeed, in our study, we observed this effect during the KT application period. However, we observed that this effect did not continue during the following untreated period. The results of one previous study showed that pain sensitivity measured with the PPT was related to the severity and duration of symptoms at the baseline [31]. Unlike previous studies, we also evaluated quality of life, and we found a significant improvement in the SF-12's physical and mental components during the third and sixth weeks. Unlike the two previous studies we have mentioned [12, 28], we applied KT for three weeks. Our conception is that pain control positively affects grip strength and function by increasing exercise compliance, which increases quality of life. Additionally, the application technique and time of the application may play a role in KT's short-term effectiveness.

One of the more popular treatments in LE is the use of a proximal FB, also known as a 'counterforce brace'. The theoretical basis of FB use is its reduction in the wrist extensor muscles' activity during functional activities [32]. The literature has proposed the two most common mechanisms of action for FB. According to the first theory, FB narrows the forearm muscle system and prevents full muscle contraction. This inhibition of muscle dilatation reduces the magnitude of muscle contraction, and accordingly, tension in the musculoskeletal unit proximal to the FB decreases. The second theory suggests that FB applies direct compression to the extensor carpi radialis brevis (ECRB) muscle belly. This compression is assumed to create a secondary origin in the lateral epicondyle. Electromyographic (EMG) studies confirmed reduced EMG activity in the forearm muscle system when treated with the forearm support band [33]. The use of a brace increases proprioception, thereby improving the biomechanics of the joint, reducing overuse, and increasing the pain threshold [34].

A placebo-controlled study reported that the use of FB to treat LE achieved a significant improvement in pain frequency and severity over the short term and at the 26th week of function. These results were preserved for one to four years of follow-up [16]. On the contrary, a study by Wuori et al. [17] found no effect on grip strength from FBs. Meyer et al. [18] reported that using a brace to treat LE decreases the muscle load and reduces pain, leading to a stronger muscle contraction and, thus, increasing grip strength. Bisset et al. [35] reported that braces' immediate effect on LE patients improved painless grip strength and the PPT. Our results showed that FB improved pain, grip strength and function at the third and sixth weeks. Improvements in PPT were observed at the sixth week. The SF-12's physical component showed a significant improvement at weeks 3 and 6, whereas the mental components showed no significant improvement. This difference might have resulted from individual variations.

Kachanathu et al. [32] showed that the application of FB in LE treatment provides significantly better handgrip strength and functional improvement than elbow taping and conventional therapy. On the contrary, Phadke et al. [36] showed that KT – as well as counterforce braces – is equally effective vis-à-vis pain, grip strength and decreasing disability in patients with LE. Our results supported the results of Phadke et al. and showed that both treatment methods similarly affect pain, PPT, grip strength, function and quality of life. Also, the cost of a roll KT and the cost of FB were similar. KT and FB also have biomechanically similar effects, and both reduce power on the lateral epicondyle

[18]. The transverse tape could simulate a counterforce brace, potentially improve pain and pain-free grip strength when applied to a similar location [37]. In our study, we applied a transverse 'fascial correction' strip band in addition to a longitudinal KT strip applied to the forearm extensor muscles for three weeks. Kachanatsu [32] used the elbow taping method for two weeks. Phadke et al. [36] used the inhibitory and space corrective method for the first three weeks and the facilitatory method for the last three weeks of treatment. Differences in application time and techniques may have led to these contradictory results.

Limitations

Our study involved a short follow-up period of six weeks and included two groups' comparisons: FB and KT. In the study by Bisset et al. [38], approximately one-third of participants in the control group also showed patient-related global improvement at the sixth week. This improvement suggests that a natural resolution of pain and function occurs within this timeframe. Therefore, we suggest randomized, controlled trials including a wait-and-see group, which should also evaluate longer-term follow-up results.

Conclusion

The results of our study showed that KT and FB treatments of LE significantly improves pain, handgrip strength, functions and quality of life. Moreover, neither method was found to be superior to the other method in this regard. Therefore, FB or KT could contribute to traditional therapy in LE treatment.

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Effects of fibrin matrix and Ishikawa cells on in vitro 3D uterine tissue cultures on a rat model: A controlled study

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Ethics Committee Approval
The ethical approval of this study was authorized by the Acibadem Mehmet Ali Aydinlar University Local Ethics Committee for Animal Experiments (ACU-HADYEK) with the decision number 2018/16 on the 9th of April 2018.
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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: In recent years, developing an embryo in in vitro conditions has been one of the most challenging and popular objectives in reproductive biology. In vitro models make observing the relationship between the two possible. Various cell culture and matrix models have been created to overcome embryonic disorganization during culturing. The primary aim of this study was to evaluate and compare the effects of fibrin, Ishikawa cell line, and a combination of both on the 3D multilayer uterine tissue cultures on a rat model, including a control group.

Methods: This study was designed as a prospective controlled cohort study. The standard uterine culture model [CNT] (N: 3) constituted the control group. In addition, fibrin matrix-supported [FIB] (N: 3), Ishikawa cells-supported [ISH] (N: 3), and a combination of both [FIB+ISH] (N: 3) culture models were designated as the exposures. All models were cultured for 14 days. Afterwards, the optimal model was determined regarding glucose consumption, lactate production, endometrial thickness and gland count (primary outcomes) with semi-quantitative and statistical methods. Finally, the optimal model was implanted with blastocytes, and the survival duration was observed (secondary outcome).

Results: There were significant differences between the groups in terms of glucose, lactate, endometrial thickness (millimeter), and the number of endometrial glands (P<0.05). FIB had the least glucose consumption, and the least lactate production was in CNT. The thickest endometrium and most endometrial glands were detected in FIB when all groups were compared, allowing for 14 days of embryo survival.

Conclusion: In embryogenesis research, the fibrin-matrix-supported culture model could be a satisfactory 3D uterine tissue culture model.

Keywords: Cell line, Tumor, Co-culture, Extracellular matrix, Fibrin, In vitro, Tissue culture techniques

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Introduction

Complete embryogenesis has been an important goal in reproductive medicine for many years. The primary determinant in embryogenesis is the quality of the relationship between the embryo and endometrium. Therefore, both a healthy embryo and endometrium are crucial for healthy embryogenesis. In vitro models make observing the relationship between the two possible. The previous studies carried out on rat models indicate that the embryos could survive in the uterine tissue and matrix and cell lines without degeneration until 14 days, and even late organogenesis was achieved with the addition of a roller culture incubator platform with a gas and pressure modulator [1, 2]. However, complete embryogenesis is yet to be achieved. Severe conditions such as infertility, implantation failures, and recurrent pregnancy losses could be prevented when long-term in vitro culturing techniques advance that far.

Some in vivo culture models that enabled the development of the post-blastocyte phase have increased the implantation, therefore, success in embryological studies. In addition, the culture models made differentiation of the three germ layers, epiblast development, amnion, and yolk sac formation possible. However, the disorganization of the embryos in these models began on days 12-13 [3, 4].

Various kinds of cell culture and matrix models have been created to overcome embryonic disorganization. These models have been studied on mice, rats, pigs, and monkeys due to the ethical difficulties regarding humans. It could be observed that the tested feeder cell culture and matrix models have been focused on three types: Embryo + cell co-culture models [5-7], 3D multilayer/organoid models [8-11], and whole organ culture models [12, 13].

Implanting embryos in different cell cultures is hypothesized to provide better receptivity and longer viability in embryo + cell co-culture models. For example, Niu et al. [5] detected gastrulation, but their co-culture model collapsed before it reached day 20. Nowotschin and Hadjantonakis [6] also studied in vitro pre- and post-implantation with different cultures until the blastocyst stage with a mouse model. Additionally, there are co-culture models derived from the endometrial stromal cells from the regularly menstruating patients obtained via endometrial biopsy. However, in vitro embryos in these models had a maximum lifespan of six to eight days [7].

Secondly, the embryo co-culture model was developed into a complex 3D multilayer/organoid structure containing multiple cell types and biomaterials to investigate whether it could prolong embryo survival even more. Bentin-Ley et al. [8] detected trophoblast invasion due to embryo implantation in their multilayer human endometrium culture model. Wang et al. [9] attempted to improve this model by combining endometrial and trophoblastic cell lines with a fibrin-agarose matrix. Different from other models, Rozner et al. [10] created a 3D model consisting of peripheral blood immune cells and decidual macrophages in combination with Matrigel® with a rhesus monkey model. Ten days of embryonic development was achieved in both studies. Afterwards, Chang et al. [11] carried out blastocyte implantations in a microenvironment consisting of Buffalo Rat Liver feeder cells with Matrigel®. 21-45 days of embryonic development was achieved. It is essential to consider the anatomical, physiological, and developmental milestones between mammals such as rats, monkeys, and humans [14-16]. These differences must be observed in molecular and histologic processes in in vitro studies to allow for better translation to clinical medicine.

Lastly, there have been two studies on whole organ culture models with swine and pig uterus. Geisler et al. [12] aimed to sustain the swine uterus ex vivo long-term with open perfusion for 8-13 hours. Han et al. [13] achieved spontaneous in vitro fertilization using pig uterus and enabled the embryo's development until the blastocyst stage. Even though the information regarding the early stages of embryogenesis is improving, the knowledge about the post-implantation phase needs further research.

The primary aim of this study was to evaluate and compare the effects of fibrin, Ishikawa cell line, and a combination of both on the 3D multilayer uterine tissue culture model in a rat model with a control group. The secondary aim of the study was to determine the duration of blastocyte survival that the optimal model enables.

Materials and methods

The ethical approval of this study was authorized by the Acibadem Mehmet Ali Aydinlar University Local Ethics Committee for Animal Experiments (ACU-HADYEK) with the decision number 2018/16 on the 9th of April 2018. The study was conducted in Acibadem Mehmet Ali Aydinlar University Laboratory Animal Application and Research Center (ACU-DEHAM).

Selection and description of rats

Twelve healthy 6-8 weeks old anestrous adult female Wistar Albino rats with an average weight of 350-400 g were purchased from ACU-DEHAM, which follows the Federation of European Laboratory Animal Science Associations (FELASA) guidelines and is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). The inclusion criterion was being healthy, and the exclusion criterion was being pregnant. The rats were kept at a room temperature of 24 °C, with a 12:12 day/night cycle with adequate water and food supply. Uteri of the Wistar Albino rats have two horns per uterus (bicornuate uterus) due to their typical anatomic structure, which provided 24 uterine horns in total.

Technical information

Two hypotheses and their research questions were developed:

Hypothesis 1: Fibrin matrix, Ishikawa cell line, and a combination of these are associated with a better uterine metabolic activity and morphology.

1. Is there a significant difference between the models in terms of metabolic activity (glucose and lactate)?
2. Is there a significant difference between the models in terms of uterus morphology (endometrial thickness, number of endometrial glands; uterine histology; estrogen and progesterone affinity of the endometrial glands)?

Hypothesis 2: If an optimal model is determined in the testing of Hypothesis 1, how long will this model enable a blastocyte to survive?

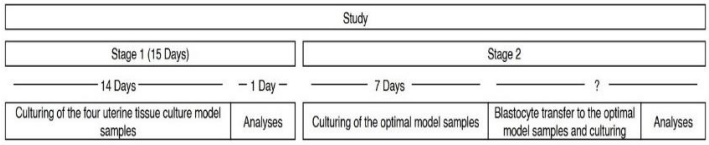
The primary outcomes were glucose and lactate measurements, endometrial thickness, number of endometrial glands, estrogen, and progesterone affinity of the endometrial glands. The secondary outcomes were embryo implantation and embryonic marker positivity.

Study Design

This study was designed as a controlled study and in two stages. Four groups, each consisting of three rats, were randomly formed. In Stage 1 (Primary Outcome), the standard uterine culture model [CNT] was the control. In addition, fibrin matrix-supported [FIB], Ishikawa cells-supported [ISH], and a combination of both [FIB+ISH] culture models were designated as the exposures. Each model was tested with three cultures. A total of 12 uterine tissues were assigned to all cultures randomly by the researcher. All models were cultured for 14 days. Lastly, metabolic and microscopic (primary outcome) analyses were carried out at the end of the 14th day (15th day).

In Stage 2 (Secondary Outcome), three uterine tissues were assigned randomly by the researcher to the model determined optimal in Stage 1. The three cultures of the optimal model were cultured for seven days. Afterwards, three blastocytes were implanted in each one of the cultures. The duration of survival of the implanted blastocytes was observed. Microscopic and molecular genetics (secondary outcome) analyses were carried out at the end. The researchers were not blinded to any data. The study flow is presented in Figure 1.

Figure 1: The flow of the study.



Chemicals, Reagents, Equipment, and Zygotes

Ishikawa cell lines (Sigma-Aldrich, St. Louis, Missouri, United States of America, SKU number: 99040201, Ishikawa Cell Line human) were tested against fungal contamination with tryptic soy broth, mycoplasmal contamination with polymerase chain reaction (PCR) method, and bacterial contamination with MALDI Biotyper® (Bruker Corporation, Billerica, MA, United States of America). Dulbecco's Modified Eagle Medium/Ham's F-12 Nutrient Mixture (DMEM/F12) medium (Sigma-Aldrich, St. Louis, Missouri, USA) and DMEM - low glucose (DMEM-LG) (Sigma-Aldrich, St. Louis, Missouri, USA), and Dulbecco's phosphate-buffered saline (DPBS) without Ca and Mg were used to culture the tissues.

ADVIA 1800 Clinical Chemistry System (Siemens Health Care Diagnostics Inc, Tarrytown, New York, USA) was used for the metabolic activity evaluations. Anti-estrogen receptor-α antibody produced in rabbit (Sigma-Aldrich, St. Louis, Missouri, USA, product number: SAB4500810), anti-progesterone Receptor antibody produced in rabbit (Sigma-Aldrich, St. Louis, Missouri, USA, product number: SAB4502184), anti-human chorionic gonadotropin (hCG) beta antibody [5H4-E2] (Abcam, Cambridge, United Kingdom, catalogue number: ab185628, mouse monoclonal), anti-cytokeratin 1 antibody [EPR17744] (Abcam, Cambridge, United Kingdom, catalogue number: ab185628), anti-vimentin antibody (Abcam, Cambridge, United Kingdom, catalogue number: ab137321, rabbit polyclonal), anti-Ki67 antibody (Abcam, Cambridge, United Kingdom, catalogue number: ab833, rabbit polyclonal) were used for immunohistochemical staining.

Nine Sprague Dawley® Rat (Strain name: RjHan:SD) zygotes were purchased from the same laboratory (Janvier Labs, Le Genest-Saint-Isle, France) to achieve standardization throughout the study. In addition, the zygotes were tested against mycoplasmal contamination with the PCR method.

Anti-Nanog antibody [23D2-3C6] (Abcam, Cambridge, United Kingdom, catalogue number: ab173368, mouse monoclonal), anti-SOX2 antibody (Abcam, Cambridge, United Kingdom, catalogue number: ab239218, goat polyclonal), Alexa Fluor® 488 (Abcam, Cambridge, United Kingdom, catalogue number: ab150077, goat anti-rabbit IgG H&L), and

Alexa Fluor® 647 (Abcam, Cambridge, United Kingdom, catalogue number: ab150079, goat anti-rabbit IgG H&L) were used for molecular genetics evaluations.

Stage 1 (Primary Outcome)

Obtainment of Uterine Tissue

All steps were carried out using sterilized surgical equipment. The rats were fixed in a supine position following general anesthesia, and the abdominal wall was shaved and disinfected with povidone-iodine. The abdominal walls were incised with a transverse incision, and total hysterectomies were performed. The removed tubular uteri were placed in sterile Petri dishes. The uteri were dissected from the corpora to the uterine horns with a single transverse incision, leaving the endometrium facing up and the parametrium down. The following dissected uteri were further dissected in approximately 10 mm in length, 5 mm in width, and 3 mm in height. The removed full-layer uterine tissues were put in a sterile isotonic solution containing 0.9% NaCl and placed in the cultures.

Standard Uterine Culture Model Preparation

The further-dissected uterine tissue measuring 10 mm in length, 5 mm in width, and 3 mm in height (3D uterine tissue) was placed in a 3 cm deep flask containing DMEM/F12 medium consisting of 1% antibiotics, and 10% fetal bovine serum (FBS) was placed in an incubator at 37 °C, 5% O_2, 5% CO_2, and 90% N_2 for the culture process. The DMEM/F12 medium was changed entirely every three days until the 14th day to prevent contamination.

Fibrin Matrix-supported Culture Model Preparation

Fibrin matrix formation: 45 ml plasma component and 4,5 ml CaCl are combined in a 50 ml Falcon tube. This mixture is then transferred to a 10 cm^2 petri dish. Afterwards, 0,5 ml transamine is added, and the mixture is quickly stirred. Finally, the Petri dish containing the mixture was placed in an incubator at 37 °C, 5% O_2, 5% CO_2, and 90% N_2 for 20 minutes for the fibrin matrix to form.

Combination of the fibrin matrix with the uterine tissue: The 3D uterine tissue measuring 10 mm in length, 5 mm in width, and 3 mm in height is gently placed in the Petri dish containing the formed fibrin matrix. 15 ml plasma component, 1.5 ml CaCl, and 0.16 ml transamine is added to the Petri dish until the upper side of the endometrium tissue is covered with the fibrin matrix solution. Next, a 10 ml DMEM-LG medium containing 1% penicillin/streptomycin and 10% FBS is added. Lastly, the final fibrin matrix-endometrium mixture is placed in an incubator at 37 °C, 5% O_2, 5% CO_2, and 90% N_2 for the

culture process. The DMEM-LG medium was changed entirely every three days until the 14th day to prevent contamination.

Ishikawa Cells-supported Culture Model Preparation

Ishikawa cell formation: The Ishikawa cells frozen in a nitrogen tank are thawed at 37 ºC. Then, they are transferred to a falcon tube in a laminar airflow cabin. Afterwards, DPBS is applied, and the mixture is centrifuged at 400 G for 10 minutes. Following this, the formed supernatant at the top of the tube is removed. The medium application and centrifuge steps are repeated three times. Next, the cells are combined with DMEM-LG in T300 flasks. The cells are cultured in an incubator at 37 ºC, 5% CO_2, and 5% O_2 for 72 hours. When the confluency of the flasks reaches 70%, the cells' mitotic ability is blocked with ten micrograms/ml mitomycin C in an incubator for 3 hours. Subsequently, the cells were removed with trypsin-EDTA and placed in a flask so that every cm^2 of the flask is coated with 3 to 5 million cells, forming the Ishikawa cell layer.

Combination of the Ishikawa cells with the uterine tissue: The 3D uterine tissue measuring 10 mm in length, 5 mm in width, and 3 mm in height is gently placed in the Petri dish containing the Ishikawa cells. 10 ml DMEM-LG medium containing 1% penicillin/streptomycin and 10% FBS is added. Lastly, the final Ishikawa cells-endometrium mixture is placed in an incubator at 37 ºC, 5% O_2, 5% CO_2, and 90% N_2 for the culture process. The DMEM-LG medium was changed entirely every three days until the 14th day to prevent contamination.

Fibrin matrix and Ishikawa Cells-supported Culture Model Preparation

The 3D uterine tissue measuring 10 mm in length, 5 mm in width, and 3 mm in height is gently placed in a Petri dish containing the fibrin matrix and Ishikawa cells which the preparations were described above. Next, a 10 ml DMEM-LG medium containing 1% penicillin/streptomycin and 10% FBS is added. Lastly, the fibrin matrix-Ishikawa cells-endometrium mixture is placed in an incubator at 37 ºC, 5% O_2, 5% CO_2, and 90% N_2 for the culture process. The DMEM-LG medium was changed entirely every three days until the 14th day to prevent contamination.

Stage 1 Analyses

Metabolic Activity (Glucose and Lactate Measurements)

On the 7th and 14th days, the mediums of the uterine tissue culture models were sampled with pipettes, and the glucose levels were measured with quantitative methods such as Trinder's glucose oxidase method using a Glucose hexokinase-3 kit and the lactate levels were measured with quantitative methods using a lactate kit.

Uterus Morphology (Histopathologic Analyses)

Cultured uterine tissues were fixated in 10% neutral formalin. Following this, the tissues were embedded in paraffin blocks following dehydration and paraffin inclusion steps. Finally, 4-micron sections were taken and stained with hematoxylin and eosin [17].

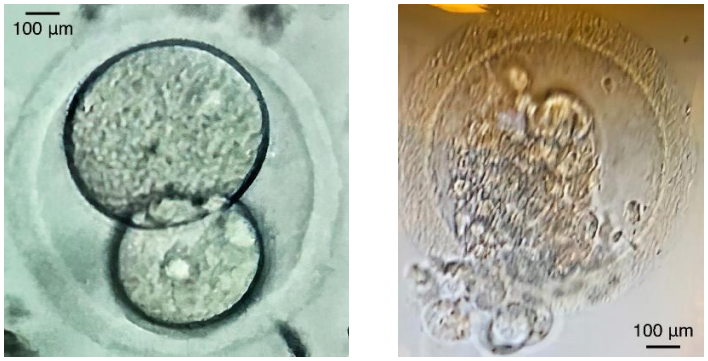
Markers selected for demonstrating the embryonic and extra-embryonic cell increase were visualized via immunohistochemical staining. The 4-micron sections were cleaned of paraffin and rehydrated following the immunohistochemical staining. Afterwards, they were stained using the streptavidin-biotin-peroxidase method [18]. The sections which were going to be applied with primary antibodies were placed in a citrate buffer solution and put in a microwave oven for 15 minutes. Subsequently, they were bathed with phosphate-buffered saline (PBS) three times. Afterwards, the endogenous peroxidase activity was blocked by applying a 3% hydrogen peroxide solution. Next, a single drop of designated primary antibodies was applied and waited for 60 minutes. The following steps were repeated with the same method for the five µL of the designated stains: ERα, PR, hCG, cytokeratin, vimentin, and Ki-67. Finally, the sections were bathed with tris buffer solution for the removal of the primary antibodies.

Afterwards, drops of the secondary antibody and streptavidin peroxidase solutions were applied and waited for 10 minutes. Next, the sections were bathed with PBS. Diaminobenzidine chromogen was applied for 20 minutes. After bathing the sections with deionized water, hematoxylin was applied for contrast staining for one to three minutes. After that, the sections were applied with a series of alcohol solutions with increasing density and xylene to achieve transparency. Subsequently, the microscopic slides were closed following the application of Entellan®. In the immunohistochemical semi-quantitative evaluations, the cells which showed positive staining in the minimum of three randomly chosen fields were evaluated under a light microscope.

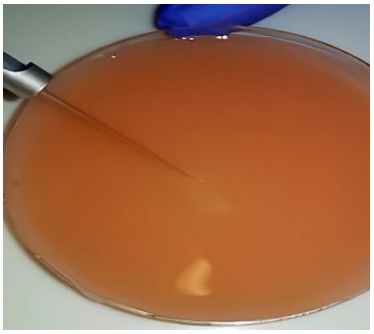
Figure 2: Embryo culturing and implantation.

A. Rat embryo on the second day of the culturing (light microscopy, x400 magnification)

B. Rat embryo on the fifth day of the culturing (light microscopy, x400 magnification)



C. Implantation of the embryo to the endometrial field in the uterine culture



Stage 2

In this stage, following the determination of an optimal uterine culture environment at stage 1, three culture models of the optimal model were prepared. First, seven days of culturing with DMEM-LG (with the medium changed every three days) in an incubator at 37 ºC, 5% CO_2, and 5% O_2 was performed. Next, the zygotes designated for implantation were cultured for five days in an incubator at 37 ºC, 5% CO_2, 5% O_2, and 90% N_2 (Figure 2.A and Figure 2.B) [19]. Afterwards, on the 7th day,

three 5-days-old blastocytes were transferred to the endometrial surface below each of the models using a Pasteur micropipette for achieving minimal trauma (Figure 2.C). Lastly, the medium was changed every 24 hours.

Stage 2 Analyses

At the end of Stage 2, evaluations were carried out macroscopically and microscopically using hematoxylin and eosin, immunohistochemical staining (ERα, PR, hCG, cytokeratin, and vimentin stains), and molecular genetics markers (NANOG and SOX2). In addition, immunohistochemical staining was carried out with the same protocol mentioned above [17].

NANOG and SOX2 Staining

The microscopic slides were fixated with paraformaldehyde solution at room temperature for thirty minutes and washed twice with DPBS (Ca^- & Mg^- free). Next, 1,5 ml phosphate-buffered saline with Tween™ was applied to the slides for 10 minutes at room temperature. Afterwards, the slides are washed with DPBS (Ca^- & Mg^--free) twice. Afterwards, 1,5 ml bovine serum albumin (BSA) solution is applied to the slides, and they are incubated at 37℃ for 30 minutes. Subsequently, the BSA solution is removed without any contact with the drop in the middle. Finally, the periphery of the drop is dried without any contact with the middle drop itself.

Anti-NANOG and anti-SOX2 stains are diluted in a 1:50 fashion for creating a 400 µl antibody solution. Afterwards, the solution is applied to the slides, and they are incubated at 37℃ in the dark. Following primary antibody incubation, the slides are washed with DPBS (Ca^- & Mg^--free) twice. For the secondary antibody incubation, Alexa Fluor 488 and Alexa Fluor 647 are diluted in a 1:200 fashion. Afterwards, the solution is added to the slides, and they are incubated at 37℃ in the dark. Following primary antibody incubation, the slides are washed with DPBS (Ca^- & Mg^--free) three times. Subsequently, the slides are incubated in a DPBS solution containing DAPI for 10 minutes at room temperature and stained. The slides are washed with DPBS (Ca^- & Mg^--free) two times to remove the residue. Lastly, the slides are left in DPBS (Ca^- & Mg^--free) and examined under a confocal microscope.

Statistical analysis

The normality test was done with the Shapiro-Wilk test. Non-parametric statistical methods were used for values with skewed (non-normally distributed, Shapiro-Wilk $P>0.05$) distribution. Descriptive statistics were presented using median and percentile 25 and 75 (Q1 and Q3) for non-normally distributed variables. Non-parametric statistical methods were used for values with skewed distribution. For comparison of more than two non-normally distributed independent groups, the Kruskal Wallis was used. For comparison of two non-normally distributed independent groups, the Mann Whitney U test was used.

Statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

Stage 1 (Primary Outcome)

The groups are described in Table 1. All analyses were carried on the 15th day. There was a statistically significant difference in terms of glucose, lactate, endometrial thickness (millimeter), and the number of endometrial glands between the groups (Kruskal Wallis test, $P<0.05$) (Table 2).

Table 1: The distribution of the experiment groups

Groups	Number	%
CNT	3	25
FIB	3	25
ISH	3	25
FIB+ISH	3	25

CNT: Standard Uterine Culture Model, FIB: Fibrin Matrix-supported Culture Model, ISH: Ishikawa Cells-supported Culture Model, FIB+ISH: Fibrin matrix and Ishikawa Cells-supported Culture Model

Table 2: Comparison of parameters according to the groups

	CNT N=3 Median (Q1-Q3)	FIB N=3 Median (Q1-Q3)	ISH N=3 Median (Q1-Q3)	FIB+ISH N=3 Median (Q1-Q3)	*P*-value
Glucose	76 (62-84)	87 (74-100)	33 (30-45)	4 (4-5)	0.021
Lactate	54.4 (35.5-75.6)	107.0 (89.5-112.0)	87 (65.6-95.2)	132.0 (120.0-135.0)	0.023
Endometrial Thickness (millimeter)	0.2 (0.1-0.25)	0.65 (0.55-0.7)	0.35 (0.3-0.4)	0.35 (0.1-0.45)	0.046
Number of Endometrial Glands	0 (0-0)	5 (4-6)	0 (0-0)	3 (2-4)	0.015

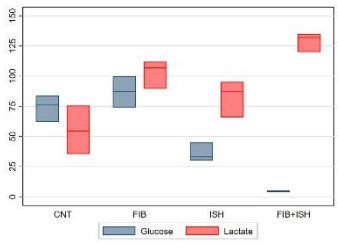
Kruskal Wallis test, CNT: Standard Uterine Culture Model, FIB: Fibrin Matrix-supported Culture Model, ISH: Ishikawa Cells-supported Culture Model, FIB+ISH: Fibrin matrix and Ishikawa Cells-supported Culture Model, N: Number

Metabolic Activity

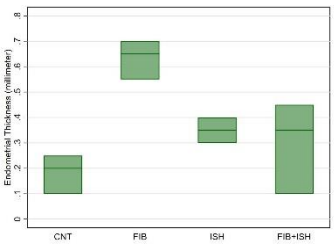
Glucose and lactate measurements were calculated as the average of the 7th and 14th-day measurements and are presented in Figure 3.A. The most glucose consumption and lactate production were detected in FIB+ISH. Conversely, FIB had the least glucose consumption, and the least lactate production was in CNT.

Figure 3: Boxplots. (CNT: Standard Uterine Culture Model, FIB: Fibrin Matrix-supported Culture Model, ISH: Ishikawa Cells-supported Culture Model, FIB+ISH: Fibrin matrix and Ishikawa Cells-supported Culture Model)

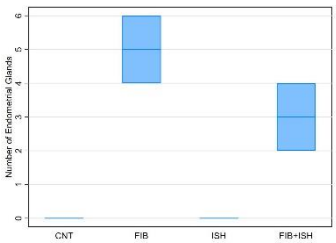
A. Glucose and lactate measurements



B. Endometrial thickness



C. The number of endometrial glands



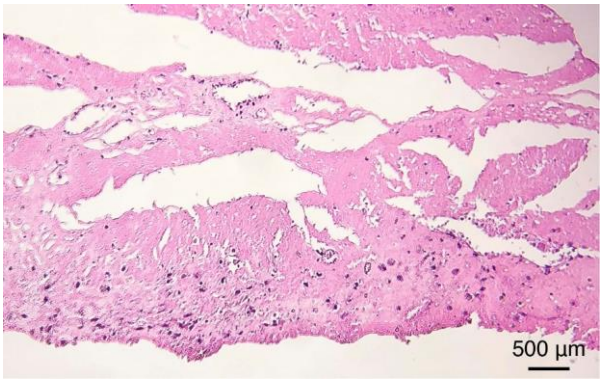
Uterus Morphology

Endometrial Thickness and the Number of Endometrial Glands

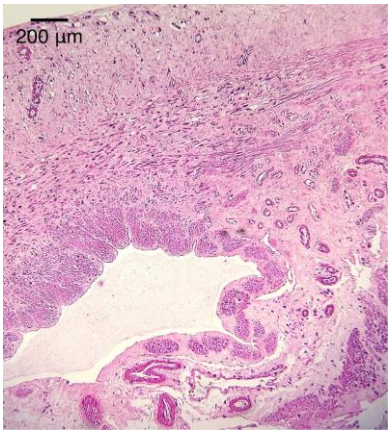
Endometrial thickness and the number of endometrial glands are presented in Figure 3.B and Figure 3.C. The thickest endometrium and most endometrial glands were detected in FIB, whereas the thinnest endometrium was in CNT. The least number of glands was detected in CNT and ISH, the gland count being zero.

Figure 4: Histologic evaluations (1 high-power field, hematoxylin & eosin).

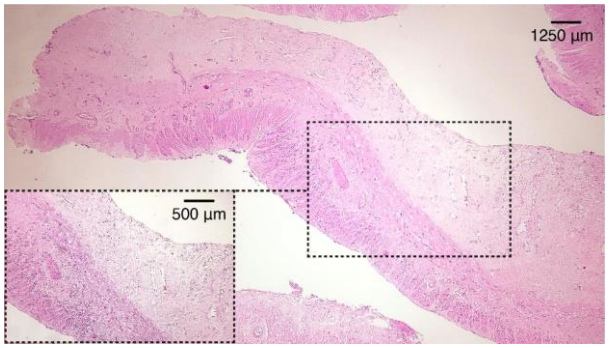
A. The control group is demonstrating a lack of development of the endometrium, myometrium, perimetrium, uterine glands, and uterine vasculature (x100 magnification)



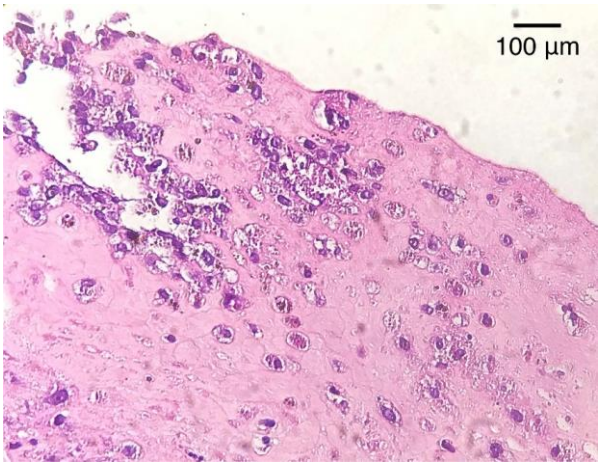
B. Fibrin-matrix supported culture model (FIB) exhibiting uterine walls composed of three layers: the endometrium, myometrium, parametrium, and containing blood vessels and uterine glands. FIB exhibiting formation of uterine vasculature (7-8%) and endometrial glands (<5%) (x200 magnification)



C. Ishikawa cells-supported culture model (ISH) displaying telangiectatic vasculature and (main image, x40 magnification; lower-left corner image, x100 magnification)



D. ISH is showing the presence of pyknotic cells (77%) (x400 magnification)



E. FIB+ISH is exhibiting uterine wall composed of three layers and connective tissue lamina propria containing large microvessels, endometrial glands, and large endometrial glandular formation. (x100 magnification)

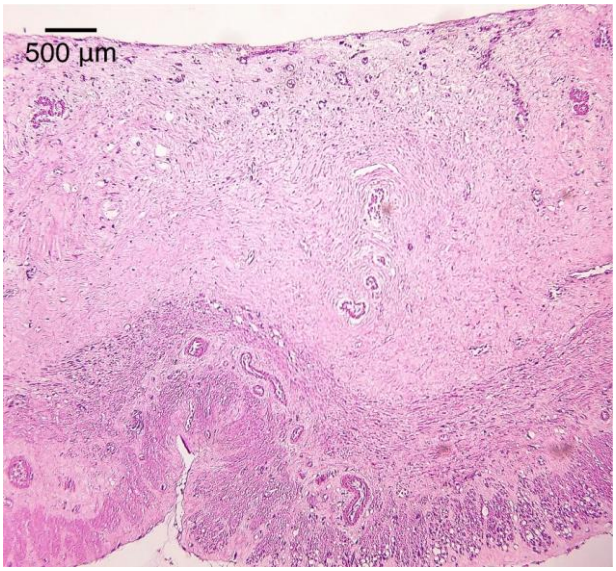
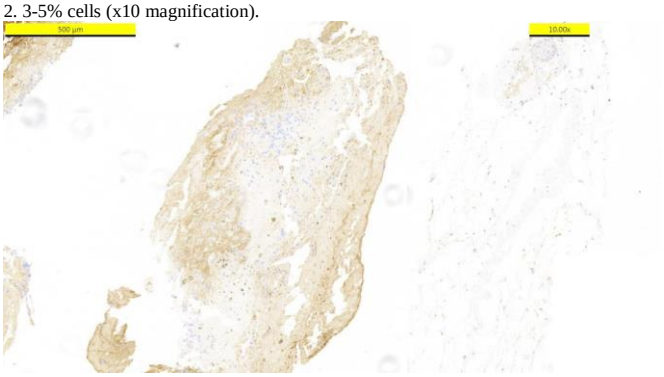
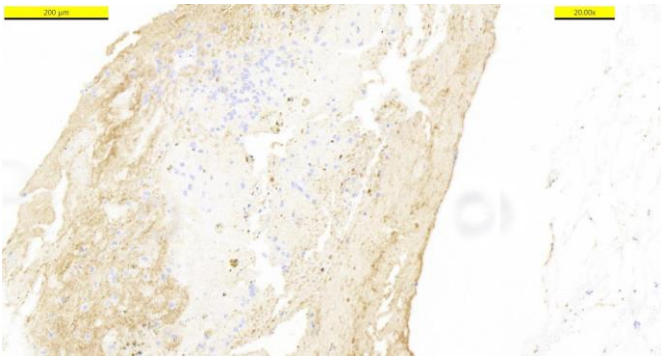


Figure 5: Estrogen affinity findings [1 high-power field, anti-estrogen receptor α (ERα) antibody]. A. Control group showing low nuclear and non-specific background staining. 1. 10-15% nuclear staining (x4 magnification)

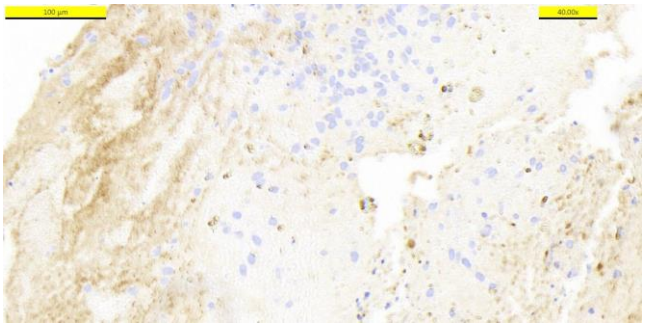
2. 3-5% cells (x10 magnification).



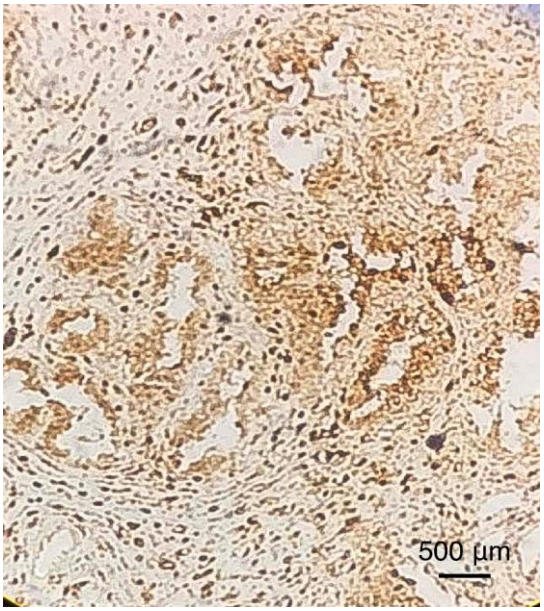
1. 3-5% cells (x20 magnification)



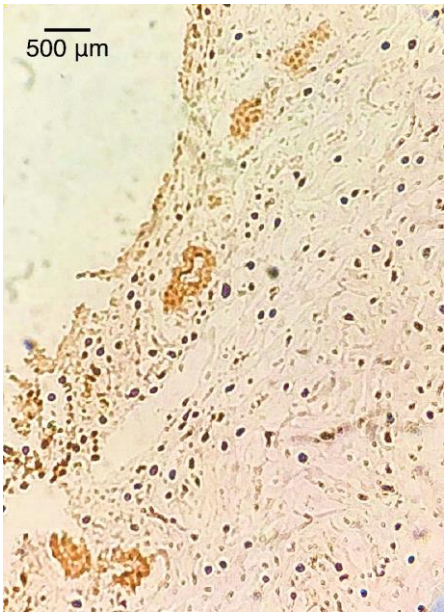
2. 3-5% cells (x40 magnification)



B. Fibrin-matrix supported culture model (FIB) exhibiting strong staining for ERα in the uterine glands (80% nuclear staining, x100 magnification)



C. Ishikawa cells-supported culture model (ISH) demonstrating ERα in the endothelial cells of the blood vessels (95% nuclear staining, x100 magnification)



D. ERα presence in the endometrial stroma and uterine glands of FIB+ISH (70% nuclear staining, x100 magnification)

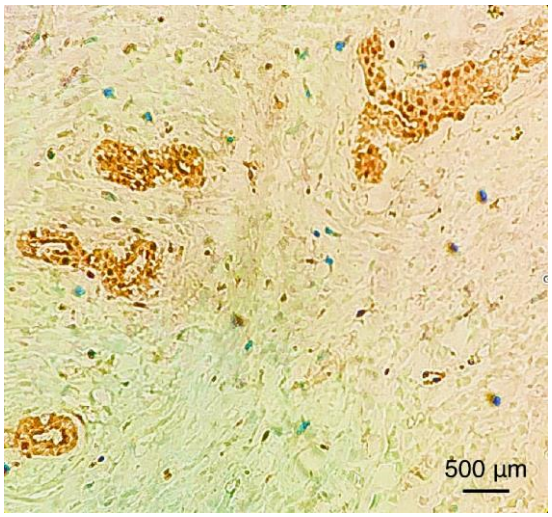
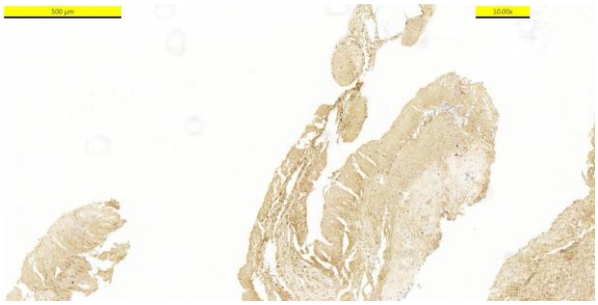
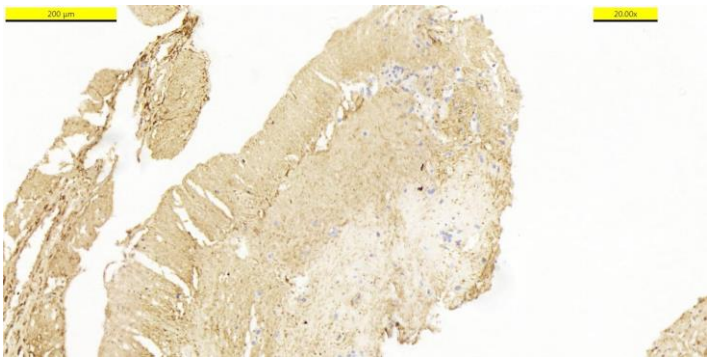


Figure 6: Progesterone affinity findings [1 high-power field, anti-progesterone receptor (PR) antibody]. A. CNT is showing no staining. 1. Diffuse background staining (x4 magnification)

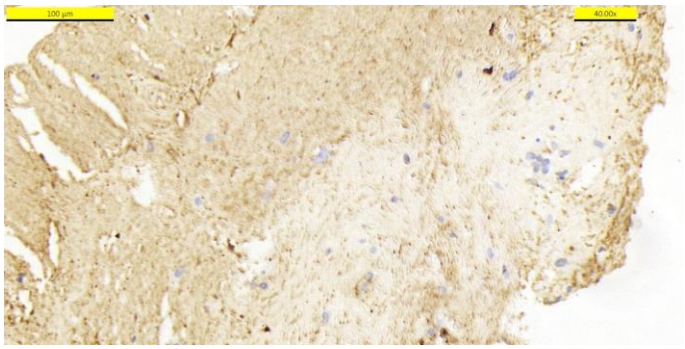
2. x10 magnification



3. x20 magnification

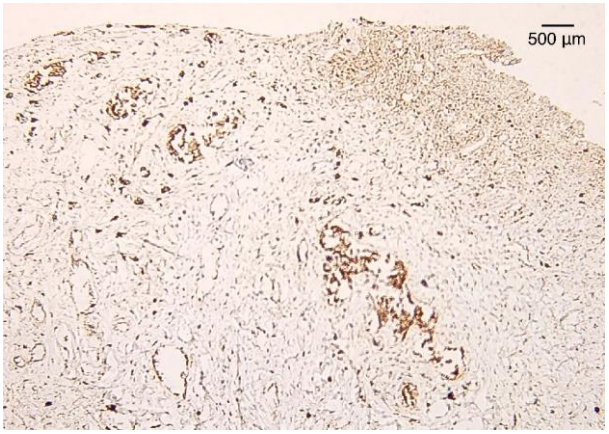


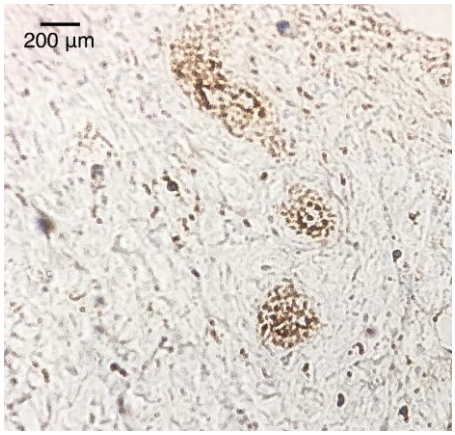
4. x40 magnification



B. Fibrin-matrix supported culture model (FIB) exhibiting PR presence in the endometrial epithelial cells and the uterine glands (55-60% nuclear staining, x100 magnification)

C. Ishikawa cells-supported culture model (ISH) demonstrating PR presence in the stromal cells and the uterine glands (70% nuclear staining, x200 magnification)





D. FIB+ISH displaying smooth muscle fibers of the myometrium and the uterine glands demonstrating weak positivity for PR antibody (55-60% nuclear staining, x200 magnification)

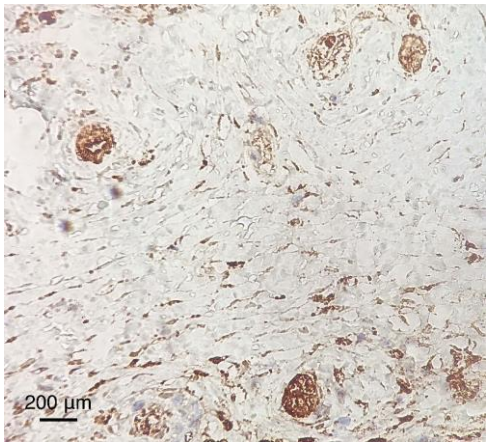
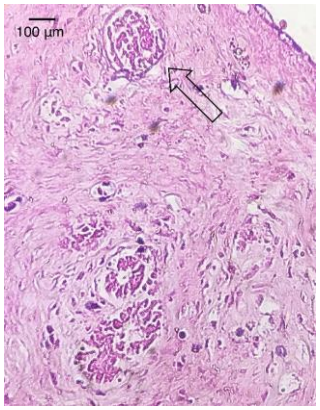


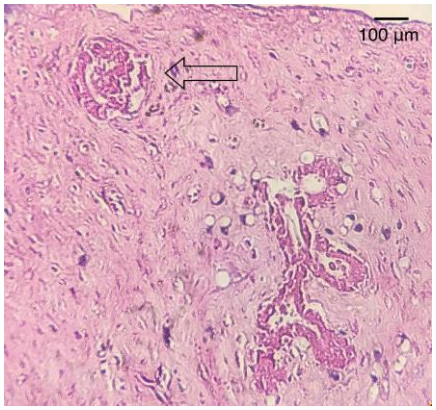
Figure 7: Implantation reaction in the Petri dish.

Figure 8: Embryos in the fibrin matrix-supported culture model (1 high-power field).

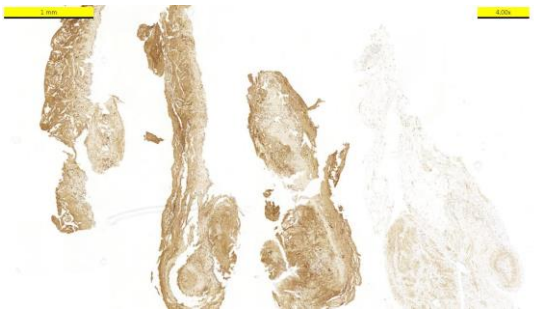
A. Embryonic body (arrow) (x400 magnification, hematoxylin & eosin)



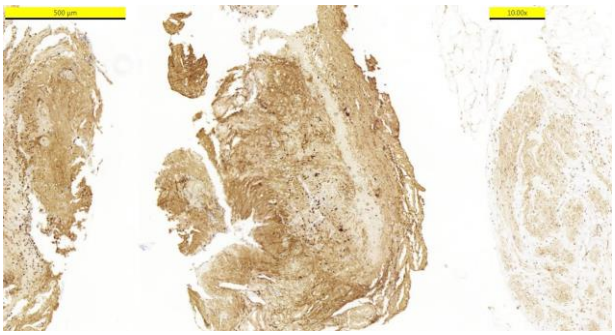
B. Embryonic body (arrow) (x400 magnification, hematoxylin & eosin)



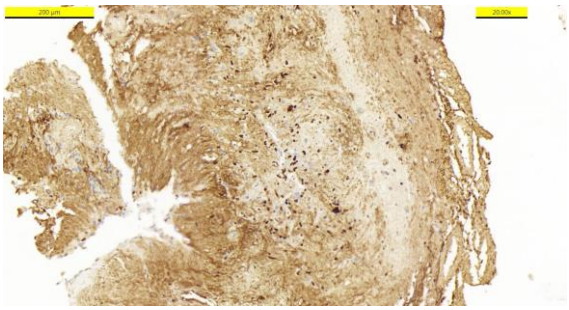
C. Estrogen receptor alpha positive cells around the uterine glands (60-70%) (x400 magnification, anti-estrogen receptor alpha). 1. x4 magnification



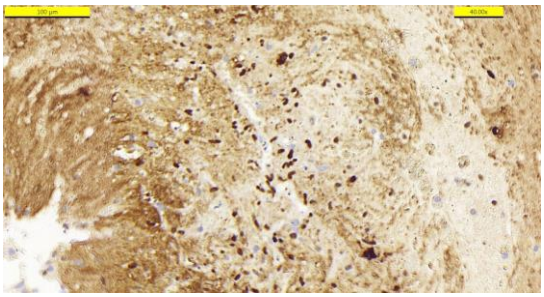
2. x10 magnification



3. x20 magnification

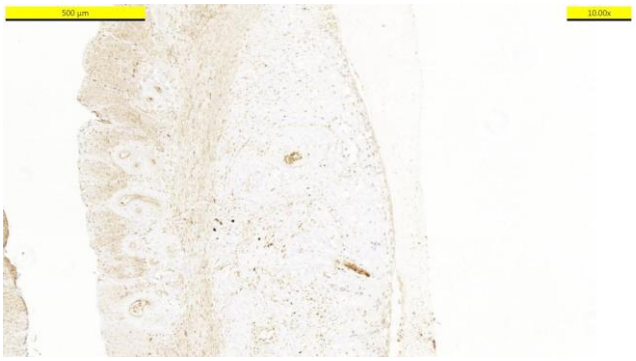


4. x40 magnification

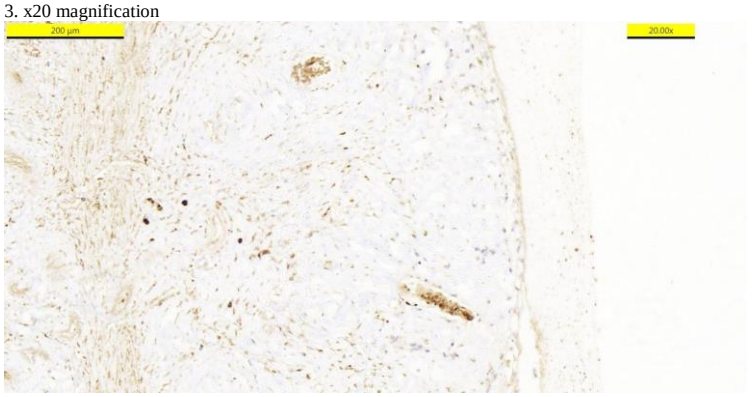


D. Progesterone receptor-positive cells in the nuclei of stromal cells (60-70%) (x400 magnification, anti-progesterone receptor). 1. x4 magnification

2. x10 magnification



3. x20 magnification



4. x40 magnification

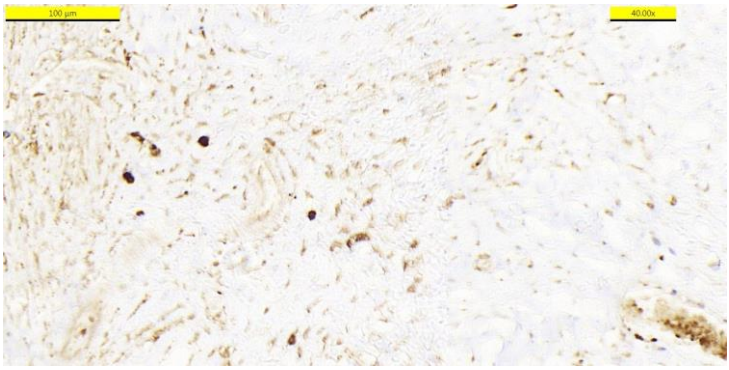
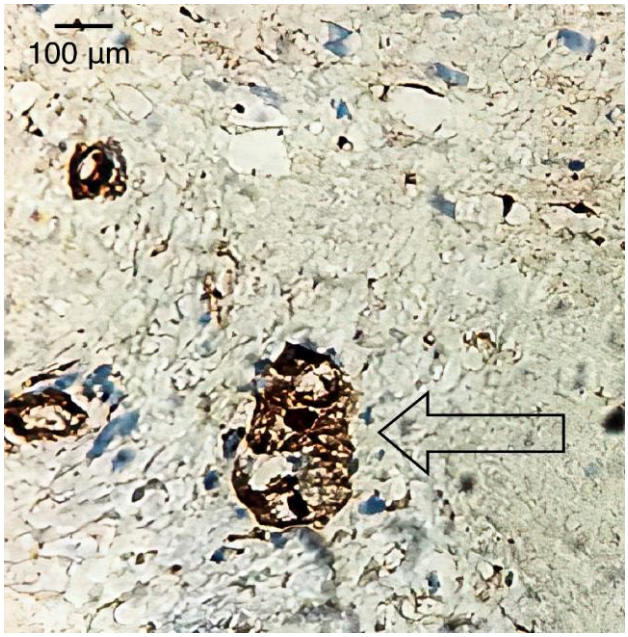
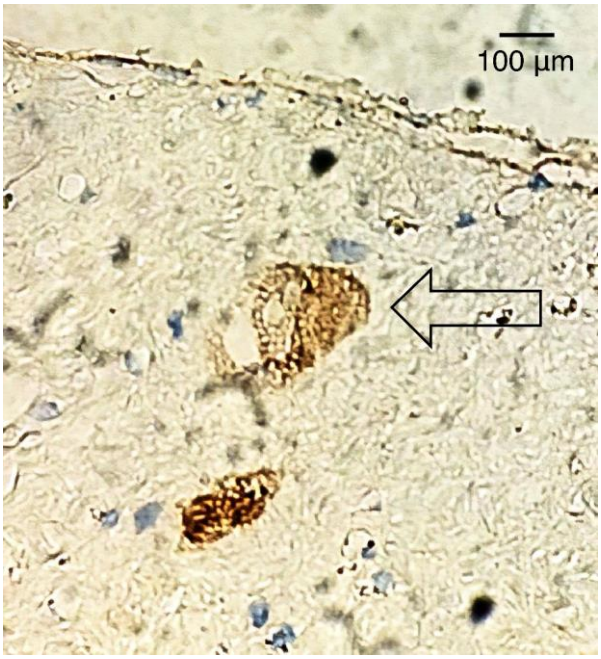


Figure 8: Embryos in the fibrin matrix-supported culture model (1 high-power field).

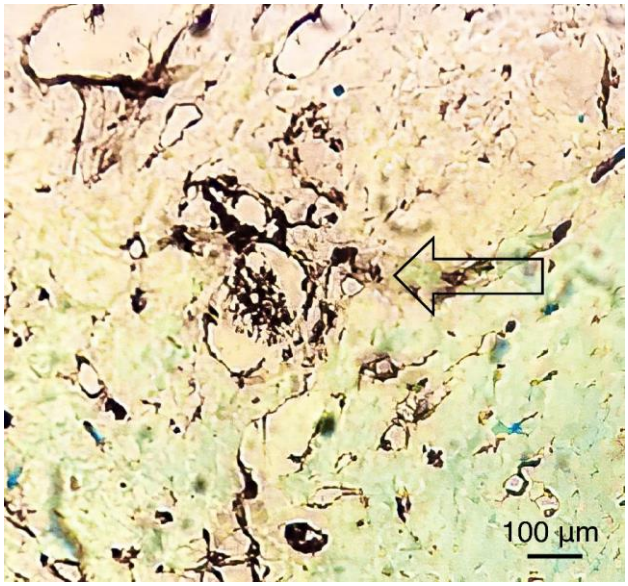
E. Embryonic body (arrow) and differentiated trophoblasts (anti-human chorionic gonadotropin antibody)



F. Embryonic body (arrow) and differentiated trophoblasts (x400 magnification, cytokeratin)



G. Embryonic body (arrow) (x400 magnification, vimentin)



H. Embryonic body (arrow) (x200 magnification, Ki-67)

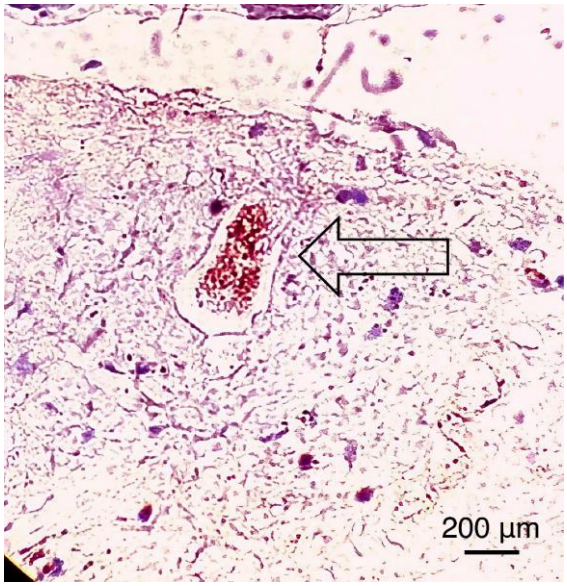
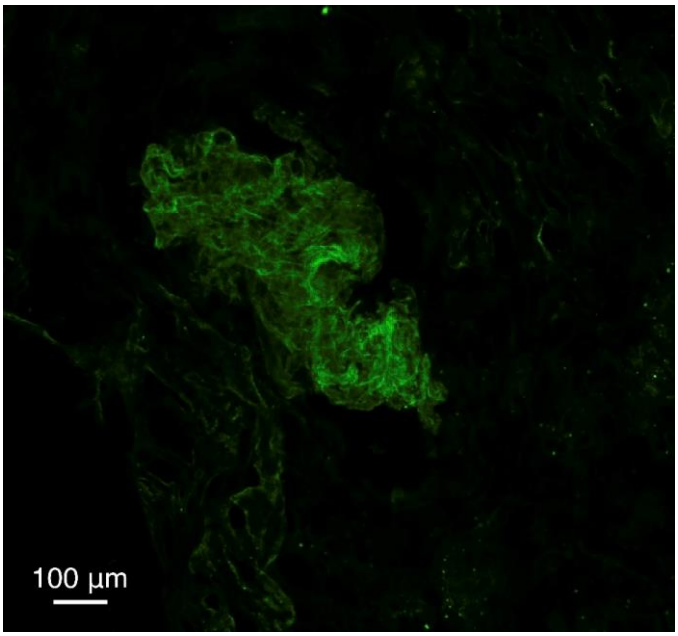
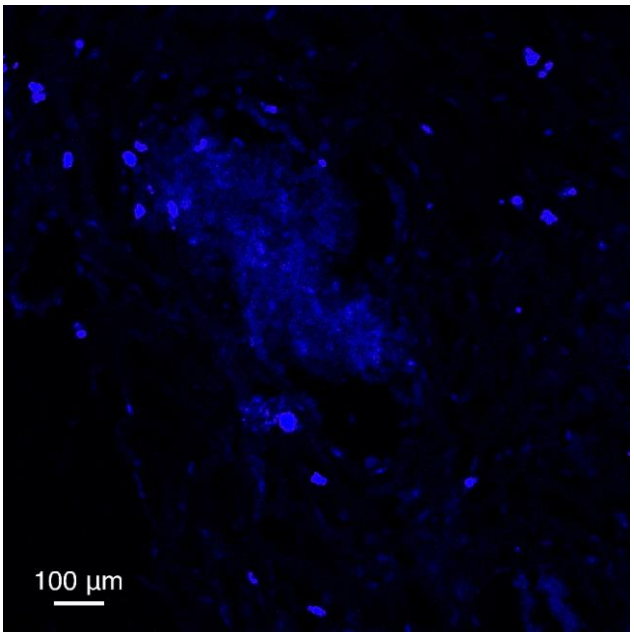


Figure 9: Embryo viability markers in the fibrin matrix-supported culture model (x100 magnification). A. Exhibiting gastrulation (NANOG)



B. Exhibiting gastrulation (SOX2)



Uterine Histology

In histopathologic semi-quantitative evaluations, in CNT, the three layers of the uterus were separated from each other, and the layers were not internally intact, and the tissue integrity was not preserved. The thickness of the endometrium was thin. These were attributed to the extensive necrosis in the endometrium and the myometrium. Additionally, the tissue itself was reduced in volume due to liquefaction. The tissue morphology was not preserved, and uterine glands were absent (Figure 4.A).

In FIB, the morphology of the endometrium, myometrium, perimetrium was intact. Additionally, uterine glands and vascularity were observed to be preserved (Figure 4.B).

In ISH, the absence of stromal cells, the sparsity of the vessels, and the presence of pyknotic cells were remarkable (Figure 4.C and Figure 4.D). Therefore, it was concluded that only the Ishikawa cells were not sufficient for uterine glands to form.

In FIB+ISH, the morphology of the endometrium, myometrium, perimetrium was intact. It was demonstrated that vascularity was preserved (Figure 4.E). Connective tissue lamina propria contained large microvessels and endometrial glands.

When all groups were compared, FIB had the thickest endometrium and the most endometrial glands. FIB+ISH was second in the number of endometrial glands, whereas CNT and ISH did not demonstrate any glands. CNT had the thinnest endometrium.

Hormonal (Estrogen and Progesterone) Affinity of the Endometrial Glands

ER-positive cells were detected in patches in the muscularis mucosa of CNT (Figure 5.A.1-4). Strong staining ER-positive cells were detected in the periphery of the submucosa and endothelium of FIB (Figure 5.B). ER positivity in the uterine glands of ISH were more prominent when compared with FIB+ISH (Figure 5.C and Figure 5.D).

PR expression was negative in CNT (Figure 6.A.1-4). PR positive cells were detected scarcely in the periphery of submucosa and endothelium in FIB (Figure 6.B). PR positive cells in ISH were more strongly stained when compared to FIB+ISH (Figure 6.C and Figure 6.D).

Stage 2 (Secondary Outcome)

All attempts had to be stopped due to macroscopic uterine tissue necrosis secondary to perfusion defect. The total duration of embryo viability was 14 days (21st day in the total duration of stage 2) in all cultures. Every culture was observed to have a single implanted embryo (Figure 7).

Embryo Staining

The embryos are shown in Figure 8.A and Figure 8.B. ERα and PR positive cells were detected around the uterine glands was present and regarded as embryonic implantation. (Figure 8.C.1-4 and Figure 8.D.1-4). hCG and cytokeratin staining detected the embryos and differentiated trophoblasts. Therefore, it was concluded as positive implantation (Figure 8.E and Figure 8.F). Additionally, vimentin and Ki-67 positive cells were detected in the laminar epithelia and trophoblastic differentiation zone (Figure 8.G, Figure 8.H).

Embryo Viability

The embryos were analyzed under a confocal microscope by staining with NANOG and SOX2 markers. The embryo tissue expressing positive signal was considered the continuing expression of three germ layers, and the integrity was preserved on the 14th day (21st day in the total duration of Stage 2). Additionally, the strong positive signals indicated that gastrulation was present (Figure 9). These correspond to embryonic day (E) 9 (E9) in embryo development. Thus, all three embryos were in stage E9.

Discussion

The main parameters contributing to the success of in vitro embryogenesis studies are the integrity of the endometrium, the positivity of embryonic markers, the presence of gastrulation, and the duration of viability [6, 8, 9, 20]. This controlled study's primary outcome was the metabolic, morphologic, and histopathologic effects of fibrin matrix, Ishikawa cells, and both on in vitro 3D uterine tissue cultures. The secondary outcome was the duration of embryo survival. Ishikawa cells were used instead of the uterine cells of the same rats due to their high metabolic energy output and the presence of estrogen and progesterone receptors.

A statistically significant difference was present between the groups in glucose, lactate, endometrial thickness, and the number of endometrial glands. Detrimentally high glucose consumption and lactate production were detected in FIB+ISH. Additionally, it had adequately preserved morphology and histology. However, it was not the best group in terms of metabolic activity and uterus morphology. These could have been due to a couple of reasons. Firstly, the rat endometrium and Ishikawa cells (human adenocarcinoma) could have damaged each other by secreting cross-species soluble factors such as cytokines such as interleukin-1β [21]. Moreno et al. [22] studied the effect of different growth factors and cytokines in addition to surfactants, embryotropic recombinant albumin, and hyaluronan without fetal calf serum and BSA on in vitro embryogenesis. It was demonstrated that the addition of cytokines and other factors positively affects embryo development.

Block et al. [23] also studied the effect of insulin-like growth factor, colony-stimulating factor 2, and hyaluronan on in vitro embryogenesis. In vivo maternal environment constitutes various growth factors, cytokines, hormones, and other regulatory molecules that affect embryo development. Transferring these molecules to a culture environment aids the development of the embryo. However, cytokine measurements and interventions were not performed in the current study. Secondly, the Ishikawa cells, which are adenocarcinoma cells that consume more glucose, could be disarranging the histologic integrity of the uterine cells by creating metabolic deprivation and harmful metabolites for the endometrial tissue. It could be prevented by changing the mediums more frequently and allowing more glucose in the uterine tissue.

The least glucose consumption was detected in FIB. It was considered a sign of adequate perfusion because the cells did not spend much energy to survive. It could also be attributed to the absence of glucose-depriving Ishikawa cells allowing the uterine tissue to survive without any deprivation and toxic

metabolites. In histopathologic evaluations, morphology and histology in FIB appeared to be preserved, and it had the thickest endometrium and the most endometrial glands. Additionally, ISH had the strongest staining for ER and PR. However, when every parameter was combined, FIB was better than ISH. Concurrent with the current results, Pelletier [24] has demonstrated positive staining for ER and PR in the pregnant rat uterine epithelial and stromal cell nuclei. Furthermore, Carvalho et al. [25] recorded that immunostaining for ERα was positive for glandular, epithelial, and stromal cell nuclei and cytoplasm of the uterus. As a result, FIB was determined as the optimal model (Stage 1).

When normal endometrium cells obtained via biopsy are cultured, it was defended that the endometrial, epithelial, and stromal cells were superior in terms of receptivity. Furthermore, it was determined that the natural killer and endometrial epithelial cells form a viable environment, especially for decidualization [26]. However, endometrial biopsies do not always provide a standard ratio of endometrial/epithelial cells. Therefore, artificial cell lines were created to overcome this issue and create a standard ratio of cells. Uchida et al. [27] created a new co-culture model using the Ishikawa cell line (human adenocarcinoma). They took advantage of the richness of estrogen and progesterone due to their adenocarcinoma nature and the adhesive properties of this cell line. However, as the current study demonstrates, this cell line was also restrictive due to the contamination caused by malignant cell formation and metabolically harmful.

Uterine tissue culture environments are attempting to be enhanced with co-cultures and biomaterials such as gels [5, 8-11], macrophages [10], stem cells [28 - 33], cell lines [34], and decellularized scaffolds [35-37]. Numerous researchers have combined uterine tissue with Matrigel®, a gelatinous protein mixture secreted by Engelbreth-Holm-Swarm mouse sarcoma cells, in different species' embryos [5, 8-11]. In the model by Rozner et al. [10], Matrigel® was combined with a matrix of maternal macrophages and pregnant monkey decidual cells. Additionally, stem cells are used and combined with Matrigel® for endometrial tissue regeneration studies [29].

In Stage 2, the study was terminated due to macroscopic necrosis on day 14. After evaluation, it was detected that each of the three models of FIB had successful implantation of a single embryo out of three. Additionally, estrogen and progesterone are essential markers of blastocyst development in addition to glandular epithelial proliferation. The endometrium is observed to have estrogen and progesterone receptors profusely when an embryo is held onto the uterus at the blastocyst stage. Blastocyte-implanted FIB was demonstrating stronger staining for estrogen and progesterone receptors than the non-blastocyte-implanted FIB. Thus, it points to successful implantation concurrent with the literature [24].

Each of the three models of FIB had successful implantation of a single embryo out of three implanted. The duration of embryo survival was 14 days. Moreover, immunohistochemical markers are essential in evaluating the multiplication and differentiation of the embryonic and extra-embryonic cells. Therefore, they were applied in the current study as well. Cytokeratin staining, a well-recognized marker to detect differentiated trophoblasts in placental cell isolates, showed areas positive for trophoblastic invasion [38]. Positive hCG staining points to the extra-embryonic cellular changes. It was also previously defined in the literature as a feature of differentiation of the trophoblasts into syncytiotrophoblasts [39]. Vimentin is a mesenchymal marker expressed from non-trophoblastic fibroblasts and endothelium when embryonic structures demonstrate growth [40]. In the current evaluations, the presence of vimentin-positive cells in the embryonic structure indicates mesenchymal growth. Ki-67 trophoblast proliferation marker was also positive [10]. In molecular genetics evaluations, NANOG and SOX2 staining demonstrated gastrulation and the embryo growth was deemed viable and classified as stage E9 (in 14-day old embryos). The literature also supported this as only onwards from stage E9 the NANOG and SOX2 markers were reported to be expressed [41]. A 14-day-old embryo matching the developmental stage, corresponding to day 9 (E9), could be contributed to the embryo's alteration of growth speed for adapting to environmental conditions [42]. It was also contributed to inadequate perfusion by the medium-only type of perfusion of the model. It is shown in the literature that when advanced perfusion tools with gas and pressure regulators are utilized, the in vitro embryo follows the same daily developmental course as a normal embryo [1]. The current study used a 3D uterine tissue culture system, and a continuous perfusion system was not used. Continuous perfusion systems are the next generation of 3D culture systems. Fibrin matrix-supported culture provides adequate perfusion for embryo development. Adding continuous gas perfusion to the current 3D model (FIB) could enable an in vitro embryogenesis model in which organogenesis could be observed. Combining the principles of the current study and Aguilera-Castrejon et al.'s [1] study could light the way for this.

In the organ perfusion models, the model by Geisler et al. [12] was designed for uterine transplant but is also considered valuable in embryonic development. In the model by Han et al. [13], monospermic insemination was achieved in ex vivo porcine uterus by in vitro fertilization. This model's embryonic development was slow; however, it is the first organ perfusion model to demonstrate monospermic blastocyte development. When the two models are evaluated, they need complex mechanisms to achieve long-term embryonic development since the organ in the model needs continuous perfusion to stay viable. Thus, the continuation of perfusion is the fundamental problem in whole organ models.

Enders et al. [43] have reported that rhesus monkey blastocyst in 2-D Matrigel® did not fully develop and had limited trophectoderm growth. Nevertheless, it was demonstrated that the trophoblastic activity was developing towards Matrigel®. Two of these embryos were followed until the 18th day, and the other two were followed until the 45th day. The embryo was sustained for a long time, but data regarding the embryonic markers in the study were not reported [11]. Rhesus monkey embryos' trophoblast development was detected until the 6th day. Afterwards, embryos were co-cultured in Buffalo rat liver cell-conditioned medium cultured using macrophages, and embryonic development was observed until the 9th day. hCG secretion was recorded until the 10th day, and the Ki-67 trophoblast

proliferation marker was detected due to staining. Thus, macrophage culture looks promising for placentation and gestation; however, long-term studies are required to validate this finding [10]. A review by Morris et al. [44] presents the culture models that support the human embryo until the gastrulation stage.

In recent years, a model by Niu et al. [5] containing Matrigel® allowed monkey embryogenesis and gastrulation findings were present after the 14th day. However, degeneration on the 20th day shows that the model enabled limited development. The current study demonstrated gastrulation similar to Niu et al.'s [5] study. However, considering the trimester of both species, 55 days per trimester for rhesus monkeys and seven days per trimester for rats, shows that when compared with the primate models, the current rat model corresponds to a more extended period of pregnancy when trimester durations between species considered. Additionally, one of the main differences of the current model with Niu et al.'s [5] study is that a uterine culture was not used for embryogenesis in the current study. Therefore, the current study's model is different due to the usage of the combined uterine culture.

There are strict ethical limits for human embryo studies, mainly focusing on the 14th day of development [45-54]. The embryo is accepted as an individual after the primitive streak is formed on day 14, and further research is prohibited [55]. Embryoids, which are animal cells taken from the intracellular matrix embryos and then cultured, behave like an early embryo (blastocyte and gastrulation stages) under culture conditions. The most significant advantage of the embryoids is that they do not possess an ethical issue, and in vitro embryogenesis research also focused on these [16, 33, 56-64]. Embryoids could also mimic specific developmental stages such as gastrulation [65, 66].

To summarize, the current results show that the fibrin matrix-supported uterine culture model supports embryogenesis and could be proposed as an adequate extracellular matrix for in vitro uterine tissue culture and embryogenesis studies. Furthermore, the embryonic cell markers being positive until the 14th day demonstrates that the model is satisfactory when the 21st-day uterus activity data of the current study and the pregnancy period of the rats are considered.

Limitations

The limitations of this study are, first, the limited number of uterine cultures and embryos. Secondly, only the optimally determined group was implanted with embryos instead of all the groups. Thirdly, cytokine and cross-species soluble factor measurements were not performed.

Further studies with larger sample sizes, including control groups, are needed for achieving a stronger generalizability. Future investigators could utilize continuous perfusion systems for maximum uterine culture survival and embryo viability. More studies on the effects of biomaterials such as cell lines and matrixes on uterine tissue cultures and implantation should be conducted on different mammalian species to better translate to clinical medicine.

Conclusion

FIB was demonstrated to be the best model for glucose consumption, endometrial gland count, and endometrial thickness. Furthermore, FIB enabled 14 days for a single embryo to survive when implanted with three embryos. In conclusion, the fibrin-matrix supported culture model could be a satisfactory 3D uterine tissue culture model for in vitro embryogenesis research.

Further studies utilizing advanced systems with continuous bioreactor systems supported by hormonal stimulation and perfusion are required. Additionally, cross-species soluble factors evaluation and adjusting are needed to achieve an even more efficient model.

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Sigmoid volvulus in pregnancy: Current approach in diagnosis and treatment

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Ethics Committee Approval
The approval for the study was obtained from the Ethics Committee of Ataturk University Faculty of Medicine (Number: 2022-88).
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: Sigmoid volvulus (SV) is an uncommon disease worldwide, while SV complicating pregnancy is extremely rare. The aim of this study is to evaluate the current diagnostic and therapeutic options in SV during pregnancy in a case series.

Methods: The clinical data of 1,046 patients with SV, including 11 pregnant women, were reviewed retrospectively. Age, gestation period, previous history of volvulus, presence of comorbidities, duration of complaints, symptoms, signs, diagnostic tools, treatment procedures and prognosis were noted. Rigid or flexible sigmoidoscopy and magnetic resonance imaging (MRI) were used in the diagnosis, while abdominal X-ray and computerized tomography (CT) were avoided. Stable patients were treated with endoscopic decompression, while emergent surgery was needed in complicated cases with necrosis, peritonitis, or unsuccessful endoscopic decompression.

Results: The mean age was 31.0 years (24-39 years). All cases were multiparous. Of the patients, 6 (54.5%) were in third trimester, 4 (36.4%) were in second trimester, and 1 (9.1%) was in first trimester. SV was diagnosed by endoscopy in 6 patients (54.5%), by magnetic resonance imaging (MRI) in 2 (18.2%), and during laparotomy in 3 (27.3%) patients. 6 patients (54.5%) were decompressed by sigmoidoscopy, while 5 cases (45.5%) were treated with surgery. One patient (9.1%) was lost due to toxic shock arising from sigmoid necrosis, while a stillbirth (9.1%) was developed following the surgical procedure in the same case.

Conclusion: Although common findings including abdominal pain, obstipation and distention are prominent clinical features of SV, some clinical findings of pregnancy may cloud the pathology during pregnancy. We recommend sigmoidoscopy or MRI in the diagnosis of pregnant patients with suspected SV. Although enlarged uterus is generally thought as an impediment factor for endoscopic decompression, flexible sigmoidoscopy is currently preferred in the treatment of uncomplicated and non-gangrenous patients, while gangrenous or complicated cases are required emergency surgery regardless of the gestation period.

Keywords: Sigmoid volvulus, Pregnancy, Endoscopy, Surgery

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Introduction

Sigmoid volvulus (SV) is a rare disease worldwide [1], though endemic in Turkey [2]. Our series included 1,046 cases with SV from June 1966 to January 2022. This is the largest single-center SV series in the world [2]. Similarly, SV complicating pregnancy is an extremely rare entity with about 110 cases reported to date [3]. In our series, 11 of 189 women (5.8%) were pregnant. This is also one of the largest single-center pregnant SV series in the world [4]. Our aim is to set forth the current diagnosis and treatment of SV complicating pregnancy.

Materials and methods

The data of 1,046 patients treated with diagnosed SV between June 1986 and January 2022 were reviewed retrospectively. Among 189 women, 11 pregnant patients were evaluated with age, gestation period, previous volvulus history, comorbidities, duration of complaints, symptoms, signs, diagnostic tools, treatment options and prognosis.

Following all of rapid and effective resuscitation, maternal and fetal clinical examination, and medical intervention including tocolytic medication or triggering an early labor in some cases, rigid or flexible sigmoidoscopy was used in the diagnosis. Magnetic resonance imaging (MRI) was also applied as a diagnostic tool in recent years, while ultrasonography (USG) was used in the evaluation of fetal health in some patients. X-ray studies including plain abdominal radiographies or computerized tomography (CT) were avoided. As a therapeutic procedure, endoscopic decompression was applied in stable patients, while emergent surgery was required in complicated cases with suspicion of necrosis, findings of peritonitis or unsuccessful endoscopic decompression. Still, elective sigmoid colectomy in the postpartum period was advised in successfully decompressed patients.

The approval for the study was obtained from the Ethics Committee of Ataturk University Faculty of Medicine (Number: 2022-88).

Statistical analysis

Quantitative parameters were performed as arithmetic mean (SD) and as number and percentages for the categorical variables. The distribution of the numerical data was evaluated histogram graphs. The software package SPSS 23.00 was utilized for the statistical analysis.

Results

As demonstrated in table 1, the mean age was 31.0 years (24-39 years). All cases were multiparous. The number of patients in first, second and third semester were 1 (9.1%), 4 (36.4%) and 6 (54.5%), respectively. Of the patients, 1 (9.1%) had chronic obstructive pulmonary disease, whereas another patient had recurrent SV history. The mean symptom period was 30.5 hours (12-72 hours). The obstipation, distention and abdominal pain were present in all cases, while 9 (81.8%) patients had vomiting. On clinical examination, abdominal tenderness and distention were found in all cases, while abnormal bowel sounds were seen in 8 (72.7%), rebound tenderness in 3 (27.3%), and melanotic stool in 1 (9.1%). One patient (9.1%) was in shock state. We diagnosed SV by endoscopy in 6 (54.5%), by MRI in 2 (18.2%), and at laparotomy in 3 (27.3%) patients. USG was used in 6 patients (54.5%) and demonstrated healthy fetus in all patients applied. In this series, sigmoidoscopic decompression was tried in 7 patients (63.6%) and 6 (54.5%) were treated with 85.7% success rate, while 5 patients (45.5%) in the whole cohort required emergent surgery. In this series of emergent surgery, one patient (9.1%) with late admission, comorbidities, and sigmoid gangrene, died due to gangrene and toxic shock, while wound infection was developed in another patient. In the decedent case, a stillbirth was developed following the surgical procedure (9.1%), while fetal health was without complication in other cases. Living 10 patients were discharged in a mean 5.0 days (1-15 days).

Figure 1: Endoscopic appearance of sigmoid volvulus (L: obstructive lumen)

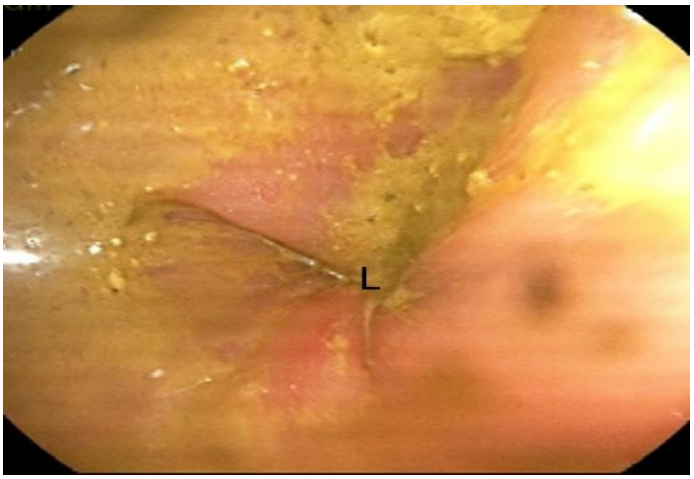
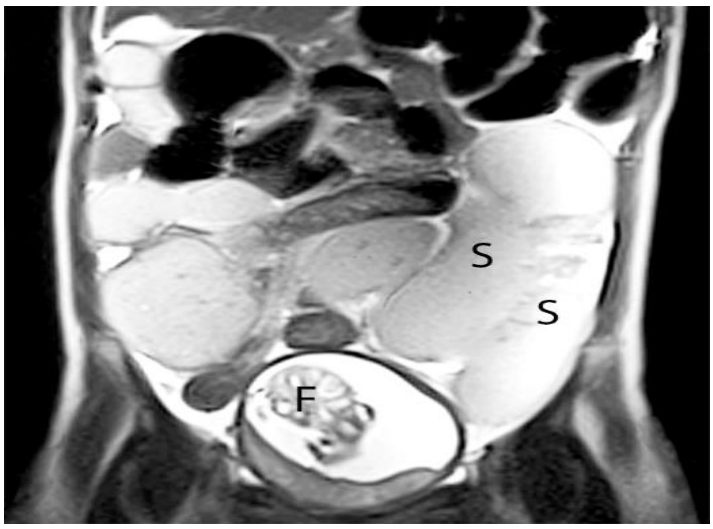


Table 1: Patients and related results

No	Age	Trimester	Symptom period (hours)	Presence of shock	Sigmoid gangrene	Endoscopy	Surgery	Mortality	Morbidity	Hospitalization Period (days)
1	36	3	24	-	-	-	Detorsion	-	Wound infection	15
2	26	2	36	-	-	Successful	-	-	-	2
3	39	3	72	+	+	-	Sigmoidectomy, Hartmann's colostomy	Toxic shock	-	-
4	30	3	20	-	-	Unsuccessful	Detorsion	-	-	8
5	31	3	24	-	-	Successful	-	-	-	2
6	27	2	36	-	+	-	Sigmoidectomy, anastomosis	-	-	9
7	24	3	12	-	-	Successful	-	-	-	2
8	33	1	22	-	-	Successful	-	-	-	1
9	29	3	18	-	-	Successful	-	-	-	1
10	30	2	48	-	+	Gangrene	Sigmoidectomy, anastomosis	-	-	8
11	36	2	24	-	-	Successful	-	-	-	2

Figure 2: Coronal T2 Weighted magnetic resonance image (S: dilated sigmoid loops, F: fetus)



Discussion

Bowel obstruction in pregnancy is a rare problem with an incidence ranging from 1.5 to 66.6 per 100,000 deliveries. However, SV is in the first two causes of intestinal obstruction complicating pregnancy, occurring in 24-44% of all cases [5, 6]. The reason of this interesting correlation in pregnant women is the presence of an enlarged uterus, blocking the spontaneous untwisting of sigmoid colon [7].

The clinical presentation of SV complicating pregnancy may sometimes be complex. In spite of modern technology, the diagnosis is made during laparotomy or autopsy, even if rare. Abdominal distention, obstipation and pain/tenderness are the main clinical features of SV in pregnancy. However, some physiologic symptoms of pregnancy, such as nausea, vomiting and abdominal pain, may cloud the clinical appearance of SV and delay the diagnosis [3-9]. Ultrasonography may be useful for evaluating fetus rather than diagnosing SV [8]. Sigmoidoscopy, preferably flexible procedure, is an effective procedure in both diagnosis and treatment of SV in pregnant women regardless of the gestation period, in addition to its being the unique method in the evaluation of the mucosal viability [10-12]. Endoscopy demonstrates a spiral twisting of the bowel (Figure 1). Similarly, the diagnostic accuracy of MRI is high in SV [4]. MRI shows the whirl sign in mesentery with a dilated sigmoid colon in addition to fetus-related material (Figure 2). If endoscopy or MRI are not available, a single abdominal X-ray radiography may be used [7, 9, 13]. Similarly, if needed, a computed tomography (CT) imaging can be taken as a terminal choice [8, 13]. But in general, X-ray studies and CT are avoided because of the probable radiation risk to the fetus. For the same reason, we prefer and recommend diagnostic flexible sigmoidoscopy or MRI in pregnant women.

The treatment requires a multidisciplinary approach involving obstetricians, neonatologists, gastroenterologists and general surgeons [3, 5, 6, 8, 13]. An effective resuscitation is essential. Medication is needed in patients with uterus irritability or fetal immaturity. Induction of delivery and abortion are decided depending on the maternal and fetal conditions [8, 12]. For solving the intestinal twisting, dilated uterus is generally thought as an impediment factor for endoscopic decompression [14]. However, according to our experience, flexible sigmoidoscopy is the best way to overcome the bowel obstruction in non-gangrenous patients. Hence, recent literature supports the importance of flexible sigmoidoscopy [10-13]. It is clear that emergency surgery is needed in gangrenous cases or in patients with unsuccessful endoscopic decompression [5, 7, 8]. Despite a clear improvement in recent years, the prognosis of SV complicating pregnancy is still relatively poor with a 6-12% maternal and 20-26% fetal mortality [7].

Although this study involves one of the largest single-center series of pregnant SV in the world, the evaluation of 11 cases is a major limitation of this study. Additionally, being a retrospective study and changing the diagnostic and therapeutic tools during the relatively long consideration period are other limitations.

Conclusions

SV complicating pregnancy is a very rare but crucial problem. We recommend flexible sigmoidoscopy or MRI in the diagnosis of pregnant patients with suspected intestinal obstruction. Flexible sigmoidoscopy may be effective in the treatment of non-gangrenous and uncomplicated patients regardless of the gestation period.

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Evaluation of chronic hepatitis B patients receiving lamivudine: Single center experience

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Ethics Committee Approval
Ethics committee approval of this study was obtained on 19.01.2022 with decision number 2022-3 from the Clinical Studies Ethics Committee of Medical Faculty at Hitit University. 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: Lamivudine (LAM), which has been used for the treatment of Chronic Hepatitis (CHB) infection for many years, is now provided for short-time use to immunosuppressive patients due to resistance. We aimed to evaluate the current state and pandemic period routine follow-ups in patients who still used LAM today due to treatment or prophylaxis in terms of virologic or serologic treatment response.
Methods: In this retrospective cohort study, we included 33 patients who received LAM treatment or prophylaxis due to CHB. Evaluations included patients' serologic results for Hepatitis B, platelet counts, comprehensive metabolic panel, HBV DNA levels, ultrasonographic (USG) evaluation of the liver, and the number and duration of outpatient visits between 01.01.2020 and 31.12.2021.
Results: Of all the patients, 51.5% (n=17) were males, and the average age was 57.3 (12.3) years. The median LAM treatment duration was found 10 (2.58) years. The ratio of receiving LAM due to immunosuppressive therapy was 27.27% (n=9). Except for HBV DNA-negative patients or patients with no accessed results, the virologic response rate of patients was found 60.7% (n=20). Within the study period, while Anti-Hbe seroconversion was found 3.2% (n=1), Anti-Hbs seroconversion was found 6.5% (n=2). One patient whose virologic response was not obtained, received the treatment without any alterations in the regimens. While the number of outpatient follow-ups in the study period was found 1.94 (0.24) on average, the duration between follow-ups was found 13.82 (12.8) months.
Conclusion: It is pleasing to obtain virologic response and Anti-HBs, Anti-HBe seroconversion in patients with low resistance profile who receive the LAM treatment. While watchful waiting is recommended for patients receiving long-term LAM treatment, our retrospective analysis showed that planned outpatient follow-ups for every three months was done in longer intervals. The treatment is not altered in one patient whose virologic response was not obtained because of inadequate number of follow-ups within the study period. Since monitoring without having prolonged follow-up durations due to the pandemic is of importance in terms of preventing complications, we believe that there is a need for further studies on this issue.

Keywords: HBV DNA, Chronic hepatitis B, Lamivudine, Seroconversion, Seroclearance, Pandemic

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Introduction

The WHO reports that around 296 million people live with the chronic Hepatitis B (CHB) infection, with 1.5 million new cases added every year [1]. Although our country is known as medium-level endemic for the Hepatitis B (HBV) virus, one in every three adults is reported to have HBV exposure [2]. The main purpose of the CHB treatment is to suppress HBV DNA levels with undetectable levels, which aims to prevent complications such as cirrhosis and hepatocarcinoma (HCC) [3]. Nowadays, nucleos(t)ide analogs are used to suppress viral replication. These antivirals used in CHB treatment are generally well tolerated. It is unknown how long these treatments would be provided, because usually they can be used for a long time without severe side effects. Lamivudine (LAM), which has been used since 1998, is a nucleoside analog with moderate strength. After a five-year application, it could cause high levels of treatment failure with high resistance levels around 80% [4, 5]. While the world has been fighting the COVID-19 pandemic since December 2019, there have been disruptions particularly in the blood tests and treatment of patients with chronic diseases. In this regard, both COVID-19 and CHB management have been very much affected by these difficult processes in patients with CHB [6, 7]. In this study, we aimed to evaluate the number of outpatient visits currently and especially during pandemic, in patients receiving the LAM treatment for CHB.

Materials and methods

This retrospective cohort study included patients who were prescribed LAM due to CHB and visited the Infectious Diseases outpatient clinic between 01.01.2020 and 31.12.2021.

Patients who received other antiviral treatments for CHB or those below 18 were excluded. Patients' demographic data, additional diseases, HBsAg, HBeAg, Anti-HBs, Anti-HBe results, hemogram parameters, AST-ALT-bilirubin and alpha-fetoprotein (AFP) values, HBV DNA levels, USG images of the liver at the beginning of the treatment and in last follow-up were evaluated. While HBsAg/HBeAg loss was defined as seroclearance, the development of Anti-HBs/Anti-HBe was defined as seroconversion. Negative-HBV DNA for virologic response was defined as an HBV DNA level of below 50 IU/ml. Detection of granular appearance was defined as progression, if it was undetected in the first USG imaging**.** Patients' routine follow-up duration was accepted as three months. The duration between the number of patients' outpatient visits between 01.01.2020 and 31.12.2021 and the duration between these visits during the pandemic was evaluated as months. Nucleic acid isolation for HBV DNA was performed using the Magnesia16 (Anatolia Geneworks, Turkey) device. The quantitative HBV DNA tests were conducted using the Montania4896 (Anatolia Geneworks, Turkey) device using real-time polymerase chain reaction (RT-PCR) in accordance with the manufacturer's instructions.

Statistical analysis

Data were analyzed using IBM SPSS 23.0 (SPSS Inc., Chicago, IL, USA) licensed by Hitit University. Data of continuous variables were expressed as mean, standard deviation and data of categorical variables were expressed as percentages. In the analyzes comparing the two groups, Mann-Whitney U test was used for continuous variables, Chi-square test and Fisher exact test were used for categorical variables, and Spearman correlation test for correlations.

Ethics

Ethics committee approval of this study was obtained on 19.01.2022 with number 2022-3 from the Clinical Studies Ethics Committee of Medical Faculty at Hitit University. The study followed the ethical principles indicated in the Declaration of Helsinki at all stages.

Results

This study included 33 patients who received LAM treatment. Of all these patients, 51.5% (n=17) were males, and the average age was 57.3 (12.3) years (32-78 years). The patients' comorbid were analyzed, which included hypertension (HT) in 24.2% (n=8), diabetes mellitus (DM) in 9.1% (n=3), rheumatologic diseases in 15.2% (n=5), chronic kidney failure (CKF) in 9.1% (n=3), kidney transplantation in 6% (n=2), multiple myeloma (MM) in 3% (n=1), breast cancer in 3% (n=1), and coronary artery disease (CAD) in 3% (n=1). Of all the cases, 27.3% (n=9) were receiving immunosuppressive treatment for different reasons. The median duration of LAM treatment was 10 (2.58) years. Table 1 demonstrates patients' ALT, total protein, albumin, total bilirubin, platelet, AFP, HBV DNA levels, and serologic results. In the beginning of the treatment period, average HBV DNA viral load of 69.7% (n=23) of the patients was 79,9026 IU/ml (131-16,000,000 IU/ml). While 21.3% (n=7) of the patients had negative HBV DNA, the HBV DNA results of 9% of the patients could not be accessed. According to the last HBV DNA evaluated, they were negative in 84.8% (n=28). Virologic response could not be obtained in a patient with HBV DNA 578 IU/ml. USG imaging of this patient indicated no liver cirrhosis. Results of 12.1% (n=4) patients could not be accessed. In the beginning, except for HBV DNA negative patients or patients with no accessed results, the virologic response rate of patients was found 60.7% (n=20).

Table 1: Patients' demographic features and laboratory values

Variable	Value	
Age (mean (SD)) (year)	57.3 (12.3) (32-78)	
Sex (n; %)	Male (17; 51.5%)	
Treatment period (years)	10 (5-15)	
	Laboratory findings at the beginning of treatment	Laboratory findings at the last follow-up
ALT (IU/L)	25.46 (14.73)	20.7 (12.37)
T. protein (mg/dL)	7.52 (0.98)	7.12 (8.66)
Albumin (mg/dL)	4.46 (0.61)	4.07 (3.8)
T. bilirubin (g/L)	0.94 (1.27)	0.73 (0.31)
Platelet (mm^3/L)	229.3 (71.9)	216.55 (81.97)
AFP	2.34 (1.67)	2.42 (1.39)
HBV-DNA (IU/mL)	799,026 (31-16,000,000)	136 (16-578)
HBeAg loss or seroconversion (n,%)		1 /31 (%3.2)
HBsAg loss or seroconversion (n,%)		2/31 (%6.5)

SD: Standard deviation, AFP: Alpha fetoprotein ALT: Alanine aminotransferase

Before the treatment, HbeAg was positive in only one patient, whereas the results of two patients could not be accessed. All other patients were positive for Anti-Hbe, which confirms that HbeAg-positive patients under treatment developed Anti-HBe seroconversion. Anti-Hbs seroconversion was determined as 6.5% (n=2).

Table 2 demonstrates the analysis of the USG findings of the liver at the beginning and in last follow-up of the treatment. From four patients not having initial USG results, two

patients had normal USG imaging, whereas remaining two had granular appearance.

Table 2: Findings in the USG imaging of the liver

	USG findings at the beginning of treatment % (n=29)	USG findings at the last follow-up % (n=33)
Normal	41.4 (12)	30.3 (10)
Hepatosteatosis	27.6 (8)	18.2 (6)
Granular appearance	24.1 (7)	45.5 (15)
Hepatomegaly	6.9 (2)	6.1 (2)

USG: Ultrasonography

During the study period, the average number of follow-up visits was 1.94 (0.24) and the average duration between follow-ups was 13.81 (1.28) months. The ratio of the delays in the routine follow-ups was 100% within the last two years. The duration between the last follow-up visits before and during the pandemic was found to be 11 (0-30) months on average.

Discussion

Globally, LAM had been the only option for the treatment of CHB for a long time. With the launch of new treatments with high resistance barriers, LAM is mainly transformed into short-term use in patients receiving immunosuppressive treatment [8]. Until recently, the first treatment option for CHB patients was supposed to be LAM or telbivudine (LdT) if their HBV DNA level was $<10^7$ IU/mL, according to the Communique on Healthcare Practices (CHP) in Turkey. With the changes in the treatment options in guidelines, treatments in Turkey have also been updated. We, therefore, aimed to evaluate the current state of patients who still used LAM nowadays.

A study that monitored the long-term outcomes of the LAM treatment, reported patients' duration of LAM use median as 16.1 (3.2-19.5) years [9]. In our study, this duration was found 10 (2.58) years. Shorter duration of LAM might be because we have been performing the follow-up of patients with CHB in our department for approximately 15 years. Initial serum biochemical, platelet, and AFP values of our patients were within normal ranges, and the last evaluations were also found to be similar with the compared study.

When the patients' HBV DNA levels were analyzed, virologic response could not be obtained in one patient. This patient was found to have findings of cirrhosis in the liver biopsy that was done before the treatment. Severe results developed under long-term treatment with nucleoside analogues, especially, patients with negative HBeAg were found to have cirrhosis of the liver in the beginning [4]. This patient's HBV DNA level was negative under treatment, but it was still high in the last evaluation, which refers to the resistance developed against LAM. Unfortunately however, when the data belonging to this patient were analyzed, it was found that the patient had not been administered test or a more potent treatment yet, due to LAM resistance. Except for HBV DNA-negative patients or patients without accessed results, the virologic response rate of patients was found to be 60.7% (n=20), in the beginning. While a study that evaluated a five-year LAM treatment reported the virologic response at levels of 30% to 35%, another study reported as 67% [4, 10]. Both studies included HBeAg-negative patients. In this study, there were HBeAg-negative patients except for one patient, and the virologic response ratio was found to be within the ranges reported in the literature. An HBeAg-positive patient was found to develop HBeAg seroconversion. A study that made a five-year follow-up of LAM treatment reported HBeAg seroconversion after 0.2-14.7 (median=5.9) years [9]. HBeAg seroconversion duration in our patient could not be detected clearly as there were no follow-up tests during the study period. The European Association for the Study of the Liver (EASL) guideline recommends that LAM treatment could be ceased with HBeAg seroconversion, yet it also reports the recurrence risk [7]. Virologic response was obtained in our patient and the LAM treatment continued. HBsAg seroclearence was detected in 11.7% of patients who received long-term LAM treatment [4]. Studies report that HBsAg seroclearance is not always accompanied by seroconversion. Two patients in our study were also found to develop Anti-HBs with loss of HBsAg. One of these two was receiving immunosuppressive therapy due to renal transplantation. This initially HBV-DNA negative patient was started LAM treatment six years ago.

In our study, we had 9 cases receiving LAM prophylaxis (27.27%), which included five rheumatologic comorbidities, two renal transplant cases, one MM and one breast cancer patient. LAM prophylaxes were started without taking a liver biopsy, as mentioned in current guidelines. The duration of prophylaxis is not certain, but based on the recommendation indicating that it should continue at least 12 months after the cessation of immunosuppressive therapy, LAM prophylaxis is still continued in all patients [7]. The other patient who was detected to have HBsAg seroclearance and HBs seroconversion was under LAM treatment for the last 10 years. According to the EASL guidelines, HBsAg seroclearance was recommended to be an ideal point for ceasing the treatment regardless of the presence of HBs seroconversion. However, even if the treatment was ceased, watchful waiting was also recommended due to the HCC risk [7]. LAM treatment has not been ceased in this patient yet considering the disruptions to be experienced in watchful waiting under the pandemic conditions.

Compared to the last evaluation, we found an increase in the ratio of granular appearance in the USG imaging or the liver. Even if a response is received in the LAM treatment, risk factors for HCC development are known as older age, male gender, and cirrhotic changes in the liver. Although we had male patients and patients with liver cirrhosis in this study, it is pleasing that HCC was not detected in any USG imaging.

As reported in the literature, while the whole world is fighting the COVID-19 pandemic, difficulties are still experienced in the diagnostic evaluation and treatment of chronic diseases like cancer [11]. Infectious diseases specialists who perform the follow-up and treatment of CHB patients were among the top in the fight against the pandemic, which particularly contributed to the disruptions experienced in the follow-up of these patients. Especially patients who receive CHB treatment are recommended to have their biochemical tests done every 12 weeks [7]. In line with this, all patients in this study were found to have delays in their follow-ups during the study period. While our patients should have had eight visits in total within this period, they were found to have 1.94 (0.24) visits on average. Hence, the duration between the follow-ups was 13.81 (1.28) months on average. Similar to the studies conducted in the world and in our country, during the pandemic period, there was

a significant decrease in the number of biopsies and CHB patients having their outpatient follow-ups regularly [12, 13]. As this study shows, the patient who did not demonstrate a virologic response should have been evaluated in terms of treatment change. Unfortunately however, due to the pandemic, the results could not be evaluated, although the patient's HBV-DNA tests were requested.

Limitations

The strengths of this study are the duration length of LAM use and the continued treatment according to the guidelines, although the patients had HBeAg and HBsAg seroconversion. The limitations of the study are being a single center, retrospective cohort study with loss of data. Due to time interval, the study could cause the exclusion of patients in both bias who received or ceased LAM treatment. Further studies including all patients receiving LAM treatment due to CHB could demonstrate the efficiency of the LAM treatment better. Besides, there is a need for further studies to evaluate the effects of the pandemic on CHB patients.

Conclusion

In conclusion, watchful waiting is recommended even if serologic or virologic response is obtained with the LAM treatment, which was excluded from being the primary treatment option due to resistance in CHB. Since when the pandemic will end is unknown, test and treatment changes in CHB patients should be done before complications develop.

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Gastric cancer during COVID-19 pandemic: What changed?

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Ethics Committee Approval
The study was granted approval by the Erzurum Training and Research Hospital ethics committee (ethics committee approval number: 2021/17-261).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: There is no doubt that oncology patients are among the most affected groups by the pandemic. The aim of this study is the evaluation of the effects of COVID-19 pandemic on patients with gastric cancer.
Methods: We carried out a retrospective cohort study in a non-clean hospital from March 1, 2020, when the pandemic became widespread in Turkey, to August 1, 2021. Patients diagnosed with gastric cancer were compared with patients in the pre-pandemic period. The cancer stages, operation types and results of the patients were compared between the groups.
Results: A total of 181 patients were included in the study. While a decrease was observed in stage 1 (P=0.01) and stage 2 (P=0.09) tumors during the pandemic period, an increase was observed in the number of stage 4A (P=0.002) and stage 4B (P=0.001) tumors on admission. Patients who received neoadjuvant chemotherapy during the pandemic were significantly less when compared with the pre-pandemic group (P=0.04).
Conclusions: When the necessary precautions are taken, surgical oncology can be safely performed even in a non-clean hospital. With the spread of similar study results, patients' anxiety-based COVID-19 fear will be overcome.

Keywords: Gastric cancer, COVID-19, Pandemic

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Introduction

Since the beginning of 2020, there has been a global fight against the COVID-19 pandemic. While the pandemic continues, oncological patients and patients with chronic diseases are undoubtedly the most affected. In a study conducted in Italy during the pandemic, there was a reduction of 70% in oncological units on the basis of hospital beds (median: 50%) and a 76% reduction in surgical activities [1]. Centers provide guidelines on what should be the appropriate approach for securing the diagnosis and treatment of other chronic and acute patients, including cancer patients, from these effects. To use the hospital more efficiently, the Centers for Disease Control and Prevention suggested rescheduling elective surgeries [2]. Later, the American College of Surgeons (ACS) and the Society of Surgical Oncology (SSO) published recommendations for elective surgeries [3, 4].

Over 1 million people are diagnosed with gastric cancer each year [5]. As with many malignant diseases, radical surgery and aggressive treatment together constitute the cornerstone of treatment. Delayed treatment results in extensive metastasis, disease recurrence, and reduced survival.

Although the centers have expressed their views on the appropriate timing for the operation during the COVID-19 pandemic, it is not clear how these will affect the results. In the current study, it was aimed to evaluate the effects of the pandemic on the diagnosis and treatment of patients with gastric cancer in a single center.

Materials and methods

Study design and patients

Patients diagnosed with gastric cancer in Erzurum Regional Training and Research Hospital between 01/03/2020 and 01/08/2021, when the pandemic was effective countrywide, were included in the study. The control group consisted of patients who applied to hospital between 1/01/2019 and 01/03/2020, just before the onset of the pandemic and were diagnosed with gastric cancer. This retrospective cohort study, in accordance with Declaration of Helsinki, was granted approval by the Erzurum Training and Research Hospital Ethics Committee (Ethics Committee approval number: 2021/17-261).

After all of the patients participating in the study were evaluated by the tumor council, patients with T1 and T2 tumors, without lymph node metastasis and without bleeding, gastric outlet obstruction, and patients with advanced age who could not tolerate neoadjuvant therapy were operated on. All other patients were operated after receiving neoadjuvant therapy.

Demographic characteristics, comorbidities, complaints on admission, preoperative laboratory parameters and imaging studies, pathological diagnosis, tumor localization, stages defined by American Joint Committee on Cancer (AJCC), neoadjuvant therapy, American Society of Anesthesiologists (ASA) scores, type of operation, total length of stay, Clavien-Dindo classification (CDC) score, postoperative tumor stages, mortality, and 30-day follow-up results after discharge were recorded. Total length of hospital stay was defined as the time between hospitalization and discharge.

Preoperative evaluation during the COVID-19 period

All of the patients who were scheduled to have surgery during the pandemic were hospitalized with their companions and isolated for 5 days. A nasal and pharyngeal swab test (polymerase chain reaction test) was given on admission and in the final 24 hours preoperatively. Patients with negative tests were operated, whereas the surgery was postponed for positive patients. The isolation rules recommended by the guidelines were followed.

Statistical analysis

SPSS Statistics for Windows 17.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Numerical variables with normal distribution were shown as the mean (SD), whereas those without normal distribution were shown as the median (minimum-maximum). Categorical variables were presented as numbers and percentages. The Mann-Whitney U and Kruskall-Wallis H tests were used for the intergroup comparisons of the numerical variables without normal distribution. Categorical variables were compared with the $\chi 2$ and Fisher exact $\chi 2$ tests. For the relationships among numerical variables, Pearson and Spearman correlation analyses were used.

Results

The study was conducted with a total of 181 patients, comprising 115 (63.5%) males and 66 (36.5%) females. Of the patients, 92 (50.8%) were evaluated in the pre-pandemic period, and 89 (49.2%) in the pandemic period. The mean age of patients during the pandemic and pre-pandemic period were 65.78 (11.68) and 63.45 (12.32), respectively (P=0.19) (Table 1).

Table 1: Laboratory results, demographic data, and procedure details of the patients

	Pandemic group n: 89	Pre-pandemic group n: 92	*P*-value
Sex (male)	59 (66.3%)	56(60.9%)	0.44
Age (mean (SD))	65.78 (11.68)	63.45 (12.32)	0.19
Hemoglobin (Hgb) (mean (SD))	10.74 (2.48)	12.61 (1.83)	<0.01**
Albumin (mean (SD))	3.88 (0.57)	4.25 (0.34)	0.49
Alarming symptoms (n)	89	92	<0.01**
Positive	80 (44.2%)	47(26%)	
Negative	9 (5%)	45 (24.9%)	
Hospital stay (days) (mean (SD))	13.08 (5.89)	8.53 (2.26)	<0.01**
Tumor localization			
Cardia (n)	42 (47.2%)	58 (63%)	0.03**
Corpus (n)	18 (20.2%)	13 (14.1%)	0.27
Antrum (n)	29 (32.6%)	21 (22.8%)	0.14
Operation type	64 (43.5%)	83 (56.5%)	0.04**
Open procedure	39 (60.9%)	64 (77.1%)	
Minimal invasive surgery (Robotic assisted)	25 (39%)	19 (22.8%)	
Total gastrectomy			
Open	31 (21.1%)	56 (38.1%)	0.02**
Robotic assisted	15 (10.2%)	10 (%6.8)	0.06
Subtotal gastrectomy			
Open	8 (5.4%)	8 (5.4%)	0.58
Robotic assisted	10 (6.8%)	9 (6.1%)	0.39
Tumor histology (n)			
Adenocarcinoma	80	84	0.74
Neuroendocrine tumor	4	2	0.11
MANEC	5	6	0.82
Morbidity (CDC)	12/64 (18.7%)	19/83 (22.8%)	0.52
Grade 1	12	15	
Grade 2	0	1	
Grade 3	0	3	
Grade 4	0	0	
Grade 5	0	0	
Mortality	0	0	

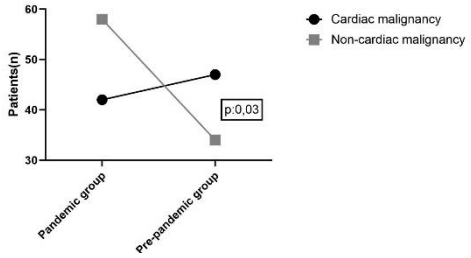
MANEC: mixed adenoneuroendocrine carcinoma, CDC: Clavien-Dindo classification, ** P<0.05 was considered as significant for the statistical analyses.

The mean length of hospital stay was 13.08 (5.89) and 8.53 (2.26) days during the pandemic and pre-pandemic period, respectively (P<0.001).

When the complaints of the patients were classified as alarming symptoms (weight loss, persistent vomiting, dysphagia, anemia) and non-specific symptoms (non-specific epigastric pain, dyspepsia, early satiety), it was observed that the patients presented with alarming symptoms are significantly dominant during the pandemic period when compared with pre-pandemic period (80 (89%) and 47 (51.1%) patients during the pandemic and pre-pandemic period, respectively) (P<0.001). In addition, alarming symptoms were found to be correlated with the clinical stage of the disease (r=0.57, P<0.01).

When the tumor localizations were evaluated during the pandemic period, tumors with antrum and corpus (distal) localization were observed more frequently, while a significant decrease was observed in proximal tumors (P=0.03) (Figure 1).

Figure 1: Gastric tumor location and periodical difference



No significant difference was observed between the groups regarding the tumor histology. The details of the pathological classification according to the tumor stages are shown in Table 2.

Table 2: Distribution of the tumor histology and stage among the groups

	Pandemic group (n)	Pre-pandemic group (n)	*P*-value
Adenocarcinoma	80 (100%)	84 (100%)	0.74
Stage 1	4 (5%)	16 (19%)	0.005**
Stage 2A	0	0	
Stage 2B	6 (7.5%)	17 (20.2%)	0.01**
Stage 3	33 (41.3%)	40 (47.6%)	0.41
Stage 4A	16 (20%)	3 (3.6%)	0.001**
Stage 4B	21 (26.3%)	8 (9.5%)	0.005
Neuroendocrine tumor	4 (100%)	2 (100%)	0.11
Stage 1	1	0	
Stage 2	0	0	
Stage 3	1	2	
Stage 4	2	0	
Mixed adenoneuroendocrine carcinoma	5 (100%)	6 (100%)	0.82
Stage 1	1 (20%)	2 (33.3%)	0.63
Stage 2A-2B	0	0	
Stage 3	0	2 (33.3%)	
Stage 4A	0	1 (16.7%)	
Stage 4B	4 (80%)	1 (16.7%)	0.03**

** P<0.05 was considered as significant for the statistical analyses.

In the clinical staging of the disease, a decrease was observed in stage 1 (P=0.01) and 2B (P=0.009) tumors during the pandemic period, while an increase in the number of stage 4A (P=0.002) and 4B (P=0.01) tumors was observed (Figure 2). In the postoperative pathological staging, significant difference was not observed between the groups (P=0.22), except the significant increase in stage 3B during the pandemic period (P=0.04) (Table 3).

Figure 2: Differences in the tumor stages between periods

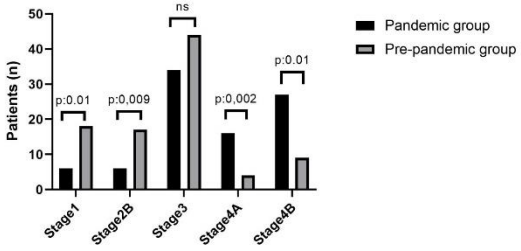
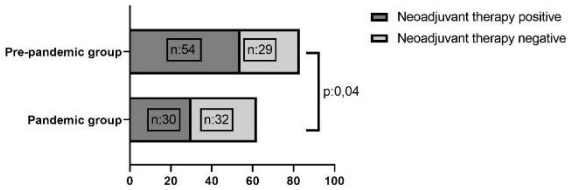


Table 3: Clinical and pathological stages of the patients

	Pandemic group (n: 89)	Pre-pandemic group (n: 92)	*P*-value
Clinical stage			
Stage 1	6 (3.3%)	18 (10%)	0.01*
Stage 2A	0	0	
Stage 2B	6 (2.8%)	17 (9.4%)	0.009*
Stage 3	34 (18.9%)	44 (24.4%)	0.21
Stage 4A	16 (8.8%)	4 (2.2%)	0.002*
Stage 4B	27 (14.9%)	9 (5%)	0.001*
Postoperative stage			
Neoadjuvant group	30/62 (48.3%)	54/83 (65%)	0.04*
Complete response	0	2 (1.4%)	0.21
Stage 1	8 (5.4%)	9 (6.1%)	0.75
Stage 2	6 (4.1%)	15 (10.2%)	0.22
Stage 3	16 (11%)	28 (19%)	0.46
Non-neoadjuvant group			
Stage 1A	2 (1.4%)	3 (2.0%)	0.87
Stage 1B	1 (0.7%)	2 (1.4%)	0.21
Stage 2A	4 (2.7%)	7 (4.8%)	0.61
Stage 2B	6 (4.1%)	2 (1.4%)	0.06
Stage 3A	10 (6.8%)	11 (7.5%)	0.68
Stage 3B	8 (5.4%)	3 (2%)	0.04*
Stage 3C	1 (0.7%)	1 (0.7%)	0.85

Patients receiving neoadjuvant therapy were found to be significantly less common during the pandemic period than the pre-pandemic period (30 (48.3%) patients vs. 54 (65%); P=0.04) (Figure 3). Minimally invasive surgery was performed on 25 (39.06%) patients during the pandemic period and 19 (22.89%) patients during the pre-pandemic period. Details of the surgical procedures applied are given in Table 1.

Figure 2: Differences between the groups in terms of neoadjuvant therapy



Mortality in postoperative first month was not observed in either groups. There was no difference between the groups regarding the postoperative morbidities (12 and 19 patients in pandemic and pre-pandemic period, respectively, P=0.52) (Table 1).

Discussion

The pandemic continues to affect life worldwide. Oncological patients are among the most affected people. In this study, it was aimed to evaluate how patients diagnosed with gastric cancer were affected by the pandemic period and to evaluate the surgical results. As a result, it was observed that patients were adversely affected during the pandemic period and usually presented with more advanced tumors.

First of all, the presence of anemia and alarming symptoms on admission was remarkable in the pandemic group. The presence of alarming symptoms and anemia in gastric cancer, which compels the patient to apply to the hospital during the diagnosis process, is quite specific for the diagnosis, but indicates a poor prognosis. In previous studies, it was found that the presence of at least 1 alarming symptom decreased the 5-year survival rate by 26% on average [6–8] and was associated with a 3-fold increase in the risk of death [6]. One of the most important reasons for the low 5-year survival rate in gastric cancer in Eastern studies (8%–26% in Eastern series, 50%–60% in Western series) is thought to be the widespread screening programs in Western regions without considering alarming symptoms [9–14].

The effect of delayed surgery on survival in gastric cancers is not clear. In a systemic review evaluating the oncological results of the time to surgery for colorectal, pancreatic, and gastric cancers between 2005 and 2020, Fligor et al. [15] stated that in case of serious resource limitations, a delay of surgery up to three months in early-stage gastric cancers and up to six weeks in advanced gastric cancers can be considered. On the other hand, Brenkmann et al. [16] analyzed the long-term survival of 2077 gastric cancer patients who were not treated with neoadjuvant therapy, and found no significant difference between patients operated in less than five weeks and those operated after eight weeks. There is not any randomized study showing the effect of the waiting time on survival in gastric cancer. Undoubtedly, it was not foreseen that the COVID-19 pandemic, which broke out in early 2020, would still continue. In this study, it was observed that patients mostly applied with advanced stage tumors during this 17-month period of the pandemic.

The current recommendations for neoadjuvant chemotherapy (FLOT) or chemo-radiotherapy are to delay extended total gastrectomy as much as possible [4, 17]. If the treatment ends during the pandemic, it is controversial how to continue the treatment. However, considering the non-negligible risk of immunosuppression, surgery can be recommended to patients with a low risk [18]. In line with these recommendations, an increase was predicted in patients receiving neoadjuvant therapy, but it was observed that the rate of patients who received neoadjuvant therapy during the pandemic period decreased as the disease progressed to an advanced stage and they could not tolerate neoadjuvant therapy. The lack of sufficient data on this subject today will become clear with the studies carried out.

Interestingly, the number of proximal gastric tumors was significantly reduced in patients who applied during the pandemic period, and gastric tumors were more distally located. Proximal gastric tumors show less clinical signs [19] and this result might be from patients not applying to the hospital without their complaints being obvious. As a matter of fact, the significantly higher number of patients with alarming symptoms in this period compared to those with non-specific symptoms supported the inference herein. Considering the histopathological features, it was also observed that patients with a diagnosis of MANEC applied more frequently with advanced tumors in this period. This may show that MANEC is a more aggressive tumor than both adenocarcinoma and isolated neuroendocrine tumors.

Although, due to the lack of data, the centers apply different protocols on the evaluation of patients for COVID-19 before the operation, isolation undoubtedly seems to be the key point to implement [20]. Thorax CT one day preoperatively is no longer recommended in the updated protocols for the detection of asymptomatic patients [21]. Patients were routinely hospitalized for 5 days, except for emergencies, and PCR test was performed at the time of admission and 1 day before the operation. There was no COVID-19 related morbidity or mortality during this period.

In addition to the fact that the results of this study were single-centered, the most important limitation of our study is the short follow-up period and the lack of long-term survival results, but still, a similar study on gastric cancer patients has not yet been published and the results are brand new in the pandemic period.

Conclusion

As a result, in this study, in which the patients who applied to our hospital due to gastric cancer within the 17-month period of the pandemic and pre-pandemic period were compared, it was found that the patients during the pandemic presented with more advanced cancer. In addition, when the necessary precautions were taken during the pandemic process, it was seen that the treatment of diseases such as cancer, for which, surgery is the basis of curative treatment, can be safely performed even in a pandemic hospital. We believe that as a result of reserving the formerly prepared departments for oncological patients and increasing similar studies, anxiety-based COVID-19 fear will be overcome and the patients will safely admit to the hospital.

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Research article

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Management and outcomes of anal sphincter injuries: A retrospective cohort study

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Ethics Committee Approval
The approval for the study was obtained from the Ethics Committee of Erzurum Atatürk University Faculty of Medicine (No:2021/11-8-22)
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: Anal sphincter injury (ASI) is a clinical condition that causes anal incontinence and can severely impair an individual's quality of life. Overlapping sphincteroplasty (OSP) is the most preferred surgical method for repairing ASI. The present study aimed to discuss the demographic and clinical characteristics of patients who underwent ASI surgical repair in light of the current literature.
Methods: Patients in two groups; males and females, who underwent an operation for grade 3-4 ASI in the General Surgery Clinic at Ataturk University between 2010 and 2021 were retrospectively analyzed. The severity of anal incontinence and quality of life post-operatively using the Wexner score were evaluated. For evaluating post-operative complications, the Clavien–Dindo Classification was used.
Results: Over 12 years, 34 adult patients with a mean age of 35.8 (22–66) years underwent ASI surgery, namely 23 (67.6%) women and 11 (32.4) men. Considering the patients' etiopathogenesis, obstetric injuries (55.9%) were the most common cause of ASI. All patients underwent overlapping sphincteroplasty (OSP), while 20.6% also underwent protective stoma. According to the Centers for Disease Control and Prevention (CDC), four patients were classified as Grade 1, four as Grade 2, seven as Grade 3 and one as Grade 5.
At a mean follow-up of 35.8 months, the mean Wexner score was 3.59 and the success rate was 88.2% (P=0.445). Males had a longer average hospital stay (P=0.021) and a higher Wexner score (P=0.445), whereas females had a greater complication rate (P=0.388). The quality of life was high, but the Wexner scores were low in all patients.
Conclusion: ASI most commonly occurs in women during childbirth. OSP has a high success rate, and opening a diverting ostomy when needed further increases this rate. The Wexner score is a simple and useful system for assessing anal incontinence.

Keywords: Anal sphincter injury, Anal incontinence, Overlapping sphincteroplasty, Wexner score system

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Introduction

Anal sphincter injury (ASI) is a clinical condition that causes anal incontinence and severely impairs an individual's quality of life. This trauma can lead to long-term psychological and physical problems. Hence, ASI has a significant effect on patients' lives [1, 2]. The overall spectrum of ASI patients ranges from mild isolated injury to severe injury with damage to the pelvic and abdominal organs, which can cause patients go into shock. ASI patients should be thoroughly examined, monitored, and followed [3].

The most common causes of fecal incontinence are damage to the anal sphincter due to obstetric injury, anorectal operations, or external trauma [3, 4]. These injuries are often managed in the acute phase by surgical units with no coloproctology experience. Coloproctological centers can perform scheduled sphincter repair procedures [3]. This injury needs to be treated without delay, and referral to experienced centers as soon as possible is crucial. This way, successful surgical repair of the anal sphincter can restore continence and improve quality of life [5].

Numerous surgical techniques for ASI exist; however, overlapping sphincteroplasty (OSP) is the most widely used method [2, 6]. The Wexner score (Cleveland Clinic Fecal Incontinence Severity Scoring System) is a system that can be easily applied easily, and it is the most frequently used system by colorectal surgeons to assess anal incontinence status and surgical success [7].

In the current study, the demographic and clinical characteristics and post-operative results of patients who underwent overlapping sphincteroplasty due to anal sphincter injury with consideration of the current literature are discussed.

Materials and methods

Approval for this study in accordance with Declaration of Helsinki was obtained from the Ethics Committee of Erzurum Atatürk University Faculty of Medicine (No:2021/11-8-22). Patients who underwent surgery for grade 3-4 anal sphincter injury in the general surgery unit of Atatürk University Research Hospital between January 2010 and December 2021 were retrospectively analyzed. Data were collected from the patients' files, hospital's electronic software system, and by contacting the patients via telephone.

Only grade 3-4 injuries were included because according to the perineal trauma classification, only these two grades involve anal sphincter injuries [8].

A vast majority of the patients had lacerations that occurred under emergency conditions, so the diagnosis was made by physical examination and the Wexner score. Computed tomography and magnetic resonance imaging (CT and MRI, respectively) were used only in a few patients. Given that anal manometry and endoanal ultrasound imaging (USG) were not available in our hospital, post-operative sphincter tone follow-ups were performed in other centers when needed.

Patients' demographic characteristics, complaints at admission, time of injury, anal sphincter laceration grade, previous operations, length of hospital stay, complications, and postoperative Wexner score were examined.

The post-operative severity of anal incontinence was evaluated using the Wexner score. The Wexner score includes questions about the frequency and type of incontinence or discomfort (solid stool, liquid stool, flatulence, use of diapers or pads, lifestyle changes) as shown in Table 1. A score of 0 corresponds to perfect continence and 20 to complete incontinence [7, 9]. We used the Clavien–Dindo (CD) classification of surgical complications to evaluate post-operative complications [10, 11].

Table 1: Anal incontinence score according to the Wexner score system [7, 9]

Type of Incontinence	Never	Rarely	Sometimes	Usually	Always
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wear Pad	0	1	2	3	4
Lifestyle Altered	0	1	2	3	4

Never: 0, Rarely: <1/ month, Sometimes: <1/ week, ≥1/ month , Usually: <1/ day, ≥1/ week, Always: ≥1/ day

Statistical analysis

Quantitative parameters were performed as arithmetic mean (standard deviation) and as number and percentages for the categorical variables. The distribution of the numerical data was evaluated using the Shapiro–Wilk and Kolmogorov–Smirnov tests and histogram graphs. The t-test was used to analyze the association between categorical covariates and postoperative results. A chi-square test was used to compare categorical data. Data were analyzed at a 95% confidence interval (CI), and *P*-value was accepted as <0.05, indicating statistical significance. SPSS version 23 software was used for statistical analysis.

Results

Over the 12-year period, 34 adult patients, consisting of 23 (67.6%) women and 11 (32.4%) men, underwent ASI surgery. These patients had a mean age of 35.8 (12.6) years (22–66). The mean age was 44.09 (13.43) years for males and 31.8 (10.2) years for females. A significant difference between the sexes in terms of mean age (P=0.012) was found.

Regarding patient etiopathogenesis, the most common causes of ASI were obstetric injuries (55.9%), cuts and puncture wounds (14.7%), traffic accidents (8.8%), iatrogenic injuries (8.8%), animal attacks (8.8%), and gunshot wounds (2.9%). Three of the obstetric injuries were of iatrogenic origin, so the iatrogenic injuries indicated in the table consist of those that occurred after colorectal surgery.

Most patients were admitted to the emergency unit; thus complete data for patients who were admitted under elective conditions could not be obtained. At admission, 79.4% of the patients had no anal tone, and 20.6% had decreased anal tone. Most (85.3%) of the patients presented with grade 3 ASI, and 14.7% presented with grade 4 ASI. Thirty-one patients underwent the operation under general anesthesia and three under regional anesthesia in the lithotomy position. Twenty-six patients (76.5%) had surgery on the day of admission. The patients who underwent surgery under emergency conditions were given ceftriaxone + metronidazole, which was continued post-operatively, and antithrombotic prophylaxis. Anal sphincter repairs were performed by three experienced colorectal surgeons under their supervision. All patients underwent OSP, while 20.6% of the patients also underwent protective stoma. For patients who underwent a colostomy, the etiological reason was external trauma. Temporary colostomy was performed in all

patients, and colostomy repair was performed after an average of five months.

The length of hospital stay was 21.9 (13.02) days for men and 15.3 (17.9) days for women with a statistically significant difference between the two groups (P=0.021).

Considering post-operative complications, 14.7% of the patients had wound infection, 8.8% had wound dehiscence, and 5.9% had urinary incontinence. Fecal incontinence, anal stricture, and rectovaginal fistula developed at a rate of 2.9%. One patient experienced mortality due to sudden cardiac arrest on the fifth post-operative day. Complications occurred in 36.4% of male patients and 52.2% of female patients. Despite the higher complication rate in females, no statistically significant difference between the sexes was observed (P=0.388).

Comparing the time of admission and complication rates, 14 of the 26 patients who underwent surgery on the day of admission developed no complications. Of the remaining 12 patients, three had CD 1 complications, three had CD 2, five had CD 3, and one had CD 5. For the patients who underwent surgery one day after admission, one had CD 1 complications, one had CD 2, and two had CD 3.

Anal function status was evaluated using the Wexner score. At a mean follow-up of 35.8 months, the mean Wexner score for the whole sample was 3.59 (3.32). The mean Wexner score was 3.39 (3.38) in females and 4 (3.31) in females. Despite the higher Wexner score among male patients, no statistically significant difference between the groups was found (P=0.445). In our sample, a Wexner score of 9 and above was observed in 11.8% of patients. It was determined that the overall quality of life was high even though Wexner scores were low.

Table 2 gives detailed information about the demographic and clinical characteristics of our patients.

Table 2: Demographic and clinical features of patients

Variable	Male	Female	Total	*P*-value
Age (mean (SD))	44.09 (13.43)	31.86 (10.29)	35.8 (12.6)	0.012*
Etyopathogenesis				
Obstetric trauma	-	19	19	
Stab and gunsut wounds	5	1	6	
Traffic accidents	2	1	3	
İatrojenik (colorectal surgery)	1	2	3	
Animal attack	3	-	3	
Hospital stay/days	21.9 (13.02)	15.3 (17.9)	17.44 (16.6)	0.0 21*
Complications rate	36.4%	52.2%	47%	0.388**
Wexner score	4 (3.31)	3.39 (3.38)	3.56 (3.34)	0.445*

SD: Standard deviation, *Independent-samples t test, ** Chi-square test

Discussion

The prevalence of anal incontinence ranges from 2% to 18% in the general population. Young female patients are at the greatest risk with obstetric injuries being the main cause [12, 13]. Research on non-obstetric injuries involving both sexes is very rare in the literature, and these studies describe 80.3%–84.6% female patients [12, 14]. In our study, the rate of male patients was 32.4%, which is higher than that in the literature. Almost all patients (11 of 12) who underwent surgery due to trauma (cuts and puncture wounds, animal attacks, traffic accidents) were male. Young male patients are exposed to trauma more frequently than young women [15]. This finding coincides with anal trauma. When considering the socio-economic structure of our region, it is expected that men would be more exposed to trauma, which could explain the high rate of male patients in this study.

A vast majority of ASI are related to obstetric injuries. Limited data on non-obstetric anal injuries are found in the literature. One study on all incontinence cases reported 72.3% obstetric causes, 13.8% fistulotomy, 9.2% nonspecific trauma, and 4.6% war injury. Some (18.5%) of these patients received stoma. In another study, 64.7% of the patients had obstetric ASI, 23.5% perineal trauma, and 11.7% iatrogenic injury [2]. Consistent with the literature, the most common cause of ASI in our study was related to obstetric injuries. However, in our research, animal attacks yielded an interesting rate of around 9%. In this regard, the literature includes only case reports, which are rare. Due to limited research on non-obstetric injuries, we believe that our study will make a significant contribution to the literature.

In the past, end-to-end sphincter repair was the most frequently used surgical technique. However, due to the high rate of failure, surgeons began to use the overlapping sphincteroplasty (OSP) technique that yielded a higher success rate in ASI cases [5, 16]. The end-to-end technique is still frequently used in milder ruptures, but the OSP is preferred, particularly for serious injuries [7]. OSP offers good and even excellent short-term results, but the long-term outcomes deteriorate over time [12]. According to previous studies, the success rate of OSP due to ASI ranges from 68% to 85% [2, 5, 17]. In our study, all patients underwent OSP, while approximately 20% also underwent protective ostomy. The success rate was very high and performing colostomy in external trauma cases led to a further increase in this rate. Accordingly, patients seem to derive many benefits from this operation.

Numerous scoring systems to determine anal incontinence status or quality of life exists; however, nowadays the Wexner score is used most frequently [7, 9, 14, 18]. The Wexner score is a very easy, well-established grading system, and unlike other quality of life scales, the result is not influenced by comorbid diseases [14]. The Wexner score accepts 9 as the threshold value for which a score of 9 or above indicates that fecal incontinence significantly impairs quality of life [19]. Moreover, Wexner scores appear to increase as the follow-up period gets longer [14]. In the present study, we used the Wexner score to evaluate the degree of anal incontinence and accepted the threshold value of 9. We found that our sample had a mean Wexner score of 3.58 at an average follow-up of 35.8 months. Despite the long follow-up period, our patients still had low Wexner scores. Thus, our results seem to be partially more successful than those reported in the literature [8, 12, 14].

Post-operative success can be affected by many factors, including the patient's age, the surgical technique, and other factors.

To improve long-term outcomes, some studies advocate the use of polydioxanone (PDS) or Prolene sutures rather than those made of vicryl or dexon due to their absorption time [20, 21]. Here, 3/0 PDS sutures in our surgeries were used. However, a control group was not included in this study, it cannot be argued that these sutures had an influence on success rates. One of the most important factors that affects treatment outcomes is the patient's age. The success rate is particularly higher in patients under 40 years of age. Again, the outcomes of iatrogenic sphincter injury are better than those of obstetric injury [12, 22].

Despite the limited number of studies involving male patients, the results in men are better than in women. However, this difference may stem from the fact that non-obstetric traumas are the main cause of injury in male patients [12].

The main reasons for our high success rate were the young ages of the patients and performance of the surgeries by three colorectal surgeons with colorectal experience. Again, 91% of our patients were admitted early, within two days at the latest, which could also be considered another factor for success.

In our sample, the most common complications were wound infection (14.7%), wound dehiscence (8.8%), and urinary incontinence (5.9%). Fecal incontinence, anal stricture, and rectovaginal fistula all developed at a rate of 2.9%. In the literature, complications, such as wound dehiscence, wound infection, colostomy-related complications, and perirectal abscess were observed at similar rates in patients who had surgery for obstetric reasons [23, 24]. Previous research reports pudendal neuropathy, traumatic cloaca, and rectovaginal fistula in patients who were admitted for external trauma [4]. Studies report complication rates ranging between 20.5% and 25% [5]. In our study, the complication rate was higher than in previous studies, but the success rate was high. This finding may stem from the high rate of low-severity complications in the CD1 and 2 classification.

For patients with poor outcomes, treatment modalities, such as post-operative sacral nerve stimulation and biofeedback should be recommended [14]. Our hospital did not have certain diagnostic methods, such as anorectal manometry and endoanal ultrasound, for evaluating anal sphincter function and anatomy, so a small number of patients were followed and treated in other centers.

Limitations

Our study had certain limitations and strengths. The main limitation was the retrospective design. Also, we only evaluated the results of emergency patients, so only data from a small number of patients who underwent surgery under elective conditions could be used. The main strength of this research was including non-obstetric injuries and contributing data in this regard to the limited literature.

Conclusion

Obstetric injuries are the most common cause of ASI. OSP has a high rate of success and patient satisfaction when performed by experienced colorectal surgeons. Diverting ostomy should be performed when necessary. The Wexner score is a useful system to determine the severity of anal incontinence. Very few articles have investigated non-obstetric ASI injuries. The need for further research on perineal injuries caused by non-obstetric reasons exists.

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Retrospective assessment of the association between inhalation anesthesia and post-operative complications in morbidly obese patients undergoing bariatric surgery

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Ethics Committee Approval
The study protocol was approved by the Ethics Committee for Clinical Studies of Marmara University Medical Faculty Istanbul Turkey (09.2022.099).
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: Today, obesity is a rapidly growing health problem. Healthcare professionals have been encountering both obese adult and adolescent patients in the operating room more and more frequently. Morbid obesity affects all body systems, thus necessitating greater care in anesthesia management. Studies conducted in recent years have failed to find clear evidence for the most appropriate anesthesia technique with minimal effect on post-operative complications. Therefore, this study was designed to compare the effects of inhalation anesthesia and total intravenous anesthesia (TIVA) on post-operative complications in morbidly obese patients who underwent bariatric surgery.

Methods: After receiving approval from the University Ethics Committee, the files of 304 patients who underwent laparoscopic gastric bypass and sleeve gastrectomy between January 2018 and December 2021 were screened. Patients with unexpectedly difficult airways, who underwent open surgery, in whom the anesthesia technique had to be changed intra-operatively for any reason, those scheduled for intensive care as decided during surgical planning, and those with liver or kidney failure were excluded from the study. A total of 278 patients were included in the study. Patients were divided into two groups according to the method of anesthesia used: (1) TIVA (Group T) and (2) inhalation anesthesia (Group I).

Results: The study was performed with 278 patients of whom 213 were women, and 65 were men. Patient demographics were similar between the two groups. Comparison of the clinical characteristics of the study groups showed that the rate of admission to the intensive care unit (P=0.032), average duration of surgery (P<0.001), and complication rate (P<0.001) were significantly higher in the TIVA group than in the inhalation anesthesia group.

Conclusion: Morbidly obese patients exhibit higher rates of anesthesia- and surgery-related complications because of their comorbidities. Anesthesia management and selection of anesthetics are important in these patients. Based on the literature and results of our study, inhalation agents may be preferred for morbidly obese patients because they are associated with fewer complications in this patient population. Although our study indicates that inhalation anesthesia is a safe and appropriate choice, extensive studies with a larger number of patients are needed.

Keywords: Bariatric surgery, Inhalation anesthesia, Total intravenous anesthesia (TIVA), Morbid obesity, Post-operative complications

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Introduction

Obesity is a growing health problem worldwide. Studies have demonstrated that morbid obesity can cause complications, such as diabetes, sleep apnea, depression, and/or heart disease. Moreover, the prevalence of morbid obesity has been steadily increasing over the last two decades. The three main treatment options for morbid obesity are lifestyle change, pharmacotherapy, and surgery. Surgical treatment has been found to be superior to the other two options because it offers a long-term and quick solution [1].

Morbidly obese patients are also at a greater risk for pre- and post-operative complications because they have more comorbidities than the normal population. General anesthesia is specific in this patient population and requires an experienced surgical team [2]. Some studies in the literature classify post-operative complications according to the Clavien–Dindo system, a grading system introduced in 2004 that provides an objective classification of post-operative complications [3, 4].

The rapid developments in laparoscopic bariatric surgery and recent increase in their use can be attributed to the reduction of post-operative complications [5]. Selection of an appropriate anesthetic agent for induction and maintenance is important for achieving favorable outcomes with laparoscopic surgery in obese patients [2, 6]. The primary aim of this retrospective study was to compare the effects of inhalation anesthesia and total intravenous anesthesia (TIVA) on post-operative complications in morbidly obese patients undergoing bariatric surgery. The secondary aim was to evaluate the relationship between laboratory data and development of complications.

Materials and methods

After obtaining approval from the Marmara University's Clinical Research Ethics Committee (approval no. 09.2022.099), the hospital database was screened, and data from 304 patients who underwent bariatric surgery between January 2018 and December 2021 were accessed. Patients with unexpectedly difficult airways, patients who underwent open surgery, patients in whom the anesthesia technique had to be changed intra-operatively for any reason, patients scheduled for intensive care as decided during surgical planning, and patients with liver or kidney failure were excluded from the study. Screening of the medical records showed that the data were only partially accessible for 10 patients; eight patients had previously undergone bariatric surgery, two patients had the method of anesthesia method changed during the operation, three patients had been switched to open surgery during the operation, two patients had initial liver enzyme levels twice the normal levels, and one patient had chronic renal failure; thus, these patients were excluded from the study. The remaining 278 patients were divided into two groups according to the method of anesthesia used: (1) TIVA (Group T) and (2) inhalation anesthesia (Group I). For bariatric surgery, our clinic uses propofol and remifentanil infusion for TIVA and desflurane or sevoflurane in combination with remifentanil infusion for inhalation anesthesia. All patients underwent electrocardiography, pulse oximetry, invasive arterial pressure monitoring, bispectral index monitoring, and capnography. Patients' demographics, admission to and length of stay in the intensive care unit (ICU), if any, duration of surgery, presence of complications, need for transfusion, choice of anesthetic agent, post-operative nausea and vomiting, pre- and postoperative lactate, blood urea nitrogen, creatinine, aspartate transaminase, and alanine transaminase levels were obtained from the screened records. Patients with a waist/hip ratio of >0.85 were evaluated as abdominally obese. Post-operative complications were classified according to the Clavien–Dindo system. The present study was designed as a retrospective cohort study.

Statistical analysis

SPSS 22.0 software was used for data analysis. Descriptive statistics were expressed as averages, standard deviations, medians, lowest and highest values, frequencies, and ratios. Variable distribution was measured using the Kolmogorov–Smirnov test. Quantitative independent variables were analyzed with the independent t- and the Mann–Whitney U tests, and quantitative dependent variables were analyzed using the Wilcoxon test. A chi-square test was used to analyze the qualitative independent data, and the Fischer's test was used when the chi-square test criteria were not fulfilled. The level of significance was set at P <0.05.

Results

The study was conducted with 278 patients, of whom 213 were females, and 65 were males. Patient demographics were distributed similarly between the study groups (Table 1).

Table 1: Comparison of demographics of the study groups (Measurable values are given in median minimum–maximum values instead of numbers and percentages)

		Group I N (%)	Group T N (%)	*P*-value
Gender	Female	131 (75.3)	82 (78.8)	0.498 [a]
	Male	43 (24.7)	22 (21.2)	
Age *		43 (22-64)	41 (21-64)	0.196 [b]
BMI*		45.8 (36.5-66.2)	46 (35.6-66.4)	0.723 [b]
Waist/ hip ratio*		0.89 (0.77-1.2)	0.93 (0.76-1.1)	0.113 [b]

[a] Chi-square test, [b] Mann Whitney U test, * In the measurement data, the median minimum-maximum values are presented instead of the number percent.

Comparison of the clinical characteristics of the study groups showed that the rate of admission to the ICU (P=0.032), the average duration of surgery (P<0.001), and complication rates (P<0.001) were significantly higher in Group T than in Group I.

The rate of obtaining low grades based on the Clavien–Dindo complication grading system was significantly higher in Group I than in Group T (P=0.003). No statistically significant difference between the study groups in terms of obesity type and post-operative nausea and vomiting (PONV) were found (Table 2).

In the 44 patients who presented complications three main complications were found: (1) atelectasis (n: 18; 40.9%), (2) hypoxia (n: 8; 18.1%), and (3) anastomotic leaks (n: 7; 15.9%). The distribution of complications by groups is presented in Table 3.

Table 2: Comparison of clinical characteristics of the study groups

		Group I N (%)	Group T N (%)	*P*-value
Obesity type	Non abdominal	36 (20.7)	22 (21.2)	0.927 [a]
	Abdominal	138 (79.3)	82 (78.8)	
Intensıve Care Unit (ICU) hospitalization	No	170 (97.7)	96 (92.3)	0.032 [b]
	Yes	4 (2.3)	8 (7.7)	
Operation duration (minute)*		100 (59-210)	110 (65-287)	<0.001 [c]
ICU duration (day)*		1 (1-4)	2 (1-8)	0.272 [c]
Complication	No	157 (90.2)	77 (74.0)	<0.001 [a]
	Yes	17 (9.8)	27 (26.0)	
Operation type	Bypass	144 (82.8)	75 (72.1)	0.036 [a]
	Sleeve	30 (17.2)	29 (27.9)	
Anesthesia agent	Desflurane	118 (67.8)	0 (0.0)	<0.001 [a]
	TIVA	0 (0.0)	104 (100.0)	
	Sevoflurane	56 (32.2)	0 (0.0)	
PONV (post-operative nausea & vomiting)	No	143 (82.2)	93 (89.4)	0.103 [a]
	Yes	31 (17.8)	11 (10.6)	
Clavien-Dindo complication scores	0	157 (90.2)	77 (74.0)	0.003 [b]
	I	1 (0.6)	6 (5.8)	
	II	7 (4.0)	8 (7.7)	
	IIIA	0 (0.0)	3 (2.9)	
	IIIB	6 (3.4)	6 (5.8)	
	IV	3 (1.7)	4 (3.8)	

[a] Chi-square test [b] Fisher test, [c] Mann Whitney U test, * In the measurement data, the median minimum-maximum values are presented instead of the number percent.

Table 3: Distribution of complications in patients who developed complications by study groups

Complication	Inhalation N (%)	TIVA N (%)	Total N (%)
Anastomosis leak	4 (23.5)	3 (11.1)	7 (15.9)
Atelectasis	6 (35.3)	12 (44.4)	18 (40.9)
Infection	0 (0.0)	4 (14.8)	4 (9.09)
Hematuria	0 (0.0)	1 (3.7)	1 (2.2)
Hypoxia	3 (17.6)	5 (18.5)	8 (18.1)
Incarcerated hernia	1 (5.9)	1 (3.7)	2 (4.5)
Bleeding	0 (0.0)	1 (3.7)	1 (2.2)
Perforation	1 (5.9)	0 (0.0)	1 (2.2)
Arrhythmia	1 (5.9)	0 (0.0)	1 (2.2)
Transfusion requirement	1 (5.9)	0 (0.0)	1 (2.2)
Total	17 (100.0)	27 (100.0)	44 (100.0)

The analysis of the relationship between clinical characteristics and complications revealed that the rate of complications was significantly higher in Group T than in Group I (P<0.001) as shown in Figure 1. Complication rates were significantly higher in patients admitted to the ICU than in patients who were not (P<0.001). The mean duration of the surgery was significantly higher in patients with complications than in those without (P<0.001). Group T had a higher rate of complications, and in Group I, patients who received sevoflurane had a lower rate of complications than those who received desflurane (P=0.001). No statistically significant difference between the two groups in terms of the type of obesity, type of operation, length of stay in the ICU, PONV, and the development of complications (Table 4).

Table 4: Relationship between clinical features and complications

		Complication No N (%)	Complication Yes N (%)	*P*-value
Obesity type	Non abdominal	51 (87.9)	7 (12.1)	0.378 [a]
	Abdominal	183 (83.2)	37 (16.8)	
Anesthesia	Inhalation	157 (90.2)	17 (9.8)	<0.001 [a]
	TIVA	77 (74.0)	27 (26.0)	
ICU hospitalization	No	234 (88.0)	32 (12.0)	<0.001 [b]
	Yes	0 (0.0)	12 (100.0)	
Duration of operation (minute)		100 (59-210)	120 (65-287)	<0.001 [c]
ICU hospitalization (day)		1 (1-4)	2 (1-8)	0.272 [c]
Operation type	Bypass	182 (83.1)	37 (16.9)	0.347 [a]
	Sleeve	52 (88.1)	7 (11.9)	
Anesthesia agent	Desflurane	103 (87.3)	15 (12.7)	0.001 [a]
	TIVA	77 (74.0)	27 (26.0)	
	Sevoflurane	54 (96.4)	2 (3.6)	
PONV (postoperative nausea & vomiting)	No	196 (83.1)	40 (16.9)	0.224 [a]
	Yes	38 (90.5)	4 (9.5)	
Clavien-Dindo classification	0	233 (99.6)	1 (0.4)	<0.001 [b]
	I	0 (0.0)	7 (100.0)	
	II	1 (6.7)	14 (93.3)	
	IIIA	0 (0.0)	3 (100.0)	
	IIIB	0 (0.0)	12 (100.0)	
	IV	0 (0.0)	7 (100.0)	

[a] Chi-square test, [b] Mann Whitney U test, * In the measurement data, the median minimum-maximum values are presented instead of the number percent.

Pre- and postoperative lactate values were significantly higher in the group with complications than in the group without complications (P=0.007 and <0.001, respectively). No significant differences were found between the groups with respect to other laboratory data and complication rates (Table 5).

Table 5: The relationship between laboratory data and the development of complications

	Complication No Median (Min-Max)	Complication Yes Median (Min-Max)	*P*-value [a]
Preop BUN	12 (5-30)	12 (7-23)	0.654
Postop BUN	13 (4-29)	13 (4-33)	0.935
Preop creatinine	0.66 (0.42-1.22)	0.67 (0,44-1,1)	0.424
Postop creatinine	0.69 (0.33-1.77)	0.73 (0.41-1.4)	0.178
Preop ALT	29 (12-64)	29 (17-54)	0.980
Postop ALT	54 (13-738)	51 (17-217)	0,727
Preop AST	27.5 (8-101)	29 (14-54)	0.264
Postop AST	52 (9-798)	57.5 (12-285)	0.532
Preop lactate	0.9 (0.3-2.8)	1.1 (0,5-3,9)	0.007
Postop lactate	0.9 (0,4-3.2)	1.2 (0.6-5)	<0.001

[a] Mann Whitney U test

Discussion

The findings of the present study showed that inhalation anesthetic agents are safe and effective in terms of complication rate in patients undergoing bariatric surgery.

Studies conducted to date have failed to yield clear results on anesthetic agents and post-operative complications [7, 8].

Obesity can affect most of the systems in the body, including the respiratory, cardiovascular, and immune systems. Obese patients experience restrictive lung disease, which manifests in the form of an increase in oxygen consumption, carbon dioxide production, alveolar ventilation, and elevated respiratory rates even in patients at rest and with reduced pulmonary compliance. These patients also have a decreased total lung capacity and functional residual capacity and increased airway resistance. Obese patients have higher rates of incidence of post-operative atelectasis, hypoxia, prolonged intubation, and lung infections compared with patients of normal weight [9]. Therefore, it is important to select the most suitable type of anesthesia.

An experimental study of obesity has shown that propofol infusion for 1 h may cause increased airway resistance and lead to atelectasis and pulmonary inflammation because of the depletion of enzymatic antioxidants and increased levels of tumor necrosis factor alpha and interleukin 6 (TNF-α and IL-6, respectively) in lung tissue [10]. In line with this finding, our study found a higher rate of atelectasis in the TIVA group. As mentioned in the literature, weakened respiratory muscles and increased oxygen consumption in obese patients cause an increase in the tendency to develop atelectasis, and the use of TIVA may further increase the risk of developing atelectasis.

Another study comparing inhalation anesthesia and TIVA in morbidly obese patients reported that oxygen saturation in the first 2 h was lower in patients who received TIVA and that the forced vital capacity, peak expiratory flow, mid-expiratory flow, and forced inspiratory capacity as measured by spirometry were lower than the initial values by 11% to 20% and lasted for 24 h [11]. Our study found similar rates of post-operative hypoxia in the two groups. High visceral fat mass in obese individuals pushes the diaphragm upward and makes the diaphragm movements harder, thus leading to hypoxia due to fat deposits between the ribs and reduced pulmonary compliance.

Therefore, it is important to select suitable anesthetic agents that do not deepen hypoxia.

In a study of respiratory mechanics during laparoscopic sleeve gastrectomy in morbidly obese patients, Ozturk et al. compared inhalation anesthetics and propofol and found no statistically significant difference. However, they reported increased airway resistance with propofol and desflurane with air in the peritoneal cavity, whereas no change in airway resistance occurred after sevoflurane administration [12]. The most common post-operative complications found in our study were atelectasis and post-operative hypoxia (40% and 18%, respectively). Respiratory complications were more common in the TIVA group. This observation could be attributed to the fact that sevoflurane, which is an inhalation anesthetic, acts on smooth muscle, suppresses smooth muscle contractility, leads to indirect inhibition of vagal reflexes, and acts as a good bronchodilator. Several studies have shown that desflurane produces bronchodilatory effects that mimic sevoflurane although desflurane also depends minimum alveolar concentration [13].

Obesity also affects the cardiovascular system and causes increased cardiac output and workload. Fat stored throughout the body can be deposited in the heart's conduction system, thereby causing conductive dysfunction in the sinoatrial node. Thus, obese patients are at a greater risk for arrhythmia and have a 1.5-fold increase in the incidence of atrial fibrillation. Studies conducted in recent years have shown that sevoflurane, an inhalation anesthetic with low solubility, has a cardioprotective effect that prevents myocardial ischemia and arrhythmia [14, 15]. In the present study, out of 278 patients, post-operative atrial fibrillation was observed in only one patient in the inhalation anesthesia group.

In recent years, clinical and experimental studies have shown that anesthetic drugs affect the immune system and the glycocalyx layer and may also affect the development of complications. It is thought that obese patients have chronic inflammation owing to the higher level of proinflammatory cytokines (TNF-α, and IL-6 and -12) compared with the normal weight population. It is also known that obese individuals have impaired macrophage and neutrophil function. A study comparing sevoflurane and propofol with TIVA found higher levels of IL6, TNF α, and other proinflammatory cytokines in the TIVA group [16]. This study was not conducted with a group of obese patients, but similar results were noted in an experimental model of obesity. The present study found no surgical site infection in the volatile anesthesia group, but four patients (14.8%) in the TIVA group developed a surgical site infection that required medical or surgical intervention.

A study investigating the effect of propofol and sevoflurane on the microcirculation reported that the capillary filtration coefficient that decreases in response to sevoflurane may result in reduced extravasation of liquids into the interstitial space and thereby reduce the need for intra-operative fluids. This finding suggests that sevoflurane may be the anesthetic agent of choice in patients susceptible to large intra-operative fluid shifts during abdominal surgery and operations involving anastomosis [17]. In the present study, the anastomotic leak rate was 23.5% in the volatile anesthesia group and 11.1% in the TIVA group.

Regarding the effects of anesthetic drugs on post-operative kidney and liver functions, the present study could not obtain a statistically and clinically significant result in the TIVA and inhalation anesthesia groups. There are reported cases of acute hepatotoxicity in non-obese patients with sevoflurane, and there is also a reported case of a patient undergoing bariatric surgery with desflurane [18]. Acute kidney damage after bariatric surgery has been reported at 6% [19]. Acute kidney damage has been defined as a ≥1.5-fold increase in creatinine levels at postoperative day 7, an increase in creatinine by 0.3 mg at 48 hours, and urine output <0.5 ml/kg/hour in 6 hours of follow-up. Our study found no significant difference between the two groups in post-operative creatinine levels. In a study with 64 patients who underwent bariatric surgery, Fernandes et al. [20] determined acute kidney damage with neutrophil gelatinase-associated lipocalin and found no significant difference between the TIVA and volatile anesthesia groups.

PONV is common, especially during sleeve gastrectomy, in morbidly obese patients [21, 22]. Although several studies have reported better results with TIVA in terms of PONV in the short term, none could find any significant results when TIVA was compared with inhalation anesthetics in the long term [21]. The present study found PONV to be more common in the inhalation anesthesia group, but the results were not statistically significant.

Our study has some limitations. First, post-operative pain levels were not recorded; indeed, pain can trigger post-operative respiratory and cardiac complications. Another limitation is the retrospective design of our study, which meant that only records of symptomatic atelectasis and complications experienced only during hospitalization could be accessed. Different results could be achieved with prospective, randomized, multicenter, and longer-term studies. The last limitation is the likelihood that metabolic conditions of the obese patients might have affected the variable and independent outcomes.

Conclusion

Patients undergoing bariatric surgery are at a risk for several complications due to obesity and the surgical method. Most studies concerning post-operative complications could not achieve clear results. Great care is needed in the selection of anesthetic agents to prevent complications in this group of patients. In view of the present study and the studies in the literature, it can be said that volatile anesthetic agents are safe and effective in terms of complications in patients undergoing bariatric surgery.

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The effect of hospital volume on mortality, morbidity and dissected lymph nodes in pancreaticoduodenectomy for periampullary region tumors

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Ethics Committee Approval
The study was approved by Gazi University Clinical Research Ethics Committee, Date: 23.06.2016, Decision no: 331.
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: Since the first pancreaticoduodenectomy (PD) surgeries, mortality, morbidity and length of hospital stay decreased, in return, the number of uncomplicated cases and dissected lymph nodes increased over the years. The aim of our study was to determine the effect of hospital volume on survival, postoperative hospital stay, fistula rate, morbidity rate and the number of lymph nodes dissected.
Methods: In this retrospective cohort study, 213 patients who were operated with the diagnosis of periampullary tumor between January 2008 and January 2016 were included in the study. The patients were divided into four groups according to the years of surgery: Group A (n=31, 2008-2009), Group B (n=46, 2010-2011), Group C (n=50, 2012-2013) and Group D (n=86, 2014-2016). The groups were compared with each other in terms of the following factors; Pancreatic fistula rates, postoperative hospital stay, mortality rates, morbidity rates, number of dissected lymph nodes.
Results: It has been observed that there is a relation between pancreatic tissue quality and duct size with fistulas (P=0.0016 and P=0.017, respectively). It is seen that as the amount of number lymph nodules increases, the quality of staging improves (P=0.009). Rates of mortality and morbidity are decreased, as the hospital volume increased (P=0.037), The same effect of hospital volume is observed in length of hospital stay and fistula rates, both improved (P=0.017 and P<0.001, respectively).
Conclusion: It is easy to state that the increase in hospital volume and surgeon's experience is directly related with patient outcomes. As the understanding of anatomy increases, quality of the surgery is assumed to be increased as well as the reduction in length of hospital stay, mortality and morbidity rates, and the increase in quantity of dissected lymph nodules.

Keywords: Periampullary tumor, Hospital volume, Pancreaticoduodenectomy

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Introduction

Periampullary region tumors (PRT) have a poor prognosis. Its incidence increases after the 5th decade. The female/male ratio is 1/2-3. Risk factors for periampullary cancers are age, gender, genetics, smoking, chronic pancreatitis, diabetes mellitus, previous small bowel surgery, and ulcer bleeding [1-3]. Pancreaticoduodenectomy (PD), which had a 20% mortality at the beginning, has become a more applicable surgery with modifications and surgical experience over time, and mortality rates have decreased to below 3% in experienced centers [4,5].

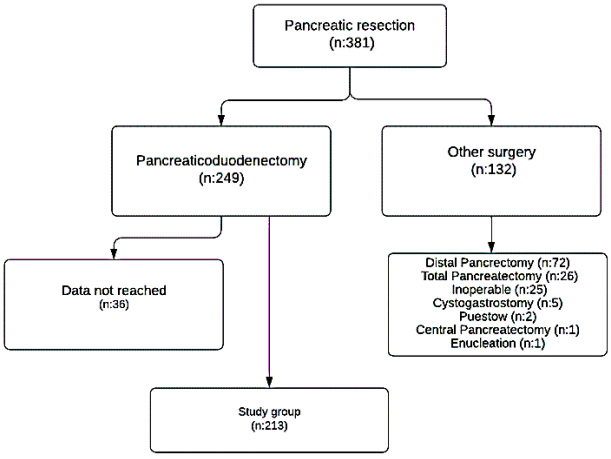
Lymph node dissection is one of the most important prognostic factors for gastrointestinal tumors. In addition, tumor size, locoregional invasion, and resection margin are also important prognostic factors [6,7]. In some studies, it has been reported that there is a positive correlation between the curability of lymph node dissection in stage I and II tumors [8]. Although up to 50% of paraaortic lymph node metastases have been observed in some previous autopsy series, dissections of these lymph nodes are not included in the standard Whipple procedure [9].

In this study, the results of PD operations performed with the preliminary diagnosis of PRT were examined. The relationship between gland texture of pancreatic tissue, pancreatic duct diameter and fistula rates was investigated in patients undergoing PD. It was aimed to determine the effect of hospital volume on survival, number of dissected lymph nodes, postoperative hospital stay and rate of fistula and morbidity.

Materials and methods

After the approval of Gazi University Clinical Research Ethics Committee (Date: 23.06.2016, Decision no: 331), 381 pancreatic surgeries performed between January 2008 and January 2016 were evaluated. PD was performed in 249 of these patients. Other surgeries were excluded from the study (Figure 1). 36 patients were excluded from the study because all data could not be accessed. Patients were staged according to the American Joint Committee on Cancer (AJCC) TNM staging system.

Figure 1: Flowchart of patients



Preoperatively with the help of CT, USG, and EUS, perioperative USG, and postoperative pathology results, pancreatic tissue was evaluated as hard and soft according to its density. The main pancreatic duct diameter was divided into 2 groups as ≤3mm and >3mm, for its relationship with rates of pancreatic fistula. The effect of dissected lymph node and metastatic lymph node numbers on survival of patients who underwent PD according to pathology results was evaluated. After that, patients were divided into 4 groups as 2008-2009 (Group A), 2010-2011 (Group B), 2012-2013 (Group C), 2014-2016 (Group D) according to the years of surgery. Pancreatic fistula rates, postoperative hospital stay, mortality and morbidity rates according to Dindo-Clavien [10], and the number of dissected lymph nodes were evaluated according to these groups.

As the definition of pancreatic fistula, the drain fluid amylase levels measured in the 3rd and 5th days after PD were accepted as being 3 times higher than the amylase levels in serum or levels determined as the upper limit by the hospital laboratory. Pancreatic fistula grading was classified according to the "International Study Group Postoperative Pancreatic Fistula" (ISGPF) [11]. The length of hospital stay was recorded as the number of days between the day of surgery and discharge.

Statistical analysis

Data analysis was evaluated with SPSS 15.0 for the Windows data analysis program. Kolmogorov-Smirnov test was performed to observe the distribution of the parameters. Descriptive statistics (frequency, percentage distribution) were used as statistical analysis. In the comparison of the two groups, Chi-Square test, one-way ANOVA, and Spearman's rho analysis methods were used. $P<0.05$ was considered statistically significant.

Results

The age distribution of patients was between 14 and 87, and the mean age was 59.71 (13.23). Of 213 patients, 87 (40.9%) were female and 126 (59.1%) were male. The mean follow-up period of the patients within the study was found 21.5 (35.5) months. The duration of hospital stay was seen as a minimum of 1 and a maximum of 85 months.

The pathological diagnosis distribution is shown in Table 1. According to the tumor stages, 107 (50.2%) were T3 tumors, whereas 53 (24.9%) were T2, 15 (7%) were T4, and 12 (5.6%) were T1. Pathological malignancy was not found in remaining 26 (12.2%) patients.

Table 1: Pathological diagnosis of patients.

Pathological diagnoses	n=213	%
Well Differentiated Adenocarcinoma	63	29.6
Moderately Differentiated Adenocarcinoma	52	24.4
Poorly Differentiated Adenocarcinoma	21	9.9
Well Differentiated Neuroendocrine Tumor	16	7.5
Chronic Pancreatitis	13	6.1
Serous Microcystic Adenoma	11	5.2
Solid Pseudo papillary Tumor	7	3.3
İntraductal Papillary Mucinous Adenoma	7	3.3
IPMN	7	3.3
Mucinous Adenocarcinoma	5	2.3
Pseudocyst	5	2.3
Signet-ring cell carcinoma	4	1.9
PAN-IN	2	0.9

IPMN: Intraductal papillary mucinous neoplasm, PAN-IN: Pancreatic intraepithelial neoplasia

The fistula was detected in 64 (30%) patients in the study. The fistula grades of the patients are given in Table 2.

Grade A fistula was not considered as a cause of morbidity. While 95 (44.6%) of the 213 patients included in the study had morbidity due to the reasons given in Table 3, 118 (55.4%) patients were considered uncomplicated.

The surgical margin was positive in 54 patients (25.4%) and negative in 159 patients (74.6%), in pathological examination.

Table 2: Percentage of patients with pancreatic fistula

Pancreatic fistula	n=64/213	%
Grade A	37	57.8
Grade B	18	28.1
Grade C	9	14.1

Table 3: Causes and percentages of morbidity

Causes and percentages of morbidity	n=95/213	%
Anastomotic leak	27	28.4
Wound Infection	18	18.9
Intraabdominal Abscess	14	14.7
Pleural Effusion	8	8.4
Kidney failure	4	4.2
Pulmonary Thromboembolism	4	4.2
Mesenteric Ischemia	3	3.1
Evisceration	3	3.1
Intraabdominal Bleeding	3	3.1
Gastrointestinal Bleeding	3	3.1
Aspiration Pneumonia	3	3.1
Biliary Obstruction	3	3.1
Intraoperative myocardial infarction	2	2.1

Pancreatic tissue was found to be hard in 71 (3.3%) patients, while the gland texture of pancreas was soft in 142 patients (66.7%). When the pancreatic fistula rates were compared, it was seen that the effect of hard or soft tissue on fistula formation was statistically significant (Table 4). The fistula was statistically less common in cases with hard pancreatic tissue (P<0.001).

The main pancreatic duct diameter widths were ≤3 mm in 118 (5.4%) patients and >3mm in 95 (44.6%) patients (Table 5). It was observed that fistula rates increased statistically in patients with a main pancreatic duct width less than 3 mm (P=0.016).

Table 4: Fistula rates by the gland texture of the pancreatic tissue

Pancreatic tissue's texture	Pancreatic fistula (+) (n=149)	Pancreatic fistula (–) (n=64)	*P*-value*
Hard (n=71)	60 (85.5%)	11 (15.5%)	0.05
Soft (n=142)	89 (62.6%)	53 (37.4%)	

*Chi-Square test

Table 5: Fistula rates by main pancreatic duct width

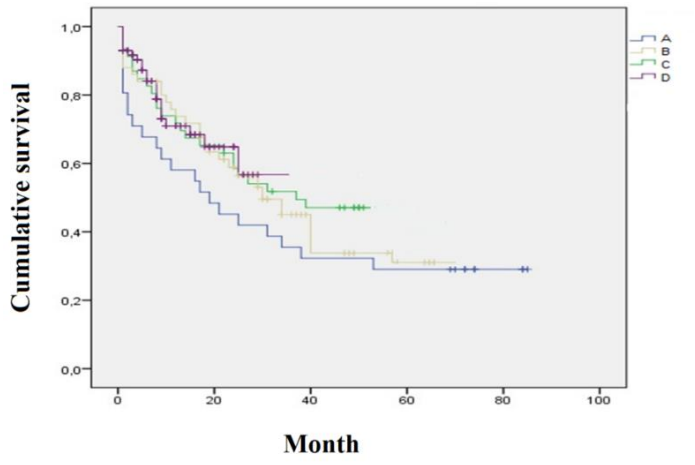
Pancreatic duct diameter	Pancreatic fistula (+) (n=149)	Pancreatic fistula (-) (n=64)	*P*-value
3mm and below (n=95)	58(61.1%)	37(38.9%)	0.016
Over 3mm (n=18)	91(77.1%)	27(22.9%)	

*Chi-Square test

213 patients were divided into 4 groups as 2008-2009 (Group A), 2010-2011 (Group B), 2012-2013 (Group C), 2014-2016 (Group D). When the groups were compared, no statistically significant difference was found according to age (P=0.789) and gender (P=0.460). The groups were homogeneously distributed.

The overall survival is shown to be increased as the number of surgeries performed and the experience are increased. This percentage increase was considered significant (Figure 2).

Figure 2: Cumulative survival by years (2008-2009 (Group A), 2010-2011 (Group B), 2012-2013 (Group C), 2014-2016 (Group D))



The 1, 3, and 5-year survivals of the patients included in the study were evaluated. The 1-year survival was calculated for all four groups. 1-year survival was 58%, 65%, 71%, and 73% in group A, B, C, and D, respectively. This increase was found to be significant. The 3-year survival was evaluated for groups A, B, and C. The survival rate was 29%, 47%, and 49% in group A, B, and D, respectively. 5-year survival was evaluated between groups A and B, which were 21% and 41% in group A and B, respectively. This increase in percentage was considered significant.

It was observed that the perioperative mortality rates decreased with the increase in hospital volume. As a result of this analysis between groups, this decrease in perioperative mortality was found to be statistically significant (P=0.037).

When the pancreatic fistula rates between the groups were compared, they were decreased as the hospital volume increased. This decrease was found to be statistically significant (P=0.017) (Table 6).

Table 6: Pancreatic fistula rates by years

Pancreatic fistula	A (n=31)	B (n=46)	C (n=50)	D (n=86)	Total (n=213)	*P*-value *
(-)	n=17	n=29	n=33	n=70	n=149	0.017
	54.8%	63%	66%	81.40%	70%	
(+)	n=14	n=17	n=17	n=16	n=64	
	45.2%	37%	34%	18.6%	30%	

*Chi-Square test

The mean length of hospital stay was found to be 15.46 (10.8) days. According to the comparison, the length of hospital stay was 18.85 (10.52), 18.48 (15.81), 14.86 (7) and 13 (8.6) days in group A, B, C and D, respectively. When these data were analyzed with one-way ANOVA test [12], it was shown that this decrease in group D was statistically significant (P=0.017).

It was clinically demonstrated that the number of dissected lymph nodes increased over the years (Table 7). The mean number of lymph nodes (LN) dissected was 13.12 (7.1). Patients were divided into three groups according to the number of dissected LNs; 0-5 LN removal (X group), 5-10 LN removal patients (Y group), 10 and more LN removal patients (Z group). When the survivals of the X, Y, and Z groups were evaluated, the cumulative survival rate of group Z was found to be statistically better (P=0.009).

Table 7: Distribution of dissected lymph node numbers by years

	A (n=31)	B (n=46)	C (n=50)	D (n=86)	Total (n=213)	*P*-value *
Mean	8.54	10.28	10.78	17.66	13.12	<0.001
SD	3.9	6.3	5.9	6.5	7.1	
Minimum	1	1	1	8	1	
Maximum	21	25	23	43	43	

SD: Standard deviation, * One-way ANOVA test

Patients with and without metastatic LN involvement were divided into 2 groups. One and three-year survivals of these patients were evaluated. 1-year survival rate of patients with LN negative was 83.9%, while it was 63% for patients with LN positive, which presents statistically significant (P=0.003). Considering the 5-year survival, it was found to be 60.8% in patients with negative LN and 24.5% in patients with positive LN. It was evaluated as statistically significant (P<0.001). 1 and 3-year survivals were statistically decreased in LN positive patients. Survival rates were decreased in patients with LN positive.

According to Dindo-Clavien classification (Table 8), they were divided into seven groups as grade I, II, IIIa, IIIb, IVa, IVb, and V. There was no statistically significant difference

between the groups (P=0.101). Although there was no statistically significant difference between the patients, all of grade I patients and patients without complications were statistically evaluated as grade I. This result was statistically significant (P=0.002). As a result, uncomplicated discharge rates decreased significantly over the years.

Table 8: Distribution of patients, according to Dindo-Clavien classification

Dindo-Clavien	A (n=31)	B (n=46)	C (n=50)	D (n=86)	Total (n=213)
Grade I	11	25	26	56	118
Grade II	5	4	3	9	21
Grade IIIa	4	4	3	5	16
Grade IIIb	3	5	5	5	18
Grade 4a	2	4	4	4	14
Grade 4b	1	2	3	2	8
Grade 5	5	2	6	5	18

Discussion

The mortality of PD surgery is less than 5% in experienced centers, and the complication rate is between 25-40%. Morbidity rates have decreased to 5-10% with the improvement of surgical technique and postoperative care conditions [13, 14].

One of the factors responsible for mortality and morbidity during or after PD is the small number of pancreatic resections performed in low-volume centers. In many studies in the literature, positive effects of hospital volume on mortality, morbidity rates, number of dissected lymph nodes, and length of hospital stay have been reported. Firstly, Luft et al. [15] put two theories in their study in 1979, for the relationship between hospital volume and outcomes. Success increases with experience, and patients should be referred to centers where more operations are performed. Van Heek et al. [16] defined hospitals where fewer than five PDs per year were performed as low-volume hospitals. Although the mortality rate is 13% in centers with pancreatic resection, it is around 2% in centers with a high number of patients [17, 18].

Three different studies confirmed that increasing hospital volume reduces mortality and morbidity [19-21]. Birkmeyer et al. [19] showed that an increase in hospital volume reduces mortality and morbidity, independent from the surgeon's volume. Bahmann et al. [22] similarly evaluated that statistically significant better survival was achieved with an increase in hospital volume. Contrary to these views, Nathan et al. [23] concluded in a study conducted in 2009 that the effect of the surgeon's patient volume is not significant. Similar to our study, the common points of these studies are that better results are obtained as the patient volume of the hospital and the surgeon increases. Because in a center where a complex surgery like PD is performed, patient selection with experience, preoperative patient evaluation, technical skills, and postoperative patient care gain importance.

One of the reasons for the decrease in mortality and morbidity in high-volume hospitals in the 2 studies conducted by Ghaferi et al. [24, 25] is the more effective management of complications in these centers. It has been shown that co-morbidities have no effect on mortality in high-volume hospitals. In a meta-analysis of 17 studies conducted by Van Heek et al. [16], only one study reported that mortality and morbidity rates in high-volume hospitals were statistically insignificantly low. It was thought that this study was also due to the inclusion of low volume centers as 2 PD per year. Today, while mortality rates are below 5% in high-volume centers, morbidity rate is around 40% despite all developments.

The most important complication after PD is the development of the pancreatic fistula. Pancreatic fistula is thought to be the cause of other major complications. Activation of enzymes secreted from pancreatic leakage causes auto digestion, which results in peripancreatic collection, intra-abdominal abscess, delayed gastric emptying, and postoperative hemorrhage. The common point in pancreatic anastomosis leaks is to protect the patient from sepsis, peritonitis, hemorrhage, and organ failure. The rate of pancreatic fistula has been reported between 2-50%. The reason for this wide range is the absence of an internationally accepted definition of fistula [5].

In this study, it was statistically shown that the rate of fistula related to hospital volume decreased over the years. Fistula rates were found to be similar in studies [26, 27]. Pratt et al. [28] showed that postoperative fistula rates decreased in high-volume hospitals by mentioning the surgeon's experience and preoperative patient preparations in a large-scale study. However, Kollmar et al. [29] defended that hospital volume showed a minimal correlation with pancreatic fistula rates.

It is a known fact that the quality of pancreatic tissue and the width of the pancreatic duct may be associated with pancreatic fistula rates. Pancreatic anastomosis, which is a complex surgery as PD, is an issue that needs to be emphasized, both in terms of its neighborhood and in terms of the tissue it contains. Pancreatic tissue evaluated preoperatively, perioperatively, and postoperatively is an important risk factor for anastomotic leakage. In a study by Yeo et al. [5] the softness of the pancreatic tissue is shown as statistically increased risk for pancreatic anastomosis leakage. Similarly, in a study of 1891 patients, Lin et al. obtained similar results [30]. However, large-scale studies have found that the size of the pancreatic duct is effective in pancreatic leakage, and the risk increases in ducts with a diameter of ≤3mm [31-33]. One study showed that each 1mm reduction in the pancreatic duct increases the risk of an anastomotic leak by 68% [28]. These data are directly proportional to our study.

As it is known, in parallel with the number of surgeries performed in high-volume hospitals, the dominance of anatomy is increasing. With increasing experience, the duration of the operation shortens and the quality of the exploration increases. In this study, it was shown that as the volume increased, the number of lymph node dissections and the number of removed lymph nodes increased statistically. It is supported by various studies that the number of dissected lymph nodes has an effect on survival and that expanded lymph node dissection provides better prognosis [34–36]. The number of lymph nodes involved in standard lymphadenectomy has been the subject of debate. Pawlik et al. [37] determined this number as 12, but in some studies, this number was accepted as ≥15 [38]. 10-15 lymph nodes are generally considered optimal [39, 40]. In our study, a mean of 13.12 (7.1) lymph nodes were dissected. This number increased statistically depending on the year.

The decrease in mortality and morbidity rates and the increase in the number of dissected lymph nodes were observed with the increase in the number of cases and experiences over the years, designed in a high-volume center as a retrospective cohort

study. However, it has been observed that the length of hospital stay of the patients has decreased over the years. It has also been found that the gland texture of pancreatic tissue and the width of the main pancreatic duct are associated with the possibility of pancreatic fistula. Fistula rates were found to statistically significantly increase in patients with soft pancreatic tissue and a main pancreatic duct smaller than 3mm. Although it has been shown that the number of dissected LNs has a percentage effect on survival, the most important point is that a better staging can be made with the increase in the number of lymph nodes resected in this complex region, which increased in every following year, with the increasing experience.

Limitations

The retrospective design of our study, and the inclusion of only PD cases can be considered as limitations. However, the number of patients is higher than most studies in terms of decision making. Future studies with larger series and more homogeneously paired groups are needed.

Conclusion

Our study showed that the quality of the surgery can be increased by increasing the volume. Accordingly, morbidity and morbidity rates decrease, the number of dissected lymph nodes increases, and the length of hospital stay decreases. It may be appropriate for low-volume centers, where preoperative diagnosis is difficult and postoperative care is difficult, to refer patients to a higher-volume hospital in hepatopancreatobiliary surgery.

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Evaluation of cancer patients receiving concurrent chemotherapy and antituberculosis treatment: Review and case series of a single-center experience

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Ethics Committee Approval
Approval of the institutional review board Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethical committee (approval date Oct 08, 2021; approval number 902)
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Abstract

Background/Aim: Cancer and tuberculosis are common in the world, and the intersection of these two diseases affects oncology practice inevitably. Fortunately, the co-occurrence of cancer and tuberculosis is rare and there are no guidelines for the management of therapy in these patients. The information on these patients is obtained from small-scaled studies. This study aimed to question the efficacy and safety of tuberculosis treatment in cancer patients receiving chemotherapy.

Methods: Twenty-two patients who were treated with chemotherapy due to cancer and followed up and treated for concurrent tuberculosis in Diyarbakır Gazi Yaşargil Training and Research Hospital Medical Oncology Clinic between February 2009 and March 2021 were included in this retrospective case-control study. The clinical laboratory and treatment data of these patients were reviewed retrospectively. Then, the clinical, laboratory and treatment data of twenty-two cancer patients of the same age, who had the same stage cancer and received the same chemotherapy treatment but did not have tuberculosis disease were compared with the patients with tuberculosis. Thus, the efficacy, safety, and effect of tuberculosis treatment on cancer treatment were investigated.

Results: Twenty-two patients were diagnosed with tuberculosis and cancer. Six (27.3%) patients were receiving single agent chemotherapy, 16 (72%) were receiving combination chemotherapy, and 5 (22.5%) were receiving a combination of chemotherapy and targeted therapy. While 10 (45.5%) patients were diagnosed with non-pulmonary tuberculosis, 12 (54.5%) patients were diagnosed with pulmonary tuberculosis. Among all patients, the rate of completion of antituberculosis treatment was 77.2%, and the success rate with initial antituberculosis agents was 72.7%. Except for elevated liver enzymes, nausea-vomiting and grade-3 neutropenia ($P<0.001$, $P<0.001$, $P=0.012$ respectively), there was no significant difference in toxicity between the patients with and without tuberculosis. The mortality rate in the first 6 months of anti-tuberculosis treatment was 18.2% in patients who received tuberculosis and cancer treatment, compared to 9.1% in cancer patients who did not receive tuberculosis treatment. There was no significant difference in the mortality rate in both groups at the end of 12-year follow-up period ($P=0.658$).

Conclusion: Our results show that the combined use of chemotherapy and antituberculosis treatment in patients with cancer and tuberculosis is effective and safe.

Keywords: Cancer, Antituberculosis treatment, Chemotherapy, Tuberculosis

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Introduction

In 2020, approximately 19.3 million new cancer cases were diagnosed around the world, and 10 million cancer patients died because of it [1]. Cancer is the second most common cause of mortality after cardiovascular diseases, which is responsible for one out of every six deaths [2]. Tuberculosis disease (TBC), which has an origin as old as human history, is the most common infectious disease with high mortality rates worldwide. According to the 2018 data of the World Health Organization (WHO), approximately one quarter of the entire world population is infected by Mycobacterium Tuberculosis. While approximately 10 million people suffer from active TBC, approximately 1.3 million people die each year due to TBC [3-4].

The cancer itself, cancer-related malnutrition, local and systemic treatments such as surgery, chemotherapy and radiotherapy lead to an immunosuppressive state in cancer patients, causing them to become sensitive to various infectious agents [5-6-7].

The intersection of these two diseases, which are common in the world, affects the practice of oncology inevitably. New and more intensive cancer treatment modalities developed since 1970, when cancer was accepted as a risk factor for the development of TBC, and increased overall survival in cancer patients, albeit rendering cancer patients more vulnerable to this disease [8-9].

Although both diseases are frequent separately, the rate of coexistence of TBC and cancer disease in the entire cancer patient population is unknown [10]. Today, although cancer is considered a risk factor for TBC disease, there is no specific guideline regarding the coexistence of the two. Information on this condition is derived mostly from case series and reviews with a small number of patients.

This study aimed to examine the patients with concomitant cancer and TBC disease in our clinic over a 12-year period and to evaluate the effect of concomitant cancer and TBC treatment on patients by comparing them with the patients diagnosed with cancer, without TBC receiving the same treatment for the same stage cancers within the same age groups.

Materials and methods

The data of 26 patients diagnosed with cancer and concurrent TBC, who were followed up and treated in Diyarbakır Gazi Yaşargil Training and Research Hospital Medical Oncology Clinic between February 2009 and March 2021, were evaluated retrospectively. Four patients were excluded from the study due to reasons such as cancer or TBC treatment incompatibility, lack of data, dropping out of follow-up, emergence of TBC disease while receiving treatment other than chemotherapy, and having hematological malignancy. The data of the remaining 22 patients were evaluated with the help of our hospital database, TBC dispensary records and the national E-Pulse health information system. In addition to demographic characteristics of patients such as age, gender, location, age at cancer diagnosis, cancer type, residental area , patient performance score (PS), chemotherapy agents used, presence of B symptoms, how the diagnosis of TBC was made, location of TBC disease, clinical data (pulmonary, non-pulmonary), antituberculosis treatment agents used, toxicities developed during treatments, how antituberculosis and chemotherapy treatments were managed in patients who developed toxicity, treatment durations, follow-up periods, cancer-related overall survival were evaluated. Then, the clinical, laboratory and treatment data of 22 cancer patients with the same cancer diagnosis and stage within the same age group, who were receiving the same cancer treatment but did not have TBC disease, were compared with the group with TBC. Thus, the safety of TBC treatment and its effect on cancer treatment were investigated. This study was conducted in concordance with the current law, Good Clinical Practice guidelines, and the ethical principles of Declaration of Helsinki. Approval of the institutional review board Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethical committee was obtained (approval date Oct 08, 2021; approval number 902).

Tuberculosis treatment

The patients who were diagnosed with TBC were started on a quadruple antituberculosis treatment consisting of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) as standard treatment. Patients who used this treatment for at least two months then received maintenance isoniazid (H) and rifampicin (R) for four months. Ethambutol (E), streptomycin (S), moxifloxacin (M), cycloserine (C) and pyridoxine (P) treatment were given to some patients who used chemotherapy agents such as paclitaxel and irinotecan or who developed recurrent liver toxicity and one patient was treated with isoniazid (H), ethambutol(E), streptomycin(S), and moxifloxacin(M) due to hepatotoxicity.

Statistical analysis

Statistical package for the social sciences (SPSS) 18.0 software was used to estimate survival rate, and descriptive data were analyzed using the same program. Kaplan-Meier curves and a log-rank test were used to analyze the survival data, and *P*-values of <0.05 were considered statistically significant.

Results

Of the 22 patients diagnosed with TBC and cancer, 13 (59.1%) were male and 9 (40.9%) were female. The male/female ratio was 1.4/1. The median age of the patients was 59 (range: 30-68) years and the median age of diagnosis of cancer was 57 years (range: 30-67). While 14 (63.6%) patients resided in the city center, 5 (22.7%) patients resided in the village and 3 (13.6%) patients resided in the district. Thirteen (59.1%) of the patients had PS: 0-1, 6(27.3%) patients had PS:2, 3 (13.6%) patients had PS:3. Of the patients, 4 (18.2%) had diabetes, 8 (36.4%) hypertension, 1 (4.5%) had COPD, 1 (4.5%) had heart failure and 1 (4.4%) had kidney failure. While 16 (72.7%) patients had type B symptoms, 6 (27.3%) patients did not. Twelve (54.5%) patients smoked, and one (4.5%) patient had a history of steroid use.

The most common cancer diagnosis was lung cancer with 7 (31.8%) patients, followed by breast cancer with 6 (27.3%) patients. Of the remaining patients, 3 (13.6%) had colon cancer, 3 (13.6%) had gastric cancer, 2 (9.1%) had prostate cancer and 1 (4.5%) had pancreatic cancer. While 6 (27.3%) patients diagnosed with TBC were receiving

neoadjuvant/adjuvant chemotherapy, 16 (72.7%) patients were receiving chemotherapy with the diagnosis of metastatic disease. Nine (40.9%) of the patients were diagnosed before starting chemotherapy, and 13 (59.1%) patients were diagnosed after chemotherapy was started. Six (27.3%) patients were receiving single agent chemotherapy, 16 (72%) were receiving combination chemotherapy and 5 (22.5%) were receiving a combination of chemotherapy and targeted therapy. While 10 (45.5%) of the patients were diagnosed with non-pulmonary TBC, 12 (54.5%) patients were diagnosed with pulmonary TBC. All patients diagnosed with nonpulmonary (Table 1) TBC were diagnosed with lymph node excisional biopsy or lymph node dissection performed during the operation. Six (50%) patients diagnosed with pulmonary TBC had cavitary lesions, 3 (25%) patients had infiltrative areas in the upper lobe of the lung, 2 (16.7%) patients had multiple nodules, and 1 (8.3%) had multiple nodules and pleural effusion. Nine (75%) patients diagnosed with pulmonary TBC were diagnosed with acid-resistant bacteria (ARB) screening in sputum, and 3 (25%) patients were diagnosed with a mycobacterial culture.

Table 1: General characteristics of patients with cancer and tuberculosis disease

	n	%		n	%
Gender			Tuberculosis diagnosis		
Male	13	59.1%	Pulmonary	12	54.5%
Kadın	9	40.9%	Non-pulmonary	10	45.5%
Performance score			Metastasis		
0-1	13	59.1%	Available	16	72.7%
2	6	27.3%	None	6	27.3%
3	3	13.6%	Chemotherapy type		
Comorbidity			Adriamycin/Cyclophosphamide	3	13.6%
Diabetes	4	18.2%	Paclitaxel/Trastuzumab	2	9.1%
Hypertension	8	36.4%	Paclitaksel	2	9.1%
ASHD/Heart failure	1	4.5%	Gemcitabine	1	4.5%
COPD	1	4.5%	Capecitabine	1	4.5%
Chronic renal failure	1	4.5%	Cisplatin/Pemetrexed	2	9.1%
B symptom			Cisplatin/Gemcitabine	3	13.6%
Available	16	72.7%	Cisplatin/Vinorelbine	1	4.5%
None	6	27.3%	FOLFIRINOX	1	4.5%
Smoke			FOLFOX/Bevacizumab	1	4.5%
Available	12	54.5%	5FU/Cetuximab	1	4.5%
None	10	45.5%	FOLFOX	1	4.5%
Cancer type			FOLFOX/Herceptin	1	4.5%
Lung	7	31.8%	Docetaksel	2	9.1%
Breast	6	27.3%	Anti-tuberculosis treatment		
Colon	3	13.6%	HRZE	16	72.7%
Stomach	3	13.6%	Quinolone based therapy	6	27.3%
Prostate	2	9.1%			
Pancreas	1	4.5%			

Chemotherapy was initiated in a median of 9 days (range: 3-21 days) in cancer patients without TBC, and a median of 24 days (range: 19-45 days) in patients with cancer and TBC. In patients diagnosed with TBC during chemotherapy, chemotherapy administration was delayed for a median of 18 days (range: 7-26 days). Eighteen (81.8%) patients were started on a quadruple antituberculosis treatment consisting of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z). Quinolone-based antituberculosis treatment was started instead of an R-containing antituberculosis combination due to the use of paclitaxel in 3 (13.6%) of the remaining patients and irinotecan in 1 (4.5%). Quinolone-based combination therapy was initiated due to hepatotoxicity in 2 (9.1%) patients who received HRZE combination therapy. ARB and culture scans became negative in 8 (66.7%) patients diagnosed with pulmonary TBC at the second month and 2 (16.7%) patients at the 3rd month. One (8.3%) patient was referred to an advanced center with the diagnosis of multidrug-resistant TBC, and 1 (8.3%) patient dropped out of follow-up. While 16 (72.7%) patients finished TBC treatment, death occurred in 4 (18.2%) patients during cancer and antituberculosis treatment. One (4.5%) patient was discontinued from follow-up and treatment and 1 (4.5%) patient was treated in an advanced center with the diagnosis of multidrug resistance (MDR) tuberculosis. The cause of death of all patients who died was due to cancer. During the same period, 2 (9.1%) cancer patients without TBC died.

The median duration of antituberculosis treatment was 192 (range: 32-553) days. The median duration of chemotherapy and antituberculosis treatment was 168 (range: 32-553) days. During the combination of antituberculosis and chemotherapy treatment, the most common side effect was liver enzyme elevation, which was significantly higher than in patients with cancer without a diagnosis of TBC (P<0.001). The rate of neutropenia and use of GCSF during treatment were similar in both groups, but grade 3 neutropenia was more common in the group receiving antituberculosis treatment (P=0.012). There was no significant difference between the two groups in terms of anemia or thrombocytopenia. Gastrointestinal side effects such as nausea and vomiting were more common in the group receiving antituberculous therapy (P<0.001) (Table 2). The chemotherapy response of cancer patients receiving TBC treatment was similar to the chemotherapy response of cancer patients without TBC during the same period (P>0.05 for all) (Table 3). At the end of the 12 year-follow-up, 15 (68.2%) patients diagnosed with TBC and cancer, and 14 (63.6%) patients with cancer without TBC died. There was no significant difference in terms of mortality rates (P=0.658) (Figure 1).

Table 2: Side effect evaluation

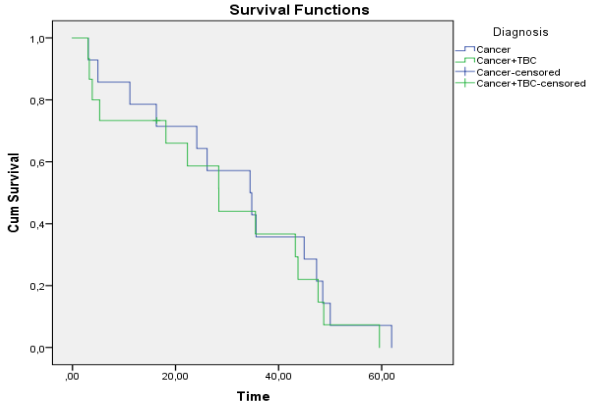
	Chemotherapy+Antituberculosis treatment group		Chemotherapy group		
	n	%	n	%	*P*-value
Neutropenia					
Grd-1	6	27.3	5	22.7	0.282
Grd-2	3	13.6	2	9.1	0.234
Grd-3	3	13.6	1	4.5	0.012
Thrombocytopenia					
Grd-1	4	18.2	3	13.6	0.286
Grd-2	1	4.5	1	4.5	0.632
Grd-3	-		-		-
Anemia					
Grd-1	4	18.2	3	13.6	0.198
Grd-2	1	4.5	1	4.5	0.610
Grd-3	1	4.5	1	4.5	0.623
AST/ALT increase	10	45.5	3	13.6	<0.001
Grd-1	5	22.7	2	9.1	<0.001
Grd-2	3	13.6	1	4.5	0.008
Grd-3	2	9.1%	0		<0.001
Nausea/Vomiting	9	40.9%	6	27.3%	<0.001
Diarrhea	6	27.3%	5	22.7%	0.308

Table 3: Response rates in the first 6 months of tuberculosis treatment

	Chemotherapy+Antituberculosis treatment group		Chemotherapy group		
	n	%	n	%	*P*-value
CR	4	18.2	5	22.8	0,276
PR	8	36.4	7	31.8	0,142
SD	6	27.3	7	31.8	0,253
PRG	4	18.2	3	13.6	0,268

CR: Complete Remission, PR: Partial Remission, SD: Stable Disease, PRG: Progression

Figure 1: Survival graph



Discussion

Our study was designed to evaluate the efficacy and safety of the combined use of TBC and cancer treatments. Our results are in line with previous studies with a small number of patients showing that antituberculous therapy can be used effectively and safely in cancer patients.

There are two theories linking TBC and cancer. The first of these is the breaking of the immune resistance to TBC infection due to the immunosuppressive environment occurring during the cancer disease and/or its treatment, and the emergence of new or reactivation TBC infection due to the broken immune defense. The second theory is the existence of factors such as smoking, chronic obstructive pulmonary disease, alcoholism, human immunodeficiency virus infection (HIV) that facilitate both cancer and TBC infection [11-13]. Apart from the fact that cancer is a facilitating cause for TBC infection, current information has shown that TBC, a chronic inflammatory disease, can stimulate carcinogenesis in the lung tissue [14]. It should also be kept in mind that tuberculosis disease can mimic lung and bone tumors in patients with suspected cancer [15].

While the incidence of TBC disease in our country is 17/100000 in the general population, this rate is 231/100000 in African countries and 3.1/100000 in the USA. Despite the TBC elimination and TBC disease treatment follow-up programs, it is still an important public health problem in our country. The highest risk for TBC in the cancer population is patients with respiratory tract and hematological malignancies, presumed to be the most susceptible group to TBC. The incidences in these patients are 892/100000 and 489/100000, respectively [9].

In the literature, there are conflicting results regarding the success rate of antituberculosis treatment in patients with cancer and TBC diagnosis. In the study conducted by Chai et al. [16] in 31 patients with lung cancer and concurrent pulmonary TBC, the completion rate of antituberculosis treatment was 87%, while the success rate of TBC treatment was 80.7%. In the case series of 30 patients by Hirashima et al. [17] the success rate of antituberculosis treatment was 70% in patients diagnosed with cancer and TBC. The reason for the difference in the success rate of antituberculosis treatment in studies seems to be that countries have different health systems and patient follow-up programs. In our study, when all patients were included, the rate of completion of antituberculosis treatment was 77.2%, and the success rate with initial antituberculosis agents was 72.7%. This rate is below the 87% TBC treatment success rate in the general population in our country. The reasons for this were thought to be the administration of antituberculosis treatment in the immunosuppressive patient population, the small patient population in our study, the high number of patients with metastatic disease, and cancer-related deaths while antituberculous treatment was continued [18].

The use of antituberculosis treatment agents in patients with lung cancer was shown to be associated with shorter survival by Shieh et al. [19]. In another study conducted by Chung Su et al. [20], the mortality rate from any cause in the first 6 months was 15.6% in cancer patients diagnosed with TBC, and the mortality rate from any cause between 6-12 months was 5%. In the same study, 12-month all-cause mortality was 20.56% in patients with cancer and TBC, and 11.84% in patients without a diagnosis of TBC. Parallel to these findings, in our study, the mortality rate in patients with cancer and TBC diagnosis during antituberculosis treatment was 18.2%, and 9.1% in cancer patients who were not diagnosed with TBC during the same period. Although the mortality rate in the first 6 months was high in our study, there was no significant difference in the number of patients who survived in both groups after 12 years of follow-up.

Most studies with a small number of patients on the coexistence of cancer and TBC also questioned the safety of using chemotherapy and antituberculosis treatment together. In a case series of 30 patients with lung cancer and TBC by Kim et al. [21], the safety of the combined use of chemotherapy and antituberculosis treatment was demonstrated. In another study conducted by Chai et al. [22] on 31 patients with lung cancer and TBC disease, combined treatment was effective and safe. In our study, there was no significant difference in hematological side effects. Although nausea and vomiting and AST/ALT elevation were more frequent in patients receiving combination therapy, it was a manageable side effect and none of the patients required interruption of chemotherapy or antituberculosis therapy.

The use of R in combination therapy stimulates cytochrome P450 enzymes such as CYP3A4 and CYP2C8. This accelerates the metabolism of chemotherapy agents such as erlotinib, irinotecan, and paclitaxel, reducing the effectiveness of chemotherapy agents. Therefore, 6 of the patients in our study received quinolone-based antituberculosis therapy at the beginning of the treatment (use of paclitaxel or irinotecan) or during the treatment period (hepatotoxicity) [23].

Limitations

Our study has some limitations, including the small number of patients and its retrospective nature. Power analysis could not be performed in our study due to the small number of patients. However, the population with cancer and TBC coexistence is fortunately small, and when we look at the literature, studies on patients with these two diseases together feature a small number of patients as well. In this respect, we think that our results will contribute to the literature. The second is the inclusion of a single center and the lack of country-wide data such as MDR tuberculosis and treatment response.

Conclusion

Our results show that the combined use of chemotherapy and antituberculosis treatment in patients with cancer and TBC is effective and safe.

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Comparison of excised breast volume, re-excision rate and margin positivity in breast-conserving surgery in breast cancer patients using and not using neoadjuvant chemotherapy

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Ethics Committee Approval
Approval for this study was granted from Gaziosmanpasa Training and Research Hospital Ethics Committee for Clinical Studies in March 2021 (reg:251).
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: One of the purposes of using neoadjuvant chemotherapy (NAC) is to evaluate the patients according to tumor-to-gland ratio, save them from mastectomy by reducing tumor dimension, and get more beautiful results cosmetically with less volume excision during breast-conserving surgery (BCS). Is it possible to achieve the goal of less volume excision after NAC? We aimed to compare the excised volume with BCS, margin positiveness and re-excision rates between the patients who received NAC and the ones who didn't receive NAC in patients with breast cancer and to calculate the increase in BCS performability with NAC.

Methods: Among 306 patients diagnosed with breast cancer between 2013 and 2021 at Gaziosmanpasa Training and Research Hospital, 105 patients who underwent BCS were included in this retrospective cohort study. Excised breast volume, surgical margin positiveness, re-excision and mastectomy rates were retrospectively compared in breast cancer patients underwent BCS with and without NAC. The patients who received BCS following NAC were named the primary chemotherapy (PC), and the patients whose treatment was initiated with BCS were named the primary surgery (PS) groups.

Results: BCS was performed to 105 breast cancer patients, of which 28 (26.7%) received NAC, and 77(73.7%) started the treatment with surgery. There were no significant differences between the PC and PS groups with respect to excision volume (755.86 (725.69) and 709 (637.36), P=0.822). Re-excision was more common in PS than in the PC group (39.0% vs 10.7%, P=0.008). Fourteen patients who were candidates for mastectomy at the beginning, became eligible for BCS by receiving NAC, which caused a 15.38% increase in BCS applicability. Surgical margin positivity was seen in only 3 patients, which is why a statistical comparison wasn't made.

Conclusions: Although the tumor size was higher in the PC group, the excised breast volume did not show a significant difference between the two groups. PC decreased the re-excision rates in the chemotherapy candidate group. This data shows that patients who are candidates for adjuvant chemotherapy might be considered for PC to increase BCS success with lower re-excision rates and equivalent excised breast volume.

Keywords: Breast cancer, Breast-conserving surgery, Resection volume, Re-excision rate

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Introduction

Historically, the first treatment for breast cancer has been wide excision. The radical mastectomy (RM) technique was presented by William Halsted in 1894 and this resulted with an increase in survival rates [1]. In this type of surgery, breast with is *enbloc* removed with the covering skin, pectoral muscles and the axillar lymph nodes. In the 1970s, Modified Radical Mastectomy (MRM) began to be performed in patients with a mobile smaller mass not invading the pectoral muscle, and it was shown that there was no difference between RM and MRM depending on survival rates [2]. Breast-conserving surgery (BCS) was first described in 1924 by Sir Geoffrey Keynes and developed in years, and additional radiotherapy resulted in an equivalent success as that in mastectomy [3].

BCS can be performed in both early-stage breast cancers and locally advanced tumors after neoadjuvant chemotherapy (NAC). In patients with large tumors who are candidates for chemotherapy, the tumor volume can be minimized, and BCS could be performed, while micrometastatic disease is eradicated [4].

Even though the prior aim in BCS is to obtain a tumor free margin (TFM) for reducing locoregional recurrence (LRR) and ensure cosmetically pleasing results, a surgical margin positivity for tumor (TIM) is reported at rates of 9-24.7%. These patients are treated with re-excision or mastectomy [5-7].

In locally advanced breast cancers, NAC before BCS is expected to yield cosmetically satisfying results by reducing resection volume. Is the excised breast tissue minimized after NAC, or does the surgeon remove more tissue to guarantee the result instead of sufficient tissue resection?

In our study, we aimed to compare resection volume, re-excision and margin positivity rates in breast cancer patients between the groups who received preoperative chemotherapy and started the treatment with definitive surgery, as well as evaluate the increase in BCS performability after NAC.

Materials and methods

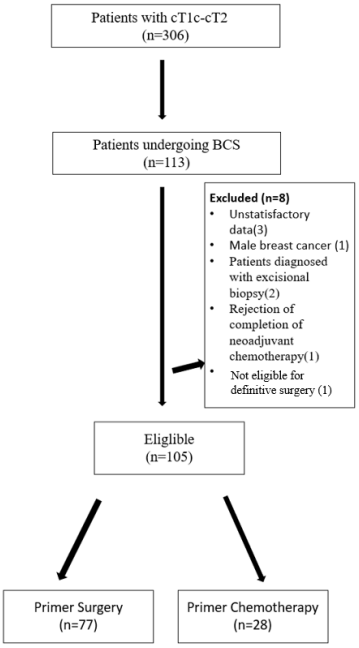
Data collections

The ethics committee approval (approval number: 251 and date: 31/03/2021) was obtained from Gaziosmanpasa Training and Research Hospital Ethics Committee, with which our hospital is affiliated. Informed consent forms from the patients were not required due to the retrospective use of anonymous administrative data.

This retrospective cohort study included 105 patients who underwent BCS, among 360 patients who received a diagnosis of stage cT1c-cT2 non-metastatic invasive breast cancer in Gaziosmanpasa Training and Research Hospital between 2013 and 2021. Patients diagnosed with excisional biopsy (n=2), those who rejected completing neoadjuvant treatment (n=1), patients not eligible for definitive surgery (n=1), those whose data cannot be reached (n=3), and males (n=1) were excluded. The data flow diagram was shown in Figure 1. Demographic, clinical, and pathological data were retrospectively collected from the medical records. Pathological data involved CNB, excision material, re-excision after BCS and mastectomy reports.

The study population was divided into two, as the primary surgery (PS) and preoperative chemotherapy (PC) groups and compared. The patients who received BCS after NAC were named the primary chemotherapy (PC) group, and the patients whose treatment was initiated with BCS were named the primary surgery (PS) groups. All patients in the PC group received 4 AC+ T (doxorubicin plus cyclophosphamide followed by paclitaxel) as the NAC regimen, trastuzumab was added to Her-2 positive patients and these patients' treatment lasted 1 year after the surgery. After NAC treatment, all patients in the PC group received definitive surgery within 3-4 weeks. The total number of patients who received BCS was low. The reasons include the patients requesting to get completely free of tumor, not accepting radiotherapy and surgeons' preferences.

Figure 1: Flow diagram of the study



Histopathological evaluation

The pathology reports of breast resection materials were examined depending on the volume of breast tissue, the biggest tumor diameter, histopathological diagnosis, histological grade, surgical margin, estrogen receptor (ER), progesterone receptor (PR), Ki-67 and Her-2 neu status. The Bloom-Richardson system, Nottingham modification was used for histological rating identification. The tumor stage was clarified in accordance with the 2017 AJCC breast cancer staging guidelines, the 8th Edition, and 2019 CAP guidelines [8, 9].

ER and PR scoring: A nuclear reaction below %1 was considered negative, and that over %1 was considered positive.

Her-2 scoring: Score 0: No reaction in tumor cells or incomplete reactions ≤ 10% of tumor cells, Score 1: 10% of tumor cells have pale, unclear incomplete membranous reactions, Score 2: > 10% of tumor cells have incomplete weak/moderate stage membranous reactions or ≤ 10% of tumor cells have complete strong membranous reactions, Score 3: > 10% of tumor cells have uniform strong membranous reactions. Score 0 and 1 were considered negative, score 2 was weakly positive and score 3 was considered positive. Score 2 patients were then evaluated with fluorescent in situ hybridization (FISH).

Clinicopathological definitions of breast cancer subtypes were made as follows [10]:

Luminal A like: ER positive, PR positive (>20%), Ki-67 low, Her-2 negative

Luminal B like: ER positive, PR low (<20%), or ER positive, Her-2 positive (3 + on IHC/amplified on FISH), any PR. Ki-67 values or low PR may be used to distinguish between Luminal A-like and Luminal B-like.

Her-2neu positive (non-luminal): ER and PR negative, Her-2 positive (3+ on IHC or amplified on FISH (for 2+ IHC results).

Triple negative (TNBC): ER, PR and Her-2neu negative

Neoadjuvant chemotherapy response was evaluated with the Miller Payne staging system [11]. According to this staging system, Grade 1 indicated no reduction in overall cellularity, Grade 2 indicated a minor loss of tumor cells (up to 30% loss), Grade 3 indicated an estimated reduction between 30% and 90% in tumor cells, Grade 4 indicated the marked disappearance of tumor cells (more than 90% loss), and Grade 5 indicated no identifiable malignant cells, although ductal carcinoma in situ may be present.

Margin status

Absence of tumor cells in the free surgical margin inked lines was defined as "no ink on the tumor''. A close margin indicated the presence of tumor cells closer to the border than 1mm [12]. Also, DCIS was present on the margin.

Calculation of the volume

To calculate excision volume (lumpectomy volume) in the surgical specimen, the ellipsoid formula, a.k.a., 4/3π (length x width x height), was used [13].

Re-excision

Re-excision was defined as any additional surgical therapy following BCS for margin positiveness, close margin, or positive palpation findings.

Statistical analysis

Normality control of continuous variables was evaluated with the Shapiro Wilk test. The continuous variables between the primary surgery and primary chemotherapy groups were compared with the Mann Whitney U test. In the analysis of categorical data, Chi-square's test and Fisher Exact tests were used. Multiple Logistic Regression analysis was used between the groups with the variables thought to be effective in the multiple models. The data were analyzed in the IBM SPSS 21.0 program. A *P*-value of <0.05 indicated statistical significance.

Results

Of the 105 patients included in the study, 28 (26.7%) were in the PC group and 77 (73.3%) were in the PS group. Patients in the PC group were younger than the patients in the PS group (*P*>0.05). The tumors of the patients in the PC group were larger (27.61 (15.42) mm, vs 17.83 (6.7) mm, respectively, *P*<0.001). Although the excised lumpectomy volume did not significantly differ, it was slightly higher in the PC group (755.86 (725.69) and 709 (637.36), respectively (*P*>0.05)). The distribution of histopathological subtypes, tumor grade and Her-2 neu status differed between the groups *(P*<0.05*).* The demographic and histopathological data of the patients and the evaluation of the surgical margin are summarized in Table 1.

Table 1: The demographic and histopathological data of the patients and the evaluation of the surgical margin

	Primer Surgery (n=77) Mean (SD)		Primer Chemotherapy (n=28) Mean (SD)		Total (n=105) Mean (SD)		*P*-value [1]
Age (year)	54 (11.07)		50.25 (8.53)		53 (10.54)		0.093
Tumor size (mm)	17.83 (6.7)		27.61 (15.42)		20.44 (10.65)		<0.001**
Lumpectomy volume (cm^3)	709 (637.36)		755.86 (725.69)		721.49 (658.8)		0.822
	n	%	n	%	n	%	*P*-value [2]
Histopathological type							
Invasive ductal	68	88.3	28	100.0	96	91.4	0.167
Invasive lobular	2	2.6	0	0.0	2	1.9	
Other	7	9.1	0	0.0	7	6.7	
Histopathological subtype							
Luminal A	53	68.8**	9	32.1	62	59.0	0.006**
Luminal B	19	24.7	16	57.1**	35	33.3	
Her2 enriched	2	2.6	2	7.1	4	3.8	
TNBC	3	3.9	1	3.6	4	3.8	
ER							
Negative	5	6.5	3	10.7	8	7.6	0.437*
Positive	72	93.5	25	89.3	97	92.4	
PR							
Negative	6	7.8	4	14.3	10	9.5	0.451*
Positive	71	92.2	24	85.7	95	90.5	
Her-2 neu status							
Negative	65	84.4**	15	53.6	80	76.2	0.001**
Positive	12	15.6	13	46.4**	25	23.8	
Margin for invasive cancer							
Tumor free margin	50	64.9	24	85.7	74	70.5	
Close margin ≤1 mm	24	31.2	2	7.1	26	24.8	0.083
DCIS involved margin	1	1.3	1	3.6	2	1.9	
Tumor involved margin	2	2.6	1	3.6	3	2.9	
Grade							
Low	9	11.7	0	0.0	9	8.6	0.010**
Moderate	58	75.3	18	64.3	76	72.4	
High	10	13.0	10	35.7**	20	19.0	

[1]: Mann Whitney U test, [2]: Chi-Square test *Fisher Exact test **: statistically significant (*P*<0.05), Tumor size: Before surgery or chemotherapy according to the clinical and radiological findings, TNBC: Triple negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor 2, DCIS: Ductal carcinoma in situ.

The rates of additional surgery differed between the PC and PS groups, and re-excision was more common in the PS group (10.7% vs 39.0%, respectively, *P*<0.05).

In the PS group, re-excision was performed 30 patients. One patient in the PS group underwent mastectomy because the surgical margin was positive, one patient underwent re-excision in a second operation due to margin positivity in the final pathology examination, and one patient, due to margin positivity in the final pathological examination. Re-excision was performed in 21 patients because of the near-margin tumors, and in 6 patients, re-excision was needed due to suspicious palpation findings although the pathology report was negative, and tumor was observed in the re-excision material in these patients.

In the PC group, re-excision was performed in 1 patient due to close margin, in 1 patient, due to marginal tumor, and in 1 patient, because of borderline DCIS. None of the patients in the PC group required a second operation. Surgical outcomes of the patients are shown in Table 2.

Because TIM was seen in only 3 patients, no statistical comparison could be made between the factors affecting margin positivity, and the findings are summarized in Table 3.

According to the multivariate analysis, the tumor size (mm) was 1.114 times higher in the PC group, while re-excision was observed 0.181 times less (*P*<0.05). Multiple logistic regression analysis results are summarized in Table 4.

BCS was initially planned for 91 of 306 patients, with a rate of 29.74%. In the PC group, 14 patients who were initially ineligible for BCS became eligible, increasing the rate to 34.31%. The absolute increase in the mean was 4.58%.

Table 2: Surgical outcomes of patients

	Primer Surgery (n=77)		Primer Chemotherapy (n=28)		Total (n=105)		
	n	%	n	%	n	%	*P*-value
Additional surgical therapy							
No	47	61.0	25	89.3**	72	68.6	0.008[a]*
Yes	30	39.0**	3	10.7	33	31.4	
Type of additional surgical therapy							
Re-excision	27	90.0	3	100.0	30	90.9	0.102
Mastectomy after re-excision	1	3.3	0	0.0	1	3.0	
Second Mastectomy	1	3.3	0	0.0	1	3.0	
Second re-excision	1	3.3	0	0.0	1	3.0	
Additional tumor in re-excision specimen							
Tumor free	25	83.3	3	100.0	28	84.4	0.745
DCIS involved	4	13.3	0	0.0	4	12.5	
Tumor involved	1	3.3	0	0.0	1	3.1	

Chi-Square test, [a] Fisher Exact test, *: statistically significant ($P<0.05$), DCIS: Ductal carcinoma in situ

Table 3: Surgical margin status

	Tumor Free Margin (102) Mean (SD)		Tumor Involved Margin (3) Mean (SD)	
Age (year)	52.86 (10.49)		57.66 (13.79)	
Tumor size (mm)	20.42 (10.77)		21.00 (6.04)	
Lumpectomy volume (cm3)	724.20 (667.40)		629.38 (248.02)	
	n	%	n	%
Histopathological Type				
Invasive ductal	93	91.2	3	100.0
Invasive lobular	2	1.9	0	0.0
Other	7	6.9	0	0.0
Subtype				
Luminal A	59	57.8	3	100.0
Luminal B	35	34.3	0	0.0
Her-2 enriched	4	3.9	0	0.0
TNBC	4	3.9	0	0.0
ER				
Negative	8	7.8	0	0.0
Positive	94	92.2	3	100.0
PR				
Negative	10	9.8	0	0.0
Positive	92	90.2	3	100.0
Her-2 neu status				
Negative	78	76.5	3	100.0
Positive	24	23.5	0	0.0
NAC response (n=28)	n=27	%	n=1	%
Miller-Payne 1	4	14.8	0	0.0
Miller-Payne 2	2	7.5	0	0.0
Miller-Payne 3	3	11.1	1	100.0
Miller-Payne 4	6	22.2	0	0.0
Miller-Payne 5	12	44.4	0	0.0

TNBC: Triple negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, Her-2: Human epidermal growth factor receptor 2, NAC: Neoadjuvant chemotherapy

Table 4: Multiple logistic regression analysis

	Odds Ratio	95% CI for Odds Ratio		*P*-value
		Lower	Upper	
Age	0.966	0.917	1.018	0.199
Tumor size (mm)	1.114	1.044	1.189	0.001*
Lumpectomy volume	1.000	0.999	1.001	0.348
Re-excision (yes)	0.181	0.038	0.857	0.031*
Tumor involved (yes)	12.393	0.470	327.028	0.132
Constant	0.401			0.541

*: statistically significant ($P<0.05$)

Discussion

NAC is successfully administered in patients who are candidates for systemic chemotherapy, showing equal overall and disease-free survival rates to adjuvant chemotherapy. One of its advantages is that it reduces tumor size and makes patients with large tumors requiring mastectomy eligible for BCS [4].

Studies report that there is an increase in the performability of BCS after NAC. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, one of the pioneering studies in this regard, it has been reported that BCS rates increased from 60% to 68%, although modest pathological complete response (PCR) was observed in patients with breast cancer after NAC [14].

Especially in TNBC and Her-2 enriched subgroups, an increase in PCR rate up to 50-70% after NAC and an increase in BCS rate were demonstrated [15, 16].

In a study of stage 2-3 TNBC patients, 42% of patients who were initially ineligible for BCS became eligible for BCS after the treatment. The results of the study show a 14% absolute increase in BCS performability [17]. Again, Golshan et al. [18] showed an increase in the rate of BCS after NAC from 41% to 64% in both positive subgroups.

In our study, 14 patients who were not suitable for BCS before NAC became eligible after treatment and this increased by 15.38% in the group of patients who received BCS. However, in our study, contrary to the literature, most patients who became suitable for BCS after PC and developed PCR were in the luminal A subgroup. This was thought to be because the patients in the TNBC and Her-2 enriched groups had smaller tumor diameters at baseline and were suitable for BCS.

By considering the volume removed, studies focused more on patients' cosmetic satisfaction, and it was reported that as the volume of the removed tissue increases, so does dissatisfaction [19, 20].

In our study, we investigated whether there was a difference in the excised breast volume between the groups that did and did not receive NAC, based on the hypothesis that the tumoral mass in the breast would shrink and less volume excision would be sufficient after NAC. The tumor size was significantly higher in the PC group, while the excised volume was not. When we evaluated according to the pathological response, the increase in PCR did not cause a change in the excised volume. Since the tumor could not be palpated in patients who received PCR, it did not cause an increase in the resection volume, although the resection margins were blindly determined by marking earlier.

When Valejo et al. [21] compared the excision volumes of the groups that did not receive NAC over 267 breast cancer patients, they showed that the resection volume was higher in patients who received NAC, regardless of tumor size, and they stated that the cause of this was the thought that the tumor did not shrink concentrically and that there might be a residual microscopic foci around the palpable mass.

Similarly, Komenaka et al. [22] found the excision volume higher in the NAC group. However, unlike these studies, Karanlik et al. [23] showed that the resection volume was lower in the patient group receiving primary chemotherapy.

There is a wide margin for post-NAC re-excision rates and TIM. In one review, the TIM rate was between 5-39.8% and 13.1-46% for patients receiving NAC and undergoing primary surgery, respectively. Accordingly, re-excision rates range from 0-45.4% to 0-76.5%, respectively [24]. In another study by Volders et al. [25], re-excision rates were 24.3% in the group operated after TIM NAC, and 10.2% in the group undergoing primary surgery. In the same study, the close margin rate after NAC was 17.7%. The re-excision rates were higher in the patients receiving NAC than in the primary surgery group (9.1% and 5.3%, respectively), and 4.9% of re-excisions in the group receiving NAC resulted in mastectomy.

Correspondingly, Devane et al. [26] showed re-excision rates of 32% in patients who received NAC, while it was 17% in the primary surgery group. Re-excision is more common, especially in patients with lobular cancer and ER+ tumor.

By examining national cancer data, Spronk et al. [27] found a TIM rate after NAC of 6.7% and a re-excision rate of

6.6%, and the margin positivity in cT3 tumors was lower than in the primary surgery group, while it was higher in cT1 tumors.

In the study of Woeste et al. [28] including 162 patients, the TIM and re-excision rates were lower in patients who received NAC than in the group who underwent primary surgery.

Christy et al. [29] also showed that re-excision rates after NAC in tumors sized 2-4 cm were lower than in the primary surgery group.

When Clement et al. [7] examined 416 patients, they found TIM or close margin in 9% of the patients and determined that 48.78% of these patients underwent re-excision, 46.34% underwent mastectomy, and 4.87% underwent both re-excision + mastectomy.

In our study, we found that 31.4% of the patients underwent re-excision due to TIM or close margin. Re-excision was performed in more patients in the PS group, its rates were 39.0% in the PS group and 10.7% in the PC group.

The limitations of our study include the small number of patients and the inability to evaluate cosmetic results because patients were lost to follow-up. In addition, since the TIM rate is low, statistical comparisons between the factors affecting margin positivity could not made. Another limitation of our study is that breast surgery in our hospital was performed not only by a team specialized in this field but by all surgical specialists in the past, affecting the surgical technique.

Conclusion

The primary goal of BCS after NAC is achieving a lower resection volume and negative surgical margins. This 8-year retrospective cohort study showed that PC significantly reduces the rate of re-excision in patients undergoing BCS without increasing the excision volume. In addition, larger tumors can be shrunk and successfully removed as well as increasing the feasibility of BCS with PC. We believe that in patients with cT1-T2 breast cancer who are candidates for adjuvant therapy, PC can be safely performed oncologically without any surgical disadvantage.

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Prognostic value of examined lymph node count in patients with lymph node negative pancreatic head carcinoma: A single-center experience

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Ethics Committee Approval
The study was approved by Local Ethical Committee of Ondokuz Mayıs University School of Medicine (2012/799).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: One of the important prognostic factors for pancreatic cancer is the count of examined lymph nodes (ELN). The ratio of metastatic to ELNs reflects survival and is required for accurate staging. The survival effect of the count of ELNs in patients with an absence of metastatic lymph nodes is unclear. However, the single-center survival outcomes related to higher ELN count based on only lymph node negative-patients are limited to a few studies with controversial results. We aimed to present the single-center experience in survival outcomes based on ELN count in patients with lymph node-negative pancreatic head cancer after pancreaticoduodenectomy.

Methods: The data of 129 patients who underwent pancreaticoduodenectomy for pancreatic cancer from October 2011-December 2021 were analyzed. Among them, those who had metastatic lymph nodes, those who died from non-PC causes, died in the first 90 days postoperatively, or had missing follow-up data were excluded. Finally, 37 patients with negative lymph nodes who satisfied our criteria were included. The cut-off value for the examined lymph node count was 15, according to the minimum LN count recommended by the International Study Group of Pancreatic Surgery and the European Society for Medical Oncology for accurate staging. Thus, node-negative patients were divided into ELN <15 and ≥15 groups. The effect of <15 and ≥15 ELN count, tumor T stage, tumor grade, presence or absence of lymphovascular invasion and perineural invasion, and the resection margin status on cancer-specific survival were evaluated by univariate and multivariate survival analyses.

Results: The median age was 63 years (interquartile range (IQR) 55.50-75.0), and 17 (45.9%) were female. The median count of examined lymph nodes was 15. The median follow-up time was 36.5 months (IQR 21.4-56.2). The 1- 3- 5- years of cancer-specific survivals were 86.2%, 61.5%, 49.6%, respectively. Seventeen patients died due to pancreatic carcinoma during the follow-up period, and 12 out of 17 patients were in the <15 group. In multivariate analyses, the examined lymph node count <15 was a negative independent risk factor for cancer-specific survival (HR: 0.293; 95% CI, 0.096-0.897; *P*=0.032). The other negative independent risk factor was a positive resection margin (HR: 5.777; 95% CI, 1.436-23.245; *P*=0.014).

Conclusion: Patients with node-negative pancreatic head cancer with <15 ELN count, and positive resection margin have shorter survival, suggesting missed metastatic lymph nodes due to assessment of too few lymph nodes. At least a 15 ELN count is required to stratify the survival more accurately in these cohorts.

Keywords: Lymph node ratio, Regional lymphadenectomy, Whipple

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Introduction

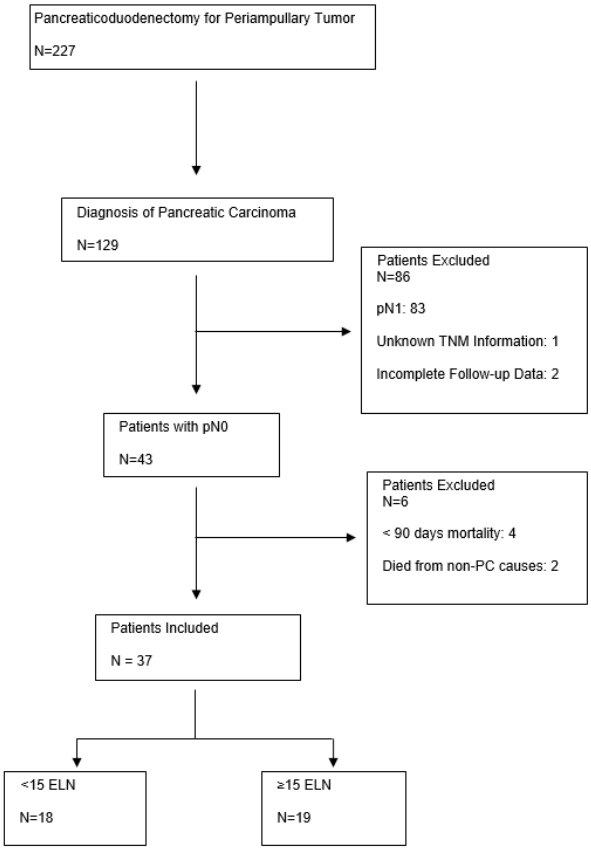
Pancreatic cancer (PC) has a poor prognosis, and it is the seventh worldwide in cancer-related deaths [1]. Although pancreatectomy is the only potentially curative treatment option for PC, overall survival is dismal [2]. Many factors, including curative resection, tumor size, lymph node (LN) status, location of positive LNs within the draining nodal basins, and locoregional invasion have prognostic significance after all types of pancreatic resections [3]. Of these, LN status is one of the most important factors, and LN metastasis is associated with worse survival and more frequent local recurrence. Accurate staging determined with LN status guides postoperative adjuvant treatment strategy [4]. In addition, the number of examined lymph nodes (ELNs) reflects survival; more ELN is associated with prolonged survival with or without the presence of metastatic lymph nodes [4-10]. Therefore, sufficient lymphadenectomy during surgery may improve pancreatic cancer survival without considering tumor localization. The objective of this study was to present the impact of ELN count on the survival of our patients who were LN negative (pN0) in the pathological examination after pancreaticoduodenectomy (PD) for PC.

Materials and methods

Patient selection and study variables

This study was approved by the research ethics committee of Ondokuz Mayıs University (2021/799). Informed consent was obtained from all patients. From October 2011-December 2021, the clinical data of 227 patients who underwent PD were prospectively recorded and retrospectively evaluated. Of these, 129 patients underwent PD for PC. We performed a standard Whipple procedure for all patients. During the surgery, regional lymphadenectomy was performed, as recommended by the International Study Group of Pancreatic Surgery (ISPGS) consensus report [10]. Pathological data were evaluated according to the 8th edition of the American Joint Committee on Cancer staging system [11]. A positive surgical margin (R1) was defined as tumor cells being closer than 1 mm to the surgical resection margin. Patients with one or more evaluated ELN in the pathology report were included in the study. Patients were excluded if they had metastatic LN, unknown TNM information, died from non-PC causes, died in postoperative first 90 days, or had incomplete follow-up data. Finally, 37 patients with pN0 satisfied our inclusion criteria. The data was evaluated in terms of age, gender, ELN count, tumor grade, lymphovascular-perineural invasion, surgical margin status, adjuvant treatment, and cancer-specific survival (CSS). The optimal cut-off value of ELN count was 15, based on the minimum LN count recommended by the International Study Group of Pancreatic Surgery (ISPGS) [10] and the European Society for Medical Oncology (ESMO) [12] for accurate staging. Then, the patients were evaluated in two groups: ELN <15 and ≥15 (Figure 1). CSS was identified as the time from the operation until death due to recurrent or metastatic disease. Patients still alive were censored. The last follow-up was on 30 November 2021.

Figure 1: ELN: Examined lymph node, PC: Pancreatic carcinoma



Statistical analysis

Survival curves were formed using the Kaplan-Meier method, and the log-rank test compared the differences between the curves. Cox proportional hazards regression models were both used to evaluate potential risk factors for survival outcomes and were used for multivariate analysis with the backward elimination method. Risk factors with a *P*-value <0.1 in univariate analysis were taken into account in the multivariate analysis. The hazard ratio (HR) and 95% confidence interval (CI) were calculated. All statistical tests were two-directional, and a *P*-value of <0.05 was considered significant. We evaluated the data using the IBM SPSS (version 26.0; IBM Corp., Armonk, New York, USA) statistical package program.

Results

The median age was 63 years (interquartile range (IQR) 55.50-75.0), and 17 (45.9%) were female. The median count of ELNs was 15 (IQR 11-26). The clinicopathological factors of the cohort were summarized in Table 1.

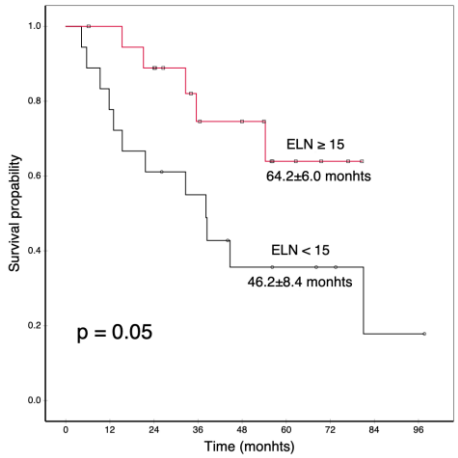
Table 1: Clinicopathological features of patients

Characteristics	Number of patients (n=37)	Percentage (%)
Age, ≥65	17	45.9
Gender, female	17	45.9
T stage		
I-II	23	62.2
III-IV	14	37.8
Grade		
Well/moderately differentiated	34	91.9
Poorly differentiated/undifferentiated	3	8.1
Lymphovascular invasion, yes	9	24.3
Perineural invasion, yes	18	48.6
Resection margin status, R1	4	10.8
ELN		
<15	18	48.6
≥15	19	51.4
Adjuvant chemotherapy, yes	29	78.4

ELN, examined lymph node; R1, positive resection margin

The median follow-up time was 36.5 months (IQR 21.4-56.2). The 1-3-5 years CSSs were 86.2%, 61.5%, 49.6%, respectively. The mean overall CSS survival was 57.8 (6.5) months, 46.2 (8.4) months for the <15 ELN group, and 64.2 (6.0) months for the ≥15 ELN group. Of the 37 patients with negative ELN, 17 died due to PC during the follow-up period, and 12 out of 17 patients were in the <15 ELN group. Patients with <15 ELN had shorter CSS than patients with ≥15 ELN (P=0.05) (Figure 2).

Figure 2: Kaplan Meier survival graph for Examined lymph node (ELN)



In multivariate analyses, ELN <15 (HR: 0.293; 95% CI: 0.096-0.897; P=0.032) and positive resection margin (HR: 5.777; 95% CI: 1.436-23.245; P=0.014) were negative independent risk factors for CSS (Table 2).

Table 2: Univariate and multivariate Cox proportional hazards regression analysis for CSS

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gender,						
Female	Reference			—		
Male	0.888	0.332—2.374	0.813	—	—	—
Age,						
<65	Reference			—		
≥65	1.333	0.513—3.466	0.554	—	—	—
T stage,						
I—II	Reference			—		
III—IV	0.615	0.216—1.749	0.362	—	—	—
Grade						
Well/moderately differentiated	Reference			—		
Poorly differentiated/undifferentiated	2.105	0.477—9.292	0.326	—	—	—
LVI,						
No	Reference			Reference		
Yes	0.201	0.027—1.524	0.085	0.341	0.043—2.732	0.290
PNI,						
No	Reference			—		
Yes	2.122	0.803—5.613	0.121	—	—	—
Resection margin status						
R0	Reference			Reference		
R1	3.924	1.099—14.008	0.035	5.777	1.436—23.245	0.014
ELN,						
≥15	Reference			Reference		
<15	0.364	0.126—1.048	0.050	0.293	0.096—0.897	0.032
Adjuvant chemotherapy,						
Yes	Reference			—		
No	1.757	0.395—7.804	0.452	—	—	—

LVI: lymphovascular invasion, PNI: perineural invasion, ELN: examined lymph node, R1: positive resection margin, HR: hazard ratio, CI: confidence interval

Discussion

LN metastasis reflects cancer survival and guides treatment strategies after surgery [4, 6, 13, 14]. Sufficient lymphadenectomy provides accurate nodal staging and prevents stage migration [4, 8]. Higher lymph node ratio (i.e., the count of metastatic LN divided by the total count of ELN) indicates a poor prognosis for PC [4-9] as well as other gastrointestinal malignancies such as gastric [15] and colorectal [16] carcinoma. Patients with more ELNs also have a better prognosis with or without the presence of metastatic LNs [4-9]. Huebner et al. [4] found that patients with >11 ELNs had better overall survival than those with <11 (HR: 1.33, 95% CI: 1.1–1.7; P=0.001) after PD for pancreatic cancer in pN0 patients. Recently, ELN >11 [5], >12 [6], and >20 [17], respectively, were associated with better overall survival in pN0 patients after undergoing distal pancreatectomy for pancreatic body/tail cancer. Slidell et al. [7] reported the importance of more than 12 ELN in identifying stratified survival for all locations of PC patients. Tomlinson et al. [9] reported that patients who underwent PD with ≥15 ELN had better overall survival than those with <15 ELN in pN0 patients. Similarly, the current study demonstrated that ≥ 15 ELN was associated with improved survival. We think complete LN dissection and detailed pathological evaluation are required to improve CSS for PC.

We found that the count of ELN was an independent prognostic factor for CSS in our cohort. Increased ELN count was reflected in improved survival in pN0 PC patients. In this study, survival rates of 1, 3, 5 years, respectively, were better than in population-based studies [4-9]. This result may be related to the small number of patients, which was the main limitation of our study. Lidsky et al. [18] reported that high-volume medical centers have higher ELN counts and improved survival. Fortunately, the median count of ELN (15, IQR 11-26) in this cohort was similar to those presented in the critical studies [6, 7].

Some scenarios may explain how an increased ELN count is associated with improved survival in pN0 patients and include the quality of surgery and pathological evaluation. False-positive pN0 patients are less likely to be observed, targeted adjuvant treatment is distinguished with accurate staging [6]. Improved survival after more LN examination is due to the understaging of patients with insufficient lymph nodes evaluated [9]. The count of ELN after PD may correlate with the type of specimen, the extent of surgery, regional nodes present in a given individual, and the technique of the pathologist [9]. It may be advantageous for this study to consist of patients who underwent surgery in a single center with a single team and the same surgical technique.

Another important issue is the role of extended lymphadenectomy during PD. Extended lymphadenectomy is related to severe postoperative complications and prolonged hospital stay [2]. In addition, no survival difference between extended lymphadenectomy and regional lymphadenectomy was presented before [19, 20]. Also, ISPGS [10] and ESMO [12] consensus reports do not recommend extended lymphadenectomy. Considering these, we performed regional lymphadenectomy on all patients, and we achieved an acceptable count of ELN and survival results.

Another negative independent risk factor in this study was the R1 resection margin, observed in only 4 patients (HR: 5.777; 95% CI: 1.436-23.245). R1 resection is associated with reduced overall survival for PC [21]. However, R1 resection

margin rates vary distinctly in the literature [22, 23]. Standardized pathological resection margin evaluation is required to stratify survival accurately [21]. According to this study, R1 resection may be more critical for survival in the pN0 cohort.

Limitations

This study had several limitations. The main limitations were its retrospective nature and the small number of patients. Others were the fact that adjuvant protocols could not be included, that different pathologists evaluated the specimens, the lymph node stations were not analyzed in detail, and disease-free survival could not be assessed. However, regional lymphadenectomy was performed by a single center and the same team, in contrast to many extensive studies, wherein the strength of our study lies [6, 17].

Conclusion

Patients with node-negative pancreatic head cancer with <15 ELN count, and positive resection margin have shorter survival, suggesting missed metastatic lymph nodes due to assessment of too few lymph nodes. At least a 15 ELN count is required to stratify the survival more accurately in these cohorts. During pancreaticoduodenectomy, complete lymphadenectomy should be performed and yield a verified negative surgical margin.

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Research article

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Coronavirus-19 pandemic and its impact on elective neurosurgical operations

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Ethics Committee Approval
This study was carried out in accordance with the Declaration of Helsinki and was approved by the Sivas Cumhuriyet University Human Research Ethics Committee (registration no: 2021-02/20). Signed statements of informed content to participation and publication were obtained from participants before the study.
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The Coronavirus-19 (COVID-19) pandemic disrupted all planned, elective surgical procedures and appointment-based health services due to the decreased capacity of hospitals, healthcare professionals' focus on fighting the pandemic and efforts to protect patients, society and healthcare workers from the pandemic. The purpose of this study was to ascertain the perspective of patients on elective surgery, who applied to neurosurgery outpatient clinics at two different centers as clean and non-clean hospitals.

Methods: This cross-sectional prospective study was performed between March 2021 and July 2021, during the COVID-19 pandemic. 160 patients who were offered elective surgery for various indications in neurosurgery outpatient clinics were enrolled in the study. To this end, a questionnaire was administered to patients that included information about their demographics, pandemic processes and their anxiety levels during this process. Age, level of education, COVID -19 infection and vaccination status were all questioned in the survey. Univariate and multivariate analysis were used to determine the factors that might influence a patient's decision towards surgery.

Results: In the univariate analysis of the factors, educational status, pandemic-induced anxiety and whether the hospital is a pandemic hospital or not were identified as statistically significant effective factors in patients' decision to accept surgery ($P<0.05$).

Conclusion: We observed that the acceptance rate of patients for elective neurosurgical operations decreased during the pandemic period, but this situation was less felt in clean hospitals. We think that separating hospitals into two parts of clean and non-clean hospital is a beneficial health policy for the continuation of elective treatment procedures.

Keywords: COVID-19, Pandemic, Neurosurgery, Elective surgery

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Introduction

While the world has been fighting with the COVID-19 pandemic for two years, which was declared a global pandemic by the World Health Organization in March 2020 [1], it seems appropriate to investigate the extent to which the pandemic has influenced patients' attitudes toward surgery, where many elective and emergency surgical interventions occur on a daily basis.

The COVID -19 pandemic disrupted all planned, elective surgical procedures and appointment-based health services due to hospitals' decreased capacity, healthcare professionals' focus on fighting the pandemic and efforts to protect patients, society and healthcare workers from the pandemic [2-4].

Apart from disrupting the routine operation of the health system, it is well established that the COVID -19 pandemic had a significant impact on the mood and feelings of society, with numerous studies confirming the existence of this panicked and fearful state [5].

The purpose of this study was to ascertain the perspective of patients who applied to neurosurgery outpatient clinics at two different centers, where COVID -19 patients were accepted and rejected, and were recommended to be operated in these departments where the surgical decision made during the pandemic period.

Materials and methods

Between March and July 2021, during the Covid-19 pandemic, this cross-sectional prospective study was conducted.

The purpose of this study was to examine the effect of the Covid-19 pandemic process and hospital status on patient acceptance of surgery in neurosurgery clinics at Sivas Numune Hospital, a pandemic hospital, and Sivas Cumhuriyet University Medical Faculty Hospitals, which isn't a pandemic hospital. The study enrolled a total of 160 patients. Considering the number of patients who applied to the neurosurgery outpatient clinic of our hospital and the other hospital in Sivas in the pandemic period, and were recommended elective surgery by us, "sample calculation in cases with known prevalence" performed to calculate the sample size with alpha: 0.05, power: 80% G*power values.

To this end, a questionnaire was administered to patients that included demographic information, information about pandemic processes and information about their anxiety levels during this process. Age, education level, Covid-19 infection status (infected before or not) and Covid-19 vaccination status were questioned in the survey.

Univariate analysis was used to determine the factors that might influence a patient's decision to accept surgery. In statistical analysis, a cut-off value of 50 years was used for the patient's age. On the other hand, educational status was classified as secondary school and below and above secondary school. Patients' anxiety levels were scored on a scale of 1 to 5, with values greater than 3 indicating that they were extremely anxious and values less than 3 indicating lower anxiety. The effect of the pandemic and hospital status on the patient's surgical admission decision was scored on a 10-point scale, with a cut-off value of 5.

Statistical analysis

The SPSS 22 software program was used to conduct the statistical analysis. The Chi-square test or the Fisher's exact test was used to compare categorical variables, as appropriate. We used univariate and multivariate analysis to determine independent variables that could influence the surgical decision. $P<0.05$ was chosen as the level of statistical significance.

Results

Of the 160 patients in the study, 69% (n = 110) were recommended for elective surgery at the Sivas Cumhuriyet University Faculty of Medicine Neurosurgery clinic, while 31% (n = 50) were recommended for elective surgery at the Sivas Numune Hospital Neurosurgery clinic. The median age of the participants was 48 (22–79). Of the patients in the study, 51% were female, and 45.4% had a high school diploma or higher education (Table 1). While 79% of patients questioned during the study stated that they were not infected with COVID-19 before, 38% stated that they had received at least one dose of COVID-19 vaccine. While 53% of patients agreed to the proposed elective surgery, the remaining desired to postpone the procedure (Table 1).

Table 1: Survey Participants Characteristics (n = 160)

Variables	n	%
Gender		
Female	82	51.3
Male	78	48.7
Vaccination status		
Yes	60	37.5
No	100	62.5
Covid-19 status		
Infected	34	21.3
Non-infected	126	78.7
Surgical indications		
Lumbar disc herniation	105	65.6
Cervical disc herniation	12	7.5
Peripheric entrapment neuropathy	8	5.0
Cranial tumors	35	21.9
Educational status		
Middle school and below	88	54.6
High school and above	72	45.4
Effect of the pandemic*		
<5	105	65.6
≥5	55	34.4
Effect of the hospital*		
<5	67	41.9
≥5	93	58.1
Consideration about the surgery		
Accepted	84	52.5
Not accepted	76	47.5

* The effect of the pandemic and hospital status on the patient's surgical admission decision was scored on a 10-point scale, with a cut-off value of 5.

In the univariate analysis of the factors that may influence patients' decision to accept surgery, educational status, the effect of the pandemic period and whether the hospital is a pandemic hospital or not were found to be statistically significant effective factors (Table 2). While it was concluded that patients with a low level of education and those who applied to the clinic at a non-pandemic hospital were more likely to accept elective surgery, it was discovered that this decision was inversely related to pandemic anxiety.

When a multivariate analysis was performed for the factors that may affect patients' decision to accept surgery, only the presence of the pandemic was found to be a statistically significant effective factor (Table 3).

Table 2: Factors affecting the decision to accept surgery - Univariate Analysis

	Consideration about the surgery				
	Accepted		Not accepted		
	N	%	N	%	*P*-value
Age					
<50	43	48.9	45	51.1	0.309
>50	41	56.5	31	43.1	
Gender					
Male	42	51.1	40	48.8	0.739
Female	42	53.8	36	46.2	
Status of vaccination					
Vaccinated	26	43.3	34	56.7	0.072
Not-vaccinated	58	58.0	42	42.0	
Educational status					
Middle school and below	53	60.2	35	39.8	0.030
High school and above	31	43.1	41	56.9	
Covid-19 status					
Infected before	19	55.9	15	44.1	0.656
Non-infected before	65	51.6	61	48.4	
Effect of the pandemic*					
<5	74	70.5	31	29.5	<0.001
≥5	10	18.2	45	81.8	
Effect of the hospital *					
≤5	45	67.2	22	32.8	0.002
>5	39	41.9	54	58.1	

* The effect of the pandemic and hospital status on the patient's surgical admission decision was scored on a 10-point scale, with a cut-off value of 5.

Table 3: Factors affecting the decision to accept surgery - Multivariate Analysis

	OR	Lower	Upper	*P*-value
Educational status				0.203
Effect of the pandemic	2.97	1.93	4.58	<0.001
Effect of the hospital				0.508

Discussion

The COVID-19 pandemic will go down in history as an extraordinary period that severely curtailed humanity's social life and had a direct impact on countries' health policies.

During the early stages of the pandemic, the unpredictable course of the disease, the lack of effective treatment and the absence of an effective preventive vaccine altered not only the dynamics of the health sector but also the approaches to intervention in both emergency and non-emergency health problems [6, 7].

The purpose of this study was to determine the factors that influenced patients' decision-making processes when they were indicated for elective neurosurgical surgery during the pandemic period. As a result, our study was conducted during a time when hospitals' capacity to perform elective surgery during the pandemic period was once again questioned. It was determined that patients with a low educational level and who were less concerned about the pandemic period were more courageous in elective surgery decision-making. Additionally, the rate of elective surgery acceptance was found to be higher in the hospital that does not serve as a pandemic hospital and does not treat COVID-19 patients. Apart from these factors, it was determined that the pandemic period lowered the rate of elective surgery acceptance.

We concluded in our study that gender and age had no effect on elective surgery acceptance during the pandemic period. In a study of 722 people recommended for orthopedic elective surgery, it was discovered that age had no effect on decision-making, but that men's attitudes toward elective surgery were more favorable [8].

Plastic surgeons reported in a study conducted during the COVID-19 pandemic that people living in low socioeconomic countries had more favorable attitudes toward aesthetic interventions, with or without surgery [9]. In our study, we discovered that individuals with low levels of education were more receptive to elective neurosurgical surgery.

Additionally, we discovered that surgical acceptance rates were lower in the neurosurgery clinic at the hospital where COVID-19 patients were followed than in the clinic that did not operate as a pandemic hospital in our study. Taking into account our country's health policy during the pandemic period, the capacity of some hospitals to combat COVID-19 and efforts to maintain some hospitals as sterile hospitals, this result is predictable and expected.

Strengths and limitations

Our study is a cross-sectional and had a sufficient sample-size study examining the factors affecting elective neurosurgical procedures during the pandemic period. Our study was conducted in a clinic where neurosurgical procedures were performed intensively before and during the pandemic. It is the first study examining the interaction of neurosurgery daily practice during the pandemic and examining the factors affecting it. Albeit sufficient sample size, our study has some limitations. Due to its design in a single city during pandemic, it may be insufficient to reflect the whole population.

Conclusion

This extraordinary period caused by COVID-19 has generated a plethora of new research topics, and any research conducted during this time period is valuable. As neurosurgeons, we sought to determine the factors that may influence our patients' attitudes toward non-emergency surgical procedures during this time period. We observed that the acceptance rate of patients for elective neurosurgical surgeries decreased during the pandemic period, but this situation was less felt in clean hospitals. We think that separating hospitals into two parts like a pandemic hospital or not, is a beneficial health policy for the continuation of elective treatment procedures. We believe that by sharing our findings, the research during this period are taken to the next level.

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Estimated glomerular filtration rate decreased by Hydroxyethyl Starch in isolated coronary artery bypass graft surgery: A retrospective cohort study

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Ethics Committee Approval
Ethical approval for this study (ATADEK-2018/18) was provided by the Ethics Committee of Acibadem Mehmet Ali Aydinlar University, on 22 November 2018.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Hydroxyethyl starches have been widely used to replace the intravascular volume. They increase the risk of renal injury in critically ill patients. In cardiac surgery, patients are at risk for cardiac surgery-associated acute kidney injury. This study aims to analyze the renal functions in coronary surgery with hydroxyethyl starches and crystalloids.

Methods: Patients who underwent isolated on-pump coronary artery bypass graft surgery between January 2017 and June 2019 were included in the study. They were categorized into two groups according to intraoperative volume replacement therapy. The non-HES group consisted of patients who had been given a balanced electrolyte solution; the HES group consisted of patients who were administered a balanced electrolyte solution and 500 ml of hydroxyethyl starch solution. A two-sided *P*-value of <0.05 was considered significant.

Results: There were no significant differences between the two groups in terms of demographic values and preoperative serum urea, creatinine, blood urea nitrogen, and estimated glomerular filtration rate levels ($P>0.05$). In the HES group, the postoperative value of creatinine was significantly higher and estimated glomerular filtration rate level was significantly lower compared to the preoperative values ($P<0.001$).

Conclusion: The intraoperative administration of 500 mL hydroxyethyl starch affected renal function in isolated on-pump coronary artery bypass graft surgery patients.

Keywords: Coronary artery bypass graft, Colloids, Hydroxyethyl starch 130-0.4, Glomerular filtration rate

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Introduction

Colloid hydroxyethyl starches (HESs) have been used fluid resuscitation to replace the intravascular volume for more than 30 years [1, 2]. Despite their efficacy, HES solutions increase the risk of renal injury and the need for renal replacement therapy in critically ill patients [3]. This has made clinicians hesitant to use HESs [4]. Furthermore, patients undergoing cardiac surgery are already at risk for renal injury, as cardiac surgery-associated acute kidney injury (AKI) occurs in 7–54% of patients [5, 6].

This study aimed to analyze the effect of HESs on renal function in isolated coronary artery bypass graft (CABG) surgery patients.

Materials and methods

The ethics approval for this study (ATADEK-2018/18) was obtained from the Ethics Committee of Acibadem Mehmet Ali Aydinlar University, on 22 November 2018. Patient data were retrieved from the electronic medical records in our institution's database. Written informed consent was waived due to the retrospective nature of the study.

Patients who underwent isolated CABG surgery between January 2017 and June 2019 were included in this study. Patients who had previous cardiac surgery, off-pump cardiac surgery, valve surgery, concomitant surgery, renal failure (dialysis patients), intraoperative ultrafiltration, perioperative or postoperative blood transfusion, and HES infusion in the ICU were excluded.

All operations were performed by the same surgical and anesthesiology team. Patients were premedicated with alprazolam (0.5 mg, orally) the night before surgery and midazolam (0.05 mg/kg, intravenously) half an hour before the surgery. The patients were monitored with a 5-lead electrocardiogram, pulse oximeter, noninvasive blood pressure monitor, and bispectral index and cerebral oximeter. Before the induction of anesthesia, the radial artery was cannulated. Anesthesia was induced with midazolam, propofol, fentanyl, rocuronium and was maintained with a fentanyl infusion and sevoflurane in an O2-air mixture. After endotracheal intubation, transesophageal echocardiography and a central venous line were inserted. The lungs were ventilated with a tidal volume of 5–6 mL/kg and 5 cmH20 positive end-expiratory pressure before and after cardiopulmonary bypass (CPB) to maintain an end-tidal CO2 value of at least 33–35 mmHg and a peripheral capillary oxygen saturation value of at least 96%. Tranexamic acid (25 mg/kg, intravenous) was infused with the induction of anesthesia.

After achieving an activated clotting time of >450 s, aortic and caval cannulation was performed and CPB was initiated. Ringer's lactate solution was used for CPB priming. The pump flow rate was set at 2.2–2.4 L/min/m2 at 30–32°C. Cold blood cardioplegia was used for cardiac arrest. In all operations, balanced crystalloid solutions (Izolen®, Polifarma, Turkey) were used for infusion during anesthesia induction and maintenance. Balanced crystalloids or 500 mL HES (Voluven®, 6% HES 130/0.4, Fresenius Kabi, Germany) were randomly used during CBP or after coming off the pump. Transesophageal echocardiography was also used for analyzing the hemodynamic status.

At the end of the operation, the patients were transferred to the ICU.

In all patients, hemodynamic monitoring, ventilation, and postoperative analgesia were managed according to a standard clinical protocol. Blood samples were obtained on the first postoperative day in the ICU.

Data on patient demographics, cross-clamping (CC), CPB, and operation duration, as well as laboratory data, including preoperative and postoperative urea, creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR) levels, ICU and hospital stay were reviewed.

Patients' data were categorized into two groups according to intraoperative volume replacement therapy. The non-HES group (n=115) consisted of patients who had been given a balanced electrolyte solution; the HES group (n=45) consisted of patients who were administered a balanced electrolyte solution and 500 mL of HES solution.

Statistical analysis

Statistical analysis was performed using the SPSS version 10 software (SPSS Inc., Chicago, IL, USA). Data were presented in mean, standard deviation (SD) or number and percentage. Student's t-test, Mann-Whitney U test, and Pearson's $\chi 2$ test were used as necessary for inter-group comparisons. The Wilcoxon test or t-test was used for related variables comparisons. A two-sided *P*-value of <0.05 was considered significant.

Results

The records of 146 patients were evaluated. Only balanced electrolyte solutions were used during surgery in 111 patients, and 45 patients were managed with both HES and balanced electrolyte solutions.

There were no significant differences in demographic and clinical characteristics between the two groups (Table 1).

The intubation period was significantly longer in the HES group than the non-HES group (6.04 (2.38) hours vs 6.64 (2.15) hours, P=0.04). There were no significant differences in ICU stay or hospital discharge times between the two groups (Table 1).

The two groups were similar in terms of preoperative serum urea, creatinine, BUN, and eGFR levels. Postoperative serum creatinine, urea, and BUN values were significantly higher and eGFR level was significantly lower in the HES group than the non-HES group. Additionally, in the HES group, there were significantly differences between preoperative and postoperative values of creatinine and eGFR values [0.99 (0.29) mg/dL vs 1.14 (0.40) mg/dL, P<0.001 and 79.56 (18.88) mL/min/1.73m2 vs 71.17 (21.84) mL/min/1.73m2, P<0.001, respectively]. There were no differences in the non-HES group in terms of preoperative and postoperative values (Table 2).

No patients required inotropic agent infusion perioperatively.

There were no new-onset strokes, new-onset dialysis, infections, sternal dehiscence, pneumonia, the need for re-exploration for bleeding or renal replacement therapy in any of the patients. There was no mortality at 1 month follow up.

Table 1: Patients' demographic and clinical characteristics

	Non-HES group (n = 111)	HES group (n = 45)	*P*-value
Age (years)	61.57 (8.67)	64.49 (9.05)	0.06
Weight (kg)	81.82 (12.75)	77.94 (10,13)	0.06
Height (cm)	170.13 (8.83)	167.15 (8.95)	0.06
Sex (female/male) (n)	16/95	9/39	0.86
Euroscore logistics (%)	3.78 (3.27)	5.99 (11.45)	0.37
NYHA Class 1 and 2 (%)	88% (n = 98)	93% (n = 42)	0.96
EF (%)	55.79 (9.0)	54.51 (10.61)	0.80
Hypertension (%)	70.3% (n = 78)	75.6% (n = 34)	0.50
Hypercholesterolemia (%)	62.2% (n = 69)	73.3% (n = 33)	0.18
Diabetes Mellitus (%)	43.2% (n = 48)	46.7% (n = 21)	0.69
Thyroid dysfunction	3.6%8n=4)	0	0.19
CVA	1.8% (n=2)	2.2% (n=1)	0.86
Smoking (%)			
Smokers	33.3% (n = 37)	33.3% (n = 15)	0.87
Former smokers	33,3% (n = 37)	35.6% (n = 16)	
Never smoked	33.3% (n = 37)	31.1% (n = 14)	
Medications			
Beta blockers (%)	53.2% (n = 59)	64.4% (n = 29)	0.19
Ca canal blockers (%)	9.0% (n = 10)	11.1% (n = 5)	0.68
ACE inhibitors (%)	31.5% (n = 35)	35.6% (n = 16)	0.62
Anti-lipids (%)	35.1% (n=39)	42.2% (n=19)	0.40
Aspirin (%)	66.7% (n = 74)	64.4% (n = 29)	0.79
Hct	40.77 (4.20)	40.88 (4.68)	0.90
CC time (min)	57.11 (16.98)	63.33 (19.89)	0.07
CPB time (min)	90.23 (23.67)	96.08 (25.43)	0.10
Number of Distal Anastomoses	3.36 (0.8)	3.68 (1.08)	0.10
Intubation time (h)	6.04 (2.38)	6.64 (2.15)	0.04
Chest tube output (mL)	398.15 (216.24)	422.88 (271.15)	0.81
Postoperative Hct	29.58 (4.30)	27.50 (4.07)	0.007
ICU duration (h)	19.55 (10.07)	19.60 (6.70)	0.13
Postoperative AF	11% (n=12)	4.4% (n=2)	0.19
Hospital discharge time(days)	6.36 (4.55)	7.41 (6.75)	0.09

BMI: body mass index, NYHA: New York Heart association, EF: ejection fraction, COPD: chronic obstructive pulmonary disease, ACE: angiotensin-converting enzyme, CC: cross clamp, CPB: cardiopulmonary bypass, ICU: intensive care unit, AF: atrial fibrillation

Table 2: Preoperative and postoperative renal values

	Non-HES group (n = 111)	HES group (n = 45)	*P*-value
Urea preoperative (mg/dL)	36.81 (13.02)	38.77 (14.48)*	0.42
Urea postoperative (mg/dL)	37.62 (14.23)	42.68 (12.83)*	0.01
BUN preoperative (mg/dL)	17.17 (6.07)	18.11 (6.79)*	0.40
BUN postoperative (mg/dL)	17.53 (6.70)	19.93 (5.99)*	0.01
Creatinine preoperative(mg/dL)	0.97 (0.24)	0.99 (0.29)#	0.67
Creatinine postoperative (mg/dL)	0.99 (0.27)	1.14 (0.40)#	0.02
eGFR preoperative (mL/min/1.73m^2)	81.69 (18.12)	79.56 (18.88)#	0,52
eGFR postoperative (mL/min/1.73m^2)	80.76 (19.22)	71.17 (21.84)#	0,01

BUN: Blood urea nitrogen, eGFR: estimated glomerular filtration rate, # $P<0.001$, * $P=0.056$: These *P*-values indicate the preoperative and postoperative differences in the HES group.

Discussion

This study shows that the intraoperative administration of 500 mL HES can increase serum urea, creatinine, BUN levels and decrease eGFR levels after isolated on-pump coronary artery bypass surgery.

Hüter et al. [7] stated that HES is used for perioperative fluid therapy and pump-priming in cardiac surgery. HES increases the intravascular volume due to osmotic pressure because of its molecular weight. The molecular weight of HES can affect glomerular filtration and cause interstitial inflammatory changes in the kidneys, leading to kidney injury [7]. HES types with a higher molecular weight and higher hydroxyethylation ratios can accumulate in the interstitial space, leading to nephrotoxicity. Those with a lower molecular weight and lower hydroxyethylation ratios are less likely to lead to nephrotoxicity [5]. On the other hand, it has been reported that HES 130/0.4 attenuates the glycocalyx response to injury and sustains vascular barrier function [8].

In three meta-analyses of randomized studies on cardiac and non-cardiac patients, HES 130/0.40 was compared with crystalloids and found to have no significant association with AKI in cardiac and non-cardiac surgical patients [1, 4, 9]. In our study, in the HES group, the postoperative values of sCr were significantly increased and eGFR was significantly decreased than the corresponding preoperative values and significantly different from the non-HES group.

Tobey et al. [4] mentioned that in cardiac surgery, the incidence of major cardiac and cerebral events is higher with a low-volume HES infusion because the need for higher amounts of crystalloids in these patients can cause edema. Momeni et al. [10] reported that a low-volume (<30 mL/kg) or high-volume (>30 mL/kg) HES infusion did not affect the incidence of renal replacement therapy and mortality, but that low-volume HES infusions can reduce the incidence of AKI. Conversely, in Bayer et al.'s [2] study including 6,478 patients who underwent cardiac surgery with CPB, treatment with 6% HES 130/0.4 was associated with a higher risk of renal failure and a greater use of renal replacement therapy than crystalloids.

Preoperative poor left ventricular function, diabetes mellitus, hypertension, previous cardiac surgery, chronic kidney disease, and prolonged CPB duration are predictive risk factors for postoperative AKI [5, 6, 11]. In our study, there were no significant differences between the groups in terms of left ventricular function, diabetes mellitus, hypertension, CC, and CPB duration.

An intraoperative blood transfusion during cardiac surgery increases the incidence of AKI [12]. Each unit of blood transfused increases the risk of AKI by 10–20 % after cardiac surgery with CPB [13]. Therefore, we excluded patients who received blood transfusions during the intraoperative and postoperative ICU periods.

Limitations

The limitations of the study included the lack of blindness due to its retrospective nature. We evaluated the biochemical renal function parameters we used in daily follow-up. Other renal biomarkers can be used in randomized controlled trials in the future. This was a single-center study which focused on isolated CABG surgery to lessen the burden of confounding variables.

Conclusion

This study suggested that intraoperative administration of as low as 500 mL of HES reduced the level of estimated glomerular filtration rate in cardiac patients.

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The impact of the COVID-19 pandemic on the quality of life of the elderly population

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Ethics Committee Approval
The study was approved first by the Ministry of Health, then by the Istinye University Clinical Research Ethics Committee (2/2020.K-068). 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 elderly population were most exposed to lockdowns worldwide. Lockdown causes many disorders in people's daily routines, and the elderly suffer the most from these disorders. Our aim is to investigate the impact of the COVID-19 epidemic, which we do not know how long will last, on the psychological status and quality of life (QOL) of the elderly population.

Methods: A total of 226 male and female volunteers over the age of 65 years and with a score above 21 in the Minimental test were included in this cross-sectional study. QOL scale SF-36 and Geriatrics Depression Scale were performed to the participants.

Results: One hundred and twenty-five (55.3%) of the participants were male, 101 (44.7%) were female, and the mean age was 69.2 (4.4) years. A significant decrease was observed in all SF-36 QOL subscale scores during the pandemic compared to before (P<0.001). Compared to those not diagnosed with COVID-19, physical functioning, role limitations due to emotional problems and physical health, general health, and pain scores were decreased significantly among those diagnosed with COVID-19 (P<0.05 for all). In 67 of the 226 cases (29.6%), deterioration was observed in their health status in terms of depression during the pandemic compared to before (P<0.001).

Conclusion: The pandemic should not be dealt with medical treatment only, but precautions should be taken to increase the QOL. For this, the factors that determine the QOL are important. Telemedicine should be widely used in the elderly, social and physical activity should be increased, and videoconferences should be made.

Keywords: COVID-19, Depression, Elderly, Geriatrics, Health-related quality of life, Lockdown, Physical activity

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Introduction

Chronologically, aging starts from at 65 years. World Health Organization (WHO) defines those aged 65 years and over as elderly [1]. The world population was 7.5 billion in 2019, while the elderly population was 700 million. Accordingly, 9.3% of the world population was formed by the elderly [2].

Aging is one of the most important reasons for decreased quality of life (QOL) because of its biological, chronological, psychological, and social aspects and is an inevitable process. The higher chronic disease prevalence and disability in the elderly than other age groups and consequently, social activity restrictions decrease the quality of life [3]. Not quality of life but biomedical results have traditionally been the primary endpoints in medical and health studies. Nevertheless, QOL has become a fundamental concept in the preceding decades and the aim in health and medicine studies. Recently, attention to QOL has increased, and more studies have been performed on this matter [4].

According to the WHO definition, quality of life means an individual's understanding of his or her situation in life concerning the value and cultural systems of his or her living environment regarding the expectations, goals, concerns, and goals [5]. The Health-Related Quality of Life (HRQOL) measures the effects of diseases, disorders, or disabilities on an individual's wellbeing and indicates how a person functions in social, mental, and physical health domains and how it affects the person's wellbeing. Understanding QOL is essential for enhancing patient care, symptom relief, and recovery. Issues that arise with the self-reported QOL of patients might cause changes and treatment progress or indicate that some treatments provide a limited advantage. Also, QOL identifies various disorders affecting patients, and this information could be utilized to understand and predict the problems that diseases can cause to patients. Also, long-term survivors and treated patients may experience persistent issues after a long time following the end of treatment. These issues can go unnoticed without a QOL assessment. Decision-making is another use for QOL because it is a treatment success indicator. Consequently, it has prognostic significance and appears to require routine evaluation of QOL in clinical studies [4].

Studies on HRQOL consist of various dimensions such as basic quality of life, wellbeing, social and psychological factors, physical function, satisfaction from life, and health status awareness. In the section on physical function, issues such as the effects of chronic diseases and their treatment methods on daily physical functions are discussed. The section on social functioning also deals with the social aspects affected by the disease, such as communication with relatives and family members and mental states such as depression, anxiety, or anger [3].

WHO named Coronavirus Disease 2019 briefly as COVID-19.

When the epidemic in Wuhan reached a global dimension, WHO declared a pandemic on Mar 11, 2020 [6]. The people most affected by the disease in the pandemic were those over the age of 65 years with serious chronic diseases. The increase in mortality due to COVID-19, directly related to old age, hospitalization and mortality rates in the geriatric age group, have shown that this age group is at high risk [7]. For this reason, all over the world, emphasis has been placed on protective measures for the elderly and a lockdown has been imposed at certain hours to protect people over 65 years of age from COVID-19.

The most important consequences of the COVID-19 pandemic for the elderly who stay at home for too long are the psychological and physical effects [8]. According to studies, the physical results of the isolation include sarcopenia, increased risk of falling, fragility, diabetes mellitus, hypertension, and increased risk of cardiovascular disease [9]. The psychological consequences of isolation are anxiety, depression, dementia, impaired cognitive functions, mental disorientation, increased suicide attempt and post-traumatic stress disorder [10].

It is important to know how much the QOL and psychological state of the elderly population are affected during the period of staying at home, in terms of precautions to be taken during the pandemic period, which we do not know how long will last [11]. This study aimed to investigate the COVID-19 pandemic impact on the quality of life of the elderly population.

Materials and methods

The study was approved first by the Ministry of Health and then by the Istinye University Clinical Research Ethics Committee (2/2020.K-068). According to the power analysis performed before the research, it needed to include at least 226 cases (85% power and 5% error level). The effect size of 0.20 was decided in line with clinical predictions. Sample size calculations were performed with the G* Power 3.0.10. (Franz Foul, Universität Kiel, Kiel, Germany) package program.

A total of 226 male and female patients with a Mini Mental Test (MMT) score of 21 and above, in accordance with the WHO definition, were included in our study. Exclusion criteria were having an MMT score of under 21 and not volunteering [12]. In October 2020 the two doctors who conducted the study first conducted MMT on the participants. Participants with a score of 21 and above were made to fill in the questionnaires twice, taking into account the pre-pandemic (February, March 2020) and current (October, November 2020) situations in Turkey, using the Short Form 36 (SF-36) and Geriatric Depression Scale (GDS), which have been proven valid and reliable in the Turkish population [13,14].

The questionnaire consisted of 9 sub-scales: Role limitation due to physical health (PH), role limitation due to emotional problems (EP), Physical Function (PF), Emotional Wellbeing (EW), Social Function (SF), General Health (GH), Fatigue (F), Pain (P) and Health Changes (HC). The higher the score of these sub-scales, the better the quality of life, and conversely, the lower the score, the lower the respondent's quality of life. For more accurate results, respondents were accompanied by a physician when answering the questionnaire.

GDS, which was used to measure depression in respondents, had 30 questions, 20 of which indicated depression if answered positive, and the rest were depressive if answered negative. GDS is a self-estimated scale, and answers were responded with yes and no. To make it more acceptable for patients, the questions were all formatted to fit in one page. 0-10

points indicated no depression, 11-13 points indicated possibly in depression, 14 and above points indicated depression.

The demographic data of the patients, their current weight (October, November 2020) and that before the pandemic (February, March 2020), exercise habits, antidepressant use history, the presence of chronic disease, whether the person was diagnosed with COVID-19, whether the person remained in quarantine, whether any of their relatives died due to COVID-19, whether there was anyone going to work every day at home were also recorded.

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normality of the distribution of continuous variables, and the Levene test was used to test the homogeneity of variances. Categorical variables were shown in numbers (n) and percentage (%) while continuous variables were given as mean (SD) or median (min-max). While the difference in status of depression between before and during COVID-19 pandemic was investigated with the McNemar-Bowker test, Wilcoxon Sign Rank test was used to compare SF-36 QOL subscale scores.

Parametric test assumptions for continuous variables were evaluated by Kruskal-Wallis or Mann-Whitney U tests based on the number of independent groups. After identifying the variables with statistically significant *P*-values through the Kruskal-Wallis test, the Dunn-Bonferroni test was used to detect the differences between the groups. Categorical data were evaluated with Pearson's χ^2 or continuity corrected χ^2 test, where applicable. Spearman's rank-order correlation test was used for the association degree between continuous variables. Multiple logistic regression analysis via the Backward LR procedure was conducted to get the best predictor(s) which effect the deterioration in depression. Variables with univariable test values of less than 0.25 were selected for the multivariate model along with other variables of clinical significance. For each independent variable, 95% confidence intervals and odds ratios were calculated. Multiple linear regression analysis was used to determine the best predictor(s) affecting the SF-36 QOL subscale scores depending on the COVID-19 pandemic. Variables with univariable test values of less than 0.10 were selected for the multivariate model along with other variables of clinical significance. For each independent variable, 95% confidence intervals and coefficient of regression were calculated. Because of non-normal distribution, logarithmic transformation was used for each component of SF-36 QOL scale in regression analysis. IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA) was used for data analysis. A *P*-value of less than 0.05 was considered significant.

Results

Table 1 contains the descriptive statistics regarding the demographic and clinical characteristics of the study participants.

Table 2 includes the frequency distribution of the cases regarding the depression status of the cases before and during the pandemic. In 67 (29.6%) of 226 cases included in the study, deterioration was observed in their health status in terms of depression during the pandemic than before (*P*<0.001). No change was observed in the depression levels of the remaining cases (except one).

Table 1: Demographic and clinical characteristics of cases

	n=226
Age (years)	69.2 (4.4)
Range of age (years)	65-85
Gender	
Male	125 (55.3%)
Female	101 (44.7%)
Living place	
At home	182 (80.5%)
Other	44 (19.5%)
Level of education	
Primary school	74 (32.7%)
High school	86 (38.1%)
University	66 (29.2%)
Marital status	
Single	37 (16.4%)
Married	189 (83.6%)
Number of children	3 (0-6)
Comorbidity	167 (73.9%)
Body weight before the pandemic (kg)	76.7 (11.3)
Current body weight (kg)	77.9 (12.0)
Smoking habit	45 (19.9%)
Alcohol consumption	53 (23.5%)
Physical examination	
No	146 (64.6%)
Not doing due to the pandemic	30 (13.3%)
Regularly doing	50 (22.1%)
Antidepressant usage	53 (23.5%)
Vitamin supplement	110 (48.7%)
Being diagnosed with COVID-19	21 (9.3%)
Exposure to lockdown	72 (31.9%)
Losing an acquaintance due to COVID-19	52 (23.0%)
Number of family member	3 (1-6)
Having someone at home going to work regularly	120 (53.1%)
Mini mental test	25 (21-30)

Table 2: Frequency distribution of cases in terms of depression status before and during the pandemic

		Before the COVID-19 pandemic			
		No depression	Possibly in depression	In depression	Total
During the COVID-19 pandemic	No depression	123 (54.4%)	1 (0.4%)	0 (0.0%)	124 (54.8%)
	Possibly in depression	27 (11.9%)	19 (8.5%)	0 (0.0%)	46 (20.4%)
	In depression	23 (10.2%)	17 (7.5%)	16 (7.1%)	56 (24.8%)
	Total	173 (76.5%)	37 (16.4%)	16 (7.1%)	226 (100.0%)

Compared to the group whose depression level did not change, the rate of women, those with a low education level, those who were in quarantine, those who lost their relatives due to COVID-19, and the absence of anyone who went to work regularly at home was significantly higher in the group whose health condition deteriorated in terms of depression (*P*<0.05 for all).

The multivariate logistic regression analysis results showed that the most effective factors in predicting the deterioration in health status in terms of depression during the pandemic than before were the absence of anyone who went to work regularly at home (OR = 3.868, 95% CI: 1.941-7.709, *P*<0.001), loss of relatives due to COVID-19 (OR = 3.863, 95% CI: 1.846-8.082, *P*<0.001), being in quarantine (OR = 2.438, 95% CI: 1.241-4.789, *P*=0.010) and being a female (OR = 1.904, 95% CI: 1.017-3.564, *P*=0.044). (Table 3).

Table 3: Determining the best predictor(s) which affect the change in depression status depending on the COVID-19 pandemic – the results of Backward LR logistic regression analysis

	OR	95% CI	*P*-value
Female factor	1.904	1.017-3.564	0.044
Exposure to lockdown	2.438	1.241-4.789	0.010
Losing an acquaintance	3.863	1.846-8.082	<0.001
Not being able to go to work	3.868	1.941-7.709	<0.001

OR: Odds ratio, CI: Confidence interval

Table 4 shows the comparisons between the SF-36 QOL subscale scores of the cases before and during the pandemic. A statistically significant decrease was observed in all SF-36 QOL subscale scores during the pandemic than before (*P*<0.001).

A significant correlation was seen between the amount of change during the pandemic period in the PF, EP, F, and P components of the SF-36 QOL scale and age compared to before

the pandemic (P<0.05 for all). However, it these correlation levels were very weak. As the population living at home increased, PH, EP, EW and HC scores significantly decreased during the pandemic compared to before (P<0.05 for all).

Table 4: The comparisons between before and during the COVID-19 pandemic in terms of SF-36 quality of life subscale scores

		Mean	SD	Median	Min	Max	*P*-value †
PF	Before pandemic	70.20	27.86	80.00	0.00	100.00	<0.001
	During pandemic	66.57	29.41	80.00	0.00	100.00	
PH	Before pandemic	71.57	35.15	75.00	0.00	100.00	<0.001
	During pandemic	51.77	36.09	50.00	0.00	100.00	
EP	Before pandemic	69.10	37.98	100.00	0.00	100.00	<0.001
	During pandemic	44.54	39.54	33.30	0.00	100.00	
F	Before pandemic	56.39	18.92	55.00	5.00	100.00	<0.001
	During pandemic	50.58	20.40	50.00	0.00	100.00	
EW	Before pandemic	64.38	17.05	61.25	12.50	100.00	<0.001
	During pandemic	60.23	18.97	60.00	8.00	92.00	
SF	Before pandemic	70.38	27.47	62.50	0.00	100.00	<0.001
	During pandemic	50.88	28.55	50.00	0.00	100.00	
P	Before pandemic	66.48	22.29	67.50	12.50	100.00	<0.001
	During pandemic	57.98	24.23	57.50	0.00	100.00	
GH	Before pandemic	58.83	18.75	55.00	15.00	95.00	<0.001
	During pandemic	53.59	18.71	55.00	10.00	95.00	
HC	Before pandemic	43.68	17.47	50.00	0.00	75.00	<0.001
	During pandemic	35.82	17.05	25.00	0.00	75.00	

† Wilcoxon Sign Rank test

The amount of change in the SF-36 QOL scale components (except the SF subscales) between women and men during the pandemic period was similar (P>0.05 for all). On the other hand, social functional subscale scores of women were significantly lower than those of men (P=0.022)

Significant differences were seen in changes in the subjects' PH, EP, F and GH sub-dimension scores according to their education levels (P<0.05 for all). Compared to college graduates, primary school graduates' PH scores decreased more during the pandemic than before (P=0.034). Compared to high school graduates, the EP and GH scores of primary school graduates also decreased more during the pandemic than before (P=0.002 and P=0.009). In addition, compared to high school graduates, EP and F scores of college graduates decreased more during the pandemic than before (P=0.032 and P=0.051).

The EP, F, SF and HC scores of those who did not have a chronic disease were significantly higher during the pandemic than those with chronic disease (P<0.05 for all).

Compared to those who were not diagnosed with COVID-19, the PF, PH, EP, P and GH scores of those diagnosed with COVID-19 decreased significantly more during the pandemic than before (P<0.05 for all).

Compared to those who were not in quarantine, the PF, PH, EP, F, P and GH scores of those who remained in quarantine were significantly higher during the pandemic than before (P<0.05 for all).

PH and EP scores of those who lost their relatives due to COVID-19 during the pandemic period were significantly lower than those who did not lose any relatives due to COVID-19 (P=0.008).

The results of multivariate linear regression analysis showed that being diagnosed with COVID-19 was an independent risk factor for the decrease in the PF sub-dimension scores of the SF-36 QOL scale during the pandemic than before (B = -0.510, 95% CI: -0.777 - -0.244, P<0.001). The most determinant factors on the decrease in PH subscale scores were having a low education level (B = -0.261, 95% CI: -0.451 - -0.071, P=0.007), losing any relatives due to COVID-19 (B = -0.487, 95% CI: -0.849 - -0.126, P=0.008) and being diagnosed with COVID-19 (B = -0.626, 95% CI: -1.220 - -0.032, P=0.039). Being diagnosed with COVID-19 (B = -1.131, 95% CI: -1.925 - -0.336, P=0.005) and the number of people living at home (B = -0.232, 95% CI: -0.434) were independent markers for the decrease in EP sub-dimension scores (B= -0.029, P=0.025). Not having chronic disease (B = 0.460, 95% CI: 0.247 - 0.673, P<0.001) and being diagnosed with COVID-19 (B = -0.432, 95% CI: -0.743 - -0.121, P= 0.007) was effective. In terms of the decrease in the P sub-dimension scores, being diagnosed with COVID-19 was an independent risk factor (B = -0.539, 95% CI: -0.791 - -0.288, P<0.001). The most determinant factor on the decrease in HC subscale scores was the number of people living at home (B = -0.141, 95% CI: -0.210 - -0.073, P<0.001) (Table 5).

Table 5: Determining the best predictor(s) which effect on the changes in SF-36 quality of life subscale scores depending on the COVID-19 pandemic – the results of Multiple linear regression analyses

	B	LL	UL	*P*-value
PF				
Age	-0.014	-0.029	0.002	0.087
Being diagnosed with COVID-19	-0.510	-0.777	-0.244	<0.001
Exposure to lockdown	0.0004	-0.164	0.165	0.997
PH				
Level of education	0.261	0.071	0.451	0.007
Being diagnosed with COVID-19	-0.626	-1.220	-0.032	0.039
Exposure to lockdown	0.309	-0.058	0.677	0.099
Losing an acquaintance	-0.487	-0.849	-0.126	0.008
Number of family members	-0.082	-0.196	0.033	0.162
EP				
Age	-0.012	-0.066	0.043	0.670
Level of education	0.054	-0.230	0.337	0.710
Comorbidity	0.324	-0.194	0.842	0.219
Being diagnosed with COVID-19	-1.131	-1.925	-0.336	0.005
Losing an acquaintance	-0.171	-0.705	0.363	0.529
Number of family members	-0.232	-0.434	-0.029	0.025
Having someone at home going to work regularly	-0.099	-0.640	0.443	0.719
SF				
Female factor	0.046	-0.143	0.235	0.632
Comorbidity	0.460	0.247	0.673	<0.001
Being diagnosed with COVID-19	-0.432	-0.743	-0.121	0.007
P				
Age	0.010	-0.004	0.025	0.167
Being diagnosed with COVID-19	-0.539	-0.791	-0.288	<0.001
Exposure to lockdown	-0.013	-0.168	0.142	0.871
HC				
Comorbidity	0.043	-0.129	0.216	0.619
Number of family members	-0.141	-0.210	-0.073	<0.001
Having someone at home going to work regularly	0.010	-0.172	0.192	0.913

B: Coefficient of regression, LL: Lower limit of 95% confidence interval for B, UL: Upper limit of 95% confidence interval for B

Discussion

Since the COVID-19 infection progressed very rapidly and pandemic decisions were made quickly, pre-pandemic scale evaluation could not be performed in our study, and the answers to the pre- and post-pandemic evaluations of the elderly were requested in the same interview. However, our study is valuable because it detects the effects of COVID-19 infection and pandemic on the quality of life of elderly people. In addition, the Short Form-36 used in this study is among the recommended scales in terms of reliability, validity, and sensitivity to change, and is recommended when a comprehensive assessment of HRQOL is required [15, 16]. One of the most important results of our study was that a significant decrease was observed in all SF-36 quality of life subscale scores during the pandemic than before. The reason may be that the health status of elderly people is mostly affected by the ability to continue daily life activities and routines. Unfortunately, physical and social isolation prevented many of the elderlies' daily activities.

Fifty (22.1%) of our participants continued their exercises regularly despite the pandemic. Thirty (13.3%) people stated that they could not exercise due to the pandemic. Suzuki et

al. assessed the impact of public health constraints on physical activity, subjective wellbeing, and health related QOL of the elderly in 165 patients in Japan. Of them, 47.3% of the participants became less active, 23.0% became more active, and 29.7% maintained physical activity levels. Subjective wellbeing and lower mental component health related QOL scores were related to an increased risk of decreased physical activity [17]. Another study in Finland examined active aging, variations of life-space mobility and QOL scores of 809 patients (75, 80, and 85-year age group) 2 years ago, and these scores were re-examined during the pandemic period. All scores were significantly lower during COVID-19 social distancing. The more physically active the elderly people are and the greater the mobility of their living space, the higher their quality of life [18]. Our results support these results.

In a multi-center study in which 928 people between the ages of 60 and 85 years were included, the relationship between health literacy and suspected COVID-19 symptoms (S-COVID-19-S) was examined. Health literacy-related factors in the study groups were age, gender, social status, ability to afford treatment costs, and education. As health literacy increased, there was an increase in healthy eating, and physical activity, and a decrease in depression rates [19]. In our study, significant differences were observed in terms of changes in PH, EP, F and GH sub-dimension scores of the subjects according to their education levels. To reduce the damage caused to the elderly in the pandemic, the use of health literacy interventions and healthy behavior training can effectively improve the mental state of the elderly.

In a study including 120 older people published in 2009, psychological factors measured by GDS and sociodemographic factors including leisure activities, income, and marital status are reported to affect QOL.

As assessed by the Geriatric Depression Scale, psychological factors and sociodemographic characteristics, such as marital status, income, and leisure activities impacted QOL. In our study, we saw that depression that increased during the pandemic period negatively affected the quality of life. The same study concluded that in the analysis models in active elderly, functional status had no impact on the QOL variable. This result can be explained by the absence of a pandemic and prohibitions in those years [20].

In 2020, a study from Spain investigated the Relationship between QOL and Sociodemographic, Physical, and Mental Health Variables in people over 65 years of age. The factors affecting the QOL were the abundance of financial difficulties, the presence of a psychological disorder, psychological and physical symptoms, while a positive factor was having a job [21].

A study about the variations of depressive indications following therapy with exercising showed that combining exercise with antidepressant medications can positively improve the symptoms of depression. The results showed that compared to other standard treatments for depression, this method could show its positive results in early 4-week periods and long 12-week periods. [22].

A 2017 study examined the relationship between physical weakness, physical activity, and depression in older women. This study showed that the risk factors associated with depression in participants with low levels of physical activity were low levels of education, diabetes, and a high risk of metabolic syndrome. The results also showed that because life expectancy and longevity are higher in women, especially after menopause, men should pay more attention to physical activity and lifestyle changes in older women to prevent a decrease in their quality of life [23]. In our study, the female gender was one of the most effective factors in predicting the deterioration of health status in terms of depression during the pandemic.

Limitations

The primary limitation of our study is that the scales before the pandemic were completed during the pandemic period, as it was not predicted before.

Conclusion

We found that the COVID-19 pandemic negatively affected the quality of life in the elderly. With the COVID-19 pandemic, the decrease in sharing with the elderly living at home decreases the quality of life and affects their mood. It is not clear how long COVID-19 pandemic and social-physical isolation will last. Therefore, enough physical activity should be encouraged for the elderly population to be less affected by this situation. Regular behavioral therapy over the phone or online, and video calls with family members and peers can help improve depression. According to our results, in behavioral therapy, priority can be given to female gender, those who lost their relatives due to COVID-19, those who remain in quarantine due to COVID-19 and the elderly population receiving COVID-19 treatment. To reduce mental issues during the pandemic, it is recommended to use health literacy interventions and teach proper health behaviors. Telemedicine should be made more available, especially in this risky group.

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What do we know about cervical cancer and HPV vaccines? A cross-sectional questionnaire evaluated by midwives and nurses

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Ethics committee approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital on 11.11.2020 with the number 2011-KAEK-25 2020/11-04.
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: Cervical cancer is a preventable disease by appropriate screening programs, treatment of pre-invasive lesions, and vaccination. Thus, the knowledge of healthcare providers about this issue is crucial. The purpose of this study was to evaluate the knowledge of nurses and midwives who were working in the obstetrics and gynecology department about cervical cancer, screening programs, and human papillomavirus vaccination.

Methods: The questionnaire comprising 17 questions about cervical cancer, screening programs, and the human papillomavirus that was created by the authors, was applied to midwives and nurses working in Bursa online. All participants were informed about the answers, cervical cancer and HPV vaccines adequately after finishing the questionnaire.

Results: The number of participants volunteering to answer the survey was 510. Of these, the rate of participants claiming that cervical cancer is a preventable disease was 97.4%. Approximately 74% of them answered that the reason for cancer was a virus, and 97.8% said that it is screened with a cervical smear. Sixty percent of the participants answered the onset age of the cervical cancer screening program wrongly. There is a great lack of knowledge about the type of vaccines, administration age, and the population vaccinated. Only 2% of the participants had been vaccinated and 34% had offered the vaccination to someone.

Conclusion: Midwives and nurses of the obstetrics and gynecology department working in Bursa have sufficient knowledge about cervical cancer, whereas they have a lack of knowledge about screening programmes and human papillomavirus vaccination. It is crucial to make everyone know that cervical cancer is preventable and that eradication is possible by vaccination. Community-based information about the cervical cancer screening program and HPV vaccines is essential.

Keywords: Cervical cancer, Human Papilloma Virus, Screening methods, Vaccination

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Introduction

Every two minutes, a woman dies due to cervical cancer worldwide [1]. Although cervical cancer is the third most common cancer in developing countries, it is the most common cancer among gynecological cancers in the world [2]. The latest data announced by the Ministry of Health of the Republic of Turkey states it is the 9th most common cancer among Turkish women, with an incidence of 3.4/100,000 [3]. The relationship between cervical cancer and Human Papilloma Virus (HPV) was shown about 40 years ago [4]. The human Papilloma Virus causes infection after entering the basal epithelial cells via micro traumatic regions, occurring during sexual intercourse. It can be eliminated by the immune system in two years. Women with persistent lesions and even those without any lesions can spread the disease. The time between the infection and the development of invasive cancer is approximately more than 10 years. It is also presented that the interval between HPV infection and precancerous lesions is 5 years, whereas it takes about 15 years for precancerous lesions to develop into invasive cancer. Preinvasive lesions are screened by the 'Pap smear test' (cervical smear). In Turkey, every woman is included in the screening program starting from the age of 30 years by the Ministry of Health, General Directorate of Public Health [5]. The community-based screening program, which starts at the age of thirty, is applied every five years with a cervical smear or HPV test. The screening program of the Ministry of Health of Turkey is presented in Table 1, and the screening program of the American Society of Obstetrics and Gynecology is presented in Table 2 [5, 6].

Table 1: Republic of Turkey, Ministry of health cervical cancer screening program

Cervical Cancer Screening Program
• All women between the ages of 30-65 years • Every 5 years, HPV DNA screening or Pap Smear • Screening is terminated in 65-year-old women whose last two tests are negative. • Women who have had a hysterectomy not for CIN II or CIN III do not need to be screened • In cases where hysterectomy was performed due to CIN II and III; three documentable report screening should be discontinued in the absence of technically adequate negative cytology and an abnormal/positive result in the last 10 years.

Table 2: American Society of Obstetrics and Gynecology Cervical Cancer Screening Program

American Society of Obstetrics and Gynecology Cervical Cancer Screening Program
• Screening recommends starting at age 21 years. Cytology is performed every 3 years between the ages of 21-29 years • Between the ages of 30-65 years, HPV DNA is screened every 5 years or Pap Smear is performed every 3 years • Screening is terminated at age 65 years (in the presence of 3 negative cytology or 2 negative HPV tests in the last 10 years and the last in the last 5 years) and benign hysterectomies • Continuation of screening for 20 years in patients with a history of CIN II and CIN III and Hysterectomy • Screening continues in those who have had the HPV vaccine

HPV is a non-enveloped DNA virus. More than 200 species have been identified. Approximately 40 types infect the genital tract [7]. It is classified as low-risk and high-risk based on oncogenicity risk. Low-risk HPV types, type 6 and 11, are especially responsible for genital condylomas, while high-risk types, 16, 18, 31, 33, 45, 52 are responsible for cervical cancers [8]. HPV vaccines are also utilized to prevent the infection. L1, which is the major capsid protein of the virus, and/or L2, which is the minor capsid protein, are used in HPV vaccines. Since it does not contain a viral genome, there is no risk of infection [9].

Increasing knowledge and experience about the cervical cancer screening program and HPV vaccines in our country is one of the most important steps in the eradication of cervical cancer. The purpose of this study was to evaluate the knowledge and experience of midwives and nurses working in the field of gynecology and obstetrics in Bursa about cervical cancer screening and HPV vaccines, and to inform them.

Materials and methods

Ethics committee approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital on 11.11.2020 with the number 2011-KAEK-25 2020/11-04. After the approval of the ethics committee, the study was conducted on the midwives and nurses who were college graduates, and still working in a state hospital department of the obstetrics and gynecology unit in Bursa, via an online questionnaire. At the beginning of the study, the participants were informed about the study, and those who agreed to participate were administered a questionnaire created by the authors.

A total of 17 questions were present in the survey, evaluating the knowledge levels of the participants about cervical cancer, screening programs, and Human Papilloma Virus vaccines. After the questionnaire was finished, a form depicting the answers and useful information about the issue was presented.

All participants were experienced nurses and midwives working in the obstetrics and gynecology department. The personal information of applicants was not used, and the respondents were not disclosed in any way. Definitions that would harm personal privacy were not used in the questionnaire. The questions and answers are presented in Table 3.

Table 3: Questionnaire form about the awareness of cervical cancer and HPV vaccines among midwives and gynecology and obstetrics nurses

1. Is Cervical Cancer a significantly preventable disease?
A.Yes B.No
2.At what age does screening start in the cervical cancer prevention program of the Ministry of Health?
A.18 B.25 ***C.30*** D.35 E.40
3. What is the method used in cervical cancer screening?
A.Blood Test B.Urine Test ***C.Smear Test*** D.Mammography
4.What is the most common cause of cervical cancer?
A.Bacteria B.Parasite ***C.Virus*** D.Smoking
5.How many types of HPV vaccines are used to prevent cervical cancer?
A.1 B.2 ***C.3*** D.4
6. How many doses of HPV vaccines are administered?
A.1 B.2 ***C.3*** D.4
7.At what age (Target Audience) should the vaccine be administered?
A.6-8 years ***B.9-12 years*** C.13-15 years D.16-20 years
8.If it is not administered in the target age range, at what age (Compensation -Catchup) is it still valuable for protection?
A.10-20 years ***B.13-26 years*** C.30-40 years
9.Can HPV vaccine cause benign or malignant diseases of the cervix?
A.Yes ***B.No***
10.Do you know about the price of HPV vaccines?
A.Yes B.No
11. Who can receive HPV vaccines?
A. Only for women B.Only for men ***C. Both women and men***
12.Do you think the HPV vaccine should be included in the Ministry of Health Vaccination Calendar?
A.Yes **B.No**
13.Are any tests (smear, blood or urine test) required before HPV vaccination?
A.Yes ***B.No***
14.Should smear screening continue after HPV vaccination?
A.Yes B.No
15.Can sexually active people get HPV vaccine?
A.Yes B.No
16. Have you had the HPV vaccine?
A.Yes B.No
17.Have you recommended the HPV vaccine to anyone?
A.Yes B.No

*The options marked in bold, underlined, and larger indicate the correct answer.

Statistical analysis

After all the participants filled the questionnaire online, all answers were evaluated. The number of the answered questions and the frequencies of the answered options were reviewed.

Results

A total of 510 participants were included in the study. Some questions were not included in the results because of the unanswered questions. Responses of the patients were demonstrated in Table 4

Table 4: The number of people who responded to the questionnaire on questioning the awareness of cervical cancer and HPV vaccines among midwives and gynecology and obstetrics nurses and their answers (N refers to the number of people who answered the question. The percentage of answers given to the question is indicated under the choices)

1. Is Cervical Cancer a significantly preventable disease? (n=508)				
A.Yes	B.No			
97.4%	2.6%			
2. At what age does screening start in the cervical cancer prevention program of the Ministry of Health?(n=504)				
A.18	B.25	***C.30***	D.35	E.40
24.2%	13.7%	38.1%	13.5%	10.5%
3. What is the method used in cervical cancer screening?(n=508)				
A. Blood Test	B. Urine Test	***C.Smear Test***	D. Mammography	
1%	0.4%	97.8%	0.8%	
4. What is the most common cause of cervical cancer? (n=509)				
A.Bacteria	B.Parasite	***C.Virus***	D.Smoking	
16.2%	2.6%	73.7%	7.6%	
5. How many types of HPV vaccine are used to prevent cervical cancer? (n=498)				
A.1	B.2	***C.3***	D.4	
22.9%	41.8%	30.6%	4.7%	
6. How many doses of HPV vaccine are administered? (n=494)				
A.1	B.2	***C.3***	D.4	
14.4%	40.9%	40.9%	3.9%	
7. At what age (Target Audience) should the vaccine be administered? (n=505)				
A.6-8 years	***B.9-12 years***	C.13-15 years	D.16-20 years	
2.4%	41.9%	13.1%	42.7%	
8. If it is not administered in the target age range, at what age (Compensation -Catchup) is it stil valuable for protection? (n=503)				
A.10-20 years	***B.13-26 years***	C.30-40 years		
9.3%	59.2%	31.5%		
9. Can HPV vaccine cause benign or malignant diseases of the cervix? (n=507)				
A.Yes	***B.No***			
38.3%	61.7%			
10. Do you know about the price of HPV vaccines? (n=503)				
A.Yes	B.No			
29.9%	70.1%			
11. Who can receive HPV vaccines? (n=505)				
A. Only for women	B.Only for men	***C. Both women and men***		
40.8%	0.4%	58.8%		
12. Do you think the HPV vaccine should be included in the Ministry of Health Vaccination Calendar? (n=507)				
A.Yes	B.No			
93%	7%			
13. Are any tests (smear, blood or urine test) required before HPV vaccination? (n=510)				
A.Yes	***B.No***			
49.6%	50.4%			
14. Should smear screening continue after HPV vaccination? (n=507)				
A.Yes	B.No			
94%	6%			
15. Can sexually active people get the HPV vaccine? (n=507)				
A.Yes	B.No			
92%	8%			
16. Have you had the HPV vaccine? (n=509)				
A.Yes	B.No			
2%	98%			
17. Have you recommended the HPV vaccine to anyone? (n=508)				
A.Yes	B.No			
34%	66%			

A total of 97.4% of the participants knew that cervical cancer was preventable, 73.7% had the knowledge that it was caused by a virus, and 97.8% answered that it can be scanned with cervical smear. Only 38% of the respondents gave the correct answer about the onset age of the cervical cancer screening program of the Ministry of Health. Considering the questions asked about Human Papilloma Virus vaccines, 30% of the respondents said that there were 3 types of HPV vaccines, 40.9% knew that they were administered in 3 doses, 41.9% were aware that the target group was between the ages of 9-12 years and 59.2% knew that it must be compensated between the ages of 13-26 years if it was not applied at the target age. A total of 61.7% of the participants had the knowledge that the HPV vaccine would not cause malignant diseases, 8.8% answered that this vaccine could be applied to both girls and boys, 70.1% of the participants did not have information about the cost of HPV vaccines, but 93% argued that this vaccine should be included in the vaccination calendar. A total of 50.4% of the participants gave the correct answer to the question regarding the necessity of pre-vaccine examination. When we asked whether sexually active people can get HPV vaccine, 92% of the participants answered correctly. The rate of correctly answering the question of the necessity of continuing screening after vaccination was 94%. It was found that 98% of the respondents did not get vaccinated and only 34% recommended the vaccine to someone.

Discussion

Cervical cancer is a preventable cancer because its etiopathology has been clearly identified. The cancer pathway consists of four steps [10]. The entry of HPV into the cervical epithelial cells is the first and the mandatory step. Approximately 75% of sexually active individuals encounter HPV at some point in their lives [11]. The persistence of HPV, which is usually eradicated from the body within 2 years by the immune system, constitutes the second step of the cancer pathway. The third step is conversion to precancerous lesions and the last step is progression to invasive cancer [10]. Although most respondents knew that cervical cancer is preventable, and caused by a viral pathogen, only 38% of the participants correctly answered the timing of the screening program. Awareness of the screening program of Turkey was also questioned in published survey studies. In a survey conducted among the healthcare professionals in our country, more than 50 percent of women stated that they had never had a cervical smear test [12, 13]. The participants in these studies reported excuses such as not seeing themselves in the risky group, having no symptoms, and abstaining from gynecological examination; however, emphasis should be placed on the fact that the screening programs should cover all the population. In the case of cervical cancer screening programs, every woman within the 30 – 65-year age range should be screened at 5-year intervals without exception [5]. No symptom or risk scoring is needed for the person to be included in screening, even if the women and her sexual partners are absolute monogamous. Many survey studies confirmed that the awareness of cervical cancer being a viral disease and the necessity of screening with smear was established, however, this awareness, unfortunately, did not make women undergo cervical smear tests [12, 14-16]. Avoidance of gynecological examination is a factor in the formation of this habit. By reaching and educating as many women as possible and providing favorable gynecologic examination conditions, establishing the practice of giving cervical smear specimens among women should be the primary concern of preventive medicine.

One of the questions in the survey was the opinion about whether the HPV vaccine could cause infection, precancerous lesions, or invasive cancer. Approximately 38% of the participants in the study thought that HPV vaccines could cause cervical diseases. The HPV vaccines consist of virus-like particles containing the L1 and/or L2 capsid protein. While these

proteins play the crucial role in the entering of the virus into the cervical epithelium, after the vaccine is administered to the person, these proteins are introduced the immune system. If the viruses even try to pass from the epithelium, the immune system can easily prevent them. Thus, the virus is rejected. Since they do not contain the virus genome, HPV vaccines do not cause any cervical lesions or cancer. Systemic immune response occurs after vaccination, so the post-vaccine immune response is stronger [17]. One of the essential points of this study was that HPV vaccines do not cause any diseases.

In 2006, the first HPV vaccine was approved by the American Food and Drug Administration (FDA). It contained virus-like particles of HPV types 16-18-6 and 11. In 2010, the vaccine containing viral particles of HPV types 16 and 18 was approved by the FDA. In 2014, the 9-valent vaccine containing HPV types 6-11-16-18-31-33-45-52-58 was approved, but it is currently unavailable in Turkey. Vaccines provide more than 90 percent protection against the viral types they contain [18, 19]. It is administered in three doses (0-1-6 months or 0-2-6 months) and no additional booster dose is required. While the American Center for Disease Control and Prevention (CDC) states that the target population should include girls and boys aged 11-12 years, The World Health Organization states that the target population of HPV vaccines should consist of girls aged 9-13 years [20, 21]. It is recommended that people who are not vaccinated at this age should be vaccinated until the age of 26 years. Although it is not routinely recommended after the age of twenty-six due to the high probability of encountering HPV types and the possibility of decreased protection, the American Food and Drug Administration (FDA) approved the use of HPV vaccine for women and men aged 27-45 years. Vaccination is not recommended during pregnancy. There is no indication for termination of pregnancy in patients who do not know that they are pregnant at the time of vaccination and routine pregnancy follow-up is recommended. No definite relationship was found between the vaccine and neonatal adverse events [22]. The HPV vaccine has been included in the national vaccination calendar of 65 countries, exclusively for girls. Both girls and boys are vaccinated in the United States, Australia, Switzerland, Austria, and Canada [23]. Our results revealed that there was a serious lack of information about HPV vaccines in the study group. Unfortunately, the level of knowledge on topics such as vaccine types and doses, the target population and age intervals were not at the desired level. In general, the participants state that HPV vaccines should be included in the vaccination calendar, but there is a lack of information about the cost. It is known correctly by the general majority that sexually active people can also be vaccinated. However, the question about the necessity of pre-vaccine examination was answered correctly by half of the participants. In studies in which the knowledge of current HPV vaccines in different populations was questioned, it was shown that most respondents had incomplete information, similar to our study [24-26]. In a survey of pediatricians, the recommendation level of HPV vaccines was high, but it was generally recommended for only girls [27]. In addition to cervical cancer, HPV can also cause diseases in men, such as genital condyloma and anal cancer. Vaccination of men should also be recommended, as men are carriers of HPV and are more likely to have risky sexual relationships. In a study, some physicians stated that they did not recommend HPV vaccination because they thought that the vaccination might lead to risky sexual intercourse. The fact is that a physician should give adequate information to the patients, and it is unacceptable for a physician to reject to inform about the vaccination due to his or her false pretenses. Another drawback was the cost of vaccination. Although the vaccine might be assumed to have a high price in Turkey, it should not be a reason not to recommend the vaccine.

Limitations

The limitation of the study was the lack of statistical comparison within the subgroups and the small number of participants. The aim was to achieve satisfactory knowledge in all participants, and not compare the knowledge. Although the number of participants could seem as a limitation, it was one of the largest in its field.

Conclusion

The lack of information about cervical cancer and especially HPV vaccines is profound. Every family should be informed about this vaccine during the administration of their routine vaccinations. In schools, children between the ages of 9-12 years should be guided to receive information about HPV vaccines through their families from the pediatrician, gynecology and obstetrics, or family medicine practitioners. Compliance with the cervical cancer screening program must be ensured and supervised. During cervical cancer screening, information about HPV vaccines should be given to mothers for their children. All hospitals, health units, social media, national media should immediately start informing about cervical smear and HPV vaccines. It should be emphasized that cervical cancer is a preventable disease. HPV vaccination is one of the most essential issues of public health.

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Can YouTube videos concerning the esophagogastroduodenoscopy experience be a reliable and satisfactory source of information for patient education in developing countries? A cross-sectional study from Turkey

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Ethics Committee Approval
The study was conducted without the approval of the ethics committee as it was performed by evaluating publicly available videos and it was done without human and/or animal participants.

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Abstract

Background/Aim: Social media has great potential for easy access to medical information especially in underdeveloped countries. We aimed to analyze the content, reliability and quality of the most viewed YouTube videos, targeting patients intending to use this social media platform as a source of information about the esophagogastroduodenoscopy (EGD) procedure.

Methods: Using the keywords “esophagogastroduodenoscopy” and “upper gastrointestinal endoscopy”, we assessed the publicly visible English-language videos available on YouTube. EGD Data Quality Score (EGD-DQS), Global Quality Score (GQS) and a modified DISCERN scale were used to assess the quality, flow and ease of use of the information and the reliability of the EGD videos.

Results: Universities/health-care professional group was the most common source of video upload (36%). The reliability score of the videos presented by physicians was significantly higher compared to all other lecturer groups (P=0.044). The reliability score, EGD-DQS and GQS score were also found to be statistically higher in the universities/health-care professional group compared to the health information websites, advertisement and patient groups (P<0.05, for all). Useful information was significantly higher in the universities/health-care professional group compared to the remaining upload sources (P<0.05). Lastly, patient-uploaded videos received more "likes" and "comments", and a higher number of subscribers.

Conclusions: YouTube is a powerful source of information for EGD procedure, especially where patients suffer to reach health care information due to inadvertent health policies. Academic sources should create videos that attract the interest of the viewers, and physicians should direct patients to online resources that present accurate and reliable information.

Keywords: Patient education, YouTube, Esophagogastroduodenoscopy, Upper gastrointestinal endoscopy, Social media, Medical information

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Introduction

The most effective method in the diagnosis and treatment of esophageal, gastric, and small-bowel diseases is performing an endoscopy targeting this system; namely, esophagogastroduodenoscopy (EGD) [1]. In 2013, an estimated 6 million EGD procedures were performed in the United States at an estimated cost of $ 12 billion [2]. When properly performed, this procedure is generally safe and well-tolerated for the examination of the upper gastrointestinal tract. However, in order to achieve a successful result in EGD procedure, not only the technical knowledge and skills of the healthcare professionals, but also the patients' knowledge and awareness of the procedure are required [3]. Although, explaining the details of this procedure is the responsibility of the physicians, patients who are planned to undergo EGD may not be able to ask healthcare professionals all questions related to the procedure under outpatient conditions, or new issues about the disease or procedure may arise after leaving the office and they may need to resort to the internet in search of further information, rather than contacting healthcare professionals. In underdeveloped and developing countries, such as Turkey, which are inadequate in the health sector and patient education, online resources have become the first and most influential source of health information for patients, and a large majority of the population uses the internet as the sole source of health information [4]. Therefore, it is important to evaluate whether the information obtained from videos on EGD is accurate and adequate or misleading since patients may turn to these sources with the hope of better understanding the disease and taking informed decisions.

YouTube, a social media platform created in 2005, is one of the most visited websites with over one billion users and provides easy access to all kinds of information, as well as health information [5]. In particular, patients with chronic diseases often rely on evidence based on the internet to manage their conditions. Individuals' health-related online searches should rely upon educative and instructive internet knowledge, since research surveys have revealed that 75% of such patients are affected by information acquired from online health searches in making decisions concerning the treatment of their condition [6]. However, the veracity and quality of the information available on this platform has been a concern since it offers uncontrollable access to both high- and low-quality information, with minimal guidelines and interventions regulating the content of the videos uploaded. Briefly, social media has great potential for easy access to medical information, but it is not always possible to ensure that this information is accurate and unbiased, and this situation can bring harm rather than benefit.

Although many previous studies on chronic diseases, self-educational skills and invasive procedures have evaluated the content and quality of information in YouTube videos [6-16], there is a lack of data evaluating the quality and content of educational videos on YouTube about EGD performance as a source of patient information. Therefore, we aimed to investigate the quality of content regarding YouTube EGD videos and determine whether this platform is a useful source for the education of patients especially whose sole information source is social media.

Materials and methods

Selection of videos

Between June 1 and 4, 2020, a You Tube search was performed on https://www.youtube.com/ using the terms "esophagogastroduodenoscopy" and "upper gastrointestinal endoscopy" to obtain all videos containing the relevant information. The search returned a total of 11.345 videos, which were then sorted by the maximum number of views to include only those that were most watched by individuals searching for both terms. In studies using online search engines, users are reported to be unlikely to go beyond the first few pages of any search result [8]. Therefore, in this study, only the first 200 videos were analyzed for both search terms (20 videos per page for the first 10 pages). The inclusion criteria were being in English language and being related to EGD. Videos which were not directly related to the EGD procedure, such as music videos, those belonging to gastric cancer awareness campaigns, and those with no sound were excluded. Duplications were excluded and videos with multiple parts were evaluated only once.

Data collection and grading of videos

Video parameters

Upon completing the search, detailed information about the videos, including the date of upload, number of days since upload, total number of views, likes, dislikes and comments, and duration were recorded.

Video sources and lecturer types

The source of videos was categorized as universities/physicians group, health information websites, advertisement, and patients. Lecturers were classified as physicians, healthcare professionals, patients, and external narrator.

Video sources and lecturer types

The videos were classified according to the target audience being healthcare professionals, or patients.

Assessment of the quality of the comprehensiveness

In order to evaluate the quality of the comprehensiveness of the EGD videos, a scoring system called the EGD Data Quality Score (EGD-DQS) was created based on an upper endoscopy education video from the website of the American Society of Gastrointestinal Endoscopy [17]. Scoring was carried out by giving +1 point for meeting the criterion in each item shown in Table 1, and 1 point was subtracted for each misleading information. The scoring method was inspired from and has been used in a similar study found in medical literature search on YouTube [13].

Assessment of the quality

A five-point validated scale, the Global Quality Score (GQS), which was developed as an evaluation tool for website resources, was also used to assess the flow and ease of use of the information presented online and the quality of the videos [18]. The videos were graded according to the criteria given in Table 2.

Assessment of reliability

To assess the reliability of the EGD videos, a five-point DISCERN tool modified by Singh et al. [19] from the original

scoring system was used (Table 2). One point was given for each "yes" response.

Table 1: EGD Data Quality Score Criteria (EGD-DQS)

Useful Information
1) Includes the definition of the EGD procedure (1 point); e.g., EGD is the process of viewing the section starting from the esophagus to the initial part of the stomach and small intestines by entering through the mouth with a thin and flexible imaging device with a camera with a light at the end.
2) Includes information that EGD is the best screening method to diagnose the gastric cancer (1 point).
3) Cites the prevalence of EGD (3,000 esophagogastroduodenoscopies are performed annually; prevalence: 3,000/250,000) (1 point).
4) Defines a gastroscope as a thin, bendable imaging device with a lighted camera on its end (1 point).
5) Gives the yearly estimation rate of gastric cancer (1 point).
6) Defines indications for EGD for diagnosis and treatment (1 point if it refers to general indications, including gastric cancer, esophageal cancer, polyp, web, diverticulum, gastritis, esophagitis, upper GIS bleeding, unexplained abdominal pain, and unexplained weight loss)
7) Includes information that EGD is the only method that allows both the diagnosis and excision of precancerous stomach lesions that are not yet detectable by a biopsy (1 point).
8) Includes information that eating or drinking should be stopped six hours before the procedure (1 point).
9) Informs the patient about how to continue the use of regular prescription drugs before the procedure (1 point).
10) States that informed consent will be obtained after explaining the benefits and risks (1 point).
11) Explains the general steps of the procedure (1 point).
12) Includes information that the procedure will be performed under intravenous sedation (1 point).
13) Encourages the patient to direct questions about the procedure to health-care professionals (1 point).
14) Includes information that the procedure takes approximately 30 minutes (1 point).
15) Lists the possible complications of the procedure (1 point if it refers to the frequency of complications, including gas, bloating, nausea, perforation, bleeding, and drug reaction).
16) Mentions that the duration of close follow-up after the procedure is approximately 30 minutes (1 point).
17) Describes what biopsy is and informs that it may take one week to obtain the results of the biopsy (1 point).
18) Includes information that the patient should not go to work or drive on the day of the procedure (1 point).
19) Mentions that the patient will need a companion on the day of the procedure (1 point).
20) Mentions that the patient can return to normal life the following day (1 point).
Misleading Information
1 point is deducted for each wrong information given below.
1) EGD is an unnecessary procedure.
2) EGD increases the risk of gastric cancer.
3) EGD does not prevent gastric cancer.
4) There is no supporting scientific evidence about EGD.
5) EGD should not be performed in asymptomatic patients.
6) EGD is a high-risk transaction.
7) EGD has a high mortality rate.
8) EGD is an expensive procedure.
9) EGD is very troublesome and is performed without sedation.
10) EGD is only performed for diagnostic purposes.

Table 2: Assessment tool for the Reliability and Global Quality Scores of EGD Videos on YouTube

Reliability Score Criteria
1. Can clear and concise information be obtained from the video and is the video understandable enough?
2. Are the sources on which the video is based (current studies or doctors) specified?
3. Is the information provided consistent and objective?
4. Are additional sources of information listed for patient reference?
5. Does the video report contradictory or ambiguous aspects?
Global Quality Score Criteria
1. Poor quality, it is unlikely to be of any benefit to patients.
2. Generally poor quality, some information is present whereas many important topics are missing, of minimal use to patients.
3. Moderate quality, some important information present, but other topics missing, somewhat useful for patients.
4. Good quality, most important information is adequately discussed, useful for patients.
5. Excellent quality, highly useful for patients.

One of the investigators is a general surgeon specialist (P.B.) certified with gastrointestinal endoscopy proficiency, and the other is an internal medicine specialist (D.A.) who has a special interest in endoscopic procedures. These two reviewers evaluated, classified and scored the videos independently and blindly. In case of a conflict between the two reviewers, a third internal medicine specialist (F.A.) evaluated the video and scored it. The study was conducted without the approval of the ethics committee as it was performed by evaluating publicly available videos and it was done without human and/or animal participants.

Statistical analysis

The data were collected and transferred to Microsoft Excel program. The Shapiro-Wilk test was used to evaluate the normality of data. Descriptive analyses were presented as median [minimum-maximum] and percentages (%) for continuous variables. Categorical variables are expressed as numbers and percentages. The Mann-Whitney U and Kruskal-Wallis tests were used for all variables that were not normally distributed in the analysis. The chi-square test was used for the analysis of categorical variables. A *P*-value of 0.05 or less was considered significant. Inter-rater agreement was determined using Cohen's kappa score. Data analyses were tested using IBM Statistical Package for the Social Sciences (SPSS) v. 26.0.

Results

We analyzed the videos returned by a search conducted on YouTube using the keywords "esophagogastroduodenoscopy" and "upper GI endoscopy". The first ten pages for the terms were evaluated, and a total of 200 videos were included in the study. After the elimination 105 videos due to the irrelevant or duplicated content, vocalization in a language other than English, or containing only animations without sound, 95 videos with a total of 17,135,764 views and a total duration of 908.58 minutes were found to be worthy for further analysis.

Among the videos enrolled in the study, the most common lecturer was physicians (40%) whereas universities/health-care professional group was the most common source of video upload (36%). Forty-six percent of the target audience consisted of patients, and the remaining 54% was health-care professionals (Table 3). When the videos were compared according to the type of lecturer, the reliability and misleading information scores were the two parameters showing a significant difference between the groups. The reliability score of the videos presented by physicians was significantly higher compared to those presented by other healthcare professionals, patients, and external narrators (P=0.044, P=0.001, and P<0.001, respectively). The misleading information scores were found to be significantly lower in the external narrator and physicians group compared to healthcare professionals and patients (P<0.05, for all) (Table 4). All the remaining parameters, including video length, time elapsed since upload, number of total views, likes, dislikes, comments, subscribers and daily views, GQS, EGD-DQS, and useful information showed no significant relationship between lecturer groups (Table 4).

Table 3: Frequency tables

Variables	n (%)
Lecturer Type	
Physicians	38 (40.00%)
Health professionals	13 (13.68%)
Individuals	22 (23.16%)
External narrators	22 (23.16%)
Upload Source	
Universities/physicians	34 (35.79%)
Health information websites	31 (32.63%)
Advertisements	19 (20.00%)
Patients	11 (11.58%)
Target Audience	
Patients	44 (46.32%)
Unclassified	51 (53.68%)
Total	95 (100.00%)

According to the results of the chi-square test, there was no significant relationship between the lecturer group and target audience whereas there was a statistically significant difference in terms of the upload source between the different lecturer

groups (P<0.001) (Table 4). The kappa statistic for inter-observer agreement was 0.87 (CI: 0.71-1.00).

Table 4: Significant differences according to the lecturer type variable (Kruskal-Wallis and chi-square tests)

	Lecturer type				
	Physicians	Healthcare professionals	Patients	External narrators	*P*-value
Length***	513.5 (368.25)	562 (371)	502.5 (319.25)	444 (411.5)	0.881
Total Views***	34445 (163179)	5634 (16046)	12211 (51417)	16099.5 (55141.5)	0.142
Duration***	43 (42.5)	17 (56)	48.5 (45)	34.5 (48.5)	0.581
Likes***	222.5 (1203.75)	54 (264.5)	258 (1198)	69 (402)	0.263
Dislikes***	16 (62.75)	1 (30.5)	11.5 (56.25)	7.5 (30.25)	0.345
Comments***	13 (81)	4 (17)	21 (52.25)	25 (77)	0.255
Subscribers***	6040 (12985.75)	1540 (11503.5)	11550 (17035)	3620 (11795)	0.157
Daily Views***	15.35 (48.09)	12.77 (15.63)	19.24 (54.59)	14.21 (36.31)	0.766
Reliability Score***	4 (1)	3 (1)	3 (1)	3 (1)	<0.001 *
EGD-DQS***	15.5 (5.25)	13 (3)	14 (3.25)	14 (3)	0.070
GQS***	4 (1)	3 (1)	3 (1)	4 (1)	0.096
Useful information***	16 (4)	16 (3)	14.5 (3.25)	15 (2.25)	0.089
Misleading information***	0 (1)	1 (0.5)	1 (1.25)	0 (1)	0.017*
Upload Source n (%)**					
Universities/physicians	22 (57.89%)	4 (30.77%)	1 (4.55%)	7 (31.82%)	<0.001 *
Health information websites	11 (28.95%)	5 (38.46%)	4 (18.18%)	11 (50%)	
Advertisements	5 (13.16%)	4 (30.77%)	6 (27.27%)	4 (18.18%)	
Patients	0 (0%)	0 (0%)	11 (50%)	0 (0%)	
Target Audience n (%)**					
Patients	19 (50%)	7 (53.85%)	9 (40.91%)	9 (40.91%)	0.769
Unclassified	19 (50%)	6 (46.15%)	13 (59.09%)	13 (59.09%)	

* Statistically significant at the 0.05 level, ** Chi-square test [n (%)], *** Kruskal-Wallis test [Median (interquartile range)]

The number of dislikes, reliability score, GQS, EGD-DQS, and useful information variables showed a statistically significant difference when compared according to the upload source. The number of dislikes significantly differed between the advertisement and universities/physicians group (P=0.006), as well as between the advertisement and health information websites groups (P=0.007). The number of dislikes in the advertisement group was statistically significantly lower compared to the other groups (P=0.027). The reliability score was also higher in the universities/physicians group compared to the health information websites, advertisement and patients (P=0.029, P=0.001 and P=0.006, respectively). The EGD-DQS scores were significantly higher in the universities/physicians group compared to health information websites, advertisement, and patients (P=0.026, P=0.002 and P=0.026, respectively). The GQS score was also statistically significantly higher in the universities/physicians group compared to the health information websites, advertisement, and patients (P=0.001, P<0.001 and P=0.001, respectively). Lastly, useful information was significantly higher in the universities/physicians group compared to the remaining upload sources (P=0.029 for health information websites, P=0.003 for advertisements, and P=0.005 for patients) (Table 5).

According to the results of the chi-square test, there was no statistically significant relationship between the upload source and target audience (P=0.559); however, a significant relationship was observed between the upload source and lecturer (P<0.001) (Table 5).

Table 5: Significant differences according to the upload source (Kruskal-Wallis and chi-square tests)

	Upload Source				
	Universities/ physicians	Health information websites	AD	Patients	*P*-value
Length***	563 (485.25)	555 (380)	451 (319)	454 (285)	0.483
Total Views***	23444 (360546)	21343 (63055)	5458 (44015)	12546 (61129)	0.197
Duration***	42 (47.75)	51 (48)	36 (43)	37 (48)	0.393
Likes***	200 (735)	221 (827)	45 (60)	438 (2177)	0.091
Dislikes***	14.5 (55.25)	12 (54)	1 (12)	12 (32)	0.027*
Comments***	14.5 (59.75)	32 (42)	5 (19)	33 (53)	0.190
Subscribers***	8020 (16599.25)	3700 (11862)	1760 (4774)	12100 (12530)	0.234
Daily Views***	15.24 (43.44)	16.32 (62.66)	5.05 (21.06)	30.92 (90.84)	0.122
Reliability Score***	4 (1)	3 (1)	3 (2)	3 (0)	0.003*
EGD-DQS***	16 (3.5)	14 (4)	13 (2)	14 (3)	0.008*
GQS***	4 (0)	3 (1)	3 (1)	3 (1)	<0.001*
Useful information***	16 (3)	15 (3)	14 (3)	14 (3)	0.004*
Misleading information***	0 (1)	1 (1)	1 (2)	0 (1)	0.531
Lecturer Type**					
Physicians	22 (64.71%)	11 (35.48%)	5 (26.32%)	0 (0%)	<0.001*
Health professionals	4 (11.76%)	5 (16.13%)	4 (21.05%)	0 (0%)	
Individuals	1 (2.94%)	4 (12.9%)	6 (31.58%)	11 (100%)	
External voice	7 (20.59%)	11 (35.48%)	4 (21.05%)	0 (0%)	
Target Audience**					
Patients	19 (55.88%)	13 (41.94%)	8 (42.11%)	4 (36.36%)	0.559
Unclassified	15 (44.12%)	18 (58.06%)	11 (57.89%)	7 (63.64%)	

AD: Advertisements, * Statistically significant at the 0.05 level, ** Chi-square test [n (%)], *** Kruskal-Wallis test [Median (interquartile range)]

Discussion

EGD is the most effective method in the diagnosis, treatment and screening of upper gastrointestinal system diseases [21]. Although EGD does not require much patient experience and knowledge during preparation and procedure, providing EGD candidates with necessary information before the procedure is very important in order to reduce their associated concerns [22]. The preparation stages, purpose, and problems that may arise in relation to the procedure should be shared with the patient. Although this is usually undertaken by physicians, most patients prefer to obtain further detailed information and access visual material on how the procedure is performed. Even information forms prepared for this purpose are sometimes insufficient, and therefore patients refer to social media and other online platforms as a source of information satisfaction [23, 24]. One of the sources used by patients to access information about EGD is YouTube. Although the contribution of an open-access platform to easy access to information is undeniable, there is also the inevitable catastrophic effect of an information provider lacking content and accuracy control. A study conducted to determine the level of health literacy of the adult population in Turkey found that 64.6% of our society is in the category of insufficient health literacy [25, 26]. Considering that individuals have different health literacy levels, it may be difficult for some to receive the same benefit from these videos. The low level of health literacy brings along concerns that patients may not be able to access accurate and high-quality information or understand what is presented even if they have such access.

In this study, we defined, analyzed and evaluated videos on EGD posted on YouTube. The total duration of the 95 videos evaluated was 908.58 minutes, and they had more than 17 million views. While evaluating the information quality of YouTube videos about EGD, we used a method similar to those employed in previous studies examining videos on various diseases and procedures [6-16]. As a result of the general analysis, we found that the videos had been mostly uploaded to YouTube by universities/physicians group (36%), and this group had the highest reliability, comprehensiveness, and quality. This led us to the conclusion that You Tube is a powerful source of information on EGD.

We concluded that the video source of upload was associated with reliability, comprehensiveness, and quality. The videos uploaded by universities/physicians were not only the most common video sources, but also had the highest EGD-DQS and GQS scores. These results are consistent with those of a previous study evaluating the colonoscopy videos which also had highest DQS, and GQS, whereas, in that study, the mean DQS of videos ⁿuploaded by professional healthcare organizations or physicians were found to be significantly lower than the upper limit [13]. This difference may be attributed to both the preparatory stage of colonoscopy and the procedure itself being more complicated than EGD. Accordingly, the total DQS was determined as 40 in the colonoscopy study since the narrators had more information to communicate to the audience. In the colonoscopy study, the second most common upload source group being patients or their relatives and the presence of videos posted by alternative medical providers may have decreased the DQS value obtained from all sources. In our study, videos in which patients shared their personal experiences ranked last as the upload source, and the sample did not contain any video uploaded by an alternative medical provider.

The most common video sources in our study were those provided by universities/physicians. However, given that these academic sources constituted one-third of the total views, we think that they are not sufficiently represented. In particular, we believe that editing videos describing interventional and stepwise processes by physicians or health care professionals will reduce misinformation In almost all of the YouTube studies, in which high reliability and accurate information were determined in the analysis of such stepwise processes, the narrator and video installer have been found as a physician or health care Professional [9, 16]. In another two studies in which videos about bowel preparation performed before colonoscopy were examined, similar results were demonstrated. In those studies, bowel preparation videos posted on YouTube by medical sources were reported to be high quality content videos [14, 15].

Description of step by step procedures, either face-to-face or on social media platforms, by different sources in health-care practices may be confusing for the targeted population. The knowledge about these stepwise procedures provided by either patients or health-care providers may cause difficulties in both understanding and keeping in mind the subsequent stages of a real-time application for individuals who have no idea or past experience about the subject [9, 12, 14, 16]. In the study assessing the YouTube videos about the information for colonoscopy bowel preparation, Basch et al. [14] reported that the accuracy of knowledge about sequencing of process steps had an indisputable positive impact on mindfulness-based learning of the target individuals. Correct and ordered information has a direct positive correlation with information retention; precisely for this reason the messages given by videos uploaded to internet platforms should contain information totally deprived of sequencing mistakes. In addition, videos containing sequencing and related logic errors may cause patients to worry about the planned procedure itself and lead individuals to take a biased attitude towards the procedure to be applied [16]. Specifically, a strict conformation while describing the steps that serve the purpose enables people to approach the subject comfortably and rationally by removing the question marks in their minds. In similar previous studies, it has been shown that the rates of reliability and useful information are undeniably high in properly designed videos with high DQS that healthcare professionals and physicians upload to social media platforms [8, 12, 16]. In the present study, we obtained similar results reaching higher reliability and EGD-DQS scores in gastroscopy videos uploaded by healthcare professionals and physicians describing the process more clearly and sequentially compared to other groups. Indeed, many healthcare professionals believe that at least websites should be evaluated for accuracy and argue that recommendations are needed for the creation of easy websites that patients can understand.

We consider that academic sources, which provide accurate and unbiased material and produce and upload informative and instructional videos to YouTube, should aim to not only inform but also attract viewers. When it comes to popularity, although statistically insignificant, the present study showed that the videos in which the patients talked about their experiences received more likes and comments, and they also had more subscribers. This finding is similar to the result of a study evaluating hypertension videos on YouTube [7]. We hypothesized that the reason for the low popularity of videos uploaded by academic sources may be the frequent use of medical terminology in academic videos, which does not attract the attention of the viewers and results in them losing interest after a while. Additionally, since video length is significantly associated with comprehensiveness, comprehensive videos not being watched from the beginning to the end may have led to this result. Therefore, we believe that a balance must be established between sophistication and viewer attention spans, and healthcare professionals need to ensure that the videos they post online are prepared in a simple language that is clear for everyone.

In our study, we found that the number of dislikes and that of comments for the videos uploaded for commercial purposes were very low compared to the other upload source groups. The durations of commercial videos were relatively shorter, and their EGD-DQS values were lower than the remaining groups. The lower number of dislikes for these videos may be because the viewers, who considered the content presented to be inadequate, chose to directly refer to other videos, without clicking on the dislike button or watching the videos to the end.

Limitations

There were some limitations to our study. First, only videos narrated in English language were evaluated. The lack of videos prepared in our own language can cause misunderstandings and unnecessary worries on patient populations who do not speak or know little foreign languages. In addition, since YouTube is a dynamic platform that is constantly changing with new videos being posted and their popularity shifting, the number of video views and search rankings may differ within days.

Conclusions

YouTube seems as a powerful source of information on EGD and we concluded that this social media platform is a reliable source for quality information about the EGD procedure.

However, although the most common video sources were professional health care providers, they may not be sufficiently represented on YouTube since these academic sources constituted only one-third of the total views. Although it seems technically difficult to audit all the information published by a constantly renewed source of information, it would be appropriate to at least periodically evaluate the most popular and most shared videos and remove scientifically inaccurate information. Especially in countries where patient education is insufficient, we believe that it will be an important step in terms of remote patient education for the relevant institutions to present patient educational videos to the patient by preparing them in corporate technique and their own language. Ideally, physicians should direct patients to online resources that provide accurate and reliable information in their native language, and the goal should be achieved by ensuring the involvement of patients in both the diagnosis and treatment stages.

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Risk factors determining bile leakage after multiple liver hydatid cyst surgery

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The study was approved by the Health Sciences University Dr Abdurrahman Yurtarslan Oncology Health Application and Research Center Clinical Research Ethics Committee .(Ethics Committee approval number:2022-03/1740)
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Abstract

Background/Aim: Biliary leaks are the main source of morbidity after liver hydatid cyst surgery. Many identified factors have been examined in predicting biliary leaks. The aim of this study was to determine the postoperative bile leakage rate and predictive factors affecting bile leakage in multiple liver hydatid cysts.
Method: In our retrospective cohort study, the data of 130 patients who underwent multiple liver hydatid surgery in our clinic between January 2007 and November 2013 were analyzed.
Results: In the 130 patients with multiple cysts, 323 hydatid cysts were detected. The number of cysts was 2 in 65.4% of the patients, and 3 or more in 34.6% of the patients. The postoperative bile leakage rate was 19.2%. According to the univariate analyses, during the preoperative period, the presence of jaundice, fever, leukocytosis, eosinophilia, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, alkaline phosphatase, and direct bilirubin increase, the largest cyst being located in the perihilar region, the mean diameter of the cyst, the diameter of the largest cyst, biliary tract dilatation on the preoperative images, and infection were associated with increased postoperative bile leakage. In the multivariate analyses, eosinophilia and biliary tract dilatation on the preoperative images were found to be independent risk factors for postoperative bile leakage.
Conclusion: In this study, the most determining factors for bile leakage after multiple liver hydatid cyst surgery were a high eosinophil rate and the presence of dilatation in the biliary tract on the preoperative radiological images.

Keywords: Liver, Hydatid cyst, Bile leak

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Introduction

Hydatid cyst is a zoonotic disease caused by infection with the larval form of *Echinococcus granulosus* and can affect almost all organs in the body but usually affects the liver (50–70%) followed by the lungs [1, 2]. Hydatid cyst is, above all, a public health problem and a preventable disease and is among the 17 neglected tropical diseases, according to the World Health Organization (WHO). It reportedly affects more than a million people around the world and results in three billion dollars in medical costs each year. Turkey is among the highly endemic regions where over 50/100,000 individuals develop hydatid cysts annually [3]. It is still a major public health problem in many parts of the world due to infected dogs, unregulated animal slaughter, and hygiene issues. Hydatid disease is endemic in many parts of the world and is quite common in countries engaged in agriculture and animal husbandry.

Currently, the preferred treatment of liver hydatid cysts is surgery. Treatment primarily aims to inactivate the parasite, empty the cystic cavity and prevent contamination, and to obliterate the remaining cavity by eliminating the germinal layer and all living components [4, 5].These principles apply to all types of surgical treatment options.

The most common complication of liver hydatid cysts is cysto-biliary communication (CBC), which was reported at a rate between 13% and 37% in the literature [6]. After the relationship of the cyst cavity with the biliary system, a clinical spectrum of disease can be seen, ranging from biliary symptoms to systemic findings. This relationship can be in the form of a major or minor relationship. A major CBC is usually associated with jaundice and cholangitis, while a minor CBC is usually asymptomatic and presents with postoperative bile leakage and the preoperative diagnosis is difficult. The postoperative biliary complication rate reported in the literature was between 2.6% and 28.6% [7]. The risk factors of this complication, which is the main source of morbidity after liver hydatid cyst surgery, have not been well defined in studies conducted to date. If these risk factors can be determined well, the biliary complication rate can be reduced by additional interventions and treatments during the preoperative and peroperative periods.

In a previous study that included only solitary liver hydatid cysts and excluded multiple cysts, we found that cyst diameter, perihilar localization, ALP elevation, and World Health Organization-International Working Groups of Echinococcosis (WHO-IWGE) stage was associated with postoperative biliary leakage [8].

Multiple cysts make up 29-38% of liver hydatid cysts [9, 10]. Studies reported that the number of cysts did not affect postoperative bile leakage but did not evaluate the differences in the identified risk factors in cases of multiple cysts.

The aim of this study was to determine the rate of biliary leakage in multiple liver hydatid cysts and the risk factors affecting it.

Materials and methods

In our clinic, a total of 370 patients underwent surgical treatment for liver hydatid cyst between January 2007 and November 2013. As per the purpose of this study, 240 patients with radical resection and/or operated for solitary cyst were excluded. Additionally, 130 patients who underwent multiple liver hydatid cyst surgery were included in the study. The data were obtained by retrospective analysis of the prospective patient records.

Preoperative Evaluation

Patients presenting with asymptomatic or different symptoms were recorded. Ultrasonography (USG), computed tomography, magnetic resonance imaging, or magnetic resonance cholangiopancreatography were used as the imaging methods for diagnosis, and the indirect hemagglutination test was used as serological test. The leukocyte count and eosinophil ratio were recorded as the hematological parameters and alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and direct bilirubin were recorded as the biochemical parameters.

Peroperative evaluation

After the general abdominal exploration, preparations were made for the hydatid cyst. In some cysts with difficult localization, peroperative USG was performed and the location of the cyst was determined. Compresses that had been soaked scolicidal agent (combination of 0.5% cetrimide and 0.05% chlorhexidine; Savlex, Drogsan, Ankara, Turkey) were placed around the cyst and then, cyst puncture was performed. Cyst aspiration was continued until the fluid inside of the cyst was had all been removed. If the cyst content was clear, a scolicidal agent was inserted inside of the cyst cavity and left therefor 10min. A scolicidal agent was not given if the cyst content was biliary or purulent. After performing the cystotomy, the cyst contents were removed along with the germinative membrane, very carefully, without contaminating the environment. After the cyst pouch had been rinsed again with scolicidal material, it was washed with 0.9% NaCl. If there was a free cyst wall, it was removed as a partial cystectomy. Continuous 2/0 absorbable sutures were used at the edges of the cyst in the event of hemostasis and bile leakage. When a cystobiliary relationship was detected, it was closed with absorbable sutures. Next, a cavity check was performed, depending on the preference of the surgeon, comprising capitonnage, introflection, or drainage. The operation was ended by placing drains in all of the patients according to the location of the cysts.

Postoperative follow-up

Oral nutrition was given to all of the patients on the first postoperative day. The drain was kept in for at least 3 days, and removed if the drainage amount was less than 30 cc and there was no bile. If the drainage content was biliary, it was considered as a biliary leak. Endoscopic retrograde cholangiopancreatography (ERCP) was performed on patients whose bile leakage lasted for longer than 10 days. Sphincterotomy, nasobiliary drain, or stent placement was performed according to these findings. Percutaneous drainage was performed and antibiotic treatment was initiated in patients with intraabdominal collections or abscesses. Despite all of these attempts, relaparotomy was performed in cases whose intraabdominal sepsis findings could not be controlled. All morbidities (Clavien&Dindo classification) and mortality, if any, that developed in the postoperative period, were recorded.

Identified risk factors

Potential risk factors for the cysts and patients were determined based on the literature information and clinical experience. Accordingly, risk factors for bile leakage after hydatid cyst surgery were determined as: age, gender, presence of recurrence, number of cysts, diameters of cysts, presence of cysts in perihilar or peripheral location, hydatid cyst classification of the WHO-IWGE, surgical procedures performed (omentopexy, introflexion, and external drainage), cyst contents (bile/infected and clear), presence of symptoms (abdominal pain, fever, and jaundice), and laboratory tests (leukocyte count, eosinophil rate, ALT, AST, ALP, GGT, and direct bilirubin). Cyst locations were defined according to preoperative imaging methods and peroperative findings. If the cyst was associated with more than one segment, the segment where it was dominant was considered the segment localization of that cyst. The cyst diameter was recorded based to the preoperative radiological imaging methods used. The nature of the cyst contents was decided according to the first cyst aspiration during surgery. The liver segmental anatomy of Couniad and Bizmuth was used while determining the perihilar and peripherally located cyst groups. Accordingly, in this study: segments I, III, IVb, and V were considered as perihilar segments, while segments II, IVa, VI, VII, and VIII were considered as peripheral segments.

Statistical analysis

All patient data were obtained from the forms prepared for this study. Statistical evaluation of the data obtained was performed using SPSS Statistics for Windows 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were shown as the mean ± standard deviation (minimum-maximum) for continuous variables, and as the number of cases and percentage (%) for the categorical variables. In the evaluations, the chisquare and Fisher exact tests were used for comparisons of the categorical variables related to bile leakage, and the t test was used for the independent samples indicated by measurement. In addition, univariate and multivariate logistic regression analyses were used to determine the factors affecting bile leakage. Statistical significance was accepted as $P<0.05$. For the multivariate logistic regression analysis, the limit for including variables in the model was accepted as 0.10. The odds ratio (OR) and 95% confidence interval (CI) for each variable were calculated.

Results

In the 130 patients with multiple cysts,323 hydatid cysts were detected. The postoperative bile leakage rate was 19.2%. Of the patients,61.5% were male and 38.5% were female. The rate of bile leakage was found to be higher in the males than in the females, but it was not statistically significant ($P= 0.275$). The mean age was 47.2 (17.7)years in the group with bile leakage and 42.5 (.1)years in the group without. The difference was not statistically significant ($P=0.224$). The rate of bile leakage was higher in the symptomatic patients than in the asymptomatic patients (20% vs. 10%,$P=0.390$). When evaluated according to the laboratory results, the leukocyte count and eosinophil rates were found to be significantly higher in the patients with bile leakage ($P=0.011$ and$P<0.001$, respectively). ALT, AST, ALP, GGT and direct bilirubin levels were also found to be statistically significantly higher in the patients with bile leakage ($P=0.002$, $P=0.017$, $P=0.03$, $P<0.001$, and $P<0.001$, respectively). With regards to the ALP level, when it is between 1 and 2 times that of the normal level, bile leakage increases by 1.2 times; when it is between 2 and 3 times, the leakage rate increases by 4.6 times; and when it is 5 times or more, the risk of bile leakage increases by 7.4 times. With each 1 mg/dL increase in the direct bilirubin level, bile leakage rate increases by 3.2 times. In the current study, bile leakage was detected as 7 times more than normal in patients with increased direct bilirubin levels. With regards to the GGT level, when it is between 1 and 2 times that of the normal level, the bile leakage rate increases by 3.7 times; when it is between 2 and 3 times, the leakage rate increases by 4.9 times; and when it is 3 or more, the risk of bile leakage increases by 15.7 times.

The number of cysts was 2in 65.4% of the patients and3or more in 34.6% of the patients. The bile leakage rate was found as 18.8% in the patients with 2cysts, and 20% in the patients with 3or more cysts, but the difference was not statistically significant ($P=0.871$). When all of the cysts were taken into account, the mean cyst diameter was 6.9 (3.2) cm. The mean diameter of the cysts was 7.9 (3.7) cm in the group with bile leakage, while it was 6.7 (3.04) cm in the group without. The difference was found to be statistically significant ($P=0.008$). When calculated only for the diameter of the largest cyst, the mean diameter of the cysts was 10.4 (3.5) cm in the group with bile leakage, while it was 8.6 (3.1) cm in the group without, and the difference was statistically significant again ($P=0.012$). Moreover, 56.9% of the patients had perihilar cysts, while 43.1% had peripheral localized cysts. While the bile leakage rate was 23% in the group with perihilar cysts, it was 14.3% in the group with peripherally located cysts. The bile leakage rate was found to be higher in the group with perihilar cysts, but it was not statistically significant ($P=0.213$). However, the bile leakage rate was found as 35.7% in patients where the largest cyst was located in the perihilar region, while it was 14.7% where the largest cyst was found to be in the peripheral location. The difference was statistically significant. ($P=0.012$). The location of the largest cyst according to the segment level and bile leakage rates are given in Table 1.

Table 1: Bile leakage rates by segment location of the largest cyst

Location	With bile leak	Without bile leak	Total
Segment I	1 (100%)	0 (0%)	1 (0.8%)
Segment II	0 (0%)	13 (100%)	13 (10%)
Segment III	1 (14.3%)	6 (85.7%)	7 (5.4%)
Segment IVa	1 (20%)	4 (80%)	5 (3.8%)
Segment IVb	4 (50%)	4 (50%)	8 (6.2%)
Segment V	4 (33.3%)	8 (66.7%)	12 (9.2%)
Segment VI	5 (27.8%)	13 (77.2%)	18 (13.8%)
Segment VII	3 (8.1%)	34 (91.9%)	37(28.5%)
Segment VIII	6 (20.7%)	23 (79.3%)	29 (22.3%)
Total	25 (19.2%)	105 (80.8%)	130 (100%)

In the patient group with bile or infected cyst contents, postoperative bile leakage rate was found to be higher (40%) than the clear group (8.2%), and the difference was statistically significant ($P<0.001$).When the bile ducts were evaluated based on the preoperative images, the bile leakage rates were 7.4% in the patients without biliary duct dilatation (BDD), 34.8% in the patients with localized bile duct dilatation, 77.8% in patients with left or right intrahepatic biliary duct (IHBD) dilatation, and 100% in the patients with diffuse IHBD and extrahepatic BDD (EHBD). When the groups were compared, as the bile duct

dilatation increased, the rate of biliary leakage increased (P<0.001).

Herein, the rate of CBC was 36.9%. In patients with CBC, the opening was closed by primary suturing. Postoperative bile leakage developed in 41.7% of these patients. However, postoperative bile leakage was prevented in 58.3% with the repair. The postoperative bile leakage rate was found as 6.1% in patients without peroperative CBC.

According to the univariate analysis, age, gender, and number of cysts were not associated with bile leakage. In the preoperative period, the presence of jaundice or fever, leukocytosis, eosinophilia, increase in AST, ALT, GGT, ALP, and direct bilirubin levels, the largest cyst being located in the perihilar region, mean cyst diameter, the largest cyst diameter, BDD on the preoperative images, and infected or bile contents of the cyst were associated with increased postoperative bile leakage. The univariate statistical analysis results of the patient risk factors determined for bile leakage after multiple liver hydatid cyst surgery are given in Table 2, and the factors for cysts are given in Table 3. In the multivariate analyses, eosinophilia and BDD on the preoperative images were found to be independent risk factors for postoperative bile leakage (Table 4).

Table 2: Univariate statistical analysis results of patient risk factors

Risk Factors	Leakage (–) n (%)		Leakage (+) n (%)		Total n	*P*-value
Age (year), mean	42.5 (15.1)		47.2 (17.7)			0.224
	105	(80.8%)	25	(19.2%)	130	
Gender						
Male	38	(76.0%)	12	(24.0%)	50	0.275
Female	67	(83.8%)	13	(16.2%)	80	
Symptom						
Yes	96	(80.0%)	24	(20.0%)	120	0.390
No	9	(90.0%)	1	(10.0%)	10	
Pain						
Yes	94	(80.3%)	23	(19.7%)	117	0.526
No	11	(84.6%)	2	(15.4%)	13	
Jaundice						
Yes	1	(10.0%)	9	(90.0)	10	<0.001
No	104	(86.7%)	16	(13.3%)	120	
Fever						
Yes	4	(33.3%)	8	(66.7%)	12	<0.001
No	100	(85.5%)	17	(14.5%)	117	
Eosinophilia						
Yes	18	(54.5%)	15	(45.5%)		<0.001
No	87	(89.7%)	10	(10.3%)		
AST level(U/L)						
Normal	90	(84.9%)	16	(15.1%)	106	0.017
High	15	(62.5%)	9	(37.5%)	24	
ALT level (U/L)						
Normal	86	(86.9%)	13	(13.1%)	99	0.002
High	19	(61.3%)	12	(38.7%)	31	
GGT value (U/L)						
Normal (≤61)	77	(91.7%)	7	(8.3%)	84	<0.001
Up to 2 times(62–122)	12	(75.0%)	4	(25.0%)	16	
More than 2times (>122)	16	(53.3%)	14	(46.7%)	30	
ALP values(U/L)						
Normal (0-40)	52	(88.1%)	7	(11.9%)	59	0.030
Up to 2 times (41–80)	31	(86.1%)	5	(13.9%)	36	
2–3 times (81–120)	13	(61.9%)	8	(38.1%)	21	
3–5 times (121–200)	7	(70.0%)	3	(30.0%)	10	
More than 5 times (≥201)	2	(50%)	2	(50%)	4	
Direct bilirubin						
Normal	89	(98.0%)	11	(11.0%)	100	<0.001
High	16	(53.3%)	14	(46.7%)	30	

Table 3: Univariate analysis results of factors related to cysts

Factors	Leakage (–) n (%)		Leakage(+) n (%)		Total n	*P*-value
Number of cysts						
2	69	(81.2%)	16	(18.8%)	85	0.871
3 or more	36	(80.0%)	9	(20.0%)	45	
Perihilar location (any of the cysts)						
Yes	57	(77.0%)	17	(23.0%)	74	0.213
No	48	(85.7%)	8	(14.3%)	56	
Diameter of the largest cyst (mean)	105	8.6 (3.1) (80.8%)	25	10.4 (3.5) (19.2%)	130	0.012
Location of largest cyst						
Perihilar	18	(64.3%)	10	(35.7%)	28	0.012
Peripheral	87	(85.3%)	15	(14.7%)	102	
Cyst content						<0.001
Bile/infected	27	(60.0%)	18	(40.0%)	45	
Clear	78	(91.8%)	7	(8.2%)	85	
BDD on imaging						
No BDD	88	(92.6%)	7	(7.4%)	95	<0.001
Localized BDD	15	(65.2%)	8	(34.8%)	23	
Right or left IHBD dilatation	2	(22.2%)	7	(77.8%)	9	
IHBD + EHBD dilatation	0	(0%)	3	(100%)	3	

BDD: bile duct dilatation, IHBD: intra hepatic bile duct, EHBD: extra hepatic bile duct.

Table 4: Risk factors detected for bile leakage in the multivariate logistic regression model

Variables	Odds ratio	*P*-value	95% CI	
			Lower limit	Upper limit
Eosinophilia	4.935	0.006	1.577	15.440
BDD on imaging				
Localized BDD	5.546	0.006	1.629	18.889
IHBD ± EHBD dilatation	48.735	0.001	8.269	287.217

The rate of intraoperative complications was 4.6%, including diaphragm injury (n=3), small intestine injury (n=1), hepatic vein injury (n=1), and hemorrhage (n=1).

Postoperative complication rate was 33.1%, the most common being bile leakage (19.2%).The remaining postoperative other complications are presented in Table 5 according to Clavien&Dindo classification.

Table 5: Clavien&Dindo classification of other complications following hydatid cyst surgery

Clavien&Dindo category *	n	%
Grade I	10	7,7
Grade II	17	13,1
Grade III	7	5,4
Grade IV	2	1,5
Grade V	2	1,5

*Some patients developed multiple complications.

Bile leakage stopped within 10 days in 7 patients and lasted more than 10 days in 18 patients. The mean duration of bile leakage was17.4 (9.9) days (range 5–45).Bile leakage was managed with medical therapy in 44% of the patients and with additional intervention in 56%.2 patients with postoperative bile leakage underwent relaparotomy due to uncontrolled biliary peritonitis. Treatments applied to patients with bile leakage are presented in Table 6.

Table 6: Treatment methods for bile leakage

Treatment of complication	n	%
Only medical follow-up	11	44
Only ERCP	7	28
Only intervention	1	4
ERCP+intervention	4	16
ERCP+intervention+surgery	2	8
Total	25	100

Mean length of hospital stay was 20.2 (9.2) days and 6.6 (5.8) days for patients with and without bile leakage, respectively.

Mortality rate was 1.5%. One patient was re-operated due to postoperative bile leakage and uncontrolled biliary peritonitis. This patient developed Budd-Chiari syndrome following reoperation and died during follow-up due to sepsis. Another patient was reoperated due to postoperative intraabdominal abscess and peritonitis and died following reoperation due to pneumonia and sepsis.

Discussion

Hydatid cyst disease is mostly located in the liver, and can be seen as a single cyst or as multiple cysts. The incidence of multiple liver hydatid cysts was reported in the literature as between 29% and 38% [10]. In the current study, 35.1% of the hydatid cyst patients treated in our clinic had multiple cysts, which was found to be compatible with the literature. Bile leakage after liver hydatid cyst surgery is one of the most important factors affecting postoperative morbidity. In the literature, the incidence ranges from 2.6% to 28.6% [7, 11]. The postoperative morbidity rate is between 12% and 63%, and most of it is due to biliary leakage [12]. Therefore, it is important to determine and prevent possible risk factors of a complication that can develop at such high rates after hydatid cyst surgery. Possible risk factors have been identified in studies conducted previously. Unlike other studies, the current study was performed only for multiple liver hydatid cysts. In the other studies performed, single and multiple cysts were evaluated together and it was reported that the number of cysts did not affect bile leakage [7]. In the current study, the rate of biliary leakage was compatible with that in the literature and was found at a rate of 19.2%. In the present study, 7.7% of the patients were asymptomatic and 92.3% were symptomatic. While the rate of bile leakage was 10% in the asymptomatic patients, it was 20% in the symptomatic patients, and the difference was not statistically significant. Some studies have reported the history of preoperative cholangitis as one of the clinical indicators of CBC. These patients should undergo preoperative ERCP, sphincterotomy should be performed according to the findings, and a nasobiliary drain should be placed if necessary [13]. In the current study, the presence of jaundice and fever in the preoperative period was associated with a significant increase in the rate of postoperative bile leakage. These patients should be evaluated in terms of CBC during the preoperative and peroperative period.

In some studies, high blood bilirubin, ALP, and GGT levels, and the presence of bile duct dilatation on the preoperative images were reported in patients with CBC [14, 15]. Demircan et al. [16] stated ALT, AST, ALP, total bilirubin, direct bilirubin and GGT elevation as predictive factors for the existence of a cystobiliary relationship. In the present study, increased ALP, AST, ALT, GGT, and direct bilirubin were found to be predictive factors for postoperative bile leakage in the univariate analysis. However, these parameters were not found as effective factors in the multivariate logistic regression model.

There are few studies in the literature investigating the relationship between leukocytosis and eosinophilia with biliary leakage. While no significant relationship was found between them in some studies, there are studies reporting otherwise. In the study of Atahan et al. [17], no relationship was found between leukocytosis and eosinophilia with occult CBC. In the study of Demircan et al. [16], leukocytosis and eosinophils over 0.09 were reported as a predictive factor for cystobiliary fistula. In the current study, the high rate of leukocytosis and eosinophils was found to be associated with postoperative bile leakage in the univariate analyses. In the multivariate analyses, the high rate of eosinophils was found to be an independent risk factor for bile leakage. Eosinophilia is not an increasing parameter secondary to cholestasis. As is known, the cyst content is a fluid with antigenic properties and it is a known complication that anaphylaxis develops as a result of hydatid cyst perforation [18]. It is our belief that in patients with cystobiliary fistula, some of the cyst fluid passes into the systemic circulation and the rate of eosinophils in the blood increases secondary to this. Therefore, when the eosinophil rate is found to be high in patients with hydatid cysts, it should be evaluated thoroughly peroperatively, considering the risk of postoperative bile leakage.

Studies have shown that the relationship between the cyst diameter and bile leakage was controversial. Some studies have emphasized that there was no relationship between the cyst diameter and biliary leakage [7, 19]. However, there are studies reporting the opposite. Recently, in the study of Zeybek et al. [13], the maximum cyst diameter was reported as 10.5 cm and was found to be associated with postoperative biliary fistula. In a study on solitary hepatic hydatid cysts, the diameter of the cyst, perihilar location of the cyst, elevation of ALP, and WHO-IWGE stage were found to be associated with postoperative biliary leakage [8]. In the current study, the mean diameter of the cysts was determined as 10.4 (3.5) cm in the patients with bile leakage, while it was 8.6 (3.1) cm in the patients without, in the evaluation performed by taking the diameter of the largest cyst, and the difference was found to be significant according the bile leakage in the univariate analyses. However, it was not found to be significant in the multivariate analyses. In the univariate logistic regression analyses, the bile leakage risk increased by 1.2 times for every 1 cm increase in cyst diameter. The risk of bile leakage in patients with the largest cyst being than 10 cm was detected as 2.25 times more than those with a cyst smaller than 10 cm. When all of the cysts were evaluated, the mean diameter was 6.7 (3.04) cm in the group without bile leakage, while it was 7.9 (3.7) cm in the group with it, and the difference was statistically significant. These results showed that although the cyst diameter was not significant in the multivariate analyses, it was an important factor in the development of postoperative bile leakage.

In this study, the detection of intrahepatic localized dilatation and/or dilatation in IHBD and EHBD on the preoperative images was found to be associated with postoperative bile leakage in both the univariate and multivariate analyses. Dilatation in the bile ducts develops secondary to the existing cyst compression or cyst material opened in the bile ducts. Herein, only intrahepatic localized biliary dilatation increased the postoperative bile leakage by 5.5 times, and dilatation in the IHBD and/or EHBD increased by 48.7 times. In these patients, ERCP should be considered during the preoperative period, and a detailed CBC investigation should be performed during the peroperative period.

CBC can develop from any cyst located in the liver. Studies have argued that cysts close to the liver hilum are more likely to rupture into the bile ducts. However, there are few studies about this issue. In addition, which segments should be considered as perihilar (central)is controversial. Dziri et al. [20] divided the liver segments into 2groups, as posterosuperior segments (II, VII, and VIII) and anterior segments (III, IV, V, and VI), according to their projections based on the diaphragm,

and no difference was found between the 2groups in terms of CBC. However, in this study, segment IV was evaluated without splitting it into its subsegments, namely segments IVa and IVb. In the current study, postoperative bile leakage was detected as 50% in segment IVb, which is a perihilar subsegment, and 20% in segment IVa, which is a peripheral subsegment. In the study of Kayaalp et al. [21], by modifying the classification of Dziri et al., it was determined that the perihilar location of the cyst is a risk factor for CBC and postoperative bile leakage. According to their study, segments I, III, IVb, V, and VI were evaluated as perihilar localized, and segments II, IVa, VII, and VIII were evaluated as peripherally localized. In this study, segment VI was accepted as a perihilar segment, but when Couniaud's liver segmental anatomy was considered, segment VI was seen to be peripherally located [22]. In the current study, the perihilar segment group (segments I, III, IVb, and V) was accepted as the peripheral segment group (segments II, IVa, VI, VII, and VIII). Herein, for solitary cysts, the perihilar location of the cyst was found to be associated with bile leakage[8].Moreover, the postoperative bile leakage rate was found as 23% in patients with at least one perihilar localized cyst, and 14.3% in patients with peripherally located cysts, and the difference was not statistically significant. However, when the location of the largest cyst was evaluated, if the largest cyst was located in the perihilar region, it was found that the bile leakage rate increased to 35.7% and was statistically significant. In light of these findings, it can be considered that with the presence of denser and wider bile ducts in the perihilar region, the possibility of contact with the bile ducts of the cysts developing there would be higher, and this possibility would increase as the diameter of the cyst increases; hence, the rate of postoperative bile leakage may be higher.

The contents of cysts with bile and/or infection are an important risk factor for bile leakage. In some studies, this has been defined as an independent risk factor for biliary fistula and high postoperative morbidity has been reported [7, 23**].** In the current study, the biliary or infected cyst contents were found to be associated with postoperative bile leakage in the univariate analysis. It was found that it increased the risk of postoperative bile leakage by 6.6 times. A detailed cystobiliary relationship should be investigated and repaired in these patients during surgery [12].

Herein, the rate of CBC was 36.9%. In patients with CBC, the opening was closed by primary suturing. Postoperative bile leakage developed in 41.7% of these patients. However, postoperative bile leakage was prevented in 58.3% with the repair. The postoperative bile leakage rate was found as 6.1% in patients without peroperative CBC. Therefore, peroperative CBC should be investigated and treated in detail. Because major CBC is usually associated with cholangitis, it is easy to diagnose during the preoperative period. However, it is difficult to show minor (occult) CBC during the preoperative period, and it is usually detected peroperatively or manifested by postoperative bile leakage, abscess, and peritonitis. Detection and treatment of occult CBC reduces the postoperative biliary leakage rate [11, 24]. Risk factors should be determined well, especially in this patient group.

Since this study was conducted with multiple cysts, the effect of the surgical procedures and cavity obliteration techniques, as well as the WHO-IWGE phase of cysts on bile leakage could not be evaluated. Because cysts at different stages could be found in a patient, it seemed impossible to obtain an objective result, because different surgical interventions and obliteration techniques were applied to each cyst in the same patient.

Strengths and limitations

Our study is strong in that the number of patients with multiple cysts is high and also our study shows that eosinophilia can be used as a marker in predicting bile leakage. Since there is more than one cyst in each patient in our study, the fact that when bile leakage develops, it cannot be determined from which cyst the leakage develops. This is one of the limitations in our study. Also the retrospective nature of our study is another limitation.

Conclusion

In conclusion, the bile leakage rate after multiple liver hydatid cyst surgery was found to be 19.2% in this study, and it was found to be consistent with the literature. The most decisive factors for this complication were a high eosinophil rate and the presence of dilatation in the biliary ducts on the preoperative radiological images. In addition, the average cyst diameter, diameter of the largest cyst, perihilar location of the largest cyst, high level of the leukocyte count, AST, ALT, GGT, ALP, and direct bilirubin, and bile and/or infection of the cyst contents were found to be associated with postoperative bile leakage in the univariate analyses. In this study, the opening was treated in patients with peroperative cystobiliary fistula, and postoperative bile leakage was prevented in 58.3% of these patients. Therefore, in patients with the risk factors identified above, ERCP should be considered during the preoperative period, and intraoperative cystobiliary fistula research should be performed and treated.

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The prognostic nutritional index is associated with mortality of patients in intensive care unit

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Ethics Committee Approval
This study was approved by University of Health Sciences, Ankara Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committees (Approval No: 13.12.2021-126/27). 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: It has been reported that the prognostic nutritional index (PNI) is), an immunonutritional index, associated with poor prognosis, especially in cardiovascular and malignant diseases. However, the clinical significance of PNI in intensive care (ICU) patients remains unclear. In this study, we aimed to measure the predictive value of the PNI in predicting mortality in patients hospitalized in the ICU.

Methods: A total of 80 patients hospitalized in the internal medicine ICU of our hospital between January 2021 and September 2021 were included in this observational cohort study. The patients' demographic characteristics, comorbidities, laboratory parameters, need for and duration of mechanical ventilation, length of stay in ICU, and mortality rates were retrospectively analyzed. The patients were divided into two groups according to their survival; the first group comprised of survivors while the second group comprised of those who died in the ICU. The two groups were compared in terms of all variables.

Results: The mean age of all subjects included in the study was 63 (18.2) years and 50% (n=40) were female and 50% (n=40) were male. When patients are grouped as survivors and non-survivors, the mean age and sex distribution were similar (P=0.23, P=0.27, respectively). The median follow-up period of the patients was 5 (IQR 3-11) days and the mortality rate was 38.7% (n=31). Those in the non-survivor group had higher APACHE II and SOFA scores (P=0.02, P<0.001, respectively), and a lower PNI level (P=0.01). In the multivariate regression analysis, PNI value [OR: 1.210 (95%CI: 1.048-1.396) P=0.009] was the negative independent risk factor and SOFA score [OR: 1.697 (95%CI: 1.201-2.398) P=0.03] was a positive independent risk factor.

Conclusion: Despite our small cohort, we believe our findings corroborate our hypothesis that as a simple and inexpensive test, PNI is a useful biomarker to assess mortality risk in ICU patients.

Keywords: Prognostic nutritional index, Intensive care, Mortality

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Introduction

The intensive care unit (ICU) is a special treatment unit equipped with high technology for rapid intervention, where patients with life-threatening organ failure and who need to be kept under constant observation are followed up and treated [1]. With the increase in the aging population, the increase in the demand for intensive care beds and the high cost of intensive care treatments require careful selection of patients who will benefit from hospitalization in the ICU [2]. Calculation of expected mortality rates of intensive care patients is important in terms of rapid identification of critical patients requiring urgent diagnosis and treatment, standardization of intensive care units, and evaluation and provision of service quality. Scales used in the ICU to determine mortality and disease severity include scoring systems such as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA). These mortality prediction models predict disease severity and risk of morbidity and mortality associated with a direct worse outcome [3].

The prognostic nutritional index (PNI) is a combined score that reflects both the immunological and inflammatory status and the nutritional status of the individual, based on serum albumin and lymphocyte values [4]. Total blood lymphocyte count is recognized as a biomarker of nutritional status of patients as well as a prognostic factor in various clinical situations. It has been previously shown that low lymphocyte count predicts increased mortality in many chronic diseases [5,6]. Another parameter indicating a poor prognosis, especially in the ICU, is low albumin levels [7]. Hypoalbuminemia in critically ill patients can have various causes, such as poor nutritional status, impaired liver function, increased loss through the kidneys, and particularly the response to systemic inflammation (negative acute phase reactant) [8]. PNI using these two parameters was also proven to have prognostic value in various clinical conditions, including malignancy, infection, and cardiovascular disease [9-12].

Incorporating simple and useful biomarkers into prognostic strategies can significantly improve outcomes for patients followed in the ICU. In this study, we aimed to measure the predictive value of PNI in predicting mortality in patients hospitalized in the internal medicine ICU.

Materials and methods

This study was designed as a retrospective, cross-sectional study. The Ethics Committee of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital approved this study regarding the principles of the Declaration of Helsinki. Written-informed consents of all patients were obtained before inclusion (App. No: 13.12.21-126/27).

Medical records of patients admitted to the internal medicine ICU between January 2021 and September 2021 were retrospectively reviewed. Patients who stayed in the ICU for less than 24 hours, those younger than 18 years old, pregnant, positive for COVID-19 PCR test and/or patients with suspected COVID-19 infection by clinical and imaging methods, patients requiring postoperative follow-up and coronary intensive care patients, patients with an indication for intensive care due to newly developed cerebrovascular disease were excluded from the study. Patients whose albumin levels were measured before the initiation of treatment in the ICU were included in the study. After the patients meeting the exclusion criteria were excluded from a total of 114 patients who were followed up in the internal medicine ICU between the specified dates, all the remaining patients (80 patients) were included in the study, and other factors that could affect survival (comorbidity, etc.) were not excluded from the study in order to avoid bias.

The patients' demographic characteristics, accompanying comorbidities, laboratory parameters on admission to ICU, need for and duration of mechanical ventilation, length of stay in the ICU, and mortality rates were retrospectively analyzed. The patients were divided into two groups according to their survival, the first group comprised survivors (survivor), while the second group comprised patients who died in the ICU (non-survivor).

SOFA and APACHE II scores were used to analyze disease severity and mortality. The data required to make the relevant calculations were collected from the hospital database on the first 24 hours in the ICU and the results were classified according to the literature. In APACHE-II scoring, twelve clinical and biochemical parameters are calculated by assigning a score between 0-4. In the calculation; age, patient's pre-existing diseases, worst value of the body temperatures, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, potassium, creatinine, white blood cell count, hematocrit, Glasgow coma scale measured in the first 24 hours of intensive care admission are evaluated; a score below 10 indicate mild disease, while a score above 15 indicate moderate-to-severe disease. In SOFA scoring, a total of six organ systems, which include respiration where arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) is calculated, cardiovascular system where blood pressure and adrenergic drug infusion are evaluated, liver where bilirubin level is scored, coagulation where platelets are evaluated, kidney where creatinine and urine output are evaluated, and Glasgow coma scale, are scored between 1 and 4, and the worst value is recorded daily. The total score ranges from 6 to 24; a higher score indicates worsening morbidity [13]. The PNI was calculated using the formula: PNI = 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (per mm3). The two groups were compared in terms of all variables.

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality of the data. The results were expressed as *n* for the number of observations, mean (SD), and median (interquartile range) values. The Chi-square test was used for comparisons of categorical variables. Ordinal variables and continuous variables that do not have normal distribution were compared by the Mann–Whitney *U* test. The Student's *t*-test was used to evaluate differences between the two groups in normally distributed continuous variables. Multivariate regression analysis was used for detecting laboratory parameters and demographic characteristics associated with patients' mortality. Data were analyzed using the Statistical Package for the Social Sciences, version 20.0 (SSPS Inc., Chicago IL, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Of the 80 patients included in the study, 50% (n=40) were female and 50% (n=40) were male. The median follow-up period of the patients was 5 (IQR 3-11) days and the mortality rate was 38.7% (n=31). When patients are grouped as survivors and non-survivors, the mean age and sex distribution were similar (P=0.23, P=0.27, respectively). The demographic, clinical and laboratory parameters of the groups are shown in Table 1. When compared in terms of co-morbidities, the non-survivor group had a significantly higher rate of diabetes mellitus (DM) (P<0.001) and malignancy (P=0.04) (Table 1). The intubation rate was higher (P<0.001) and the duration of mechanical ventilation was shorter in the non-survivor group (P=0.01) (Table 1). Those who did not survive had higher APACHE II and SOFA scores (P=0.02, P<0.001, respectively), and a lower PNI level (P=0.01) (Table 1). In the multivariate regression analysis, PNI value [OR: 1.210 (95%CI: 1.048-1.396) P=0.009] was a negative independent risk factor, SOFA score [OR: 1.697 (95%CI: 1.201-2.398) P=0.03] was a positive independent risk factor (Table 2).

Table 1: Demographic, clinical, and laboratory parameters of patients followed in the ICU, grouped as survivors and non-survivors

Variables	Total	Survivors	Non-survivors	*P*-value
n, (%)	80 (100)	49 (61.3)	31 (38.7)	
Age	63 (18.2)	61.5 (19.3)	66.5 (16.3)	0.23
Sex				
Male, n (%)	40 (50)	24 (49)	16 (51.6)	0.27
Female, n (%)	40 (50)	25 (51)	15 (48.4)	
Co-morbidity				
DM, n (%)	30 (37.5)	16 (32.7)	14 (45.2)	<0.001
HT, n (%)	37 (46.3)	19 (38.8)	18 (58.1)	0.09
CCF, n (%)	10 (12.5)	6 (12.2)	4 (12.9)	0.93
CKD, n (%)	5 (6.3)	3 (6.1)	2 (6.5)	0.95
CAD, n (%)	17 (21.3)	10 (20.4)	7 (22.6)	0.81
COPD, n (%)	13 (16.3)	7 (14.3)	6 (19.4)	0.54
Malignancy, n (%)	21 (26.3)	9 (18.4)	12 (38.7)	0.04
WBC, (10^3/µL) median (IQR%25-75)	8.91 (6-15.9)	9.02 (6.29-13.86)	8.64 (5.74-18.89)	0.51
Lymphocyte, (10^3/µL) median (SD)	0.9 (0.7)	1.03 (0.6)	0.92 (0.7)	0.45
Hemoglobin, g/dL median (SD)	10.4 (2.5)	10.4 (2.5)	10.2 (2.6)	0.74
Platelet, (10^3/µL) median (SD)	203 (1.5)	210 (1.2)	192 (1.9)	0.6
Creatinine, mg/dL median (IQR%25-75)	0.99 (0.61-2.2)	0.91 (0.55-1.73)	1.35 (0.73-2.67)	0.3
Albumin, g/dL median (IQR%25-75)	3.57 (2.71-4.48)	2.95 (2.36-3.26)	2.5 (2-3.03)	0.009
AST, U/L median (IQR%25-75)	33 (18-66)	28 (15.5-46.5)	51 (26.4-162)	0.06
ALT, U/L median (IQR%25-75)	25 (11-50)	17 (10-37)	45 (17-100)	0.02
CRP, mg/L median (IQR%25-75)	58.6 (23-145)	44 (15-126)	101 (52-194)	0.47
PO2 mmHg median (IQR%25-75)	88 (75-137)	93.4 (76.3-141)	86 (64-113)	0.29
PaCO2 mmHg median (SD)	32.8 (11)	32.1 (9.5)	34 (13.1)	0.44
Length of stay in the ICU, days median (IQR%25-75)	5 (3-11)	6 (3-11)	5 (2-12)	0.85
Intubation (%)	34 (42.5)	12 (24.5)	22 (71)	<0.001
Mechanical ventilation time, days median (IQR%25-75)	4 (2.75-9)	9 (5.2-15.5)	3 (2-4)	0.01
APACHE II score median (SD)	20.6 (8.4)	18.4 (7.3)	24.4 (8.8)	0.02
SOFA at admission median (SD)	5.4 (3.5)	4.08 (2.8)	7.7 (3.4)	<0.001
PNI median (IQR%25-75)	43.9 (31.4-56)	32.8 (28.1-39.8)	30.5 (24.6-35.5)	0.01

DM: Diabetes mellitus, HT: Hypertension, CCF: Congestive cardiac failure, CKD: Chronic kidney disease, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, PaO2: Partial pressure of oxygen, PaCO2: Partial pressure of carbon dioxide, APACHE-II: Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, PNI: Prognostic nutritional index

Table 2: Multivariate logistic regression analysis to determine the independent risk factors for mortality according to PNI and SOFA

	Odds Ratio	95% Confidence Interval	*P*-value
PNI	1.210	1.048- 1.396	0.009
SOFA	1.697	1.201- 2.398	0.03

PNI: Prognostic nutritional index, SOFA: Sequential Organ Failure Assessment

Discussion

This study showed that PNI was significantly lower in non-survivor ICU patients and was associated with mortality. The PNI had a performance similar to SOFA score in assessing mortality in patients in ICU.

Patients followed in the ICU is a heterogeneous group with various complications and different clinical conditions, and it is known that the mortality rate of these patients is high. SOFA, one of the mortality estimation models used in the ICU, was first developed to determine the severity of organ dysfunction in septic patients, but later it was determined that it could also be an indicator of disease severity in critically ill patients in ICU, and it started to be used as a mortality indicator in recent years [14-16]. In our study, expectedly, the SOFA score was higher in the non-survivor group. Moreover, in patients followed in the ICU, the SOFA score was effective in indicating increased mortality.

Scorings such as SOFA are commonly used but are comprehensive, difficult to calculate, and time consuming for patients followed in the ICU because they utilize multiple physiological variables from different organ systems. Clinicians need a clinically applicable, inexpensive, and easy to interpret biomarker which will be helpful for early determination of serious disease and poor outcome. PNI is a combined marker that reflects both the immunological and inflammatory status and the nutritional status of the individual [4]. Hypoalbuminemia indicates the patient's malnutrition, which is the main reason for the relationship between albumin and patient prognosis [17]. However, since albumin has a long half-life, it does not have sensitivity to detect acute changes in nutritional status. Therefore, it is not recommended as an indicator of nutritional assessment alone. There is also evidence to suggest that albumin also reflects disease severity [18]. Albumin, a negative acute phase reactant, is more susceptible to acute inflammation as it is inhibited by proinflammatory cytokines in case of systemic inflammation [19]. The importance of lymphocytes, another determining factor of the PNI index, in the human immune system has been proven in many studies [20,21]. Progression of inflammation is the decisive factor in consequence of critically ill patients. In addition, there is an inverse relationship between the progression of inflammation and the lymphocyte count [22].

PNI, on the other hand, was initially defined to determine the surgical risk and perioperative immunonutrition status in patients undergoing initial gastrointestinal surgery [23]. It was later reported to be useful in evaluating malnutrition and prognosis in cardiovascular diseases [24]. Keskin et al. [25] reported that it is an independent predictor of mortality in patients undergoing coronary artery bypass surgery; Hayashi et al. [26] found that higher PNI scores were associated with shorter mechanical ventilation time, shorter follow-up time in ICU, and lower infection ratio in patients undergoing cardiovascular surgery. Again, there are also studies in the literature showing that there is a relationship between low PNI and poor prognosis in different cancer types [4]. In our study, we found PNI as an independent predictor of mortality in patients followed in the ICU. Due to the combined effect of two immunonutritional markers (albumin and lymphocyte) reflecting

the severity of the disease, we believe that low PNI may be a marker of poor survival in ICU patients.

Our main limitations are the lack of data on long-term clinical events due to the retrospective nature of the study and the small sample size. Another limitation is that patients' nutritional status was not analyzed prior to admission to ICU.

Conclusion

In our study, we identified PNI as an independent predictor of mortality in patients followed in the ICU. In intensive care, instead of comprehensive mortality estimation scores, which are complex to calculate and subjective to evaluate, the use of easy to calculate objective markers such as PNI, which can eliminate inter-clinician variability, can be considered. However, these data should be corroborated by prospective multicenter studies. We think that the evaluation of markers such as PNI together with mortality prediction scores will help clinicians to quickly assess the severity of disease and improve patient prognosis.

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Laparoscopic cholecystectomy - A safe and feasible procedure in patients with mild-moderate acute cholecystitis: A single center, prospective, observational study

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Ethics Committee Approval
This study was approved by IEC-CS Apollo Hospitals Bilaspur (No. AHB/IEC-CS/28, 02.05.2019).
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: Laparoscopic cholecystectomy (LC) is the gold standard modality for treating the gallstone disease. However, it is associated with perioperative complications. Moreover, some of the patients with acute cholecystitis (AC) require conversion to open cholecystectomy (OC). Thus, the aim of this study is to assess the safety and feasibility of LC in patients with AC.

Methods: This was a single center, prospective, observational study performed, over a period of 18 months (March 2019 to August 2020), in Department of General Surgery of a tertiary care center located in Central India. 96 patients fulfilling Tokyo guidelines (2018 diagnostic criteria for AC) were included. The feasibility was assessed in terms of conversion to OC, while safety was assessed in terms of postoperative complications in the first 30 days.

Results: During LC, none of the patients required conversion to OC due to difficulty in dissection or anatomy. On postoperative day 1, the mean VAS score for pain was 2.1 (0.56), meaning of low pain. Mean length of hospital stay was 2.34 (0.61) days, thereby inferring shorter hospital stay. Mortality was not observed. During the follow-up period, 2 patients developed epigastric port-site infection, while other 2 reported port-site bleeding. Moreover, 2 patients had intra-abdominal collection. All the complications were managed conservatively.

Conclusion: The study confirms that LC is feasible and safe in patients with AC, among the age group studied. LC can be a method of choice for AC due to decreased conversion rate, short hospital stays, reduced morbidity, and swift transition to routine.

Keywords: Acute cholecystitis, Cholelithiasis, Feasibility, Laparoscopic cholecystectomy, Safety

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Introduction

Gallstones (GS) are one of the most common gastroenterological conditions with a prevalence of 10-15% in adults. Obstruction of the cystic duct due to GS can lead to distension of gallbladder (GB) and biliary colic. Prolonged obstruction results in acute cholecystitis (AC), a condition characterized by infection, inflammation, and ischemia, in severe cases [1]. AC accounts for one of the most frequent causes of emergency hospitalization in surgical care [2]. Etiologically, 90-95% cases of AC are due to GS, while remaining 5-10% are due to acalculous cholecystitis [3]. Following the trend in western countries, prevalence of GS is on rise in India and is estimated to be between 3%-6% [4]. While the majority of the patients with GS remains asymptomatic, about 1-2% of patients turn symptomatic annually. Among them, 10% progress to AC. Recurrent attacks of AC can lead to chronic cholecystitis with several changes in GB including atrophy of mucosa, wall thickening, and scarring [1].

For the past several decades, open cholecystectomy (OC) has been the standard treatment for symptomatic GS disease [5]. Subsequently, less invasive, but expensive methods including contact dissolution agents, oral desaturation agents, and extracorporeal shock wave lithotripsy were introduced. However, they were limited by size, number, and composition of GS [6]. Moreover, these non-surgical methods could not guarantee a permanent cure. In the last decade, introduction of laparoscopic cholecystectomy (LC) has revolutionized the treatment of GS disease. Compared to OC, LC is associated with several advantages including less postoperative pain, short recovery time, short duration of hospitalization, decreased expenditure, improved cosmetic results and patient satisfaction, and quick resumption of daily routine without added morbidity [7].

However, LC is limited by higher rates of complications including injuries to bile duct, liver, and bowel that are significantly increased with less experience and training of the surgeon [8]. Moreover, around 1.8-27.7% of LCs are converted to OC and the increased conversion rate counters the advantages of LC. Converted cases have higher postoperative complications leading to longer post-operative hospitalization, and higher rates of morbidity and mortality [9]. With improved surgical skills and laparoscopic instruments, LC is now considered safe for AC [10]. In a developing world such as India, where absenteeism from work and high healthcare expenditure form the primary concern, we speculated that LC could be a safe and feasible alternative in patients with mild-moderate AC. Thus, in the present study, we aimed to assess the safety and feasibility of LC in patients with mild to moderate AC.

Materials and methods

Study design and setting

This was a single center, prospective, observational study performed over a period of 18 months (May 2019 to October 2020) in the Department of General Surgery of a tertiary care hospital located in Central India. The study was conducted after the approval of study protocol by the Institutional Ethics Committee, Ramkrishna Care Hospital, Raipur (AHB/IEC-CS/28, Dated May 2, 2019) and obtaining written informed consent of the patients.

Eligibility criteria

Patients of either sex, belonging to the age group of 18 to 70 years, undergoing LC, fulfilling the Tokyo Guidelines 2018 (TG18) diagnostic criteria for AC, and with mild-moderate AC were included in the study [11]. In contrast, patients with severe AC, acute hepatitis, obstructive jaundice, malignancy, patients planned for OC, pregnant patients and medically unfit patients for general anesthesia were excluded from the study.

Study procedure

A total of 110 patients presenting with upper abdominal pain, nausea, vomiting, or fever were screened for eligibility. Of these 110 patients, 7 did not give consent, 5 were planned for OC, and 2 were found to have obstructive jaundice. Thus, these 14 patients were excluded and 96 patients were enrolled in the study. Based on laboratory (complete blood count, C-reactive protein (CRP), and liver function test) and radiological (chest X-ray, abdominal ultrasonography) investigations, the diagnosis of AC was established as per the TG18 Criteria. All the patients were operated by a single experienced surgeon and the standard 4 ports technique was used for performing LC. Both the feasibility and safety outcome measures were noted. Post-operatively, pain was assessed on postoperative day 1 with the help of visual analogue scale (VAS) ranging from 0 to 10, where 0 and 10 suggested none and excruciating pain, respectively. Sutures were removed on postoperative eighth day. All 96 patients were followed-up at first month, for any complications and recurrent symptoms.

Outcome measures

Assessment of feasibility

The feasibility of performing LC was assessed, intra-operatively, in terms of conversion rate i.e., the number of patients requiring conversion of LC to OC.

Assessment of safety

The safety associated with LC was evaluated in the intra- and post-operative period. It was assessed in terms of intra-operative injury to organs including common bile duct, bowel, or liver; discontinuation of LC due to unclear or difficult anatomy; undue intra-operative bleeding leading to intra- or post-operative resuscitation and blood transfusion; post-operative complications including bleeding from port-site, port-site infection, jaundice, drain dislodgement, and readmission; post-operative intra-abdominal collection requiring drainage; and repeated laparoscopy following the primary LC.

Statistical analysis

Data was collected and collated with Microsoft Office Excel 2013. The data was analyzed with SPSS v23.0 (IBM, Armonk, NY, USA) for Windows. Continuous and categorical variables were represented as mean (standard deviation (SD)) and frequencies (percentages), respectively. Independent sample t-test was used to assess any association between continuous variables. A two-tailed probability value of <0.05 was considered as statistically significant.

Sample size calculation

Sample size was calculated on the basis of the proportion of patients with severe AC undergoing LC and requiring OC i.e., 6% [12].

The sample size was determined on the basis of the following formula:

$$\frac{Z^2_{1-\frac{\alpha}{2}}p(1-p)}{d^2} = \frac{(1.96)^2 \times 0.06(1-0.06)}{(0.05)^2} = \frac{3.84 \times 0.0564}{0.0025} = 86.63$$

Where,

p = prevalence of conversion of LC to open cholecystectomy = 6% = 0.06

d = Absolute precision required on either side of the proportion = 5 % = 0.05 (2-sided)

$Z_{0.025}$ = 1.96 for 95% confidence interval

Thus, sample size was calculated to be 87. Considering the drop-out of 10%, a total of 96 patients were included.

Results

The present study had female (61.46%) predominance with female to male ratio of 1.6:1. Majority of the patients belonged to the age group of 51-60 years (30.21%). The mean age of the study population was 48.47 (13.36) years and mean age of males was significantly greater than that of females (p=0.021). The majority of the patients (62.5%) had leukocytosis (WBC count >10000 /dl). The mean WBC count and CRP levels were 11527.11 (4149.1) /dl and 41.26 (34.02) mg/dl, respectively. In all patients, USG was suggestive of acute calculus cholecystitis. Moreover, majority of the patients had moderate AC (56.25%) (Table 1).

Table 1: Baseline demographic and clinical characteristics

Characteristics	n	%
Sex distribution		
Male	37	38.54
Female	59	61.46
Age group (years)		
21-30	12	12.5
31-40	18	18.75
41-50	19	19.79
51-60	29	30.21
61-70	18	18.75
Mean Age (years)		
Male	52.43 (12.47)	-
Female	45.98 (13.39)	-
Total	48.47 (13.36)	-
USG suggestive of acute calculus cholecystitis		
Yes	96	100
No	0	0
WBC count (/dl)		
< 10000	36	37.5
> 10000	60	62.5
Severity of AC		
Mild	42	43.75
Moderate	54	56.25
Mean WBC count (/dl)	11527.11 (4149.1)	-
Mean CRP mg(/dl)	41.26 (34.02)	-

WBC: White blood cells, CRP: C Reactive protein, USG: Ultrasonography

The majority of the patients had double presenting symptoms (54.17%). Pain (95.83%) followed by dyspepsia (40.63%) were the most common solitary presenting symptoms. Moreover, pain + dyspepsia (29.17%) and pain + vomiting + fever (15.62%) were the most frequently observed double and triple presenting symptoms, respectively (Table 2).

Assessment of VAS score demonstrated that majority of the patients had a VAS score of 2 (91.67%). Moreover, the mean VAS score was 2.17 (0.56), suggesting low postoperative pain (Table 3).

Table 2: Presenting symptoms

Presenting symptoms	n	%
Number of symptoms		
One	22	22.92
Two	52	54.17
Three	22	22.92
Presenting symptoms		
Pain	92	95.83
Dyspepsia	39	40.63
Vomiting	33	34.38
Fever	28	29.17
Combination of symptoms		
Pain + Dyspepsia	28	29.17
Pain	21	21.88
Pain + Vomiting + Fever	15	15.62
Pain + Vomiting	15	15.62
Dyspepsia + Pain + Fever	7	7.292
Pain + Fever	6	6.25
Vomiting + Dyspepsia	3	3.125
Dyspepsia	1	1.043

Table 3: Distribution of patients according to VAS score

VAS pain score	n	%
2	88	91.67
4	8	8.33
6	0	0
Mean VAS score	2.17 (0.56)	-

Assessment in terms of surgical difficulties demonstrated that none of the patients had difficult anatomical structures and none required conversion to OC. Thus, the conversion rate was 0%. The mean operative time was 57.39 (14.7) minutes (Table 4).

Mean length of hospital stay was 2.34 (0.61) days, suggesting shorter length of hospital stay. Assessment of postoperative complications revealed that 2 patients developed epigastric port-site infection, while other 2 reported port-site bleeding within the 30-days follow-up period. Port-site infection required oral antibiotics and drainage of abscess on an out-patient basis and thus, was managed conservatively. The port-site bleeding was reported on postoperative day 1 and was managed conservatively with suturing and required no further intervention. Two patients developed intra-abdominal collection which required USG-guided pigtail drainage of the collection. The drain output subsided gradually and drain was removed by postoperative day 18. No mortality was reported in post-operative period during the 30-day follow-up (Table 5).

Table 4: Intra-operative characteristics of patients

Characteristics	n	%
LC Abandoned due to difficult anatomy		
Yes	0	0
No	96	100
Patients converted to laparotomy due to difficult anatomy		
Yes	0	0
No	96	100
Mean Operating time (Mins)	57.39 (14.7)	-

Table 5: Post-operative findings of patients

Parameter	n	%
Post-op complications		
Port-site infection of epigastric port	2	2.08
Bleeding from port-site	2	2.08
None	92	95.84
Post-operative intra-abdominal collection requiring drainage		
Yes	02	2.08%
No	94	97.92%
Mortality		
Yes	0	0
No	96	100
Mean hospital stay (Days)	2.34 (0.61)	-

Discussion

The principal findings of the present study suggested that LC is feasible as well as safe in patients with mild-moderate AC among the age group studied. With regards to feasibility, successful completion of the laparoscopic procedure as planned at the outset without any intra-operative complications that might lead to conversion to OC was observed. LC resulted in reduced

intra-operative complications, abandoning of surgery due to unclear or difficult anatomy, and post-operative complications, thus increasing the safety of patients with mild-moderate AC.

In the present study, none of the patients were converted to OC. Moreover, difficult anatomy was not encountered in any of the patients and thus, all the patients underwent LC successfully. Available literature suggests that around 1.8-27.7% of LCs are converted to OC [9]. Sippey et al. [13] reported a conversion rate of 6%. Terho et al. [14] reported a conversion rate of 22.5%, and the most common reasons were severe inflammation and difficulty in identification of anatomy. Thus, the conversion rate observed in the present study is significantly lower than that documented in literature. We attribute the 0% conversion rate to the fact that we rigorously practiced the primary principles of laparoscopic surgery including employing Veress needle, having sufficient visual field, nominal use of electrocautery in the Calot's triangle, clipping preceded by exhibition of the structures in the Calot's triangle, sufficient traction in an appropriate direction, employing gauge dissection in cases with difficult anatomy, and repeated confirmation of the anatomy. We excluded patients with severe AC and LC was performed in a single center with the same laparoscopic surgeon, which was mainly responsible for attaining 0% conversion rate, as has been reported in other studies [15]. Moreover, critical view of safety was used for identification of all the structures in the hepatocystic triangle and thus, bile duct injury was avoided. Singh et al. documented a conversion rate of 0.42%. They observed that out of 22.66% difficult cases, conversion was required only in 1.86%. Thus, highlighting the fact that LC can be successfully performed even in difficult cases by following the basic principles of laparoscopic surgery [16].

In the present study, the overall complication rate of 4.2% was less than the complication rates of 9-20% reported by other studies [17, 18]. Within the 30 days follow-up period, 2 patients each reported epigastric port-site infection and bleeding from port-site. All the patients were managed conservatively. Similarly, Lohiya et al. [19] reported minimal post-operative complications with LC. They observed that 2 patients had prolonged bile leak, and 1 each had post-operative hemorrhage and surgical site infection, and all patients were treated conservatively. In another study, Singh et al. reported that only three patients had developed surgical site infection, and all were managed with daily dressings [16].

In the present study, 1 patients developed fever on post-operative Day 2, while another patient had right upper quadrant discomfort on post-operative Day 4. On USG, both were found to have intra-abdominal collection which required USG-guided pigtail drainage of the collection. The collection subsided and drain was removed between post-operative Day 14 and 18 in both the patients. Thus, intra-abdominal fluid collection was successfully managed with drain placement. Similarly, Alberto et al. reported a case of intra-abdominal fluid collection after LC which was successfully managed with drain placement [20]. Chau et al. reported two patients complicated by post-LC leakage of cystic stump. Both the patients were successfully treated by percutaneous drainage of the intra-abdominal collection under ultrasound guidance [21].

In the present study, mean hospital stay was 2.34 (0.61) days and no mortality was reported during the 30-day follow-up period. Singh et al. reported the mean hospital stay of 1.5 days following LC [16]. Another study by Karim et al. [22] observed a mean hospital stay of 3.7 days post-LC. Contrarily, Jeong et al. [23] observed significantly longer hospital stay of 10.3 days, however, it was shorter compared to patients that underwent OC (17.7 days).

In a recently published randomized trial, Kiviluoto et al. [24] found that LC does not result in increased mortality rates in patients with AC but that the morbidity rates are substantially lower than that observed following OC. Similar to the present study, Johansson et al. [25] reported no mortality during or after LC. Similarly, Pessaux et al. [26] reported no mortality in patients undergoing LC, but 4 patients died following OC.

In the present study, majority of the patients had WBC count >10000 /dl and all the patients had CRP levels of >3 mg/dl. Moreover, the mean WBC count and CRP levels of the study population were 11527.11 (4149.09) /dl and 41.26 (34.02) mg/dl, respectively. Similarly, Chau et al. reported leukocytosis in 61.3% of the patients [21]. In another study, Terho et al. [14] reported the mean WBC count of 13000/dl, ranging from 2500 to 32000/dl. Moreover, the median CRP levels reported by Johansson et al. were considerably greater than the present study. They reported the median CRP levels of 140 mg/l, ranging from 23 to 290 mg/l [25]. Similarly, Terho et al. [14] reported elevated median CRP levels of 123 mg/l, ranging from 3 to 524 mg/l. Thus, in the present study, median CRP levels were considerably less than those cited in literature, thereby suggesting lower levels of inflammation among the enrolled patients.

In the present study, USG of abdomen was suggestive of AC in all the patients and this was supported by the findings on LC. None of the patients had suspected complications of AC and thus, CT of abdomen was not performed. Similarly, Lohiya et al. [19] and Haziraka et al. [27] used USG of abdomen as the main investigation to diagnose GS disease and reported the presence of GS in all the patients. However, Terho et al. [14] reported that, even if USG is the main choice of imaging in patients with clinical suspicion of AC, they used CT in patients who presented with severe or diffuse symptoms, and magnetic resonance imaging in patients with suspicion of bile duct stones, in addition to AC. Thus, in the present study, USG abdomen was found to have a high diagnostic accuracy.

In the present study, 4-port technique was used and the operating time ranged from 35 to 96 minutes, with mean of 57.39 (14.7) minutes. Considerably greater median operating time was documented by Johansson et al. They used 4-port technique and reported the median operating time of 90 minutes, ranging from 30 to 155 minutes. While, significantly shorter time was observed in patients that underwent OC. This difference was attribute to the longer time taken for the converted procedures (median 125 min) [25]. In contrast, Chau et al. reported no significant difference between LC and OC in terms of the mean operation time (92.5 (25.5) vs 84.8 (41.0) minutes) [21]. Thus, the mean operating time in the present study was considerably less than that documented in the literature. The reason for reduced operating time was due to experience of the surgeon and

use of advanced laparoscopic technology (such as 3D laparoscopic cholecystectomy).

As the present study was not comparative in nature, randomization was not performed. Moreover, the patients underwent surgery, so blinding was not done. However, standard operative procedures were followed and LC was performed by single laparoscopic surgeon, thereby eliminating the chances of performance bias.

In the present study, majority of the patients had the post-operative VAS pain score of 2 and the mean score was 2.17 (0.56). Johansson et al. reported that the median pain score at discharge was not statistically different with OC and LC [25]. Similarly, Enes et al. [28] reported that post-operative VAS was lower in patients operated by LC than OC. This difference was pronounced throughout the entire postoperative period. In another study, Kum et al. reported that patients who underwent LC had significantly less pain on the day of operation (mean VAS score 3.8 vs 7.7) and on the first post-operative day (mean VAS score 2.8 vs 6.2) than those who underwent OC [29].

Conclusion

The findings of the present study support the safety and feasibility of LC in patients with mild-moderate AC among the age group accentuated. If possible, LC should be used to minimize the postoperative complications in terms of shorter length of hospital stay and lower morbidity rates. However, OC should not be avoided if necessary, to ensure patient safety in severe cases or those with difficult anatomy. Moreover, major focus should be on training the surgeons regarding the appropriate technique for performing LC.

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Analysis of the psychiatric consultations requested for hospitalized COVID-19 patients: One year results from a major pandemic hospital

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Ethics Committee Approval
Ethical approval of the study was obtained from the Ethics Committee of Marmara University Medical School (protocol no:092021590)
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: Coronavirus 2019 (COVID-19) has brought unprecedented challenges to the practice of consultation-liaison psychiatry. Moreover, it is probable that the characteristics of psychiatric consultations and administered treatments have varied and will continue to vary significantly over time. Given the relative lack of prior research concerning this issue, this study aimed to provide a multi-dimensional analysis of the psychiatric consultations requested for inpatients diagnosed with COVID-19 and to examine the temporal course of the selected variables throughout the pandemic.

Methods: In this retrospective cohort study, the medical records of 232 patients who underwent psychiatric consultation between May 1, 2020 and April 30, 2021 were reviewed in detail. Data were obtained for a series of variables, including reasons for consultation, diagnoses after assessment, medical comorbidities, past psychiatric history, treatment arrangements, and clinical outcomes, after which the data were systematically classified to be included in the multi-dimensional analysis.

Results: The mean age of the patients was 66.79 (17.18) years (61.21% were males). The most common reasons for consultation were psychomotor agitation, anxiety, and treatment non-compliance, while adjustment disorder and delirium were the most common diagnoses after psychiatric evaluation. Among the reasons for consultation, the shortest durations from admission to consultation were associated with psychomotor agitation, assessment for drug interaction, and treatment non-compliance while among the diagnoses, the duration was shortest for dementia, mental retardation, bipolar disorder, and psychosis. The most frequently prescribed medications were antipsychotics, antidepressants, and benzodiazepines. The number of consultations and rates of delirium and death showed a significant increase over the course of the study. Delirium and medical comorbidities were found to be the strongest predictors of death as a clinical outcome.

Conclusion: Knowledge and experience in the field of consultation-liaison psychiatry might contribute to the accurate diagnosis of COVID-19-related neuropsychiatric syndromes in addition to implementation of appropriate treatment interventions.

Keywords: COVID-19, Consultation-liaison psychiatry, Neuropsychiatry, Psychopharmacology, Delirium, Adjustment disorder

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Introduction

The wide range of clinical presentations among patients treated in Coronavirus 2019 (COVID-19) wards or intensive care units (ICUs) has led to the understanding that the disease is much more frequently associated with multisystemic involvement than previously expected [1, 2]. The most frequently reported clinical manifestations associated with COVID-19 are neuropsychiatric symptoms, which are likely to involve heterogeneous and potentially complex pathophysiological processes [3, 4]. The underlying mechanisms might include several parameters: a) common psychological reactions in response to having the disease, hospitalization, social isolation, severe clinical course, and others; b) direct or indirect effects of the virus on central nervous system (CNS) functions; c) direct effects of medications used for the treatment of COVID-19 or interaction with other drugs; and/or d) abrupt cessation of medications used for an underlying neuropsychiatric disease [5–7]. Aside from anxiety and depressive symptoms that are commonly experienced resulting from psychological stress due to the disease, the most common neuropsychiatric manifestations in the acute period are reported to be delirium/encephalopathy, psychosis, mood changes, and insomnia [8].

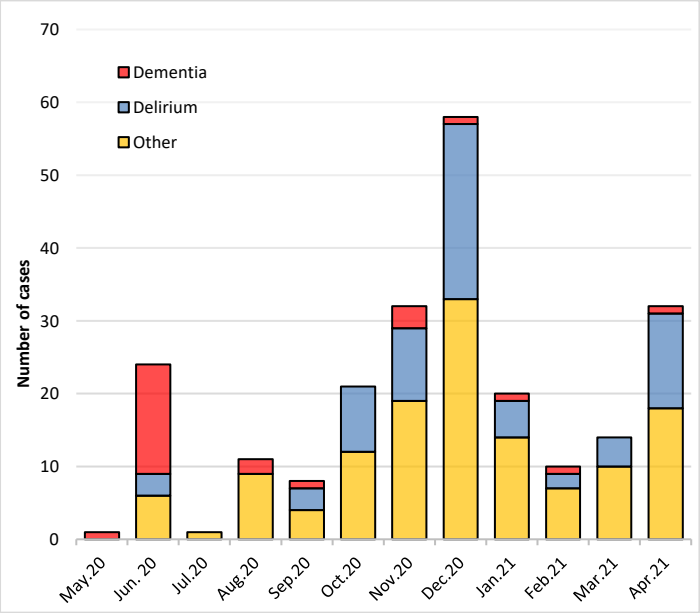
As in other fields of expertise, COVID-19 has brought uncertainty and clinical struggles in the practice of consultation-liaison psychiatry (CLP). The chaotic course of the disease results from multisystemic involvement, frequent updates of treatment protocols, and significant heterogeneity in clinical approaches between hospitals, making it difficult to elucidate the etiology of the neuropsychiatric symptoms in question in addition to developing reliable treatment algorithms [9]. The only known study to date on the characteristics of psychiatric consultations for Turkish patients with COVID-19 was conducted at the initial phase of the pandemic (n = 89) in which it was reported that the most common reason for psychiatric consultation was psychomotor agitation, whereas the most common psychiatric diagnosis was delirium [10]. However, considering the complex interactions among a number of substantial factors (such as the ever-increasing number of infected individuals, frequent updates in treatment algorithms, initiation of vaccination program across the country as of January 2021, and unpredictable mutations in the virus genome), it seems highly probable that the clinical profile of the inpatients and characteristics of psychiatric consultations in COVID-19 wards might exhibit significant changes over the time course of the study.

Taking the above-mentioned limitations into consideration, the present study aimed to provide a multidimensional picture of the characteristics of psychiatric consultations requested for patients hospitalized with a diagnosis of COVID-19 during the one-year period from the onset of the pandemic in Turkey and to assess the cross-sectional relationships between these features in addition to their temporal pattern throughout the pandemic. The variables of interest include the sociodemographic characteristics of the patients, the main characteristics of the psychiatric consultations (reasons for consultation, diagnoses after psychiatric evaluation, past psychiatric diagnoses, treatment protocols, and others) in addition to the clinical features of the cases (medical comorbidity, length of hospital stay, need for intensive care, clinical outcomes, and others).

Materials and methods

The study sample consisted of adult (>18 years old) inpatients admitted to the pandemic hospital (Marmara University, Prof. Dr. Asaf Ataseven Hospital) with a diagnosis of COVID-19 between May 1 2020 and April 30, 2021 and who underwent psychiatric consultation during their hospital stay (the hospital has been serving as the leading center for the treatment of COVID-19 patients in Istanbul since the onset of the pandemic with around 6000 inpatients treated during the first year of service). Data collection was based on the retrospective screening of the patients' medical records, psychiatric consultation files, and other relevant medical information through the hospital's database. Patients with uncompleted procedures (missing information, unsubmitted consultation, and other parameters) or those with unavailable data on corresponding fields were not included in the final sample. Accordingly, a total of 285 psychiatric consultation records (30 cases with two or more files) over a one-year period were examined in detail, and 232 patients who met the criteria were included in the final sample (the monthly distribution of the consultations is shown in Figure 1).

Figure 1: One-year course of the psychiatric consultations requested for inpatients diagnosed with Coronavirus 2019 (COVID-19) and monthly distribution of the psychiatric diagnoses



For each patient, the medical records regarding a series of variables (reasons for psychiatric consultation, diagnoses after evaluation, and medical comorbidities, among others) were reviewed twice and independently by two researchers to reduce potential bias after which the data were systematically classified under corresponding categories, which were determined in accordance with the frequency and clustering tendencies (such as psychomotor agitation, treatment non-compliance, and others, which were coded as the categories for reasons for consultation; psychotic disorders, dementia, and others were coded as psychiatric diagnoses after evaluation).

To include all the relevant data in the statistical analysis, additional levels were provided for the variables potentially consisting of more than one component (such as up to three

levels for reasons for consultation, and up to two levels for diagnoses after consultation). Ethical approval of the study was obtained from the Ethics Committee of Marmara University Medical School (protocol no: 092021590).

Statistical analysis

SPSS (version 24.0) was used for statistical analysis. Descriptive statistics are given as numbers (n), percentages (%), means and standard deviations (SD), median, minimum and maximum values. Normal distribution was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. A chi-square test was used to compare the distribution of categorical variables between two independent groups, a Mann–Whitney U test was used to compare non-normally distributed continuous or ordinal variables, Student's-t test was used to compare normally-distributed continuous variables, and Spearman's correlation test were used for the analysis of bidirectional relations between the variables of interest. Logistic regression was used to determine the factors predicting death as an outcome among the patients who underwent psychiatric consultation. Statistical significance was determined as $\alpha = 0.05$.

Results

Sociodemographic and clinical characteristics of the sample

Ninety (38.79%) of the patients were women. The mean age was 65.92 (18.66) (median = 71) for females, 67.33 (16.22) (median = 70) for males, and 66.79 (17.18) (median = 70) for the entire sample. Over half of the patients (54.7%) did not have any psychiatric diagnosis or treatment history prior to hospitalization. Of the 105 patients with a history of psychiatric diagnosis (86 single, 19 two diagnoses), 47.61% (n = 50) had dementia, 24.76% (n = 26) had anxiety disorder, and 12.38% (n=13) had psychotic disorder. It was found that all patients were diagnosed with dementia, bipolar, and/or psychotic disorders; 93.75% (n = 15) of those diagnosed with depressive disorder and 68.18% (n = 15) of those diagnosed with anxiety disorder also had these diagnoses during the pre-admission period. Seventy-two (31.03%) of the patients were actively using at least one psychotropic medication before hospitalization while 10.77% (n = 25) were using other types of CNS drugs (antidementia, antiepileptic, antiparkinsonian, and others). One-hundred forty-two (61.20%) of the patients of the patients had at least one medical comorbidity. Fifty-one (35.91%) had diabetes mellitus (DM), 18.30% (n = 26) had chronic obstructive pulmonary disease (COPD), and 59.85% (n = 85) had other chronic diseases.

General characteristics of the psychiatric consultations

The reasons for the psychiatric consultations and the characteristics of the diagnoses after psychiatric evaluation are shown in Tables 1 and 2. The consultation requests involved two major reasons in 31.89% (n = 74) of the cases and three major reasons in 3.01% (n = 7). On the other hand, 9.05% (n = 21) of the patients received two diagnoses after the psychiatric evaluation. Psychomotor agitation (25.63%, n = 82), anxiety (15%; n = 48), treatment non-compliance (14.69%; n = 47), insomnia (14.06%; n = 45), and confusion (10%; n = 32) were the most common reasons for consultation requested by the treating physicians. The most common reason for consultation was psychomotor agitation in men (29.76%; n = 61) and anxiety in women (19.13%; n = 22). The mean duration from admission to the first consultation was 7.19 (7.77) days (median = 5). In terms of the reasons for consultation, the shortest durations were associated with a request for the evaluation for drug–drug interactions with 2.07 (0.26) days (median = 2), treatment non-compliance with 5 (2.32) days (median = 5), and psychomotor agitation with 5.89 (6.13) days (median = 4). The most common diagnoses established by the consultant psychiatrists were adjustment disorder (AD) (29.25%; n = 74) and delirium (28.85%; n = 73) for the whole sample; delirium was the most common diagnosis among males (32.45%; n = 49) and AD among females (30.39%; n = 31). Among the primary diagnoses, the mean age was highest for dementia (79.58 (8.23) years) and delirium (76.41 (11.99) years) and lowest for bipolar disorder (44.50 (21.92) years) and alcohol/substance use disorder ([ASUD], 31 (1.41) years) as shown in Table 2. Finally, the highest rates of medical comorbidity were observed among patients diagnosed with AD with depressed mood (AD-D) at 76.47%, delirium (75.34%), and depressive disorder (62.50%). However, these rates were 52.63% and 36.36% for AD with anxiety (AD-A) and anxiety disorder, respectively.

Table 1: Characteristics of the psychiatric consultations requested for inpatients diagnosed with Coronavirus 2019 (COVID-19)

Reasons for consultation					Gender distribution*		Duration until consultation request (day)**	
	RC 1 % (n)	RC 2 % (n)	RC 3 % (n)	Total % (n)	Women % (n)	Men % (n)	Mean (SD)	Median (min-max)
Anxiety	18.96 (44)	24.69 (2)	28.57 (2)	15 (48)	19.13 (22)	12.68 (26)	10.09 (10.76)	6.50 (1–54)
Confusion	9.48 (22)	12.34 (10)	-	10 (32)	10.43 (12)	9.76 (20)	7.82 (8.17)	4 (1–32)
Depressive symptoms	6.46 (15)	1.23 (1)	-	5 (16)	10.43 (12)	1.95 (4)	8.60 (6.92)	7 (2–26)
Evaluation for drug–drug interactions	6.03 (14)	1.23 (1)	-	4.69 (15)	6.96 (8)	3.41 (7)	2.07 (0.26)	2 (2–3)
Poor sleep	11.21 (26)	20.98 (17)	28.57 (2)	14.06 (45)	13.91 (16)	14.15 (29)	7.12 (5.96)	4.5 (1–25)
Alcohol–substance use	0.43 (1)	1.23 (1)	-	0.63 (2)	0	0.98 (2)	5	5
Psychomotor agitation	31.46 (73)	11.11 (9)	-	25.63 (82)	18.26 (21)	29.76 (61)	5.89 (6.13)	4 (1–32)
Psychotic symptoms	1.72 (4)	1.23 (1)	14.28 (1)	1.88 (6)	1.74 (2)	1.95 (4)	10.75 (14.88)	4 (2–33)
Death/suicidal ideation	1.29 (3)	3.70 (3)	-	1.88 (6)	0.87 (1)	2.44 (5)	7.33 (5.85)	5 (3–14)
Treatment noncompliance	4.74 (11)	41.97 (34)	28.57 (2)	14.69 (47)	10.43 (12)	17.07 (35)	5 (2.32)	5 (2–9)
Evaluation for somatization	1.72 (4)	1.23 (1)	-	1.56 (5)	2.61 (3)	0.98 (2)	8 (7)	8 (1–15)
Treatment arrangement	6.46 (15)	1.23 (1)	-	5 (16)	5.22 (6)	4.88 (10)	8.60 (9.86)	5 (1–38)
Total	100 (232)	100 (81)	100 (7)	100 (320)	100 (115)	100 (205)	7.19 (7.77)	5 (1–54)

RC: Reason for consultation, * According to all reasons for consultation, ** According to primary reason for consultation

Table 2: Patients' characteristics and clinical features according to psychiatric diagnoses established after evaluation

Psychiatric diagnoses				Gender distribution*		Age*		Duration until consultation request **		Hospital stay**		Past diagnosis*	Medical comorbidity*	ICU*	Death*
	D1 % (n)	D2 % (n)	D3 % (n)	Women % (n)	Men % (n)	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	% (n)	% (n)	% (n)	% (n)
Anxiety dis.	8.19 (19)	14.29 (3)	8.70 (22)	4.90 (5)	11.26 (17)	58.37 (18.56)	52 (24-89)	13.74 (13.73)	10 (1-54)	23.84 (21.58)	16 (2-84)	68.18 (15)	36.36 (8)	9.09 (2)	4.54 (1)
Bipolar dis.	0.86 (2)	9.52 (2)	1.58 (4)	3.92 (4)	0	44.50 (21.92)	44.5 (29-60)	2.50 (0.71)	2.50 (2-3)	5 (4.24)	5 (2-8)	100 (4)	50 (2)	50 (2)	0
Delirium	31.47 (73)	0	28.85 (73)	23.53 (24)	32.45 (49)	76.41 (11.99)	77 (40-100)	6.41 (6.75)	4 (1–32)	14.99 (9.30)	12 (2–44)	34.24 (25)	75.34 (55)	50.68 (37)	45.20 (33)
Dementia	11.21 (26)	33.33 (7)	13.04 (33)	16.67 (17)	10.60 (16)	79.58 (8.23)	81 (61–91)	2.19 (0.98)	2 (1-5)	16.08 (10.09)	12 (5-37)	100 (33)	45.45 (15)	39.39 (13)	21.21 (7)
Depressive dis.	4.74 (11)	23.81 (5)	6.32 (16)	9.80 (10)	3.97 (6)	60.73 (14.71)	60 (27–80)	7.27 (5.02)	6 (2-20)	11 (6.35)	9 (4–24)	93.75 (15)	62.50 (10)	12.5 (2)	0
İnsomnia dis.	3.88 (9)	0	3.56 (9)	2.94 (3)	3.97 (6)	64.67 (13.80)	67 (48-82)	9.78 (6.94)	8 (4–25)	22.38 (17.97)	14.50 (9-64)	22.22 (2)	55.55 (5)	0	0
Drug side-effect	0.86 (2)	0	0.79 (2)	0	1.32 (2)	68.50 (6.36)	68.50 (64-73)	20.50 (17.67)	20.50 (8–33)	27 (26.87)	27 (8–46)	50 (1)	100 (2)	0	0
Alcohol/substance use disorder	0.86 (2)	4.76 (1)	1.19 (3)	0	1.99 (3)	31 (1.41)	31 (30-32)	3 (2.82)	3 (1-5)	6.50 (0.71)	6.50 (6-7)	100 (3)	0	66.66 (2)	0
Mental retardation	0.86 (2)	0	0.79 (2)	0	1.32 (2)	40 (8.48)	40 (34-46)	2	2	5.50 (2.12)	5.50 (4-7)	100 (2)	0	0	0
Psychotic dis.	3.45 (8)	4.76 (1)	3.56 (9)	3.92 (4)	3.31 (5)	59.13 (15.01)	63.50 (27-72)	2.54 (0.74)	2.50 (2-4)	11.13 (5.69)	8 (6–21)	100 (9)	44.44 (4)	22.2 (2)	0
Somatoform dis.	0.43 (1)	0	0.40 (1)	0	0.66 (1)	88	-	18	-	32	-	100 (1)	100 (1)	0	0
Adjustment dis. (anx)	23.71 (55)	9.52 (2)	22.53 (57)	19.61 (20)	24.50 (37)	57.84 (16.32)	57 (28-88)	8.13 (7.57)	6 (1-35)	17.60 (12.44)	14 (1-54)	19.29 (11)	52.63 (30)	28.07 (16)	10.52 (6)
Adjustment dis. (depr)	7.33 (17)	0	6.72 (17)	10.78 (11)	3.97 (6)	61.18 (16.50)	64 (24-85)	8.41 (6.50)	6 (2-26)	21.71 (13.50)	21 (5-49)	23.52 (4)	76.47 (13)	17.64 (3)	5.88 (1)
No psychiatric diagnosis	2.16 (5)	0	1.98 (5)	3.92 (4)	0.66 (1)	67.80 (20.46)	72 (33-87)	6 (5.24)	4 (2-15)	16.80 (17.19)	12 (3-45)	20 (1)	60 (3)	60 (3)	60 (3)
Total	100 (232)	100 (21)	100 (253)	100 (102)	100 (151)										

D: Diagnosis, ICU: Intensive care unit, * According to all diagnoses, ** According to primary diagnosis

Table 3: Reciprocal distributions of the reasons for consultation according to psychiatric diagnoses and diagnoses according to reasons for consultation

Diagnosis		No diagnosis		Anxiety dis.		Bipolar dis.		Delirium		Dementia		Depressive dis.		Insomnia dis.		Drug side effect		Alcohol-substance use dis.		Mental retardation		Psychotic dis.		Somatoform dis.		Adjustment dis. (anx)		Adjustment dis. (depr.)	
Reason		→ Reasons for consultations according to psychiatric diagnoses (%)→																											
Anxiety	↓ Diagnoses according to reasons for consultation →	0	0	29.4	55.6	0	0	3.9	1.9	2.0	2.2	3.9	9.1	0	0	0	0	0	0	0	0	0	0	0	0	56.9	36.3	3.9	7.7
Confusion		0	0	0	0	0	0	75.7	26.4	16.2	13.3	0	0	0	0	0	0	2.7	20	0	0	2.7	7.7	0	0	2.7	1.3	0	0
Depressive symptoms		6.3	20	0	0	0	0	0	0	0	0	18.8	13.6	6.3	10	0	0	0	0	0	0	0	0	0	0	0	0	68.8	42.3
Evaluation for drug-drug interaction		0	0	0	0	5.0	25.0	0	0	70.0	31.1	15.0	13.6	0	0	0	0	0	0	5.0	33.3	0	0	0	0	5.0	1.3	0	0
Poor sleep		0	0	8.5	14.8	0	0	2.1	0.9	2.1	2.2	10.6	22.7	19.2	90	0	0	0	0	0	0	0	0	0	0	44.7	26.3	12.8	23.1
Alcohol-substance use		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	66.7	40	0	0	33.3	7.7	0	0	0	0	0	0
Psychomotor agitation		2.27	40	3.4	11.1	0	0	58.0	48.1	15.9	31.1	2.3	9.1	0	0	0	0	0	0	1.1	33.3	2.3	15.4	1.1	100	11.4	12.5	2.3	7.7
Psychotic symptoms		0	0	0	0	0	0	33.3	1.9	16.7	2.2	0	0	0	0	16.7	50	0	0	0	0	33.3	15.4	0	0	0	0	0	0
Death/suicidal ideation		0	0	12.5	3.7	12.5	25.0	0	0	0	0	12.5	4.6	0	0	0	0	0	0	0	0	0	0	0	0	37.5	3.8	25.0	7.7
Treatment noncompliance		2.0	20	2.0	3.7	0	0	42.0	19.8	16.0	17.8	4.0	9.1	0	0	0	0	0	0	2.0	33.3	4.0	15.4	0	0	22.0	13.8	6.0	11.5
Evaluation for somatization		16.7	20	0	0	16.7	25.0	0	0	0	0	0	0	0	0	16.7	50	0	0	0	0	0	0	0	0	50	3.8	0	0
Treatment arrangement		0	0	17.7	11.1	5.9	25.0	5.9	0.9	0	0	23.5	18.2	0	0	0	0	11.8	40	0	0	29.4	38.5	0	0	5.9	1.3	0	0

The white lines (from left to right) show the distribution of the reasons for consultation according to the diagnoses, and the gray columns (from top to bottom) show the distribution of the diagnoses according to the reasons for the consultation.

Table 4: Correlations between demographics, clinical features, and outcomes

		1. Age	2. Gender	3. Duration until consultation	4. Hospital stay	5. Past psychiatric diagnosis	6. Medical comorbidity	7. Delirium	8. Intensive care admission	9. Death
1. Age	r_s	-								
	P	-								
2. Gender (f-m)	r_s	0.022	-							
	P	0.744	-							
3. Duration until consultation	r_s	-0.166[c]	0.129[a]	-						
	P	0.011	0.049	-						
4.Hospital stay	r_s	0.088	0.118	0.472[c]	-					
	P	0.183	0.076	<0.001	-					
5. Past psyciatric diagnosis (-/+)	r_s	0.183[b]	-0.094	−0.302[c]	-0.147[a]	-				
	P	0.005	0.155	<0.001	0.027	-				
6. Medical comorbidity (-/+)	r_s	0.215[b]	0.002	0.095	0.045	-0.040	-			
	P	0.001	0.981	0.148	0.503	0.541	-			
7. Delirium (-/+)	r_s	0.385[c]	0.082	–0.075	-0.041	−0.150[a]	0.197[b]	-		
	P	<0.001	0.212	0.252	0.536	0.022	0.003	-		
8. Intensive care admission (-/+)	r_s	0.142[a]	0.063	0.037	0.255[c]	–0.075	0.044	0.260[c]	-	
	P	0.031	0.338	0.573	<0.001	0.253	0.503	<0.001	-	
9. Death (-/+)	r_s	0.229[c]	0.101	–0.005	0.090	–0.101	0.210[b]	0.410[c]	0.685[c]	-
	P	<0.001	0.125	0.940	0.173	0.125	0.001	<0.001	<0.001	-

Significant correlations are shown in bold font. [a] $P<0.05$, [b] $P<0.01$, [c] $P<0.001$.

Relationships between reasons for consultation and psychiatric diagnoses

Table 3 shows the reciprocal distribution of the reasons for consultations reported by the treating physicians and the diagnoses established by the consultant psychiatrist after the evaluation. Accordingly, delirium was diagnosed in 75.68% of the cases who had a consultation due to confusion and in 57.95% of those who were reported to exhibit psychomotor agitation. On the other hand, confusion was reported in 26.42% and psychomotor agitation in 48.11% of the cases diagnosed with delirium. Moreover, delirium was diagnosed in 42% of the cases reported to exhibit treatment non-compliance and in 33.33% of those with reported psychotic symptoms. The most common reasons for consultation for patients diagnosed with psychotic disorder were a request for treatment arrangement (38.46%) and psychomotor agitation and treatment non-compliance (15.38% for both). Finally, 70% of the requests for evaluation of drug–drug interactions involved patients with dementia.

Characteristics of treatment protocols

Notably, psychopharmacological treatment was started in 83.6% (n = 194) of the patients after the psychiatric evaluation. Accordingly, antipsychotic (AP) agents were used in 128 individuals, benzodiazepines (BZD) in 34 subjects, and antidepressants in 54 subjects with combination therapy being used in 10.83% of the patients. In terms of diagnoses, the most frequently adopted protocol for patients with delirium was AP monotherapy (91.42%). Haloperidol was the most frequently prescribed agent (n = 40) followed by an AP-BZD combination (7.14% using lorazepam in all cases). It was found that among those who were diagnosed with AD, 55.93% were started on antidepressants, 32.20% on APs, and 23.72% on BZDs, with a remarkable difference in the treatment choice between AD-A and AD-D. For the whole AD group, mirtazapine (48.48%) was the most frequently prescribed antidepressant followed by selective serotonin reuptake inhibitors (SSRIs) at 30.30%, whereas quetiapine (55.55%) and lorazepam (73.33%) were the most preferred AP and BZD agents, respectively. As for the patients with dementia (mostly treated for symptoms such as psychomotor agitation), 78.94% were started on APs (most frequently olanzapine) and 31.57% on BZDs (most frequently lorazepam) as monotherapy or in combination. It was also seen that among those diagnosed with anxiety disorders, 50% were started on antidepressants (most frequently escitalopram), 38.88% on APs (most frequently quetiapine), and 33.33% on BZDs (most frequently lorazepam) as monotherapy or in combination. Regarding the remaining less common diagnoses, patients with depressive disorder were most frequently started on antidepressants (77.77%) and SSRIs in particular, whereas quetiapine monotherapy was the most preferred regimen (66.66%) for insomnia.

Relationships between the disease course and clinical features

The mean hospital stay of the patients was 16.88 (12.71) days (median = 13). The longest durations were recorded in patients diagnosed with anxiety disorder with 23.84 (21.58) days (median = 16) and insomnia with 22.38 (17.97) days (median = 14.50), while the shortest durations were found for patients with bipolar disorder with 5 (4.24) days (median = 5) and mental retardation with 5.50 (2.12) days (median = 5.50). It was seen that 31.46% (n=73) of the patients had the need for IC during the treatment course. The rate of IC unit admission in women was found to be significantly lower than in men (27.77% versus 33.80%; P=0.001). In terms of diagnoses, 50.68% of the patients diagnosed with delirium, 28.07% of those diagnosed with AD-A, and 17.64% of those diagnosed with AD-D had a history of ICU admission (Table 2).

It was found that 20.69% (n = 48) of the patients who underwent psychiatric consultation died during their stay in the hospital with the mortality rate being significantly lower in women than in men (15.55% versus 24.46%; P=0.001). Of note, the highest mortality rate (60%) was recorded in a small number of patients who underwent consultation due to treatment non-compliance (such as unwillingness to wear an oxygen mask) but were not diagnosed with a psychiatric condition at the end. Not surprisingly, among those with an established psychiatric diagnosis, the highest mortality was observed in the delirium group (45.20%). Again, 67.12% of those with delirium were males, and the mortality rate among male delirium patients was significantly higher than that of women (48.97% versus 37.5%; P=0.003). The rates of delirium and mortality among the patients without a history of chronic diseases were 20% and 10%, respectively, whereas the rates were 38.73% and 27.46%, respectively, for those having medical comorbidities. Similarly, 75.34% of the delirium cases and 81.25% of the deceased patients had at least one medical comorbidity.

Correlations between variables of interest

Inter-correlations are shown in Table 4. The duration from admission to psychiatric consultation positively correlated with the length of hospital stay and negatively correlated with having a past medical history of psychiatric diagnosis (P<0.001 for both). Notably, a history of psychiatric diagnosis was also associated with a shorter hospital stay and a lower rate of delirium (P=0.027 and 0.022, respectively). Not surprisingly, the presence of medical comorbidities, delirium, need for IC, and death during the treatment course were strongly inter-correlated.

Temporal course of the consultation requests and the distribution of psychiatric diagnoses

In terms of the monthly distribution of the psychiatric consultations, it can be seen that 25% (n = 58) of the consultations were requested in December 2020, while the lowest number of consultations were recorded during the first months after the hospital had open for service (Figure 1). It was also observed the rate of dementia was highest in June 2020 (62.5%; n = 15), moreover, these patients constituted 45.45% of all dementia cases over a 1-year period. As for delirium, which was relatively infrequent during the first months of the pandemic, the total number of the cases exhibited a significant increase between October and December 2020 with remarkably high rates of 42.85%, 31.25%, and 41.37%, respectively. Following a two-month decline, the increase resumed as of March 2021 reaching a rate of 40.62% (n = 13) by April 2021. Finally, the total number and the rates of patients diagnosed with AD were highest in October and December 2020 (34.37% and 37.93%, respectively).

In terms of the temporal pattern of the use of psychotropic medications, it was observed that the preference for

haloperidol became increasingly significant over time compared to other APs, whereas no such change was evident for the BZDs and antidepressants. As for delirium, for which APs are the most common treatment options, the rate of haloperidol usage gradually increased from 0% (the first four-month period) to a strikingly high percentage of 82.60% by the last four-month period.

Logistic regression for the prediction of death

In the logistic regression analysis, the occurrence of death over the course of COVID-19 treatment was determined as the binary outcome variable of interest (0: lived, 1: deceased). Accordingly, death over the course of treatment was predicted by the presence of delirium (test–retest reliability [TRR] = 7.01, 95% confidence interval [CI] = 3.43–14.32; $P<0.001$) and medical comorbidities (TRR = 2.58, 95% CI = 1.12–5.93; $P=0.026$). Taken together, the regression model predicted survival and death among the patients with an accuracy of 85.3% and 58.3%, respectively ($P<0.001$).

Discussion

The present study aimed to provide a multidimensional view of the psychiatric consultations requested for inpatients admitted to a specialized pandemic hospital with a diagnosis of COVID-19 over a one-year period from the onset of the pandemic in Turkey. The main research objectives were to examine the characteristics of and relationships between several clinical variables, including patients' socio-demographics, the reasons for psychiatric consultation, psychiatric diagnoses and treatment arrangements after evaluation, clinical courses and outcomes of the inpatient treatment, and temporal course of these variables during the pandemic.

Demographics and clinical characteristics

It can be seen that the rate of male patients was significantly higher than females and the mean age of the sample was strikingly high compared to the general CLP practice. These findings are likely to related to the overall demographic profile of the inpatients with COVID-19, given that both male gender and older age are associated with a more severe clinical prognosis and increased need for hospitalization during the pandemic [11–13]. From a broader perspective of "neuropsychiatric disorders", it is seen that the most common premorbid diagnosis among patients was dementia (on the other hand, the reason for consultation and the treatment arrangements was directly linked to dementia only in a minority of these patients). Strikingly, a significant portion of psychiatric consultations regarding patients with dementia were requested in June 2020. A detailed examination of the records revealed that the observed surge was mostly due to the mass hospitalizations of infected elderly patients from nursing homes regardless of their clinical status on the grounds that isolation measures could not be provided in their institutions. Accordingly, the main reasons for psychiatric consultations for these patients mostly consisted of treatment non-compliance, agitation, and/or the evaluation for the drug–drug interactions between the psychotropics and the medications used for the treatment of COVID-19 (especially hydroxychloroquine). On the other hand, the rate of delirium and/or death was remarkably low in these patients. In line with these findings, in their systematic review, Simonetti et al. [14] reported that the most common symptoms among dementia patients with COVID-19 are apathy, anxiety, and agitation, which could all be partially attributed to the effects of hospitalization and long-term social isolation. On the other hand, the high mortality rate (62.2%) reported among dementia patients hospitalized due to a more severe clinical condition (COVID-19 pneumonia, and others) [15] indicates that the prognosis may be detrimental in special subgroups.

Several factors, such as the rapid spread of the disease, increasing pressure on the health system, increase in the knowledge and clinical experience about the disease, and initiation of the vaccination program in elderly patients as of January 2021 seem to have resulted in substantial changes in the clinical profiles of the patients admitted to hospitals. Indeed, as the impact of the pandemic gradually became more and more detrimental, the proportion of the psychiatric consultations requested for patients with a primary diagnosis of dementia decreased, while the rates of delirium and overall mortality exhibited dramatic increases.

One of the strengths of our study is that the reasons for psychiatric consultation (as stated by the treating physicians) and the diagnoses established by the consultant psychiatrist after evaluation were systematically categorized and analyzed as separately parameters. Accordingly, the most common reasons for consultation in our sample were found to be psychomotor agitation, anxiety, treatment non-compliance, insomnia, and confusion. After psychiatric evaluation, approximately three-fourths of all cases were diagnosed with delirium, AD, and/or dementia. This distribution seems consistent with the findings of a few previous studies conducted on smaller samples [10, 16]. Aside from delirium and dementia, which are neuropsychiatric syndromes characterized by neurocognitive dysfunction, the most common psychiatric diagnosis established after hospitalization was found to be AD. Notably, it can be seen that only one-fifth of those diagnosed with ADs had a past medical history of psychiatric disorders, and only 1/7 of them had used psychotropic medications before hospitalization. On the other hand, the majority of those diagnosed with anxiety disorder and/or depression do have a history of psychiatric diagnosis before hospitalization, and more than half had used psychotropic agents. These two diagnoses may therefore not be directly associated with the effects of COVID-19 infection and related stressors for the affected individuals in our sample. Of course, the symptoms associated with premorbid depression and anxiety disorders may have become exacerbated during hospitalization as also supported by previous evidence [17]. Nevertheless, the cross-sectional nature of our study prevents us from drawing any further inference on this matter.

It is noteworthy that approximately three-fourths of those diagnosed with AD met the characteristics of AD-A, which is in line with previous studies indicating that anxiety symptoms are more common than depression among patients with COVID-19 [18]. Indeed, physical problems caused by the disease and/or the treatment (dyspnea, intubation, and others.), challenging conditions specific to treatment (social isolation, uncertainty about the disease and treatment efficacy, and others), and the flow of distressing information in the media (high mortality rates, among others) might potentially elicit further anxiety and

fear of death among patients [19, 20]. In a prospective cohort study conducted with 44 patients with COVID-19, an increase in anxiety and depression scores was reported in 36% and 29%, respectively, of the patients as per the admission. The rates for high anxiety and depression decreased to 9% and 20%, respectively, after two weeks of follow-up [21].

Another striking finding is that the rate of medical comorbidity was significantly higher in patients diagnosed with AD-D or depressive disorder than in those diagnosed with AD-A or anxiety disorder. Similarly, the rates of AD-D and depressive disorder among those with a medical comorbidity were two and three times higher, respectively, than in the group without such a comorbidity. Although causal underpinnings of this observation extend beyond the scope of our study, the finding is consistent with previous literature in the sense that chronic medical comorbidities have been strongly associated with depression [22, 23].

The findings of our study additionally indicate that insomnia might stand as another common psychiatric condition that is in close association with COVID-19 and/or hospitalization. Indeed, several studies indicate that insomnia stands out as a common clinical condition associated with COVID-19, especially among inpatients [24, 25]. One possible mechanism for the insomnia might be irregular circadian rhythms caused by the disease, treatment process, and/or protective measures [18, 26]. A recent study reported that 40% of 402 inpatients with the diagnosis of COVID-19 exhibited clinically significant insomnia symptoms by the first month after discharge [27]. A multicenter cohort study from the United States found that insomnia was among the most frequent newly diagnosed psychiatric disorders occurring within 14 to 90 days after the disease [18]. Finally, a meta-analysis of 31 studies on the prevalence of psychiatric symptoms in patients with COVID-19 found that the prevalence for sleep disorders was 34% [28].

Our findings show that a relatively small number of the consulted patients had a premorbid diagnoses other than anxiety/depressive disorders, namely patients with bipolar disorder, psychotic disorders, mental retardation, and ASUD collectively constitute a small portion (7.5%) of the diagnoses established after evaluation. Notably, a substantial proportion of the reasons for consultation in these patients consisted of requests for treatment arrangements, evaluation for drug–drug interactions, and treatment non-compliance. Some case reports in the literature suggest that isolated manic or psychotic episodes might occur due to COVID-19 infection although a causal link between COVID-19 and bipolar/psychotic disorders has not been established [29–31]. Of note, no such case was present in our sample.

Treatment non-compliance has become an important agenda in the COVID-19 wards. Indeed, adherence to the strict treatment protocols can be extremely challenging for many patients. In our sample, psychomotor agitation and/or treatment non-compliance were cited as the reasons for psychiatric consultation in approximately one-third of the patients diagnosed with psychotic disorders, two-thirds of those with mental retardation, and nearly half of the patients with dementia. It has been reported that patients with psychosis experience more problems in complying with preventive measures and treatment protocols, and that these patients are more reluctant to accept vaccinations and isolation protocols [32]. Similarly, patients with mental retardation are also reported to be at increased risk of abuse due to their difficulties in understanding and adapting to special requirements [33]. From this point-of-view, it seems imperative for policy makers to develop multidimensional strategies to include care institutions, social service units, non-governmental organizations, and healthcare workers to increase treatment compliance among these vulnerable subgroups [34].

Treatment protocols

It is noteworthy that some agents were more frequently prescribed than others in the same class and that the preference pattern varied within the temporal course of the pandemic. During the pandemic, many psychiatrists working in the field of CLP had to make critical decisions and needed to improve their knowledge about specific medications (hydroxychloroquine, tocilizumab, favipiravir, remdesivir, azithromycin, and others) in addition to possible drug interactions that they were aware of at an anecdotal level [35, 36]. For example, in the early periods when hydroxychloroquine was extensively used for treatment, the use of haloperidol was largely avoided (possibly due to the risk of cardiological side effects and interactions). However, it was observed that the preference for olanzapine turned in favor of haloperidol as treatment protocols and patient profiles changed over time. Indeed, olanzapine is known for its anticholinergic side effects that have been associated with an increase in delirium severity in elderly hospitalized patients [37, 38]. Again, mirtazapine, sertraline, and escitalopram, which were the most preferred antidepressants, and lorazepam, which was the most commonly administered BZD in our sample, stand out as plausible treatment options that are mostly in line with the recommendations of the corresponding guidelines [39, 40].

In our study, the fact that the shortest durations for psychiatric consultations were associated with psychomotor agitation and treatment non-compliance might reflect the hierarchy of requirements in the pandemic wards in which compliance with treatment protocols and preventive measures are of vital importance. In this context, determining the early needs of all hospitalized patients, increasing treatment compliance, planning preventive approaches, and providing psychoeducation stand out as highly important aspects of CLP practice during the pandemic [41, 42].

Delirium and death

Not surprisingly, the highest rates of intensive care requirements and mortality were recorded among the patients diagnosed with delirium [20]. Findings from different studies indicate that the incidence of delirium in patients diagnosed with COVID-19 varies between 9% and 14.8% [43, 44]. The logistic regression model created with the variables examined in our study showed that delirium and medical comorbidities were the strongest predictors of death among COVID-19 patients who underwent psychiatric consultation. Similarly, a study conducted on 707 inpatients in Brazil reported delirium as an independent predictor of hospital deaths due to COVID-19 in patients over 50 years of age [45]. In another study conducted in Spain, delirium and a history of mood disorder were associated with high mortality [46]. In this regard, early recognition of delirium in COVID-19 patients (in our study, a significant proportion of the

patients diagnosed with delirium were consulted for non-specific reasons other than confusion), and consideration of the most appropriate treatment options on an individual basis still constitute a critical agenda in CLP practice in hospitals.

Strengths and Limitations

The findings of our study should be approached within the framework of several methodological limitations. The fact that the sample consisted only of patients who underwent psychiatric consultation limits the generalizability of the findings concerning the characteristics of neuropsychiatric symptoms and the rates of psychiatric disorders among inpatients with COVID-19. Considering that the number of inpatients admitted to our hospital was around 6000 over the first one-year period, it is likely that the incidence of these conditions might actually be higher than reflected in psychiatric consultations. Furthermore, due to the fact that a large number of psychiatry residents have been assigned as ward physicians during the pandemic, many clinical situations might have been handled without being subject to official psychiatric consultations through the hospital's medical record system. Another limitation is that information about the dose and duration of the treatments were not included in the data analysis due to technical restrictions.

On the other hand, the fact that the present findings and observations on psychiatric consultations reflect the general profile of COVID-19 patients treated in one of the largest pandemic hospitals in our country, the inclusion of several well-defined clinical variables in the multidimensional analyses and the emphasis on the temporal course of these variables throughout the one-year period from the onset of the pandemic stand out as the strengths and distinguishing features of our study. In addition, systematic and multi-level classification of the variables of interest (such as the reasons for consultation and post-evaluation diagnoses under separate headings) and the distinction between clinical entities (such as the subtypes of AD) might contribute to a better understanding of the relationship between the observed symptoms and underlying clinical diagnoses.

Conclusion

As in other fields of public health, the COVID-19 pandemic has caused a detrimental and multi-faceted impact on psychiatric treatment services. Neuropsychiatric symptoms and syndromes associated with the disease have become a focus of interest during daily CLP practice in several institutions, such as in the pandemic hospitals, in which inpatient COVID-19 treatment is delivered. In the present case, our findings collectively indicate that AD and delirium were the two most common diagnoses among COVID-19 patients who underwent psychiatric consultations during the first year of the outbreak. It should also be noted that the characteristics of the consultations and the treatment preferences exhibited significant variability over the course of the pandemic.

During the ongoing struggle against COVID-19, the knowledge and experience gained in the field of CLP might contribute to the recognition of disease-related neuropsychiatric syndromes and the implementation of appropriate treatment interventions in the coming years. We also believe that the treatment experiences gained with COVID-19 patients having severe mental disorders might provide guidance for the development of specialized treatment strategies and social policies to target these specific groups.

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Surprise in hernia sacs: Malignant tumor metastasis

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Ethics Committee Approval
The study was approved by the Hatay Mustafa Kemal University Non-interventional Clinical Research Ethics Board (approval number: 37, date: 17.06.2021).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Malignant tumors are rare in the hernia sac, and there are very few studies on this subject in the literature. We aimed to investigate the malignancies in surgically resected hernia sacs and their clinicopathological features in the last ten years in our institution.
Methods: The hernia sac specimens sent for pathological examination between 2010 and 2021 were included in this retrospective cohort study. The age and gender of the patient, the type of hernia and known malignancy history of all patients were recorded. Cases with malignancy in the hernia sac were selected and their slides were re-evaluated. The cases with and without malignancy in the hernia sac were compared in terms of age, gender and known cancer history.
Results: There were 455 hernia sac specimens belonging to 448 patients which underwent pathological examination between 2011 and 2021. Malignancy was detected in ten (2.20%) hernia sacs. Eight were malignant tumor metastases (1.75%). The remaining two were secondary involvement of another malignancy. Five malignant tumors were ovarian serous carcinoma, one was vulvar squamous cell carcinoma, one was appendiceal mucinous cystadenocarcinoma, one was malignant melanoma metastasis, one was undifferentiated pleomorphic sarcoma, and one was non-Hodgkin lymphoma. The incidence of hernia sac malignancy was similar in male and female patients (3.5% and 1.4%, respectively; P=0.190). There was a known cancer history in 70% (n=7) of ten patients with malignancy in the hernia sac. The incidence of malignancy in the hernia sacs of patients with a known cancer history was significantly higher (P<0.001). Malignancies were present in 0.95% (n=2) of inguinal hernias, 1.67% (n=2) of abdominal hernias and 5.45 % (n=6) of incisional hernias. Gross pathology was detected in the macroscopic examination of all malignant inguinal hernias, but not in any of the abdominal hernias.
Conclusion: We recommend the microscopic examination of hernia sacs, even if there is no macroscopic abnormality, especially in the elderly and/or patients with a history of malignancy, in order to detect incidental metastases.

Keywords: Hernia sac, Incidental, Malignant tumor, Metastasis, Pathological findings

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Introduction

Malignant tumors are rare in the hernia sac. Urachal carcinoma, malignant mesothelioma, and umbilical cord liposarcoma are primary tumors of the hernia sac and are extremely rare. Malignant tumor in the hernia sac may occur as a metastasis or the secondary involvement of another cancer. Most metastatic tumors are malignant epithelial tumors, and colorectal carcinoma metastasis is most frequently observed in the hernia sac [1-6]. Metastases originating from ovarian, prostate, pancreatic, appendix, peritoneum, endometrium, and stomach cancers have also been reported [1-4, 7-14]. Rarely, the hernia sac may be the first presentation of an unknown malignancy. Clinicopathological correlation and detailed immunohistochemical studies are required to determine the origin. Although some authors are strong advocates of routine histological examination of hernia sacs, others suggest that hernia sacs should be discarded after gross examination [9]. There are a very few studies on malignant tumors in the hernia sac in the literature. Those that have been published are usually case reports [1-4, 9, 10]. In these studies, the rate of malignant tumor detection in the hernia sac ranged from 0.07% to 0.7% [1-4, 9, 10].

We aimed to investigate the malignancies in surgically resected hernia sacs and their clinicopathological features in the last ten years in our institution.

Materials and methods

The hernia sac specimens sent for pathological examination between 2010 and 2021 were included in this retrospective cohort study by examining the pathology database of Hatay Mustafa Kemal University. Our routine practice is to perform a histologic examination of every hernia sac material sent to our pathology laboratory, even if gross pathology is not detected. The age, gender, symptoms, type of hernia and known malignancy history of all patients were recorded. The cases with and without malignancy in the hernia sac were compared in terms of age, gender and known cancer history. Cases with malignancy in the hernia sac were selected and their slides were re-evaluated. Primary tumor focus, macroscopic features of the hernia sac, and histopathological features of the tumor were evaluated in these cases.

The study was approved by the Hatay Mustafa Kemal University non-interventional Clinical Research Ethics Board (approval number: 37, date: 17.06.2021) and conducted according to the ethical standards of the Helsinki Declaration.

Statistical analysis

All data were analyzed in the SPSS 21 package program (SPSS Inc., Armonk, NY, US). The number, and the frequency of the qualitative data were given. The median, interquartile range (IQR), minimum (min) and maximum (max) values of the quantitative data were given. The Fisher-exact test was used to compare qualitative data. The Mann-Whitney U test was used in the analysis of the quantitative values between the two groups. A value of $P<0.05$ was considered significant.

Results

There were 455 hernia sac specimens belonging to 448 patients who underwent a pathological examination between 2011 and 2021. An average of 2.6 paraffin blocks was prepared per case. The median age of the patients was 52.95 (IQR: 42-65, min:1 max:97) years. Of 448 patients, 170 (37.9%) were female and 278 (62.1%) were male. Twenty-three percent (n=103) had umbilical hernias, 46.9% (n=210) had inguinal hernias, 1.3% (n:6) had femoral hernias, 24.6% (n=110) had incisional hernias, 0.9% (n=4) had ventral hernias, 3.1% (n=14) had epigastric hernias and 0.2% (n=1) had parastomal hernias.

Malignancy was detected in ten (2.20%) hernia sacs. Eight were malignant tumor metastases (1.75%). The remaining two were secondary involvement of another malignancy. Five of ten cases (50%) were ovarian serous carcinoma metastases, one was squamous cell carcinoma of the vulva (10%), one was appendix mucinous cystadenocarcinoma metastasis (10%), one was malignant melanoma metastasis (10%), one was undifferentiated pleomorphic sarcoma (UPS) (10%) and one was non-Hodgkin lymphoma (NHL) (10%) (Table 1). NHL and UPS were considered secondary involvement of another malignancy.

Six of the ten cases were female (60%) and four were male (40%). In the general cohort, the incidence of hernia sac malignancy was similar between the male and female patients (3.5% and 1.4%, respectively; $P=0.190$).

The median age of the patients with and without malignancy in the hernia sac were 60.70 (IQR: 51.2-66; min:45, max:88) years, and 52.77 (IQR: 41-65; min:0, max:97) years, respectively ($P=0.277$).

In the entire cohort, the rate of patients with a known cancer history was 6% (n=27). The incidence of malignancy in the hernia sacs of patients with a known cancer history was significantly higher ($P<0.001$). Twenty of 438 patients (4.6%) without a tumor in the hernia sac had a known cancer history. There was a known cancer history in 70% (n=7) of ten patients with malignancy in the hernia sac. Of these, four had a history of ovarian serous carcinoma, one had a history of vulvar squamous cell carcinoma, one had a history of appendiceal mucinous adenocarcinoma, and one had a history of malignant melanoma. Postoperative ovarian cancer was detected in one patient. In these cases, the classification of tumor origin in the hernia sac was confirmed by clinical and histomorphological comparisons and limited immunohistochemical studies (Figure 1). Two (20%) patients had a suspicion of malignancy before the operation, and three (30%), during the operation. Two of the five patients with no suspicion of malignancy in the hernia sac had a metastatic mass in the peritoneal tissue. The median time between the first primary tumor diagnosis and the presentation of hernia sac malignancy was 23 (range: 7-51) months.

Gross pathology was observed in 50% (n=5) of hernia sacs macroscopically. Malignancies were present in 0.95% (n=2) of inguinal hernias,1.67% (n=2) of abdominal hernias (umbilical+ventral+epigastric), and 5.45 % (n=6) of incisional hernias (Table 2). Gross pathology was detected in the macroscopic examination in all malignant inguinal hernias, but in none of the abdominal hernias (Table 1).

Figure 1: A: Serous carcinoma metastasis (Hematoxylin-eosin X40) and immunohistochemical studies show that tumor cells are positively stained with p53 (above right). B: Well-differentiated squamous cell carcinoma metastasis is observed (Hematoxylin-eosin X40). C: Melanoma metastasis (Hematoxylin-eosin X40). In the immunohistochemical study, it is seen that tumor cells are positively stained with Melan-A (above right).

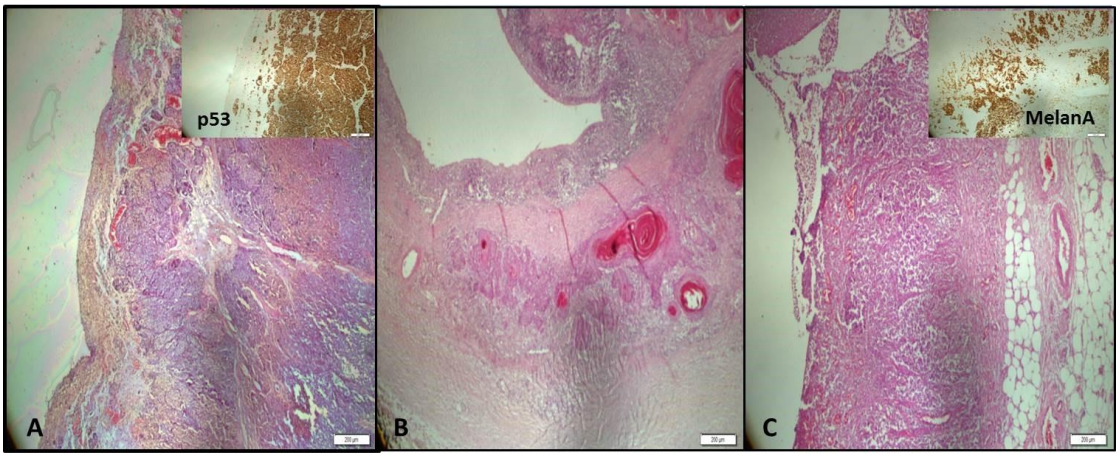

Table 1: Clinicopathological features of patients with malignancy in the hernia sacs

Case no	Gender	Age	Complaint	Hernia type	Diagnosis	Primary site	Macroscopic abnormality	Known cancer history
1	F	45	Abdominal pain	Incisional	Serous carcinoma	Ovary	Absent	Present
2	F	59	Abdominal pain	Incisional	Serous carcinoma	Ovary	Present	Present
3	F	60	Abdominal pain, vomiting	Umbilical	Serous carcinoma	Ovary	Absent	Absent
4	F	53	Abdominal swelling	Incisional	Serous carcinoma	Ovary	Absent	Present
5	F	58	Abdominal pain	Incisional	Serous carcinoma	Ovary	Absent	Present
6	F	88	Pain	Incisional	Squamous cell carcinoma	Vulva	Present	Present
7	M	61	Abdominal pain	Incisional	Mucinous adenocarcinoma	Appendix	Present	Present
8	M	81	Abdominal swelling	Epigastric	Malign melanoma	Skin	Absent	Present
9	M	52	Inguinal swelling, pain	Inguinal	Undifferentiated pleomorphic sarcoma	-	Present	Absent
10	M	49	Abdominal pain	Inguinal	Non-Hodgkin Lymphoma	Lymph node	Present	Absent

Table 2: Distribution of malignancy by hernia types in our cohort

Hernia type	Count	Malignant diagnosis in hernia sac n(%)
Incisional	110	6 (5.45)
Inguinal	210	2 (0.95)
Femoral	6	0 (0.00)
Ventral+epigastric	4+13	1 (5.88)
Parastomal	1	0 (0.00)
Umbilical	103	1 (0.97)

Table 3: Review of the literature and summarizing key points

Article	Hernia count	Malignant diagnosis in hernia sacs n(%)	F/M	Median age	Known cancer history	No gross abnormality	Primary tumor site
Nicholson et al.[1]	22816	15 (0.07)	4/11	65	60%	0%	GIS 40%,ovary 20%,prostate 13%,mesothelium 13%,unknown 13%
Wang et al.[10]	1426	10 (0.7)	5/5	76.5	70%	50%	Cholangiocarcinoma 10%, CLL 20%, prostate 10%, peritoneum 10%, ovary 20% endometrium 10%, pleomorphic sarcoma 10%,pancreas 10%
Roberts et al. [9]	3117	11 (0.35)	9/2	68	30%	73%	Ovary or fallopian tube 45.5%, breast 9.1%, prostate 9.1%. unknown 36.3%
Val-bernal et al.[2]	8435	12 (0.14)	4/8	67	50%	25%	GIS 50%, gynecological 25%, lung 8.3%,peritoneum 8.8%, unknown 8.3%
Topal et al.[3]	556	9 (0.61)	7/2	60	66.7%	22.2%	GIS 55.5%,ovary 22.2%, epididymis11.1%, breast 11.1%
Zhang et al.[4]	4301	21 (0.49)	7/14	65	66.7%	40%	GIS 52%, pancreatobiliary 24%, gynecological 24%,
This Study	455	10(2.20)	6/4	60.7	70%	50%	Ovary 50%, vulva 10%, appendix 10%, melanoma 8.3%, NHL10%, pleomorphic sarcoma 10%

GIS: Gastrointestinal system, CLL: Chronic lymphocytic lymphoma, NHL: Non-Hodgkin lymphoma

Discussion

An abdominal hernia is a common condition and a surgically removed hernia sac is a highly common sample for pathologists. Malignant tumors in the hernia sac are very rare and may occur as the first finding in a patient with no previous history. In that case, like in any other pathological diagnosis, tumor histomorphology, immunohistochemical profile, clinical information, imaging findings, and serum tumor markers are all required to help identify the tumor origin. Until now, no definite common etiology was found for abdominal wall hernias and any type of cancer. However, obesity can be mentioned as the common denominator of these two separate diseases. There is evidence of a relationship between obesity and many different cancers, including breast, liver, colorectal, pancreatic, prostate, endometrial, and renal cell carcinoma [15-17]. Metabolic changes caused by obesity may directly or indirectly initiate cancer development [18]. On the other hand, it has been reported that obesity is a predisposing factor for abdominal hernias and increases the risk of recurrence [17, 19].

Although there is no proven cause and effect relationship between hernia and cancer, data are in support of this relationship. In addition to the publications advocating that cancer increases the risk of hernia, there is also literature showing that the hernia itself can cause cancer [17]. The pathway for tumor cells to spread into the hernial sac remains unclear. Lymphatic or hematogenous spread, direct invasion, and localized peritoneal carcinomatosis are possible mechanisms of metastasis. The hernia sac is not essentially a normal anatomical structure, and a voluminous tumor itself may cause a hernial sac with mass effect and increased intra-abdominal pressure [4, 17].

Especially advanced stage cancers may cause enlargement of the peritoneum with the formation of ascites or mucinous cancers causing pseudomyxoma peritonei with the effect of space-occupying mucin. As a result, the tumor mass can spread into the hernia sac with the effect of increased intra-abdominal pressure and gravity [4]. Sugarbaker [20] detected metachronous or synchronous inguinal hernia in 9.6% (n=17) of 178 pseudomyxoma peritonei cases secondary to mucinous neoplasm of the appendix. In addition to these, chemotherapy and/or radiotherapy may also be a risk factor for the development of incisional hernia [21].

There are limited studies in the literature investigating malignant tumors in the hernia sac [1-4, 9, 10]. The incidence of cancer in the hernia sac in these cohorts ranged from 0.07 to 0.7%. In our study, malignancy was detected in ten (2.20%) of 455 hernia sacs. Our metastatic tumor rate in the hernia sac was 1.75% (n=8), which was above the rates reported in the literature. The reason for this may be that we are the only tertiary center hospital in the region and therefore the rate of cancer patients followed in our hospital is high. In the literature, it has been reported that patients with tumors in the hernia sac have a history of malignancy at rates varying between 30% and 66.7% [1-4,9,10]. However, no history of malignancy of the general cohort was mentioned in any of these studies. In the entire cohort, the rate of patients with a known cancer history was 6% (n=27). Twenty (n=20) of 438 patients (4.6%) without a tumor in the hernia sac had a known cancer history. There was a known cancer history in 70% (n=7) of ten patients with malignancy in the hernia sac (P<0.001). This indicates that the probability of finding cancer in the hernia sac is higher in patients with a history of cancer than in patients without.

Colon carcinoma metastasis is most frequently detected in the hernia sac [1-6]. Among studies investigating metastatic carcinomas in the hernia sac, Zhang et al. [4] presented the largest cohort with 21 cases. In their study, they found the most common metastases originating from the pancreaticobiliary and gynecological systems in the hernia sac. They reported that the primary focus was serous carcinoma of the ovary in female patients and gastrointestinal or pancreatobiliary malignancy in male patients [4]. Providing the second largest cohort, Nicholson et al. [1] reported the most common malignant formation as GIS (40%) and second as ovary originated malignancies (20%); however, the most common ovarian cancer metastasis in women in their cohort is 75%. In our study, ovarian serous carcinoma metastasis was found most (50%, n=5). Metastases originating from the GIS were detected only in 10%. This may be since 60% of our patients with malignancy were women.

Very few cases of squamous cell carcinoma (SCC) metastasis in the hernia sac have been reported in the literature [22-24]. Katsourakis et al. [23] and Quayumi et al. [24] reported cases of SCC in the bladder herniated into the inguinal canal. Best et al. [22] reported metastatic squamous cell carcinoma originating from the bladder in the hernia sac. Christofi et al. [25] reported a case of SCC originating from the cervix in the incarcerated small bowel tissue in the umbilical hernia sac in a 59-year-old patient. In our study, there was a case of SCC originating from the vulva in an incisional hernia sac in an 88-year-old female patient. In the patient's history, vulva SCC was diagnosed 14 months ago. In our review of the English literature (search: PubMed, date: 22.06.2021, key words: hernia, squamous cell carcinoma), no case of SCC metastasis of the vulva in the hernia sac was found so far.

Undifferentiated pleomorphic sarcoma (UPS) is very rare, and its incidence is 0.08-1 per 100,000 [26]. So far, pleomorphic sarcoma has been detected in abdominal wall hernia in only one case (search: PubMed, date: 22.06.2021, keywords: hernia, pleomorphic sarcoma) [10]. In our study, UPS was detected in the inguinal hernia sac in a 55-year-old male patient, as the second case in the literature.

The American College of Pathologists recommends the pathological examination of all resected hernia sacs and microscopic examination of all abdominal hernias but leaves the decision of microscopic examination of macroscopically normal inguinal hernias to the discretion of the pathologist/institution [27]. The study of Wang et al. [10] and Topal et al. [3] supports this view. Val-Bernal et al. [2], on the other hand, recommends pathological examination of all hernia sacs without distinguishing them as inguinal or abdominal hernias, and microscopic examination only for those with macroscopic pathology. Nemer et al. [28] recommended sampling only the sacs with patients older than 50 years of age, positive oncology history, or unusual gross findings. However, in the literature, it is remarkable that 22.2-73% of cases with malignancy in the hernia sac were not found to have gross pathology [1-4, 9, 10] (Table 3). In this study, there was no gross pathology in 50% of the cases with malignancy in the hernia sac. A gross macroscopic pathology was observed in all malignant inguinal hernias and in none of the abdominal hernias.

Conclusion

In conclusion, the incidence of malignancy in hernia sacs in this study was 2.2%, and the majority were metastatic tumors. While ovarian serous carcinoma metastasis is most common in female patients, no particular system dominance was detected in the male patients. We recommend the microscopic examination of hernia sacs, even if there is no abnormality in the macroscopic examination, especially in the elderly and/or patients with a history of malignancy, to detect incidental metastases.

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Diabetic retinopathy treatment and management during the COVID-19 pandemic

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Ethics Committee Approval
This study was approved by the University of Health Sciences, Gazi Yaşargil Education Research Hospital, 16.10.2020 / 598.
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: Diabetic macular edema (DME) is a common retinal disease and is the most common cause of vision loss due to diabetic retinopathy. During the COVID-19 pandemic, there has been a serious decrease in hospital visits due to both the measures taken by governments and the anxiety of patients fearful of contracting COVID-19. The aim of this study is to determine the problems occurring during the COVID-19 pandemic period in patients treated with intravitreal (IV) injection for diabetic retinopathy, and to provide recommendations for treatment management in these patients.

Methods: Twenty-nine eyes of 17 patients who were diagnosed with DME were included. The frequency of hospital visits, treatments performed, and detailed ophthalmological examination findings, including optical coherence tomography findings and glycated haemoglobin (HbA1c) values, were recorded in the period before the COVID-19 pandemic. During the COVID-19 pandemic period, the detailed ophthalmological examination findings and HbA1c values were noted after the patients who had delayed their routine control time (>90 days) applied to the hospital. New treatments were planned according to the current situation.

Results: Seventeen patients were included in the study; 10 were female (58.8%) and seven were male (41.2%). The mean time interval between following visits was 45.5 (5.9) days during the pre-pandemic period, but it increased to 110.4 (13.5) days during the COVID-19 pandemic period (P<0.001). Visual acuity (LogMAR) was 0.4 (0.4) in the pre-pandemic period and 0.8 (0.5) during the COVID-19 pandemic period (P=0.003). Central macular thickness was 300.1 (85.6) µm in the pre-pandemic period and it increased to 387.1 (144.5) µm during the COVID-19 pandemic period (P=0.007). In three patients, complications of diabetic retinopathy that could not be cured by medical treatment developed and surgical treatment was recommended.

Conclusions: Delays in the treatment of diabetic retinopathy may cause permanent impairment in visual functions. The COVID-19 pandemic has caused an increase in the hospital visit intervals of patients, and this situation has resulted in disruptions in the follow-up and treatment of patients with diabetic retinopathy. Alternative diagnosis and treatment practices are needed in order to manage these and similar processes smoothly.

Keywords: COVID-19, Diabetic retinopathy, Intravitreal injection, Optical coherence tomography

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Introduction

Diabetic macular edema (DME) is a common retinal disease and is the most common cause of vision loss due to diabetic retinopathy [1]. The prognosis of DME depends on various factors, such as age, glucose regulation and other systemic diseases (e.g. hypertension, renal disorders) [2]. Direct fundus examination and fundus fluorescein angiography are used for the diagnosis of DME. Furthermore, there have been important advances in the diagnosis and treatment of DME following the development of optical coherence tomography (OCT) technology, which plays an important role in the diagnosis and follow-up of, and treatment planning for diabetic patients [1].

The most important step in DME treatment is metabolic regulation, and while laser photocoagulation is often the first treatment option, anti–vascular endothelial growth factor (VEGF) agents have also entered the ophthalmology practice, resulting in changes in treatment algorithms. VEGF is an important mediator that causes abnormal vascular permeability in DME [3]. There are different anti-VEGF agents used as an intravitreal (IV) injection in the treatment of DME to supress rising VEGF levels [4-6]. In addition to anti-VEGF agents, long-acting IV steroid injections are also used in the treatment of DME [7, 8]. Routine ophthalmological controls are performed in certain periods in patients with a diagnosis of diabetic retinopathy, and IV injections are applied according to various treatment protocols.

The coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus was first identified in Wuhan, China, by the ophthalmologist, Dr Wenliang Li, at the end of 2019 [9]. The disease spread worldwide in a short period of time, and the World Health Organization declared COVID-19 as a pandemic on March 11, 2020 [10]. The transmission of the disease through droplets caused many countries to take local precautions, and routine examinations and practices in healthcare facilities became limited except for in the cases of emergencies and semi-emergencies [11]. With the spread of cases in March 2020 in Turkey, the government implemented some restrictive measures in order to control the distribution rate of the virus, similar to other countries.

During the COVID-19 pandemic, there has been a serious decrease in hospital visits due to both the measures taken by governments and the anxiety of patients fearful of contracting COVID-19, which has led to morbidity and mortality due to delays in treatment of some acute and chronic diseases. The aim of this study is to examine the anatomical and functional results of diabetic macular edema in diabetes mellitus (DM) patients due to the prolongation of routine periodic examination intervals during the COVID-19 pandemic, and to provide recommendations for treatment management in these patients during the pandemic.

Materials and methods

This was a prospective, observational study conducted in Diyarbakır Gazi Yaşargil Training and Research Hospital. Ethics Committee approval was obtained for the study (University of Health Scıences Gazi Yaşargil Education Research Hospital, 16.10.2020 / 598), written informed consent form was obtained from all participants and the principles in the Helsinki Declaration were followed.

29 eyes of 17 patients who were followed-up with and treated for DME in one or both eyes in the ophthalmology clinic were examined in this prospective cohort study. Patients were selected from those who were previously diagnosed with type 2 DM, had developed DM-related posterior segment complications in one or both eyes during the follow-up period, and applied IV anti-VEGF injection and/or panretinal laser photocoagulation. Patients who underwent a long-acting IV steroid injections were excluded from the study due to its longer potency. In addition, patients with visual impairment due to anterior or posterior segment complications, such as age-related macular degeneration or cataracts, were also excluded.

The patients were selected from those who were followed-up with and treated at regular intervals due to diabetic retinopathy, but were unable to attend for routine controls for at least 90 days due to the COVID-19 pandemic. The time that the patient was absent from the hospital was calculated by subtracting the time they last came to the hospital in the pre-pandemic period from the time of their visit to the hospital during the COVID-19 pandemic period. Patients who developed visual impairments due to complications such as cataract and glaucoma during the period when they could not come to the hospital for routine controls were excluded from the study. Ophthalmological examination findings and OCT measurements during the last examination before and during the pandemic period were noted. Treatments performed during the follow-up period were also noted. In addition, the glycated haemoglobin (HbA1c) values of the patients were recorded at the last examination during their controls in COVID-19 pandemic period.

After the pupil was dilated (with 1% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride), spectral domain OCT (SD-OCT) was performed by the same experienced physician at the same time interval (2.00-4.00 pm) using Heidelberg's Spectralis OCT (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). Real-time eye tracking using the TruTrack Active Eye Tracking function was used, and automatic real-time image averaging was set at 100 images. After the stabilization of the eye, six radial macular scans with equal angular orientation and 200 μm spacing were performed with an infrared camera in the centre of the fovea. The value at the centre of the scan was determined and recorded as central macular thickness (CMT). Patients with poor image quality due to anterior or posterior segment complications, and those who could not comply with SD-OCT imaging were excluded from the study. Fundus fluorescein angiography (TRC-50DX, Topcon) was performed in patients as deemed necessary. Based on these results, new treatment plans (IV injection and/or panretinal laser photocoagulation) were determined.

Statistical analysis

All of the data were recorded using the Statistical Package for the Social Sciences for Windows (version 20; SPSS Inc., Chicago, IL, USA). The categorical variables were presented as mean (standard deviation). An independent t test was used for comparisons between two groups of numerical

variables. A *P*-value of <0.05 was considered to be statistically significant.

Results

Seventeen patients who were treated for DME were included to the study; 10 were female (58.8%) and seven were male (41.2%). The mean age of the patients was 63.0 (5.5) years (range 56-74 years). Twelve (70.6%) patients presented with bilateral DME and five (29.4%) patients presented with unilateral DME. The mean time interval between follow-up visits was 45.5 (5.9) days in the pre-pandemic period, but it increased to 110.4 (13.5) days during the COVID-19 pandemic period (*P*<0.001). HbA1c values were 8.0 (1.2%) in the pre-pandemic period, it increased to 8.6 (1.6%) during the COVID-19 pandemic period (*P*=0.245). Visual acuity was 0.4 (0.4) LogMAR in the pre-pandemic period and 0.8 (0.5) LogMAR during the COVID-19 pandemic period (*P*=0.003). CMT was 300.1 (85.6) µm in the pre-pandemic period and it increased to 387.1 (144.5) µm during the COVID-19 pandemic period (*P*=0.007) (Table 1).

Table 1: Demographic characteristics of the patients, and visual acuity (logMAR) and central macular thickness values at different visits

	Before the COVID-19 pandemic	During the COVID-19 pandemic	*P*-value *
Gender (M/F) n, %	10 (58.8%) / 7 (41.2%)		
Age (years)	63.0 (5.5		
Unilateral/Bilateral, n, %	5 (29.4%) / 12 (70.6%)		
HbA1c (%)	8.0 (1.2)	8.6 (1.6)	0.245
Days of visits (days)	45.5 (5.9)	110.4 (13.5)	<0.001
BCVA (logMAR)	0.4 (0.4)	0.8 (0.5)	0.003
CMT (µm)	300.1 (85.6)	387.1 (144.5)	0.007

Results are denoted as mean (standard deviation), M: Male F: Female Hb A1c: Hemoglobin A1c BCVA: Best-corrected visual acuity, CMT: Central macular thickness µm: micron meter, *: Independent t test (*P*<0.05 statistically significant)

Demographic findings of all patients, HbA1c values, findings of the last pre-pandemic ophthalmologic examination, visit intervals and applied treatments were noted. The duration of delay in days, current ocular examination findings and planned treatments during the visits in pandemic period were recorded and are detailed in Table 2. The OCT images of the first two patients taken in the pre-pandemic and during pandemic periods are shown in Figure 1a, 1b, 2a, and 2b.

Figure 1a: OCT images of the first patient taken at the last hospital visit before the pandemic, 1b: OCT images of the first patient taken at the hospital visit during the pandemic period. (* OCT: Optical coherence tomography)

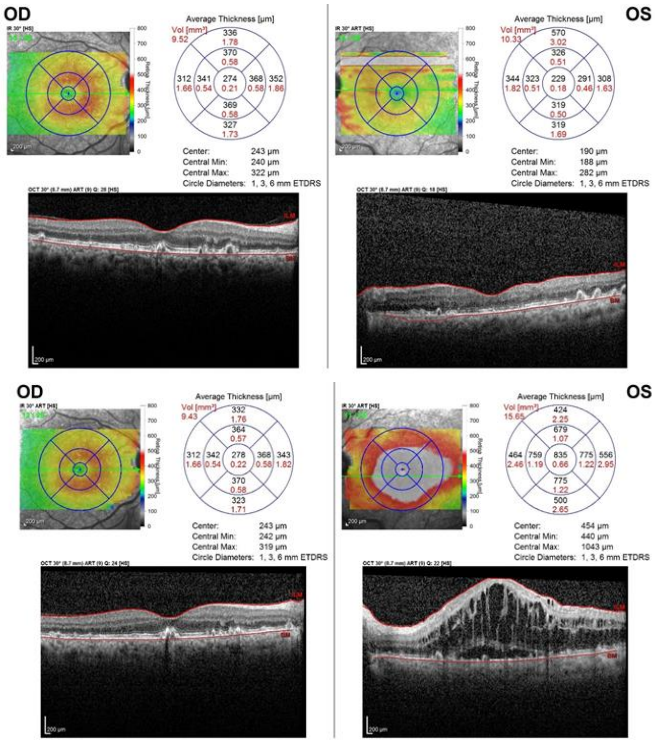

Figure 2a: The OCT images of the second patient taken at the last hospital visit before the pandemic, 2b: The OCT images of the second patient taken at the hospital visit during the pandemic period (* OCT: Optical coherence tomography)

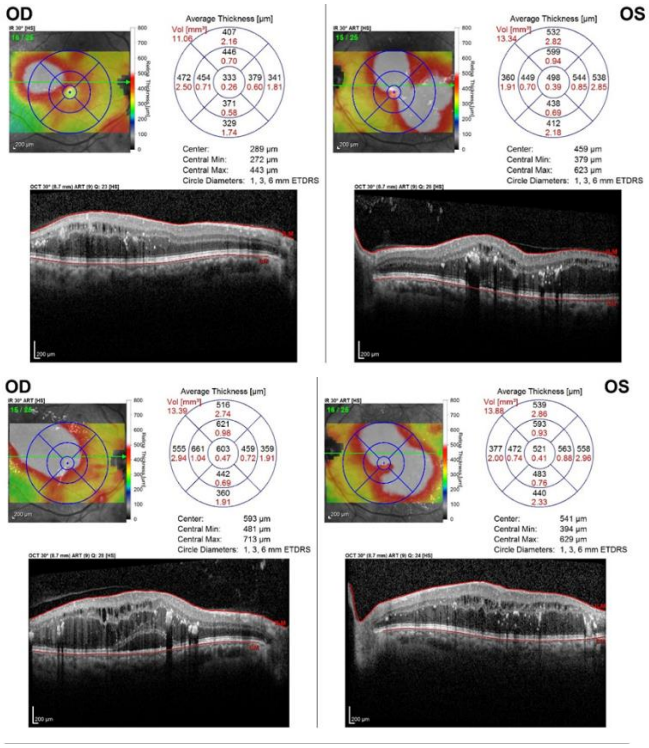

Table 2: Detailed information about the demographic, clinical features, ocular examination findings, and treatment plans of patients with diabetic retinopathy whose treatment is delayed due to the Covid 19 pandemic.

No, Gender, Age (years)	Last HbA1c* (%)	Current HbA1c** (%)	Laterality	Previous treatments (number of IV injections)	Pre-pandemic visit frequency (days), total number of visits	Elapsed time after last visit (days)	Last BCVA at pre-pandemic examination (RE/LE) (logMar) CMT (µm) (RE/LE)	Current BCVA (RE/LE) (logMar) CMT (µm) (RE/LE)	Current ocular examination results	Planned treatment
1, F, 67	6.2	6.7	Bilateral	RE: IV injection (4) LE: IV injection (5)	38.6 (7)	126	0.2 / 0.3 274 / 229	0.3 / 1.3 278 / 835	LE: DME	LE: IV injection
2, M, 56	7.2	7.8	Bilateral	RE: IV injection (3)+ Panretinal Laser LE: IV injection (2)+ Panretinal Laser	42.4 (5)	97	0.4 / 0.5 333 / 498	1.3 / 0.7 603 / 521	Bilateral: DME	Bilateral: IV injection + Panretinal Laser
3, F, 58	6.7	8.8	Unilateral	LE: IV injection (5)	41.1 (7)	104	0.1 / 0.3 251 / 339	0.1 / 0.7 265 / 454	LE: DME	LE: IV injection
4, M, 61	8.7	8.4	Bilateral (RE: NVG)	RE: IV injection (9)+ Panretinal Laser LE: IV injection (7)+ Panretinal Laser	34.3 (13)	92	- / 0.5 -/ 288	- / 1.0 -/ 346	LE: DME	LE: IV injection
5, F, 60	8.6	7.7	Bilateral	RE: IV injection (3)+ Panretinal Laser LE: IV injection (4)+ Panretinal Laser	39.7 (6)	128	0.5 / 0.5 545 / 549	1.0 / 1.0 652 / 668	Bilateral: DME	Bilateral: IV injection
6, F, 64	10.4	8.3	Bilateral	RE: IV injection (5)+ Panretinal Laser LE: IV injection (4)+ Panretinal Laser	52.3 (7)	135	1.3 / 1.3 345 / 306	1.6 / 1.5 - / 486	RE: VH LE: DME	RE: PPV LE: IV injection
7, M, 57	8.7	7.8	Bilateral	RE: IV injection (2)+ Panretinal Laser LE: IV injection (3)+ Panretinal Laser	44.3 (4)	103	0.2 / 0.5 254 / 296	0.3 / 1.3 304 / 442	Bilateral: DME	RE: IV injection+ Panretinal Laser LE: IV injection
8, M, 71	6.3	6.7	Bilateral	RE: IV injection (7)+ Panretinal Laser LE: IV injection (5)+ Panretinal Laser	48.6 (10)	112	0.2 / 0.2 242 / 238	0.4 / 0.2 314 / 248	RE: DME	RE: IV injection
9, F, 63	9.4	7.2	Unilateral	LE: IV injection (1)	48.5 (2)	129	0.2 / 0.4 236 / 276	0.3 / 0.4 334 / 298	Bilateral: DME	Bilateral: IV injection
10, F, 67	8.1	11.7	Bilateral	RE: IV injection (5)+ Panretinal Laser LE: IV injection (6)+ Panretinal Laser	56.7 (9)	132	1.5 / 1.3 -/ 312	1.6 / 1.3 -/ 352	RE: VH LE: DME	RE: PPV LE: IV injection
11, M, 74	7.2	6.9	Unilateral	RE: IV injection (2)	46.7 (3)	95	0.3 / 0.2 262 / 254	0.5 / 0.2 336 / 248	RE: DME	RE: IV injection
12, F, 60	8.8	8.0	Unilateral	LE: IV injection (2)	38.5 (4)	117	0.1 / 0.4 232 / 287	0.2 / 0.7 268 / 298	Bilateral: DME	Bilateral: IV injection LE: Panretinal laser
13, M, 72	7.5	6.9	Bilateral	RE: IV injection (4) LE: IV injection (3)	45.3 (6)	99	0.3 / 0.2 246 / 234	0.5 / 0.3 354 / 246	RE: DME	RE: IV injection
14, F, 60	10.2	7.8	Bilateral	RE: IV injection (3) LE: IV injection (2)	50.3 (4)	92	0.3 / 0.5 284 / 322	0.7 / 0.7 414 / 406	Bilateral: DME	Bilateral IV enjeksiyon
15, M, 57	8.8	8.1	Unilateral	LE: IV injection (6)	46.1 (8)	124	0.2 / 0.3 238 / 226	0.2 / 0.7 234 / 306	LE: DME	LE: IV injection
16, F, 64	12.1	9.4	Bilateral	RE: IV injection (4)+ Panretinal Laser LE: IV injection (3)+ Panretinal Laser	49.8 (5)	128	0.4 / 0.4 304 / 264	1.6 / 1.3 - / 457	RE: VH LE: DME	RE: PPV LE: IV injection
17, F, 60	10.4	7.2	Bilateral	RE: IV injection (2) LE: IV injection (2)	50.7 (3)	106	0.2 / 0.3 281 / 296	0.7 / 0.5 344 / 302	Bilateral: DME	Bilateral: IV injection

F: Female M: Male Hb A1c: Hemoglobin A1c IV: Intravitreal, BCVA: Best-corrected visual acuity RE: Right Eye LE: Left Eye, CMT: Central macular thickness µm: micron meter NVG: Neovascular glaucoma, DME: Diabetic macular edema VH: Vitreous hemorrhage PPV: Pars plana vitrectomy, *: HbA1c values before the pandemic period, **: HbA1c values during the pandemic period

Discussion

The COVID-19 outbreak that emerged at the end of 2019 has led to numerous cases of severe respiratory distress that have led to death, and has affected the whole world in a short period of time. The fact that COVID-19 is transmitted especially by the respiratory tract has led to the implementation of serious isolation practices [10]. In the fight against the pandemic, governments have applied restrictive measures, including restrictions on attendance to public places, curfews, travel restrictions and quarantines in order to prevent the uncontrolled spread of the virus. While the COVID-19 pandemic continued, other diseases unfortunately did not stop their progression, especially chronic diseases such as diabetic retinopathy. The pandemic has revealed a side effect resulting from the disruption of follow-up and treatment protocols and the cancellation of surgical services, in addition to the public health effects of the disease itself: Hospital admissions have decreased significantly, and many patients have been unable to attend their routine examinations and, thus, their treatments have been delayed [12, 13]. Unfortunately, the negative consequences of pandemic have emerged and still continue to emerge. In this study, we

demonstrated that the COVID-19 pandemic significantly delayed the in-person visits and subsequent possible IV procedures in diabetic retinopathy follow-up. More importantly, we proved that this deferral was significantly associated with worsened short-term outcomes in patients with diabetic retinopathy.

Some vascular diseases of the retina that require IV injection are on the list of emergencies that need to be treated during the pandemic period [12, 13]. Diabetic retinopathy is the most common among them. After DME—which is the most common cause of vision loss due to DM—develops, the most important treatment is to achieve glycaemic control [1]. However, researchers have revealed that there have been problems related to achieving glycaemic control in patients with DM during the pandemic period. Zhou et al. [14] observed that 56.6% of 881 diabetic patients who were hospitalized for COVID-19 had abnormal blood glucose levels. However, poorly controlled levels of hyperglycaemia in diabetic patients are also known to increase the severity of COVID-19 and thus mortality [15]. It is necessary to raise the awareness of diabetic patients about glycaemic control, nutrition and physical exercise, and to reduce the number and duration of hospital admissions as much as possible. To this end, diabetic patients should be encouraged to use telemedicine and teleconference-like applications. The COVID-19 pandemic should be turned into opportunities to develop innovative management strategies for DM and other chronic diseases.

Periodic routine controls performed in the ophthalmology department on diabetic patients are of great importance in maintaining and improving visual acuity. However, the risk of close contact and contamination in the examination room during patient examinations poses a risk for both the doctor and the patient, since tears can contain the virus [16]. Therefore the need to close, face-to-face ophthalmologic examinations have increased the postponement of patient examinations. In this respect, many preventive measures have been taken instead. In some retina clinics in Europe and America, biomicroscopic examinations were not considered appropriate for the routine follow-up of retina patients; instead, it was deemed appropriate to evaluate the patients' visual acuity and macular evaluation using OCT [17, 18]. With the developing technology, it will be possible to evaluate patients in terms of diabetic retinopathy without applying to the hospital in the future. For this purpose, deep learning algorithms and systems can help patients to have an idea about the presence and progression of their diabetic retinopathy without applying to the hospital [19, 20]. The integration of these systems with smartphones can make life easier for DM patients in the current and similar times of crisis [21].

Delays and cutbacks in IV injection therapy have been associated with reduced efficacy and decreased visual acuity, as well as increased retinal thickness [22-24]. However, the fact that the patients who most need IV injections are generally elderly and those with comorbid diseases is worrisome. Borrelli et al. [25] reported a 59.6% decrease in the number of patients who were applied to a tertiary eye centre who received IV injections due to DM, and they found a decrease in the average age of the patients who applied. However, in two prospective studies in which more than 100 IV injections were made during the pandemic period, no complications were found in patients or healthcare workers, as long as the anti-sepsis rules were followed [26].

The duration of treatment and its applications show changes during the pandemic period. The main goal is to keep the number of visits to a minimum, but not to hinder treatment. It is recommended that it would be more appropriate to choose a 'treat-and-extend' regimen for patients who will be newly starting treatment during the pandemic period, and that patients following up with this protocol should be monitored for the longest and safest intervals possible [27]. Antaki et al. [28] stated that 'treat-and-plan', which is a combination of the 'treat-and-extend' and 'observe-and-plan' strategies, may be more effective in patients who have started treatment, and thus the number of hospital visits required to monitor the disease may be fewer. In addition, in crisis periods such as during the COVID-19 pandemic, choosing long-acting anti-VEGFs and extending treatment regimens should be considered as an alternative treatment option.

Borelli et al. [25] examined cases of patients who applied to retina clinics due to age-related macular degeneration during the COVID-19 pandemic quarantine in Italy. They examined the cases who applied to the retina unit in March and May 2020 and those who applied to the retina unit in the same period of 2019, and they found a significant decrease in the number of patients who applied to the hospital in pandemic period. Researchers found that a worse visual acuity at a visit during a real-life emergency setting may indicate that a longer time interval between visits may be causing a reduction in visual acuity in age-related macular degeneration patients. Salah et al. [26] reported that diabetic patients in need of IV injection presented to the hospital with a delay of 6.4 weeks. In these patients, it was observed that visual acuity decreased from 20/55 to 20/70, and mean CMT values increased from 344 µm to 381 µm. The authors also reported progress in diabetic retinopathy staging in these patients.

Limitations

There are some factors limiting our study, most importantly, a larger case series is needed. A second important data is that studies comparing patients treated with long-acting anti-VEGF and patients treated with anti-VEGF agents are needed.

Delays in the treatment of diabetic retinopathy may cause permanent impairments in visual functions and a decrease in quality of life. The most important step in preventing complications due to DM is blood glucose regulation. For this purpose, new threshold levels should be determined in these patients and methods such as teleconsultation and telemedicine should be developed. In addition, in order to eliminate the gaps in diagnosis, digital technology should be integrated more into our lives and home-based OCT applications should be brought into our daily practices as soon as possible. In this way, only patients in severe need will be directed to hospitals, and the potential viral load of patients and ophthalmologists will be reduced. However, in the current and similar pandemic periods, the use of long-acting anti-VEGFs, should be evaluated as an alternative treatment method in suitable patients who need IV injection.

Conclusions

In this study, we evaluated 17 patients with diabetic retinopathy who came to their routine controls before March 2020, but could not come to their routine controls due to the pandemic in the post-March 2020 period, which resulted in anatomical and functional losses in their ocular structures. We observed that these patients had a mean delay of 8.6 weeks in their hospital visits. We found that this delay caused the development of DME, the progression of diabetic retinopathy and a severe decrease in visual acuity. In addition, posterior segment diabetic retinopathy complications, such as vitreous haemorrhage, occurred in three patients that could not be treated medically, so a surgical course of treatment was recommended instead. These results are important in terms of drawing attention to the negative consequences of the failure to provide timely and effective treatment to patients with diabetic retinopathy during the epidemic period.

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Nurses' assessment of nutrition awareness in the critical patient

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Ethics Committee Approval
Ethical approval date and numbered 07/13/2021, 2012-KAEK-15/2345 was taken from Kecioren Training and Research Hospital Clinical Research Ethics Committee.
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Healthcare professionals need sufficient knowledge and practice regarding nutrition in terms of early diagnosis and treatment of malnutrition. This study aims to investigate and evaluate nurses' awareness and knowledge of nutrition among critical patients.
Methods: In this cross-sectional study, the knowledge levels of the nurses (n: 55) who have worked for at least two months in the intensive care or palliative service were measured using the Nurses' Nutrition Support Awareness Questionnaire for the Critical Patient, and the answers were statistically evaluated and interpreted.
Results: Nurses' average age was 27.7 and 21.8% of them were men and 78.2% were women. In terms of education status, 16% of them were high school graduates, 33% had associate degrees and 51% were university graduates. In addition, 76% of the nurses had more than two years of professional experience. According to the rate of correct answers in the questionnaire, the level of knowledge about starting nutritional support with the evaluation of the patient, the way and route of TPN administration, and the products and drugs that can be given together were evaluated as "good" with scores of 80-84%. The level of knowledge about the time to start support for the patient with insufficient oral intake, which products were preferred initially, the way to administer enteral products, and the duration of consumption were evaluated as "medium" with 60-65%. Nurses scored 40-50% on fluid support and feeding the patient without swallowing reflex, which was deemed "insufficient."
Conclusion: This study reveals that nurses have sufficient knowledge about the necessity of nutritional support and TPN. In addition, it indicates that the level of knowledge about enteral nutrition, fluid support, and nutrition of patients who do not have a swallowing reflex need to be supported by theoretical and practical training.

Keywords: Malnutrition, Enteral nutrition, Parenteral nutrition, Nurse

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Introduction

Nutrition is the maintenance of tissue and organ functions and adequate intake of all necessary nutrients for growth and regeneration [1]. Malnutrition causes complications, such as growth retardation, delay in wound healing, suppression of the immune system, the loss of skeletal muscle mass, atrophy of the intestinal mucosa, widespread edema, and decline in cognitive functions. Due to malnutrition, hospital stay, morbidity and mortality are also increasing [2, 3].

Healthcare professionals need to have sufficient knowledge and practice regarding nutrition in terms of early diagnosis and treatment of malnutrition. Nurses are in an ideal position to determine the nutritional status of the patient first and best, as they are the healthcare workers who first accept the hospitalized patient and perform daily follow-up and care. In a study conducted on this subject, 86% of nurses stated that nurses focused on nutritional problems in the clinics in which they worked, and 27% reported that doctors had this responsibility [4].

Nutrition of patients in palliative services and intensive care units should be a priority as much as treatment. Having sufficient knowledge and interest in nutrition of all healthcare personnel will reduce costs, as it will help patients recover faster and with fewer complications [5, 6].

This study is aimed at evaluating the knowledge, opinions, and perceptions of nurses regarding nutritional status assessment and support since they are aware of the nutritional status of the patients and play an active role in the process.

Materials and methods

Ethical approval dated July 13, 2012, and numbered KAEK-15/2345 was provided from Kecioren Training and Research Hospital Clinical Research Ethics Committee to start the study. Nurses who had worked in the intensive care or palliative service in the hospital for at least two months or had worked in the past voluntarily participated in this survey. They were asked to answer the Nurses' Nutrition Support Awareness Questionnaire for the Critical Patient consisting of 24 questions. The answers were then statistically evaluated and interpreted. The inclusion criteria for participating in the survey were volunteering and having worked in the intensive care or palliative service for at least two months.

Statistical analysis

Statistical analyses were evaluated using the Statistical Program for Social Sciences (SPSS 22.0). In the evaluation of the data, frequencies and percentages are given for qualitative data. Kolmogorov-Smirnov test was applied to determine the normal distribution of quantitative data. For quantitative data, mean and standard deviation values from descriptive statistical methods were given and for qualitative data, frequencies and percentages were given. Correct answers to the questions on general nutrition knowledge, oral enteral supplementation, enteral nutrition, and total parenteral nutrition were given 1 point, and incorrect answers were given 0 points. By dividing the total scores by the number of questions, the average scores of the participants in each section were calculated. Average scores from questions based on learning status were evaluated using the Kruskal Wallis test. All statistical calculations were evaluated in the 95% confidence range and at the $P<0.05$ significance level.

Results

A total number of 55 volunteer nurses participated in the study. The average age of the interviewers was 27.7; 21.8% of them were male and 78.2% were female. Of the participants, 23.6% were in their first year of professional life. In addition, 45.5% had two to ten years of professional experience and 30.9% had more than ten years. The units in which the interviewees worked at the time they answered the questionnaire were as follows: service (14.5%), palliative service (16.4%), and intensive care (69.1%). When the working years of the interviewees were examined, it is seen that six people worked in the same department for three years or less and the remainder had worked in the same unit for one to two years (Table 1).

Table 1: Demographic data of surveyed participants

		n	(%)
1. Age			
2. Gender	Female	43	(78.2%)
	Male	12	(21.8%)
3. Education Status			
	High School Graduates	9	(16.4%)
	Associate Degree Graduates	18	(32.7%)
	University Graduates	28	(50.9%)
	Post Graduates	-	
4. How many years have you been working in your profession?			
	0-1 year	13	(23.6%)
	2-10 years	25	(45.5%)
	10 years or more	17	(30.9%)
5. In which department do you work?			
	Service	8	(14.5%)
	Palliative Care	9	(16.4%)
	Intensive Care	38	(69.1%)
6. How many years have you worked in your department?			
	1 year	20	(36.4%)
	2 years	29	(52.7%)
	3 years or more	6	(11%)

The nutritional information of the interviewees was evaluated with 7-24 questions (Table 2).

To the question of “Is it necessary to give nutritional support to every hospitalized patient?” 81.8% responded, "It is necessary to evaluate."

To the question of "When should nutritional support be given to a patient with insufficient oral intake?" 67.3% stated "as soon as it was detected," while 9.1% stated "when signs of dehydration are given" and others (23.6%) stated that it would be more appropriate to wait a few days.

Only about one-third of the interviewees evaluated that "oral enteral supplementation should be given" to the question of “Which product provides nutritional support to the elderly patient with reduced oral intake? Other interviewers, however, stated that nutritional support should be provided to the patient with "enteral product by inserting nasogastric" and "total parenteral nutrition."

Awareness of starting fluid support for a patient with insufficient fluid intake was found in 58.2% of those interviewed, and the rest waited for signs of dehydration for fluid support.

In response to the question, "What should be the nutritional support of the patient who does not have a swallowing reflex?", 49.1% preferred "enteral feeding with the correct nasogastric tube."

Table 2: Distribution of answers to questions related to nutrition knowledge

	n	(%)
7. Do you think it is necessary to provide nutritional support to every hospitalized patient?		
Yes	6	(10.9%)
No, medical treatment should be done first	4	(7.3%)
Need to evaluate	45	(81.8%)
8. If the inpatient's oral intake is insufficient, on which day of hospitalization is nutritional support required?		
As soon as detected	37	(67.3%)
The third day	13	(23.6%)
If the patient shows signs of dehydration	5	(9.1%)
9. Which product provides nutritional support to an elderly patient with reduced oral intake?		
Oral enteral supplementation	18	(32.7%)
Enteral product with nasogastric insertion	17	(30.9%)
Total parenteral nutrition	20	(36.4%)
10. When should fluid support be given to a patient with insufficient oral fluid intake?		
As soon as detected	32	(58.2%)
The third day	1	(1.8%)
If the patient shows signs of dehydration	22	(40.0%)
11. If the patient does not have a swallowing reflex, which method should be used first for feeding?		
Total parenteral nutrition	26	(47.3%)
Enteral feeding with nasogastric insertion	27	(49.1%)
Should be supported with oral enteral supplementation	2	(3.6%)
12. How long does total parenteral nutrition last?		
Peripheral and central are indefinite	2	(3.6%)
Peripheral 14 days; central 14 days	23	(41.8%)
It is necessary to switch from peripheral to central as soon as possible.	30	(54.5%)
13. Are total parenteral products sufficient for nutrition?		
Yes	13	(23.6%)
No	42	(76.4%)
14. When should the set of patients receiving total parenteral nutrition be changed?		
12 hours	46	(83.6%)
24 hours	9	(16.4%)
It is not changed unless necessary		
15. Can the patient's treatment drugs be added to the parenteral nutrition solution?		
Yes	11	(20.0%)
No	44	(80.0%)
16. What is the reason for adding fatty acids, glutamine, vitamins and trace elements into total parenteral products?		
Since these substances are not present in TPNs, they cannot provide adequate nutrition on their own.	33	(60.0%)
Enabling patients to take more vitamins and minerals	17	(30.9%)
It is added to prevent bedsores.	5	(9.1%)
17. Which of the following is true?		
Peripheral nutritional solutions can be given through the central venous route.	13	(23.6%)
Central nutritional solutions can be given through the peripheral vascular pathway.	-	
Peripheral nutrition solutions should be given from the peripheral vein; central nutrition solutions should be given from the central route.	42	(76.4%)
18. Does a patient who is given oral enteral supplement support need to eat?		
Yes	15	(27.3%)
No	40	(72.7%)
19. In which of the following situations should enteral feeding be stopped? Multiple markings can be made.		
Melena (gastrointestinal bleeding)	47	(85.5%)
Intraoral wounds	4	(7.3%)
Ileus (intestinal obstruction)	43	(78.2%)
Absence of swallowing reflex	19	(34.5%)
20. Which of the following is true?		
Patients should be fed in a position with the head upright at 45 degrees.	54	(98.2%)
Patients with PEG and nasogastric can be fed in a lying position.	1	(1.8%)
Only patients at risk of aspiration should be fed in a position where the head is in an upright position of 45 degrees.		
21. Can enteral and parenteral nutrition be given simultaneously?		
Yes	44	(80.0%)
No	11	(20.0%)
22. Within how many hours should the enteral product placed in the feeding bag be consumed (at room temperature)?"		
24 hours	11	(20.0%)
12 hours	9	(16.4%)
8 hours	35	(63.6%)
23. How many hours should the first feeding be after the newly opened percutaneous endoscopic gastrostomy (PEG)?		
It can start immediately.	3	(5.5%)
After 4 hours. it can be started with water.	9	(16.4%)
Nothing is given for 24 hours	43	(78.2%)
24. Which type of diet is easiest to feed your patients?		
Oral feeding of the patient. even with assistance	34	(61.8%)
Nasogastric or enteral feeding with PEG	6	(10.9%)
Total parenteral nutrition by peripheral route	2	(3.6%)
Total parenteral nutrition by central route	13	(23.6%)

Table 3: Distribution of answers to questions related to general nutrition, oral enteral supplementation, enteral nutrition information, and TPN information

	n	(%)
Correct Response Rates in General Nutrition Knowledge		
7. Do you think it is necessary to provide nutritional support to every hospitalized patient?		
Need to evaluate	45	(81.8%)
8. If the inpatient's oral intake is insufficient, on which day of hospitalization is nutritional support required?		
As soon as detected	37	(67.3%)
10. When should fluid support be given to a patient with insufficient oral fluid intake?		
As soon as detected	32	(58.2%)
11. If the patient does not have a swallowing reflex, which method should be used first for feeding?		
Enteral feeding with nasogastric insertion	27	(49.1%)
24. Which type of diet is easiest to feed your patients?		
Oral feeding of the patient, even with assistance	34	(61.8%)
Correct Response Rates in Oral Enteral Supplement Knowledge		
9. Which product provides nutritional support to an elderly patient with reduced oral intake?		
Oral enteral supplementation	18	(32.7%)
18. Does the patient who is given oral enteral supplement support need to eat?		
Yes	15	(27.3%)
Correct Response Rates in Enteral Nutritional Knowledge		
19. In which of the following situations should enteral feeding be stopped? Multiple markings can be made		
Melena (gastrointestinal bleeding)	47	(85.5%)
Intraoral wounds	4	(7.3%)
Absence of swallowing reflex	19	(34.5%)
20. Which of the following is true?		
Patients should be fed in a position with the head upright at 45 degrees.	54	(98.2%)
21. Can enteral and parenteral nutrition be given simultaneously?		
Yes	44	(80.0%)
22. Within how many hours should the enteral product placed in the feeding bag be consumed (at room temperature)?"		
24 hours	11	(20.0%)
23. How many hours should the first feeding be after the newly opened percutaneous endoscopic gastrostomy (PEG)?		
After 4 hours, it can be started with water.	9	(16.4%)
Correct Response Rates in Total Parenteral Nutrition (TPN) Knowledge		
12. How long does total parenteral nutrition last?		
It is necessary to switch from peripheral to central as soon as possible.	30	(54.5%)
13. Are total parenteral products sufficient for nutrition?		
No	42	(76.4%)
14. When should the set of patients receiving total parenteral nutrition be changed?		
24 hours	9	(16.4%)
15. Can the patient's treatment drugs be added to the parenteral nutrition solution?		
No	44	(80.0%)
16. What is the reason for adding fatty acids, glutamine, vitamins and trace elements into total parenteral products?		
Since these substances are not present in TPNs, they cannot provide adequate nutrition on their own.	33	(60.0%)
17. Which of the following is true?		
Peripheral nutritional solutions can be given through the central venous route.	13	(23.6%)

For the TPN administration route, a large proportion of the interviewees (76.4%) stated that the peripheral product should be administered via the central route. Of the total respondents, 83.6% did not have an awareness that parenteral sets should be changed every 24 hours and 76.4% believed that TPN was not sufficient for full nutrition. Sixty percent believed that fatty acids, glutamine, vitamins, and trace elements should be added to total parenteral products and 80% knew that treatment drugs should not be added to TPN. The rate of those who knew that peripheral nutrition solution could be given via the central route was 23.6%, but all the interviewees were aware that central nutrition solution could not be given via the peripheral route.

Regarding oral enteral supplements (OES), 27.3% of the nurses answered “yes” to the question, “Does the patient taking OES need to eat?” To the question, “In which of the following situations should enteral feeding be stopped? Multiple markings can be made,” 85.5% marked melena (gastrointestinal bleeding), 7.3% marked intraoral sores, 78.2% marked ileus (intestinal obstruction), and 34.5% marked absence of swallowing reflex. Almost all (98%) of the interviewers knew that the feeding position (oral / NG with enteral / enteral with percutaneous

endoscopic gastrostomy (PEG)) was in a 45-degree head position. Eighty percent responded "yes" to the question, "Can enteral and parenteral nutrition be given together?"

In response to the question, "Within how many hours should the enteral product placed in the feeding bag be consumed (at room temperature)?" 63.6% answered correctly by saying "eight hours.

To the question, "After how many hours should the first feeding be given to the patient after the newly opened PEG?" 78.2% responded “24 hours.” The question, “Which type of diet is easiest to feed your patients?” evoked the following answers from nurses: 61.8% said that the patient should be fed orally, even with assistance, and 23.6% responded that the patient should receive TPN via the central route.

The correct answer rates for general nutrition, oral enteral supplementation, enteral nutrition information, and TPN information of the interviewers are given in Table 3. There was no statistically significant difference between the answers to general nutritional information, oral enteral supplement, enteral nutrition, and total parenteral nutrition questions according to age (Table 4), gender (Table 4), or education status (Table 5) among the nurses participating in the survey.

Table 4: Nutrition knowledge by age and gender

	Age				*P*-value
	Under 29 (n:32)		30 and above (n:23)		
	$\bar{X}$	SD	$\bar{X}$	SD	
General Nutrition Information	0.64	0.18	0.63	0.19	0.607
Oral Enteral Supplementation	0.28	0.36	0.33	0.36	0.596
Enteral Nutrition	0.59	0.15	0.63	0.16	0.508
Total Parenteral Nutrition	0.49	0.21	0.56	0.20	0.213
	Gender				
	Female		Male		
General Nutrition Information	0.63	0.20	0.67	0.13	0.518
Oral Enteral Supplementation	0.26	0.32	0.46	0.45	0.147
Enteral Nutrition	0.60	0.17	0.62	0.10	0.759
Total Parenteral Nutrition	0.51	0.22	0.54	0.19	0.633

Table 5: Nutrition information by education status, years of work in the profession, department, and years of work in the department

	Education Status						*P*-value
	High School Graduates		Associate Degree Graduates		University Graduates		
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
General Nutrition Information	0.69	0.15	0.59	0.19	0.65	0.19	0.421
Oral Enteral Supplementation	0.28	0.44	0.36	0.33	0.27	0.35	0.531
Enteral Nutrition	0.67	0.17	0.58	0.17	0.61	0.14	0.463
Total Parenteral Nutrition	0.63	0.20	0.48	0.21	0.51	0.21	0.141
	Years of Work in the Profession						
	0-1 Year		2-10 Years		10 Years or more		
General Nutrition Information	0.65	0.15	0.65	0.23	0.61	0.15	0.801
Oral Enteral Supplementation	0.27	0.26	0.16	0.28	0.53	0.41	0.007
Enteral Nutrition	0.54	0.15	0.64	0.14	0.61	0.17	0.136
Total Parenteral Nutrition	0.50	0.20	0.47	0.24	0.61	0.14	0.097
	Department						
	Service		Palliative Care		Intensive Care		
General Nutrition Information	0.73	0.15	0.56	0.13	0.64	0.20	0.142
Oral Enteral Supplementation	0.63	0.44	0.44	0.17	0.20	0.32	0.003
Enteral Nutrition	0.63	0.13	0.56	0.19	0.62	0.15	0.539
Total Parenteral Nutrition	0.60	0.12	0.39	0.20	0.53	0.22	0.087
	Years of Work						
	1 year		2 years		3 years or more		
General Nutrition Information	0.68	0.16	0.59	0.18	0.73	0.21	0.129
Oral Enteral Supplementation	0.30	0.34	0.33	0.36	0.17	0.41	0.459
Enteral Nutrition	0.54	0.13	0.64	0.15	0.67	0.16	0.045
Total Parenteral Nutrition	0.51	0.19	0.52	0.23	0.53	0.19	0.884

The rate of correct answers to oral enteral supplementation questions was statistically significant and high among nurses who had been in the profession for ten or more years (Table 5). Similarly, the rate of correct answers to oral enteral supplementation questions among nurses working in the service is statistically significant and high (Table 5). Nurses who worked in the department for three years or more gave a statistically significant and highly accurate answer to the enteral nutrition questions (Table 5).

Discussion

Enteral and parenteral nutrition practices are of great interest to nurses and are common in clinics, especially in intensive care and palliative services. Nursing follow-up and initiatives are extremely important in effective implementation of nutrition practices and prevention of possible complications. It is among the responsibilities of the nurse to determine the need for nutritional support, to maintain the feeding tube or nutrition set, to choose the right nutritional product, and to manage the speed and time of the feeding product, expiration dates, and storage conditions.

This study shows that nurses are aware of the need for nutritional support in critical patients and adopt this role. In the study of Kalaldeh et al. [7] on intensive care nurses, it was determined that nurses perceived clinical nutrition practices as a secondary nursing role. In another study conducted by Yılmaz [8], nearly half of the nurses stated that they had no idea about the occurrence of malnutrition in the clinics where they worked, and that nutritional problems were primarily the responsibility of the physicians. In our study, we think that this awareness of duty is due to in-service training.

The most accurate and most incorrectly answered questions of nurses were examined in the present study. The most accurately answered question was that patients should be fed in a position where the head is in an upright position at 45 degrees. The most incorrectly answered question was the preference of invasive feeding methods instead of oral enteral supplement support for "the diet of the elderly patient with impaired oral intake."

Nurses were more familiar with TPN and its management. The necessity of choosing large and central veins in parenteral nutrition applications [9] was answered correctly by 80%. In Çelebi's study, nurses' awareness of parenteral nutrition and its complications were similar to our study [10]. Unlike our study, the research of Akın indicated that TPN products, according to their osmolarity, were the least known question among nurses. In the same study, it was determined that the questions related to the storage location and duration of enteral nutrition products, gastric residual volume, and drug administration through enteral feeding tubes were the questions most frequently answered incorrectly [11]. However, in our study, the level of enteral nutrition knowledge was evaluated as moderate.

In the survey conducted by Akın and Koçhan [11], the least correct answers for the questions involved storage conditions for the enteral product. Our study did not include questions about the storage condition, but the rate of correct

answers to the questions about enteral nutrition was evaluated as moderate with 60-68%.

Percutaneous endoscopic gastrostomy (PEG) is a simple, inexpensive, effective and low complication rate method preferred in patients with normal gastrointestinal system functions and need long-term enteral nutritional support [12]. In our hospital, the PEG procedure is performed laparoscopically by a gastroenterologist. For the feeding time after PEG, 78.2% of the nurses gave the incorrect answer, indicating that the feeding time should wait one day. However, after a four-hour waiting period, low volume (20cc/h) nutrition can be started. If there are no complications and the patient can tolerate them, feeding can start at this time.

No difference was found between educational status, age, gender, and nutritional knowledge in the current research.. However, the correct answer to the questions about enteral nutrition was found to be significantly higher in those who had worked in the department for more than three years and in the profession for more than ten years.

Oral enteral nutrition support questions were among the questions with a high correct answer rate by hospital service nurses. We think that this difference is related to the higher need and use of oral enteral supplements in patients treated in the service.

Insufficient information and deficiencies in practice should be determined through knowledge-level studies on issues. Continuity of education should be ensured with effective in-service training programs.

This study does contain limitations. Since our aim was directed at single-center (a chest diseases hospital) and critically ill nutritional support, only nurses working in the intensive care and palliative service participated in the survey and their numbers were limited. For future studies, observational studies are proposed on the level of knowledge reflected not only by the survey but also by the application.

Conclusion

Nurses have sufficient knowledge about the necessity of nutritional support and TPN. It is seen that the level of knowledge about enteral nutrition, fluid support, and nutrition of patients without swallowing reflex needs to be supported by theoretical and practical training. Therefore, it is necessary to support the knowledge level of healthcare professionals on patient nutrition support with theoretical and practical training.

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Color kinesis-dobutamine stress echocardiography pinpoints coronary artery disease

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Ethics Committee Approval
The study has been approved by Istanbul Atlas University Clinical Research Ethics Committee on 21.12.2021 with protocol number E-22686390-050.01.04-10993.
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: Dobutamine stress echocardiography (DSE) can identify significant coronary artery disease (CAD) and where it is localized. However, determining endocardial borders with poor echocardiographic views may create unsatisfactory results. Color kinesis (CK) shows endocardial movement with color, and allows easier and more objective evaluation of ventricular wall motion. In this study, our aim was to evaluate the role of CK in determining CAD localization during DSE.
Methods: The study group consists of patients whose CAD diagnosis was confirmed with coronary angiography (CA). Patients with atrial fibrillation (A-Fib), left bundle branch block, poor echocardiography image quality, left ventricular (LV) ejection fraction < 40%, and non-ischemic LV wall motion abnormality were excluded. CK-DSE and dobutamine stress-induced myocardial perfusion scintigraphy (MPS) was done in all patients and compared to CA.
Results: A total of twenty patients [16 males (80%) and 4 females (20%)] were included in the study. CK-DSE results were consistent with CA in determining CAD localization (kappa 0.66). Vessel-based kappa values for LAD, RCA, and Cx were 0.81, 0.70 and 0.61, respectively. Consistency between MPS and CK-DSE was evaluated by the area under curves (AUC) within a ROC curve analysis (P>0.05, 95% CI).
Conclusion: Our study showed that CK allows for rapid, objective, and automatic evaluation of segmental wall motion. In addition, CK-DSE is consistent with CA results.

Keywords: Color kinesis, Coronary artery disease, Stress echocardiography

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Introduction

Coronary artery disease (CAD) is the world's leading cause of morbidity and mortality. Due to improved primary prevention and healthcare services, mortality has decreased over the past three decades [1]. Its prevalence in Turkey is estimated to be around 2.8% [2]. CAD is approximately 40% and 50% of all mortality in men and women, respectively. Patients may have insignificant symptoms or be asymptomatic. Sudden cardiac death increases in all forms with silent ischemia. Early diagnosis is critical, so that all available data is considered and easy-to-apply, with reliable diagnostic methods. Invasive and noninvasive diagnostic methods are also widely used in this respect. Other techniques are resting electrocardiography (ECG), the exercise stress test, myocardial perfusion scintigraphy (MPS), echocardiography, and coronary computed tomography angiography (CCTA) [3].

Transthoracic echocardiography and dobutamine stress echocardiography (DSE) help in the detection of myocardial infarction (MI), visualization of proximal coronary arteries, examination of wall motion abnormalities, evaluation of systolic and diastolic functions of the ventricles, and risk stratification of CAD [4-9]. Difficulties in locating endocardial borders and poor echocardiographic windows may cause unsatisfactory results. With these limitations, color kinesis (CK) was developed with acoustic quantification (AQ). CK, based on coding the inward and outward movements of the endocardium with color cues, helps with objective evaluation of wall motion abnormalities [10,11].

Stress echocardiography is another frequently-used method, dobutamine being the most used pharmacological agent for this [12]. Objective wall motion analysis can be performed by stress echocardiography in association with CK [5]. In this study, we aimed to evaluate the role of dobutamine stress echocardiography in association with color kinesis (CK-DSE) to determine the localization of coronary artery disease (CAD).

Materials and methods

Study population

The minimum number of patients to test consistency between CK-DSE and CA was 20 patients, statistically. Patients with atrial fibrillation (A-Fib), left bundle branch block, poor echocardiographic image quality (< 30% visible endocardial border), left ventricular (LV) ejection fraction < 40%, and non-ischemic LV wall motion abnormality (Wolf-Parkinson-White syndrome, and a previous history of cardiac surgery, pacemaker rhythm issues, cardiomyopathies, and severe aortic and mitral valve insufficiency) were excluded. The background of all patients was recorded, resting ECGs taken, exercise ECGs, CK-DSE, and MPS examinations performed. Thirty-two patients who met the above criteria enrolled in the study. Ten patients for whom CA was not performed and 2 patients with poor echocardiographic image quality were later excluded. As per protocol, enrollment was ended after achieving the target patient number, with the study group consisting of 20 patients after all exclusions. Written informed consent was obtained from participants, and the study was conducted in accord with the principles of the declaration of Helsinki (1964): its protocol was also approved by the institutional review board.

Evaluation of CK-DSE

All evaluations were performed with Hewlett Packard (Palo Alto, CA, USA) Sonos 2500 echocardiography, using a 2.5-3.5 MHz transducer. Anti-ischemic and anti-hypertensive drugs were discontinued at least 2 days before the examination, after 4 hours of fasting. The parasternal long and short axes, and the apical two- and four-chamber echocardiographic windows were used for evaluation. AQ resting in two-dimensional echocardiographic views was used for CK recordings thereafter. Dobutamine infusion was started with a dose of 5 mcg/kg/min and increased every three minutes to 10, 20, 30, and 40 mcg/kg/min. ECG, blood pressure, and patient heart rate were recorded with each step. Age-adjusted target heart rate was calculated as follows: 220-age (years) x 0.8.and 0.25 mg IV atropine injection was used as the last step for patients who could not reach a target heart rate. Two-dimensional and CK images were recorded for at least 3 cycles. Dobutamine infusion was terminated in patients who had angina pectoris, hemodynamically significant arrythmia, ≥ 2 mm of ST depression on ECG recordings, and ischemia-induced echocardiographic findings.

Two-dimensional and CK dobutamine stress echocardiographic recordings were evaluated by an experienced cardiologist, unaware of the patients' history, MPS, and CA reports. Segments with color layers from red to blue in CK analysis were accepted as having inward endocardial movement and as normokinetic. Segments with thin color layers were interpreted as hypokinetic, but those with thin layers of color (red-orange) were interpreted as akinetic; segments with outward movement and thin layers of color (red-orange) were interpreted as dyskinetic. CK-DSE findings with the presence of ischemia are summarized in Table 1.

Table 1: Interpretation of CK-DSE

Resting wall motion	Wall motion at maximum stress	Interpretation
Normal	Hyperkinetic	Normal
Normal	Hypokinetic	Ischemia
Normal	Delayed contraction (tardokinesia)	Ischemia
Hypokinetic	Increased contractility	Normal
Hypokinetic	No change	Ischemia
Hypokinetic	Decreased contractility	Ischemia
Hypokinetic	Akinetic	Infarction
Akinetic	Not evaluated	Infarction

LV wall motion was evaluated at rest; however, for all steps of the stress test and then during the recovery period, this was done with CK. Broderick's classification system was used to define left ventricle wall segments [13]. Septum, anterior, anteroseptal wall, and apical segments were accepted as the left anterior descending artery (LAD), lateral and posterior wall segments were accepted as the circumflex artery (Cx) and inferior wall, while interventricular septum basal segments were accepted as right coronary artery (RCA) territory. Apical inferior and lateral segments were accepted as overlapping. If septal or anterior wall motion accompanied a lateral apical segment wall motion abnormality, it was considered LAD territory. Posterior or posterolateral wall motion abnormality with lateral apical segment wall motion abnormality was considered Cx territory. For inferior wall apical segment evaluation, accompanying inferior wall motion abnormality was considered RCA territory,

while anterior or anteroseptal wall motion abnormality was considered LAD territory [14, 15].

Myocardial perfusion scintigraphy (MPS)

When the maximum heart rate was reached during CK-DSE, 10 mCI Tc 99m MIBI was injected for scintigraphy evaluation. After 45 minutes, stress images were taken. Rest images were taken three hours later, 45 minutes after the MIBI injection. All images were taken with single-photon-emission computed tomography (SPECT).

Perfusion defects in the anterior, lateral, and apical wall segments were considered LAD territory, lateral and posterior wall segments were considered Cx territory, inferior wall, and posterior and interventricular septum basal segments were accepted as RCA territory. MPS findings were evaluated by an experienced nuclear medicine specialist who was unaware of the patients' history, CA, and CK-DSE results.

Coronary angiographic evaluation

Coronary angiographies and left ventriculography evaluations were performed with a Toshiba CC-i angiography device (Minato, Tokyo) by interventional cardiologists with standard methods. A coronary artery with > 70% percent stenosis was seen as an ischemia-related artery.

Statistical analysis

Variables are expressed as numbers and percentages. CK-DSE and dobutamine MPS's compatibility with angiography was generally and individually evaluated for all coronary arteries. Cohen's kappa coefficient was used for CK-DSE and MPS to test the consistency of CA. A kappa value ≥ 0.7 was considered high, and between 0.4 and 0.7 was considered moderate consistency. Kappa values for MPS and CK-DSE were analyzed with receiver-operating characteristic (ROC) curve analysis, while consistency between tests was evaluated by comparison of area under curves (AUC) with 95% confidence interval (CI) as previously described by DeLong et al. [16]. All statistical procedures were performed with SPSS v.16.0 (IBM-SPSS, Inc., Armonk, NY, USA). A *P*-value < 0.05 was seen as statistically significant.

Results

In 13 (65%) patients, DSE was completed, but was ended early in 5 patients due to angina pectoris, and in 2 patients due to ≥ 2 mm ST segment depression. There were no significant side effects during DSE; 11 patients had no side effects, while others experienced dizziness, palpitations, headaches, and burning sensations, which was eliminated by terminating the test.

Resting wall motions were normal in 8 (40%) patients. During the dobutamine challenge, segmental wall motion abnormality developed in all patients, despite normal resting wall motion. Four developed wall motion abnormality in Cx territory, 3 developed it in LAD territory, and 1 developed it in RCA territory.

Twelve (60%) patients had abnormal resting wall motion of various degrees. Wall motion abnormalities remained unchanged or deterioriated in 10 patients. One had resting hypokinesia in Cx territory, which was resolved during the dobutamine challenge and accepted as normal. Three patients had akinetic or dyskinetic segments of LAD territory, 4 had akinetic segments of RCA territory, having had previous MIs. In 5 patients, resting hypokinesia of LAD territory was increased during the dobutamine challenge and considered to be ischemia. In one patient, resting hypokinetic segments in RCA territory became akinetic during a dobutamine challenge and the patient was found to have had a previous MI.

According to the CK-DSE results, 1 patient was considered normal, 11 (55%) as having single-vessel disease, 2 (35%) as having two-vessel disease, and 1 (5%) as having three-vessel disease. As per the MPS results, 1 patient was considered normal, 8 (40%) had single-vessel disease, 9 (45%) had two-vessel disease, and 2 (10%) had three-vessel disease.

More than 70% percent with stenosis of the coronary arteries were related to inducible ischemia, yet accepted as significant CAD. CA had shown single-vessel disease in 10 (50%), two-vessel disease in 9 (45%), and three-vessel disease in 1(5%). Nine LAD, 11 RCA, and 11 significant Cx lesions could detect CA. Left ventriculography had shown segmental wall motion abnormality in 9 (45%) patients, and apical aneurysm in 3 (15%).

The kappa coefficient of CK-DES was 0.66 in determining CAD localization. Vessel-based kappa values for LAD, RCA, and Cx were found at 0.81, 0.70, and 0.61, respectively.

The kappa coefficient of dobutamine MPS was found to be 0.67 for all coronary vessels. Vessel-based kappa values for LAD, RCA, and Cx were 0.79, 0.70, and 0.59, respectively. According to the ROC curve analysis, comparison of AUC for kappa values of MPS and CK-DSE in determining CAD was found to be statistically insignificant (*P*>0.05, 95% CI).

Discussion

The following factors were considered while preparing our study protocol: 1- Reflecting routine daily cardiology practice, 2- Performing necessary and non-time-consuming procedures for patients, 3- Objective interpretation of the tests. The combination of these factors was obvious in patient selection, evaluation of data, and determination of diagnostic methods.

In this study, our aim was to determine the presence and localization of significant CAD. The population consists of a mixed group of patients, some of whom had a previous diagnosis of CAD, while others did not. Clinical, resting ECG, and echocardiography findings were evaluated and CK-DSE examination was only performed in suitable patients: MPS or CA was also recommended in them. Unnecessary CA was avoided in patients with a low probability of significant CAD in noninvasive tests. Two of 32 patients were excluded, as they were not eligible for CK-DSE, with 10 excluded from the study, not having an indication of CA. This approach increased the likelihood that CK-DSE and dobutamine MPS would yield similar results with CA. CK-DSE and MPS were performed for the same dobutamine challenge, so repeated dobutamine administration was avoided. Although it was not mentioned in the study protocol, the exercise stress test was performed in all patients to preclude unnecessary CA.

Mor-Avi et al. [17] performed CK-DSE in 20 patients, suggesting that CK allows for objective and rapid evaluation of CAD. Our impression was similar. Although we did not evaluate

patients with poor echocardiographic image quality, endocardial borders could be seen clearly with CK. A previous study had evaluated the role of DSE in determining ischemia-related coronary artery, but Segar et al. had shown that sensitivity was similar for each coronary artery [10]. Our study found that CK-DSE was consistent with CA results in determining CAD localization (kappa=0.66); however, predictive probability was different among all coronary arteries. This difference was mainly due to a lower predictive value in Cx lesions; it simulated a previous DSE study in which Geleijnse et al. [18] reported the sensitivity of DSE in determining LAD, RCA, and Cx lesions as 72%, 75%, and 55%, respectively. We explained the lower resolution of the lateral wall and differences in the Cx coronary artery.

DSE is a valuable diagnostic tool in determining CAD: in a recent study, its sensitivity and accuracy was reported as 85% and 90%, respectively [6, 19]. Studies comparing MPS and DSE to determine CAD localization found similar diagnostic performance [20]. The optimal test changes according to patient characteristics, laboratory conditions, and availability. The main advantage of DSE is that it allows for detection of additional information about cardiac disorders. It is also less expensive, radiation-free, and can be done at the bedside.

Limitations

The main limitation of our study was that it was conducted with a relatively small number of patients. Given ethical considerations, 10 patients without a CA indication were not included, although we had already performed CK-DSE. Further studies conducted with a large patient population, comparing CK-DSE and CA in all patients, were needed. In our research, patients with an ejection fraction of < 40% and A-Fib were not included in the study, such that these findings should not be extrapolated to this patient population. Although CK allows for more objective evaluation of wall motion abnormalities, there is a group of patients in whom healthy evaluation cannot be done due to poor image quality (n=2 in our study). New techniques and improved CK may transcend image quality issues in this population.

Conclusion

In determining CAD localization, CK-DSE led to results close to CA. Compared to MPS, no significant difference was found between methods. While their compatibility with CA was higher in determining ischemia in LAD and RCA territories, consistency was found as moderate for Cx territory. Although both CK-DSE and MPS produce similar results, CK-DSE has some advantages: it is easy to apply, less expensive, and detects accompanying cardiac disorders. The CK method allows for rapid, objective, and automatic evaluation of segmental wall motion. In our study, CK was used with DSE, with high diagnostic accuracy achieved.

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Analgesic efficacy and opioid sparing effect of erector spinae plane block in oncologic breast surgery: An observational study

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Ethics Committee Approval
The study protocol was approved by the Ethics Committee for Clinical Studies of Marmara University Medical Faculty Istanbul Turkey (date: July 24, 2020; number: 09.2020.125).
The study was registered to ClinicalTrials.gov with identifier NCT04824300.
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: Erector spinae plane block (ESPB) is a fascial plane block technique suitable for perioperative analgesia. This study aimed to evaluate the value of ESPB performed under ultrasound guidance and with ANI (Analgesia Nociception Index) monitoring in terms of intraoperative opioid need and postoperative pain management, in patients undergoing oncological breast surgery.
Methods: This prospective case-control study includes forty-two female breast cancer patients who underwent unilateral modified radical mastectomy with axillary lymph node dissection. Patients were allocated to receive (ESPB group) or not receive (controls) ultrasound guided ESPB before anesthesia induction based on patient preference, and the groups were compared in terms of total intraoperative opioid consumption (with the guidance of ANI) and postoperative pain. Visual analogue scores (VAS) were obtained during the 12-hour postoperative follow-up.
Results: Total intraoperative remifentanil dose required was significantly lower in the ESPB group when compared to controls (361.9 (108.3) vs. 1560.0 (4), $P<0.001$). ESPB group had significantly lower visual analogue scores at all postoperative time points. None of the patients in the ESPB group but all controls required additional analgesia during the 12-hour postoperative follow-up period.
Conclusion: Ultrasound guided ESPB together with ANI monitoring is an effective and relatively safe perioperative analgesia method in patients undergoing mastectomy. Together, they provide an effective postoperative analgesia and reduce intraoperative opioid use consumption. Further studies will shed more light on the role of ESPB in this setting.

Keywords: Erector spinae plane block (ESPB), Oncological breast surgery, Perioperative pain, Opioid

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Introduction

Oncologic breast surgery is associated with significant acute and chronic postoperative pain, leading to reduced quality of life following surgery. Multimodal analgesia and regional analgesia are frequently utilized to alleviate pain after breast surgery. Pharmacological treatments to reduce pain in these patients include intra- and post-operative paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), preoperative gabapentin or pregabalin, single dose dexamethasone to reduce pain and nausea, and intraoperative opioids and postoperative opioids for rescue analgesia [1]. Other recommended pain management strategies in oncologic breast surgery include local anesthetic infiltration at the wound site, paravertebral block, pectoral nerve block (PECS1-PECS2), and erector spinae plane block (ESPB) [2].

Although local anesthetic infiltration leads to reduced postoperative pain and opioid use, its efficacy lasts for only a brief period. On the other hand, regional anesthetic administration is associated with reduced opioid use, better alleviation of postoperative nausea and vomiting, and lower postoperative pain scores, as compared to general anesthesia alone and local anesthetic infiltration at the wound site, in addition to shortened length of hospital stay [1]. Since paravertebral nerve block is performed at an anatomical site close to pleura, it is associated with the risk of pneumothorax, even if performed under ultrasound guidance [3]. Furthermore, the risk of total spinal block cannot be eliminated.

Erector spinae plane block (ESPB) is the most recently described fascial plane block technique to be utilized for analgesia in patients undergoing breast surgery [4]. There is considerable distance between the site of procedure and the pleura [5], reducing the risk of serious complications such as pneumothorax. ESPB provides all benefits associated with the gold standard thoracic epidural anesthesia for postoperative pain management, and is devoid of hemodynamic side effects [6]. Despite a surplus of studies since the first description of ESPB in 2016, most publications have reported on its effects on postoperative opioid use, with few studies examining intraoperative opioid use with ANI (Analgesia Nociception Index) monitoring. Furthermore, the increased use of opioids for postoperative pain in patients receiving general anesthesia only is associated with side effects. In recent years, we have also witnessed an alarming increase in opioid dependency and opioid-related mortality.

In the absence of a reliable monitor, the assessment of intraoperative pain intensity and opioid need is generally based on the change in hemodynamic parameters, although this approach is non-specific. In more recent years, ANI device has been introduced as an objective means for continuous perioperative pain measurement. ANI reflects the balance between nociception and analgesia using an analysis of heart rate variability against a scale of 0 to 100 and determines the intensity of pain stimuli via heart rate and arterial pressure. This allows opioid administration in accordance with the patient need [7].

The main objective of our study was to examine the effect of ESPB performed under ultrasound guidance and with ANI monitoring on intraoperative opioid need in comparison with controls. In addition, the time to first need of analgesia postoperatively and postoperative pain scores were analyzed.

Materials and methods

Patients

A total of 42 consecutive female breast cancer patients aged between 25 and 70 years with ASA scores of 1-3 who underwent unilateral modified radical mastectomy with axillary lymph node dissection were included in this prospective non-randomized observational cohort study. Exclusion criteria were as follows: Severe respiratory or cardiac condition, hepatic or renal failure, coagulopathy, local infection at the injection site, deformity of the vertebra or chest wall, allergy against study drugs, opioid abuse, or patient unwillingness. The study protocol was approved by the Ethics Committee for Clinical Studies of Marmara University Medical Faculty Istanbul Turkey (date: July 24, 2020; number: 09.2020.125) and the study was conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent prior to study entry. The study was registered to ClinicalTrials.gov with the identifier NCT04824300.

Study groups and outcome measures

Patients were allocated to receive (ESPB group) or not receive (controls) erector spinae plane block (ESPB) before anesthesia induction based on patient preference. The primary outcome measure was total intraoperative opioid consumption with the guidance of analgesia nociception index (ANI), and the secondary outcome measure was the change in postoperative pain as assessed by visual analogue scale (VAS). Sample size estimation revealed that a total of 21 patients per group would be necessary to detect a mean difference of at least 40% reduction in intraoperative opioid consumption between the two treatment groups, with an alpha error = 0.05 and beta = 0.2 (power = 0.8). Thus, 21 consecutive patients preferring and not-preferring ESPB were included in the ESPB group and controls, respectively. The study groups were compared in terms of study outcomes.

Erector spinae plane block technique

In the ESPB group, ESPB was performed by the same experienced anesthesiologist before the induction of general anesthesia. The procedure was carried out at the operation side in sitting position and under ultrasound guidance using a linear probe (6-13 MHz). Injection site was identified and marked at 3-cm lateral to the T3 spinous process. The injection was performed using in-plane technique and a 22G block needle (100mm, B-Braun, Germany). The needle was advanced in the cranio-caudal direction and 1-2 ml saline was injected to separate erector spinae muscle from the transverse process. Following the separation, 20 ml 0.5% bupivacaine and 100 mg (5 ml) lidocaine were injected. Diffusion of the drug in erector spinae plane at cranio-caudal line was ensured. No analgesic or sedative was used during the procedure.

Intraoperative management

Anesthesia induction was done with 2 mg/kg propofol and 0.6 mg/kg rocuronium and an endotracheal tube was placed. Anesthesia was maintained by propofol and remifentanil with the guidance of ANI and BIS. Electrocardiography, non-invasive

blood pressure, bispectral index (BIS, Medtronic, Mineapolis), and ANI were monitored and recorded every 15 minutes.

ANI was monitored to objectively evaluate perioperative pain and to prevent unnecessary intraoperative opioid administration. Two ANI electrodes were placed on the sternum and at the level of left nipple (to the same places with V1 and V5 ECG electrodes, respectively). ANI was continuously displayed at 1 Hz frequency throughout the surgical procedure. Patients received a maintenance dose of 0.3 mcg/kg/h remifentanil. Remifentanil dose was adjusted to keep ANI values between 50 and 70. A 1 mg/kg remifentanil dose was administered when ANI < 50, and remifentanil infusion dose was reduced when ANI > 70. Total remifentanil dose was recorded for each patient.

Patients were monitored with BIS (Aspect Medical Systems, Natick, Mass, ABD) to help assess anesthesia depth, which uses bispectral analysis and monitors the effect of anesthesia based on electroencephalogram (EEG). Maintenance propofol infusion dose was 6-8 mg/kg/h, which was adjusted to keep BIS value at 40±5, and the total propofol dose was recorded.

Fifteen minutes before the completion of the surgical procedure, both groups received 1 g paracetamol and the control group received 100 mg tramadol.

Postoperative assessments

Patients received instructions before the surgery on how to assess their pain postoperatively, using 0 to 10-point visual analogue scale (VAS): 0 indicated no pain, while 10 indicated the worst imaginable pain. A physician blinded to patient allocations recorded self-assessed VAS scores of all patients upon awakening and at 6 and 12 hours. In addition, the timing of the first analgesic requirement was recorded. If VAS ≥ 4, 100 mg tramadol was given as rescue analgesic.

Statistical analysis

Sample size was calculated based on changes in opioid consumption. It was determined that at least 42 (sample size calculator) patients should be included in the study, with the expectation that there would be a 40% reduction in α=0.05, β=0.2 opioid consumption, based on significant difference.

SPSS (Statistical Package for Social Sciences) version 21 software was used for the analysis of data. Descriptive data were expressed in mean (standard deviation) or median (range), where appropriate. The normality of continuous variables was tested using both hypothesis tests and graphical methods. Intergroup comparisons of continuous variables were made using the student t test for independent samples or Mann-Whitney U test, depending on data distribution. The two-way ANOVA test for repeated measurements was used to examine the significance of differences between the groups in postoperative VAS scores and intraoperative measurements over time. Two-sided *P*-values of <0.05 were considered indication of statistical significance.

Results

Patients

A total of 42 female patients were included: 21 in the ESPL group and 21 in the control group. The patients in the ESPB group were significantly younger when compared to the controls: 45.2 (13.8) vs. 53.0 (9.4) years, respectively (P=0.040). The two groups were similar regarding intraoperative changes in heart rate, mean arterial pressure, analgesia nociception index, and bispectral index over time (P>0.05 for all).

Analgesia requirement

None of the patients in the ESPB group required additional analgesia during the 12-hour postoperative follow-up period. All patients in the control group required analgesia following surgery after a mean duration of 3.6 (0.7) hours (median, 4; range, 2-5). At the time of analgesia requirements, the mean VAS score was 6.7 (1.1) (median, 7; range, 5-8).

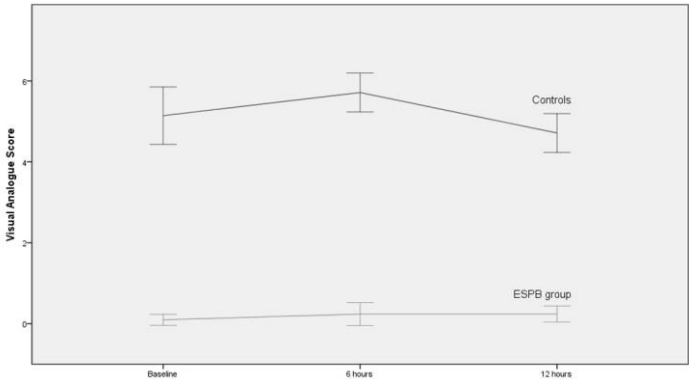
Intraoperative narcotic requirement

Total intraoperative remifentanil dose required was significantly lower in the ESPB group, when compared to controls (361.9 (108.3) vs. 1560.0 (491.6) µg, P<0.001). In addition, ESPB group required less intraoperative propofol (453.3(168.3) vs. 599.0(127.2) mg, P=0.001).

Changes in VAS scores

Figure 1 shows changes in postoperative VAS scores over time (at baseline when awakening, at 6 and 12 hours), where a significant difference in VAS scores was evident over time between the two groups (P<0.001). ESPB group had significantly lower VAS scores at all-time points (P<0.001 for all).

Figure 1: Changes in mean postoperative VAS scores over time. Upper line, control group; lower line, ESPB group. Error bars indicate 95% confidence intervals for the mean.



Discussion

In this study, ultrasound guided ESPB was associated with a significant reduction in the need for intraoperative opioid use and satisfactory level of pain control over a 12-hour period in patients undergoing unilateral modified radical mastectomy with axillary lymph node dissection. In patients undergoing oncological breast surgery, to the best of our knowledge, no studies have examined intraoperative opioid use and pain management with ESPB via ANI monitoring.

In our study, utilizing nociception measurement-guided analgesia monitoring, intraoperative opioid infusion settings were adjusted at an ANI of ≥50. Successful analgesia could be delivered to patients using ESPB, resulting in an effective intraoperative analgesia and reduced opioid use. In routine clinical practice, analgesic administration is generally based on clinical pain symptoms elicited by the activation of the autonomous nervous system. However, this approach has been reported to lack sensitivity and specificity, due to the role of many confounders (e.g. autonomic, hormonal, or metabolic alterations) as well as due to intra-individual differences [7]. In a study by Dundar et al. [8], ANI monitoring significantly lowered

opioid consumption and could provide guidance on evaluation of blockade efficiency and determination of the need for analgesia in patients undergoing concomitant regional anesthesia and general anesthesia [8].

Also, despite the inclusion of a different group of surgical patients, Melvin et al. [9] found significantly lowered peri-operative opioid use in patients undergoing lumbosacral spine surgery when ESPB was performed at T10-T12 prior to incision.

Since the analgesic efficacy of the block continued into the postoperative period, a satisfactory level of opioid-free analgesia could be achieved. Since the recent introduction of opioid-free anesthesia, anesthesiologists have started to utilize multi-modal analgesia management in addition to general anesthesia in many surgical settings. Reduced use of opioids is associated with significant clinical benefits in terms of patient care as well as quality of life. Pain control with nerve blocks has been reported to yield superior results as compared to opioid-centered analgesia with respect to early mobilization, rapid recovery of body functions, and lack of dependency risk [10], underlining the importance of opioid-free anesthesia. In many studies exploring postoperative opioid consumption, ESPB was found to reduce the need for opioid use. For example, in Gürkan et al.'s [11] study, ESPB and control groups were compared in terms of postoperative analgesia and opioid use during the first 24 postoperative hours in patients undergoing breast surgery. Although a 65% reduction in opioid consumption was observed at postoperative 24 hours with ultrasound guided ESPB, postoperative pain scores were not significantly different [11]. Similarly, Yao et al. [12] found reduced morphine consumption and adequate analgesia with ESPB following breast surgery. In a review of 85 publications involving 242 cases undergoing ESPB, a significant proportion of patients had reduced postoperative opioid utilization [13]. A recent study from Korea included 40 patients who underwent breast-conserving surgery and received preoperative ESPB or not (controls). In the postoperative period, ESPB was associated with lower pain scores for breast but not for axilla. The two groups did not differ in terms of postoperative use of non-steroid anti-inflammatory agents [14]. ESPB has been found to provide adequate analgesia and to reduce postoperative opioid consumption in many types of surgery other than breast surgery. For instance, reduced postoperative opioid consumption with ESPB was reported following mitral valve surgery in a study by Leyva et al. [15].

In our ESPB group, patients required no additional analgesia for the first postoperative 12 hours. In contrast, control patients had a VAS score of 7 approximately 4 hours after surgery, and all subjects required additional analgesia. Postoperative VAS scores were significantly lower in the ESPB group. The stress response to postoperative pain and surgical trauma may lead to several changes in the release of hormones such as cortisol, prolactin, and adrenocorticotrophic hormone, potentially resulting in adverse metabolic and cardiovascular effects. Hence, postoperative analgesia has an important role in the stress response attenuation. As shown by Gad et al. [16], ESP block is associated with reduced stress hormone levels and pain scores. In another study, ESPB reduced pain scores significantly in breast surgery, similar to our observations [17]. In contrast to our findings, in another study, the patients were divided into 3 groups to compare pain scores with paravertebral block, ESP block, and control treatment, and no differences were found between ESP block and control treatment [18]. Wang et al. compared postoperative pain with serratus anterior plane block, ESP block, and general anesthesia only in patients undergoing radical mastectomy and found lower VAS scores in both block groups than general anesthesia [19]. A previous meta-analysis also reported significant efficacy in providing 24 h postoperative pain control and opioid reduction with ESPB in patients undergoing breast surgery [20]. Elsabeeny et al. [21] reported better analgesia with ESPB in comparison with iv opioid analgesia in patients undergoing radical mastectomy, in addition to reduced postoperative opioid use, longer time to first dose of analgesic, and reduced number of side effects.

ESPB under ultrasound guidance provides abdominal or thoracic segmental analgesia depending on the level of injection [22]. The injected agent spreads to the thoracic paravertebral area via costa-transvers foramina; thus, ESPB blocks dorsal and ventral rami of spinal nerves [23]. In a cadaveric MRI study, it has been shown that the spread of analgesia extends to a large area from a single injection point [24]. ESPB has gained popularity as a regional anesthesia technique in several painful surgical and non-surgical conditions. In the current study, the cranio-caudal spread of the local anesthetic along the transverse process at T3 level was ascertained using ultrasound, and sensory block at T1-T6 dermatomes was confirmed with pin-prick test.

In our study, ESP blocks were performed by the same senior experienced anesthesiologist with no complications. While the use of ultrasound reduces the risk of complications, paravertebral blocks are associated with a significant risk of severe pneumothorax and pleural puncture [25]. Since ultrasound cannot fully guarantee prevention of dangerous complications, many clinicians are reluctant to utilize these blocks. ESPB, on the other hand, is associated with a lower risk of serious complications, when performed under ultrasound guidance at a tissue plane distant from potentially problematic structures [26]. It also represents a safer alternative to paravertebral block due to the use of the transverse process as a barrier, avoiding needle injury to the pleura [27]. Ueshima [5] reported only one patient developing pneumothorax following ESPB, although no clear information was provided whether patients with bullous lung disease were excluded from the study. No local toxicity due to local anesthetic was reported by Krishna et al. [28] in their patients undergoing bilateral ESPB for pain control after cardiac surgery. However, Tulgar et al. [29] administered bilateral ESPN at T9 level prior to laparoscopic umbilical hernia repair in their patient, who experienced reduced general muscle tone and loss of consciousness. The authors stated that this was likely to represent a neurological complication of local anesthetic [29]. A previous study reported stable hemodynamics following ESPB despite sympathetic block [30].

Since ANI monitoring can reduce unnecessary opioid use due to its ability to instantly reflect perioperative pain using heart rate, it may offer an additional means to lower opioid consumption in patients undergoing ESPB and to closely monitor the success of the block.

A major limitation of our study is the lack of randomization. Further randomized studies may provide more valuable information on the efficacy of ESPB performed in conjunction with ANI monitoring. Group assignment was based on patient discretion, and ESPB was preferred by younger patients, which may represent a confounding bias and reduces generalizability, although this alone may not account for the differences observed.

Conclusions

Ultrasound guided ESPB together with ANI monitoring is an effective and relatively safe perioperative analgesia method in patients undergoing mastectomy. Together, they reduce intraoperative opioid use, and provide satisfactory postoperative analgesia. Further studies will shed more light on the role of ESPB in this setting.

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Research article

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Investigation of postero-anterior mobilization in the lumbar spine: A finite element analysis study

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Ethics Committee Approval
Approval for the study was obtained from the Clinical Research Ethics Committee of Amasya University with the decision numbered 14. 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: Postero-anterior (PA) mobilization is a non-invasive treatment method traditionally used to treat low back pain (LBP) in many countries. However, the effects of PA mobilization on lumbar spine biomechanics are still unknown. The aim of this study is to determine the maximum von Mises stresses on the lumbar vertebra (L5), with force applied at different angles during PA mobilization therapy using finite element analysis (FEA).

Methods: L5 vertebra CT images of a 34-year-old male patient were modeled in three dimensions (3D) with MIMICS software to examine the PA mobilization biomechanics. The resulting L5 spine model was submitted to the finite element software ANSYS (version 19) to evaluate the effects of PA mobilization. To simulate PA mobilization on the L5 vertebra, a static force of 100 N was applied over the spinal process in three different directions. The distribution of von Mises stresses occurring in the L5 spine was determined in the analyses.

Results: During PA mobilization, the stress distributions on the vertebra caused by the static force applied in three different directions in the L5 vertebra spinal process was determined. As a result of the analysis, higher stress values were found in the posterior elements of the vertebra in all directions compared to the vertebral corpus. However, when compared according to the direction of application, the lowest stress values were detected in the pedicles and laminas in PA mobilization applied toward the spine center.

Conclusion: Vertebral pedicles, laminae, and spinous process are critical areas prone to fracture. It was argued that the change in the direction of PA mobilization applied in the L5 vertebral spinal process affects the von Mises stress distributions occurring in the pedicles and laminae.

Keywords: Postero-anterior mobilization, Finite element analysis, Lumbar vertebra

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Introduction

Lower back pain (LBP) is one of the most prevalent health issues referred to doctors [1]. Approximately 40% - 70% of the global population experiences at least one LBP attack during their lifetime [2]. LBP can be caused by problems with any part of the spinal muscles, ligaments, bones, discs, and nerves in the lumbar spine that may be interrelated [3]. Conservative treatment of low back pain consists of medical therapy, electrotherapy, exercise therapy, and manual therapy.

Manual therapy is a widely used clinical technique for diagnosing and treating human joints and soft tissues [4, 5]. This involves massage, mobilization, and manipulation [6]. Postero-anterior (PA) mobilization is a low-speed passive movement technique used in physical therapy. One of the manual therapy procedures, PA vertebral mobilization, can be used to evaluate and treat patients with low back pain. This procedure involves posterior-to-front movements that occur with the application of manual force applied to a single vertebra above or lateral to the midline [7]. Pain relief, reduced spinal stiffness, and increased spine range of motion are all benefits of PA mobilization [8-10].

PA mobilization is performed on the vertebra in different directions and with different force, increasing the stress within the bone tissue. However, the processes underlying the effect of PA lumbar mobilization on the vertebra remain unclear. We can use finite element analysis (FEA), which has become popular in recent years, to better understand lumbar biomechanics, make better choices, and formulate therapeutic decisions. It can be used as a non-invasive method to evaluate the biomechanical efficacy and properties of new and existing treatments [11, 12]. In addition, there are a limited number of studies in the literature evaluating the biomechanical effects of PA mobilization [13]. The force applied in the PA mobilization studies was generally applied in one direction [13, 14]. However, since mobilization is a dynamic process, changes in the direction of application force may occur during treatment. For this reason, the aim of our study is to investigate the effect of static force applied at different angles during PA mobilization on L5 vertebra geometry using the FEA method.

Materials and methods

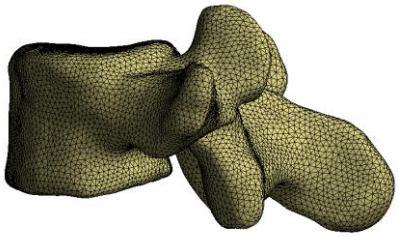
Creation of the 3D model

The anatomical geometry of the L5 vertebra was obtained from a computed tomography (CT) scan of a 34-year-old healthy male patient (height: 175 cm, weight: 74 kg) without osteoporosis or previous history. Approval for the study was obtained from the Clinical Research Ethics Committee of Amasya University with the decision numbered 14. The research was carried out in conformity with the principles of the Helsinki Declaration. CT images were recorded in the Digital Imaging Communication in Medicine (DICOM) format from a Toshiba Aquilion CT scanner at the Department of Radiology, Faculty of Medicine, Amasya University. Images were acquired at 135 kV with a pixel size of 0.625 mm and a resolution of 512×512 pixels. The resulting images were segmented using MIMICS 12 (Materialise, Leuven, Belgium) 3D image processing software and the L5 vertebra were modeled in 3D. The geometries were converted to stereolithography format with MIMICS software and sent to reverse engineering software Geomagic Studio 12.0 (Geomagic, Cary, North Carolina, USA) in order to edit the surface defects in the modeled vertebra and obtain the correct geometry. The resulting 3D model was transferred to ANSYS Workbench for FEA.

Mesh and properties of material

The L5 vertebra model tetrahedral mesh structure was created using ANSYS Workbench (Version 19.0) software, as shown in Figure 1. For mesh convergence, the element size in the 3D model was increased by 0.2 from 0.2 mm spacing to 3 mm. For bone structures, Solid187 tetrahedron element types and mesh size of 1.2 mm were selected. Our models consisted of 46,2471 nodes and 327,788 elements. The material properties of L5 vertebra are defined as linear elastic and isotropic. Cortical and trabecular bones have Young's modulus values of 12.0 GPa and 100 MPa, respectively. The Poisson ratio was chosen as 0.3 for cortical bone and 0.45 for trabecular bone [15-18]. Nonlinear analyses were performed according to the Newton-Raphson method.

Figure 1: Mesh structure of the model



Boundary conditions

This study simulated static loading applied on L5 vertebra in different directions during PA mobilization. The lower endplate and upper endplate of the vertebra were considered fixed. To simulate PA mobilization, a force of 100 N was applied from the spinal process toward the lower endplate (Figure 2a), toward the center of the corpus (Figure 2b), and toward the upper endplate (Figure 2c).

Figure 2: The loading and boundary conditions a) toward the lower endplate b) toward the center of the corpus c) toward the upper endplate

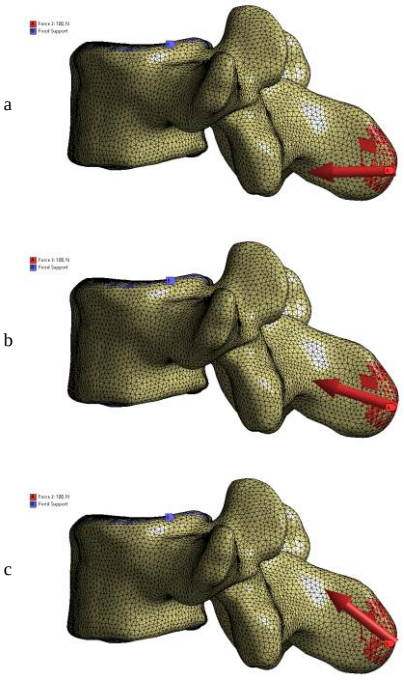
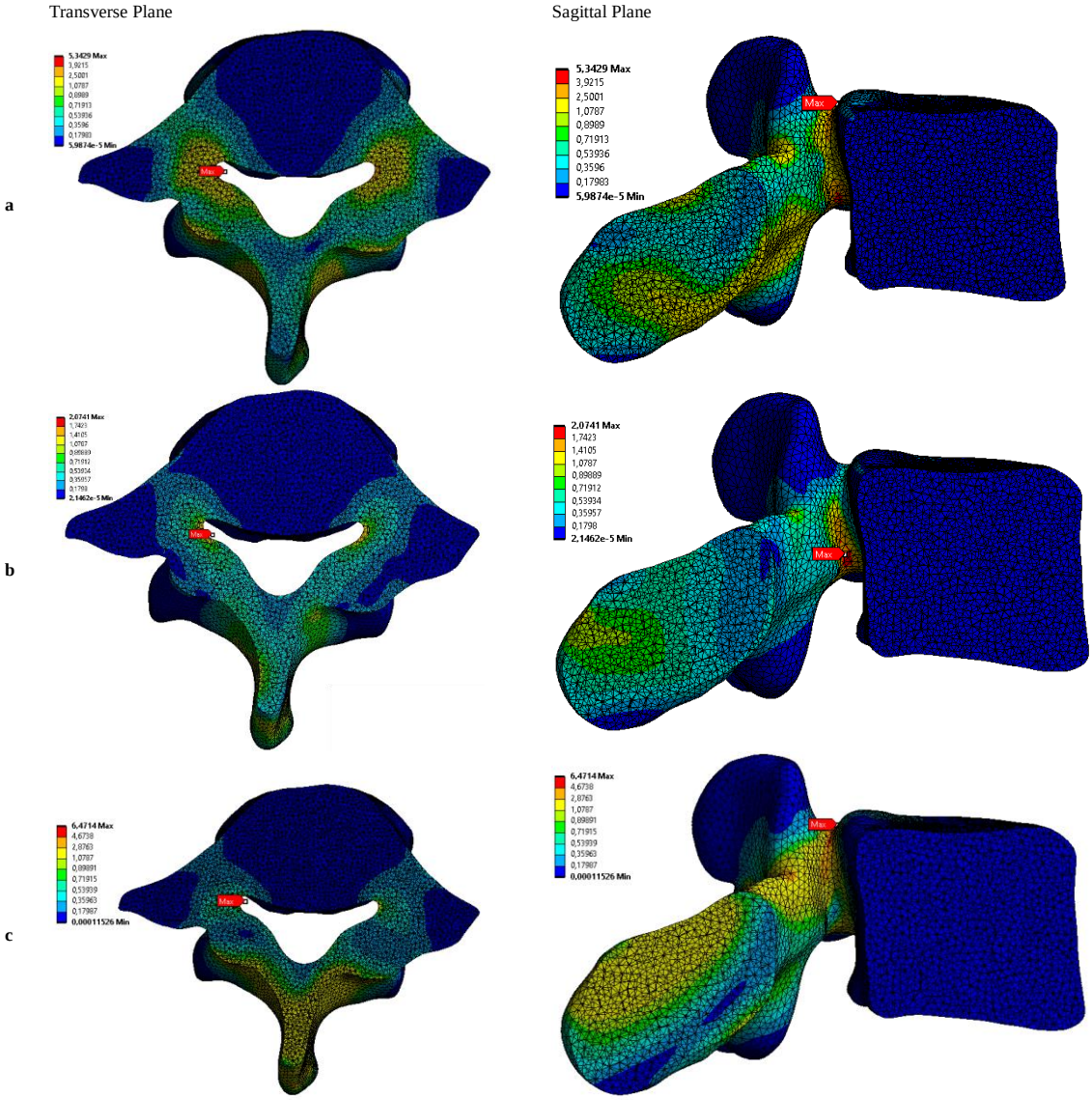


Figure 3: Stress distributions in the transverse and sagittal planes as a result of the analyses a) toward the lower endplate b) toward the center of the corpus c) toward the upper endplate



Results

Stress distributions occurring in the L5 vertebra during PA mobilization therapy, which is widely used in the treatment of LBP, were determined using the FEA method. Stress distributions occurring on the L5 vertebra under loads applied at different angles were performed on the transverse and sagittal planes as seen in Figure 3.

When the analyses were examined, the maximum stress values according to the force directions were obtained as 5.3429 MPa when applied toward the lower endplate, 2.0741 MPa when applied toward the center of the corpus, and 6.4714 MPa when applied toward the upper endplate. In addition, it was observed that the maximum stress was on the pedicles in all models. However, it was noted that the force applied in the direction of the upper and lower endplate of the maximum stress was in the upper part of the pedicles, and the force applied in the direction of the corpus was in the central part of the pedicles.

Discussion

There are a limited number of studies examining the effects of PA mobilization on the vertebra, and the biomechanical results remain unclear. In our study, the effect of PA mobilization applied in different directions on the geometry of the L5 vertebra on the maximum stresses occurring in the anatomical parts of the vertebra was investigated using finite element analysis.

Mobilization is a complementary and alternative medical practice that is widely used mainly for spine and soft tissue treatment [19]. Mobilization consists of low-speed, variable-intensity, repetitive passive movements within the range of normal joint motion [20]. There are many specific mobilization techniques that vary according to patients' needs. However, the forces and directions applied during these spinal techniques may vary among clinicians depending on the treatment area and patient characteristics [21]. In addition, it is not fully known whether clinicians adhere to mobilization techniques in daily practice [22]. Various complications may develop during treatment sessions for low back and neck pain. Reported complications have included disc herniation, vertebral fracture, and cervical arterial strokes [23-25]. It is important to

determine the intensity and direction of the force to be applied in order to prevent possible complications.

In our study, with the application of static 100 N force in three different directions, it was observed that there were more stress distributions in the posterior elements of the L5 vertebra, consisting of the spinal process, laminas and pedicles, compared to the corpus. Boonyoung et al. [14] found that the lumbar vertebral pedicle and lamina regions of an elderly male patient were susceptible to fracture. They also showed that in severe osteoporosis, not only the pedicles, but also the spinal process is a high-risk fracture site. Another in vivo study has shown that the spinous process is displaced anteriorly during PA mobilization [26]. As a result, more loading occurs on the pedicles during the anterior movement of the spinous process. In our study, the highest maximum stress values were observed especially in the pedicles, which act as a bridge in connecting the posterior bone components and the corpus. Therefore, pedicles are critical structures during mobilization.

One of the most important results of our study is that after force was applied from the spinal process to the center of the corpus, the maximum tension in the pedicles was found to be significantly lower than the forces applied in the upper and lower endplate directions. This information can be helpful in preventing complications that may develop during vertebral mobilization applications, especially in high-risk patients. In addition, changes in the direction of the force applied during PA mobilization significantly affect the stress distributions created by the vertebra on the bone elements. Thus, effective and appropriate use of power can be ensured and the success of the treatment can be achieved.

Limitations

Our study has several limitations. First, the material properties of bone are defined linearly. Secondly, real environment experiments were not carried out. Disc and vertebral ligaments were not included in our model. Therefore, it may not clearly reflect the complex structure of this region. In addition, only static loading was applied in our study. However, both static and dynamic loads occur during PA mobilization. Due to the limitations of FEA, outputs may not accurately reflect real-life situations; however, even approximate results can provide useful information.

Conclusion

In this study, we investigated the stress distributions that occur after force is applied at different angles over the L5 spinal process. It was observed that loading applied at different angles can increase the maximum tension, especially in the pedicles. It was found that as a result of the force applied toward the center of the corpus, less stress was created than in other directions. These results are important in terms of predicting and preventing damages that may occur in the vertebra during mobilization. They can also be used to increase the effectiveness of treatment.

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Comparison of high-dose, short-term steroid and low-dose long-term steroid use in ARDS caused by COVID-19: Retrospective cohort study

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Ethics Committee Approval
Biruni University's non-interventional clinical research ethics committee (no: 2021/53-05, Date: 16.06.2021)
ClinicalTrials.gov Identifier: NCT05047874.
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Given the increasing incidence and mortality caused by coronavirus 2019 (COVID-19) worldwide, beneficial and effective treatment for patients in the early pulmonary phase is still of great importance. Fifteen-day continuous hemodynamic, laboratory, and clinical courses of patients with acute respiratory distress syndrome (ARDS) due to COVID-19 who received short-term high-dose and long-term low-dose systemic methylprednisolone were compared.

Methods: Two hundred and two patients were reported to have ARDS due to COVID-19 in the intensive care unit between June 1, 2020 and February 1, 2021. The patients were divided into two groups: (1) short-term high-dose and (2) long-term low-dose systemic methylprednisolone. Age, gender, Acute Physiology and Chronic Health Evaluation (APACHE II) scores, steroid treatment protocol, intubation duration, length of stay (LOS), Neutrophil/Lymphocyte Ratio, C-reactive protein (CRP), procalcitonin, lactate levels, cytokine filter requirements, the prognosis, and total costs were obtained from their records.

Results: It was determined that elderly patients tended to be given low doses of steroids. No significant differences between the two treatment protocols in terms of other parameters were found. It was determined that high doses of steroids affected only CRP levels ($P<0.05$).

Conclusion: No differences in lactate, PCT levels, NLR, intubation and weaning times, hemoperfusion requirements, hospital stay, and prognosis between administration of different doses and durations of methylprednisolone for the treatment of COVID-19 ARDS were found.

Keywords: Methylprednisolone, COVID-19, ARDS, Prognosis

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Introduction

Since coronavirus 2019 (COVID-19) was appeared in China in late 2019, the number of infected people continues to rise. If the COVID 19 infection is not eradicated by proper and powerful immune responses, pulmonary fibrosis, shortness of breath, decreased O_2 saturation, acute respiratory failure syndrome (ARDS), and mortality owing to the resulting cytokine storm can occur [1].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been found to cause a cytokine storm in COVID-19 patients who are in the intensive care unit (ICU) high plasma levels of inflammatory cytokines have been linked to illness severity and prognosis [2].

Glucocorticoids and immunosuppressive therapy can cause a reduction in respiratory tract inflammation and prevent cytokine storm and ARDS induction in COVID-19 patients. Because no effective specific therapeutic agents for the disease are available, glucocorticoids and immunosuppressive therapy can. lead to a reduction in respiratory tract inflammation and prevent cytokine storm and ARDS induction [3].

The 15-day continuous hemodynamic, laboratory, and clinical course of COVID 19 patients who received short-term (3 days) high-dose (10 mg/kg/day) systemic methylprednisolone versus COVID 19 patients who received low-dose long-term (1 mg/kg/day) systemic methylprednisolone in this retrospective study was compared.

Materials and methods

After receiving approval from Biruni University's non-interventional clinical research ethics committee, this project was started as a retrospective cohort study (Ethics committee no: 2021/53-05; Date: 16.06.2021 ClinicalTrials.gov Identifier: NCT05047874). Patients over the age of 18 who were hospitalized in the General intensive care unit of Biruni University Medical Faculty Hospital with the diagnosis of COVID 19 between June 1, 2020 and February 1, 2021, diagnosed with ARDS, and over the age of 18 were included in the study. In the retrospective study, the sample size was not calculated to screen all patients who met the inclusion criteria. Identification of SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal swab or sputum specimens and/or abnormal lung computed tomography (CT) scans with 90% oxygen saturation at rest (bilateral, subpleural, peripheral ground glass opacities) were considered positive-for the diagnosis of COVID-19. If the ARDS was caused by COVID 19, patients who received high flow nasal oxygen (HFNO), non-invasive mechanical ventilation (NIV), or invasive mechanical ventilation (IMV) due to acute hypoxemic respiratory failure associated with SARS-CoV-2 pneumonia [4] were included in the study. In the context of COVID-19, this definition is fully consistent with the pathophysiological logic that supports the Berlin Definition for ARDS (Table 1).

Patients with a diagnosis of steroid allergy or those who developed an allergy during therapy, pregnant or breastfeeding women, patients with active malignancies, and patients receiving any immunosuppressive drug were all excluded from the trial.

Table 1: Characteristics of the pragmatic definition of coronavirus 2019 acute respiratory distress syndrome (COVID-19 ARDS) [4]

Feature of definition	Berlin Criterion	COVID application
Associated with COVID-19	No restriction by pathogen	Limited to patients with SARS-CoV-2 pneumonia
Acute	< 7 days since onset	5–14 days is common; most important factor is that the respiratory failure be from COVID-19
Bilateral opacities	Bilateral opacities consistent with pulmonary edema "may be very mild, patchy, and asymmetric"	COVID-19 pneumonia is generally a bilateral process
Hypoxemic	Positive pressure ventilation with PEEP ≥ 5 cm H2O and PaO2:FIO2<300 (Kigali modification SpO2:FIO2<315 and eliminates PEEP and positive pressure ventilation requirements)	Hypoxemic respiratory failure treated with HFNO, NIV, IMV (FIO2 ≥ 0.35 guarantees SpO2:FIO2<315 regardless of SpO2)
Not primarily cardiogenic / hydrostatic	Clinical assessment and judgment	Respiratory failure primarily due to COVID-19 pneumonia

PEEP: positive end-respiratory pressure, PaO2: partial pressure of oxygen in arterial blood, FIO2: fraction of inspired oxygen, SpO2: oxygen saturation, HFNO: high-flow nasal oxygen, NIV: non-invasive ventilation, IMV: intermittent mandatory ventilation

In the study, information from the file records of 202 patients hospitalized with the diagnosis of ARDS due to COVID 19 in the General intensive care unit of XX University Medical Faculty Hospital between June 1, 2020 and February 1, 2021; patients' age, gender, Acute Physiology and Chronic Health Evaluation (APACHE II) scores, steroid treatment protocol (low dose steroid therapy [1 mg/kg/day] for 15 days or high-dose steroid therapy [10 mg/kg/day] for three days) were tapered off after three days. low dose continued for up to 10 days) intubation time (Day), weaning time (days), hospital stay time (days), prognosis: (death/survival), cost (Turkish Lira), and daily neutrophil lymphocyte ratio for 15 days (NLR), C-reactive protein (CRP), PCT Procalcitonin (PCT), lactate levels, and the need for cytokine filter (HMP) were recorded.

After obtaining ethics committee and chief physician approval, a "data processor" who was not involved in the study anonymized the patients who met the study's inclusion criteria between these dates, and after ensuring that their identity information was hidden, the data in the case registration form was accessed and recorded from the computer records. The primary aim of the study was to compare the 15-day continuous hemodynamics, laboratory findings, and clinical course of COVID 19 patients.

Statistical analysis

The results were presented for categorical variables as numbers and percentages, and for continuous variables as mean (standard deviation (SD)). Comparison of the categorical variables between groups was done using a chi-square or Fisher exact test. For comparison of independent continuous variables between two groups, the Student's t- or Mann–Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. Similarly, for dependent continuous variables paired samples t- or Wilcoxon signed rank test was used.

SPSS version 21.0 for Windows was used for statistical evaluation (IBM Software, New York, United States), and $P < 0.05$ was considered statistically significant.

Results

The mean age of 202 patients included in the study was 66.64 (14.9) years and 57.4% were male. Over half (67.3%) of the cases were extubated when they were admitted to the first intensive care unit, (ICU) and their mean APACHE II score was

26.32 (12.1). While the mean day of intubation was 2.19 (3.7) days, mean weaning days were 5.86(6.8) days. A total of 78 (38.6%) patients were administered short-term (three days) high-dose (10 mg/kg/day) systemic methylprednisolone, and it was observed that 51 (25.2%) patients needed HMP. The mortality rate was 59.4%, the duration of hospital stay was 10.99 (7.8) days, and the cost was mean 30243,378 (36596.2) TL (Table 2).

Table 2: Descriptive Statistics

		N	Mean (SD) (min–max)
Female		86	42.6%
Male		116	57.4%
Age (year)		202	66.64 (14.9) (25–93)
APACHE-II		202	26.32 (12.1) (2-62)
Intubation Time (Days)		202	2.19 (3.7) (0–25)
Weaning (Days)		202	5.86 (6.8) (0–40)
Arrival Status	Extubated	136	67.3%
	Intubated	66	32.7%
Methylprednisolone	None	124	61.4%
	Yes	78	38.6%
HMP	None	151	74.8%
	Yes	51	25.2%
Prognosis	Death	120	59.4%
	Discharge	82	40.6%
LOS (days)		202	10.99 (7.8) (1–49)
Cost (Turkish Liras)		202	30,243,37 (36,596,2) (208,2–307,721,2)

* HMP: hemoperfusion, LOS: length of stay; APACHE: Acute Physiology and Chronic Health Evaluation, SD: standard deviation

The planned 15-day follow-up of 202 patients included in the study was included in the first 10-day follow-up calculations so as not to cause errors in the calculations due to the deficiencies in the continuous data with the increase in deaths after the 10th day. These 10-day NLR, lactate, PCT, and CRP levels are shown in Figures 1 and 2.

Figure 1: Changes of neutrophil/lymphocyte ratio (NLR) and lactate over time (days)

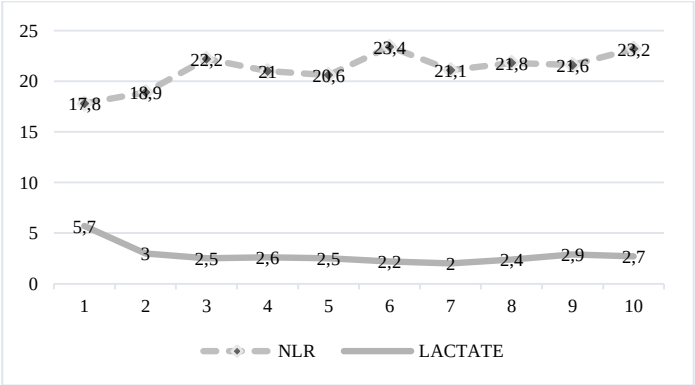
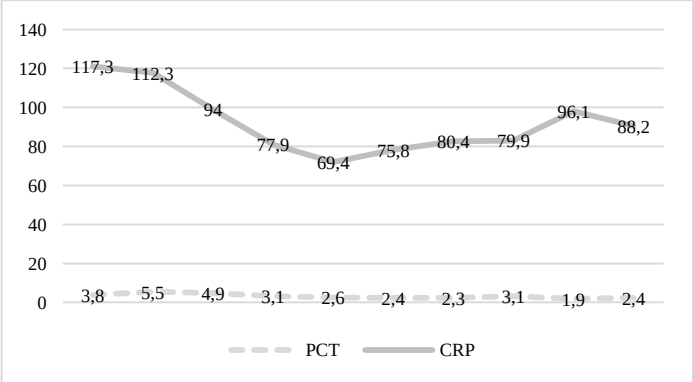


Figure 2: Changes of procalcitonin (PCT) and CRP over time (day)



The comparison of COVID 19 patients (n=78) who were received short-term (three days) high-dose (10 mg/kg/day) systemic methylprednisolone and low-dose (n=124) long-term (1 mg/kg/day) systemic methylprednisolone is shown in Table 3. It was determined that elderly patients tended to be given low-dose steroids. In addition, it was observed that high-dose steroid therapy was preferred mostly in extubated patients, while low-dose long-term steroid therapy was preferred in patients who were intubated (P<0.05). No significant differences between the two treatment protocols in terms of gender, APACHE II, intubation and weaning time, need for hemoperfusion, prognosis, LOS, and costs were found (Table 3).

Table 3: Comparisons between groups

		Group		*P*-value
		High dose (n=78) Mean (SD)	Low dose (n=124) Mean (SD)	
Sex	Female	31	55	0.309
	Male	47	69	
Age (year)		62.7 (14.1)	69.0 (15.0)	0.003
Status of arrival	Extube	61	75	0.006
	Intube	17	49	
APACHE II		25.1 (12.6)	27.0 (11.7)	0.299
Intubation time (Days)		2.5 (3.9)	1.9 (3.5)	0.344
Weaning (Days)		5.5 (6.6)	6.0 (6.9)	0.655
HMP	Yes	15	36	0.083
	None	62	87	
Prognosis	Death	45(57.7%)	75 (60.5%)	0.402
	Discharge	33	49	
LOS (Days)		11.4 (7.4)	10.7 (8.1)	0.530
Cost (Turkish Liras)		27535.1 (25873.8)	31946.9 (41978.2)	0.357

* ANOVA: analysis of variance ** chi square, HMP: hemoperfusion, LOS: length of stay

When changes in laboratory values of high- and low-dose steroid treatments over time were examined, it was found that high-dose steroid only affected CRP levels (table 4), but there was no difference in mortality rate (P=0.402).

Table 4: C-reactive protein (CRP) levels between groups over time

		Mean (SD)	*P*-value
CRP 1st day	Low dose	105.4 (85.4)	0.012*
	High dose	136.2 (81.6)	
CRP 2nd day	Low dose	109.8 (82.8)	0.596
	High dose	116.3 (85.4)	
CRP 3th day	Low dose	99.0 (78.2)	0.267*
	High dose	86.3 (76.0)	
CRP 4th day	Low dose	90.4 (74.6)	0.004*
	High dose	59.3 (59.3)	
CRP 5th day	Low dose	83.9 (73.1)	0.001*
	High dose	48.9 (63.1)	
CRP 6th day	Low dose	95.2 (85.4)	0.001*
	High dose	47.0 (74.8)	
CRP 7th day	Low dose	101.8 (92.2)	0.001*
	High dose	50.2 (77.7)	
CRP 8th day	Low dose	99.3 (84.4)	0.003*
	High dose	53.0 (80.1)	
CRP 9th day	Low dose	142.6 (119.4)	0.081
	High dose	60.4 (95.3)	
CRP 10th day	Low dose	110.5 (95.7)	0.007*
	High dose	59.2 (87.2)	

* one-way analysis of variance (ANOVA)

Discussion

In rheumatic illnesses, methylprednisolone is a glucocorticoid medication that produces a decrease in autoimmune and inflammatory reactions [5]. Previously, some studies have been conducted with the thought that methylprednisolone administration in the hyperinflammatory stage in COVID-19 patients may have possible benefits due to the suppression of the cytokine storm, but the results of these studies are inconsistent. Studies that claim to be useful include a randomized controlled study conducted by Maryam et al. [2] in which they found that giving methylprednisolone in a pulse at the start of the early pulmonary phase of the disease cut the death rate in half, enhanced recovery, and led to a decrease in the length of hospital stay by half [2]. In the same study, they found that methylprednisolone caused an improvement in pulmonary involvement, oxygen saturation, dyspnea, heart rate, respiratory rate, and inflammatory markers, such as CRP and interleukin 6 (IL-6) in patients, and that methylprednisolone could be an effective therapeutic agent for severe COVID-19 patients during

the pulmonary phase. In meta-analyses by Li [6] and Sterne [7] it was found that systemic glucocorticoids are associated with a decrease in all-cause mortality in COVID-19-positive critically ill patients. Investigations that claim to be ineffective include studies by Hu [8] and Rodrigez Molinerio [1] in which it was found that glucocorticoid treatment had no significant effect on the clinical course, side effects, or outcome of COVID-19 pneumonia. In a cohort study by Wang et al. [9], it was shown that patients treated with methylprednisolone had a faster recovery in oxygen saturation and a decrease in CRP and IL-6 levels and were less likely to require invasive ventilation. However, they did not observe significant differences in mortality between the groups. Hu et al. [8] focused on the impact of low-dose glucocorticoid therapy in COVID-19 pneumonia patients and found that glucocorticoid medication had no effect on the clinical course, side effects, or outcome of COVID-19 pneumonia in their retrospective analysis.

In these studies, the dose of methylprednisolone was different, and 1 mg/kg was used as the high dose. The observed differences could be related to disparities in therapy dosage and duration, limited sample sizes, the patients' ages, and disease severity. In reality, patient characteristics, duration of administration, and pulmonary phase are key factors in the effectiveness of corticosteroid therapy. So et al. [10], who reported the sole case report in the literature involving administration of 1000 or 500 mg/day methylprednisolone for three days, theorized that high-dose corticosteroid treatment could prevent tissue damage and hence, cause less lung damage. Five-hundred milligrams per day of methylprednisolone followed by 1 mg/kg once daily and then a reduction by 10 or 20 or 30 mg was administered. They finished with 10 mg/day oral prednisolone. They claimed that giving patients methylprednisolone intravenously led to lowering of their temperature, cause a 100% survival rate, reintubation rates were 0%, and ventilator support could be removed in all cases within seven days. In our study, it was determined that short-term high-dose methylprednisolone only led to a decrease in CRP values and had no effect on lactate, PCT, NLR levels, intubation time, weaning time, hemoperfusion requirement, hospital stay, or prognosis. Our study has limitations in that it is a single-center report with a small number of cases. Because clinical course findings, such as fever, heart rate, inotrope need, and oxygenation level are not available in computerized form and can only be collected from handwritten nursing records, they were not included in the study to avoid a faulty or biased conclusion.

Conclusion

It was discovered that varied doses and durations of methylprednisolone for the treatment of COVID-19 ARDS had no effect on lactate, PCT, NLR levels, intubation time, weaning time, hemoperfusion requirements, hospital stays, and/or prognosis. The time and dosage of glucocorticoids for the treatment of COVID-19 ARDS still require in-depth and systematic investigations to ensure that they limit the inflammatory response in COVID-19 ARDS.

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Posterior ocular parameters following extraocular muscle surgery: an optical coherence tomography study

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Ethics Committee Approval
The study was approved by the Ordu University Ethics Review Committee (approval date/no: 2020/41).
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: Muscle trauma, vascular injury, and compensatory vasoconstriction during strabismus surgery may cause changes in the choroidal circulation in the early postoperative period. This study aims to evaluate the effect of extraocular muscle surgery on posterior ocular parameters, including central subfield thickness (CST), average retinal thickness (ART), choroidal thickness (CT), and macular volume (MV).

Methods: This prospective cohort study included 26 eyes of 26 strabismic patients who underwent single medial or lateral rectus recession surgery using a fornix-based conjunctival incision. All participants underwent detailed ophthalmologic evaluation, including axial length (AL) and spherical equivalent (SE), uncorrected (UCVA), and best-corrected visual acuity (BCVA). Retinal and choroidal images were obtained using spectral-domain optical coherence tomography (OCT). All measurements were performed preoperatively and repeated 1 week and 1 month after surgery.

Results: All patients received satisfactory results in terms of deviation. None of the patients showed changes in AL, SE, UCVA, and BCVA. No significant differences were noted in CST and MV values (P=0.472 and P=0.182, respectively). Although subfoveal CT and ART showed statistically significant decreases 1 week after surgery (P=0.012 and P=0.046, respectively), no significant differences in these values were observed 1 month after surgery (P>0.05). No significant differences exist in the measurements between the preoperative, postoperative first week, and first month in nasal and temporal CT (P>0.05).

Conclusion: Extraocular muscle surgery performed with the fornix-based conjunctival incision is a safe procedure for posterior ocular parameters, including CST, ART, CT, and MV.

Keywords: Choroidal thickness, EDI-OCT, Retinal thickness, Recession surgery, Strabismus

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Introduction

Strabismus surgery aims to achieve a proper ocular alignment, prevent or treat amblyopia and improve binocular visual function in children [1-3]. Strabismus is one of the most common surgical indications in ophthalmologic practice [4]. Extraocular muscle disinsertion and reinsertion during surgery may affect other ocular tissues. The effect of strabismus surgery on anterior segment circulation is well-known. Muscle trauma, vascular injury, and compensatory vasoconstriction during strabismus surgery may cause changes in the choroidal circulation in the early postoperative period. However, the effect on the posterior segment is still unclear.

The choroid functions in outer retinal supplementation, thermoregulation, secretion of growth factors, and thus scleral growth, refractive focus, and emmetropisation [5]. Age, gender, refractive errors, and even diurnal rhythm affect choroidal thickness (CT) [5-7]. Changes in CT may result in retinal and retinal pigment epithelial diseases [8,9]. Thus, several studies are being conducted on retinochoroidal analysis at an increasing rate to understand the pathophysiology of many disorders. Optical coherence tomography (OCT) is an important tool for the diagnosis and treatment of chorioretinal diseases [10]. The enhanced depth imaging-OCT (EDI-OCT) provides comprehensive choroidal imaging and helps understand the pathophysiology of ocular disorders.

Limited studies evaluating the effect of different strabismus surgeries on CT or macular changes are available in the literature [11-13]. Thus, this study aims to evaluate the effect of extraocular muscle surgery on posterior ocular parameters, including central subfield thickness (CST), average retinal thickness (ART), CT, and macular volume (MV).

Materials and methods

This prospective study was conducted following the Helsinki Declaration and was approved by the Ordu University Ethics Review Committee (approval date/no: 2020/41). Written informed consent was obtained from all participants or their parents.

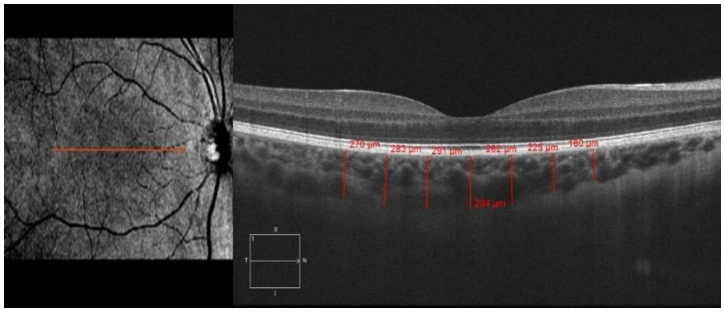
This study included 26 eyes of 26 patients diagnosed with horizontal strabismus and underwent single medial rectus (MR) or lateral rectus (LR) recession surgery between April 2020 and December 2020. Patients with a history of prematurity, chronic systemic diseases, vascular abnormalities, craniofacial anomalies, nystagmus, sensory or restrictive strabismus, retinal or macular pathologies, glaucoma, orbital pathology, ocular trauma, previous ocular or extraocular muscle surgery were excluded. Similarly, patients who underwent vertical rectus or oblique muscle surgery, horizontal muscle resection surgery, and who could not cooperate for the OCT imaging were also excluded.

All participants underwent detailed ophthalmologic evaluation, including uncorrected (UCVA) and best-corrected visual acuity (BCVA) using the Snellen chart, cycloplegic refraction, slit-lamp biomicroscopy, and dilated fundus examination. The angles of near and distance deviations were measured using an alternate prism cover test and recorded in terms of prism dioptres (PD). Abnormal head position, extraocular muscle overaction, and eye movements in nine cardinal positions were also noted. Axial length (AL) was measured using ultrasonic biometry (Pac-Scan 300p, Sonomed Escalon, New Hyde Park, NY, USA). Retinal and choroidal images were obtained using the spectral-domain OCT (SD-OCT; Cirrus HD-OCT 4000, Carl Zeiss Meditec Inc., Dublin, CA, USA) before pupillary dilation. Cycloplegic refraction was measured using an autorefractometer (Tonoref III, NIDEK Co., Ltd., Tokyo, Japan) 30 min after instillation of 1% cyclopentolate hydrochloride (Siklopleji n®, Abdi Ibrahim Pharmaceuticals, Istanbul, Turkey) twice at an interval of 5 min. All measurements were taken between 09.00 and 12.00 a.m. to exclude diurnal variation.

All patients were operated on using the same technique under general anesthesia by a single surgeon (AU). A fornix-based conjunctival incision was used to reach extraocular muscles. Single muscle recession surgery (MR recession for esodeviation and LR recession for exodeviation) was performed in all patients. The muscles were inserted into the sclera using absorbable double-armed 6-0 vicryl (polyglactin 910) suture, and the conjunctiva was closed with absorbable 8-0 vicryl (polyglactin 910) suture. Topical moxifloxacin (0.5%)–dexamethasone (0.1%) combination (Moxidexa®, Abdi Ibrahim Pharmaceuticals) was prescribed four times daily for two weeks, postoperatively.

SD-OCT images were obtained by a single experienced technician. Those scans with a signal strength of ≥7/10 were taken. CST (the average thickness of macula in the central 1-mm diameter circle) and ART scans were performed using a macular cube 512 × 128 scan protocol (128 consecutive line scans). This protocol has a scan area of 6 × 6 mm of the retina, and macular thickness is calculated in microns in an area corresponding to the Early Treatment Diabetic Retinopathy Study grid. CT was obtained using SD-OCT with EDI modality. The CT was measured from the outer part of the hyperreflective line corresponding to the retinal pigment epithelium, perpendicular to the inner surface of the sclera (Figure 1). CT was measured in 7 points: at the foveal center (one point) and within the horizontal temporal (three points) and nasal (three points) positions at 500-μm intervals to a distance of 1,500 μm from the foveal center. Furthermore, CT measurements were manually evaluated by two experienced masked ophthalmologists (AU and AKS) via the Cirrus HD-OCT software caliper, and the measurements were averaged for analysis.

Figure 1: Enhanced depth optical coherence tomography image of choroidal thickness in a patient



Detailed ophthalmologic evaluation, angle of deviation, AL, and retinal and choroidal measurements were performed preoperatively and then repeated at 1 week and 1 month after surgery. All participants completed the study.

Statistical Analysis

All data were analyzed using the SPSS statistical software package, version 21.0 (SPSS Inc., Chicago, IL, USA). The sample size is based on the literature of the difference observed in CT after strabismus surgery. A power of 80% and a confidence level of 95% yielded the sample size. The Shapiro–Wilk test was used to determine whether variables are normally distributed. Data are given as mean and standard deviation or median (minimum-maximum) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. The normally distributed repeated measurements were analyzed with the paired t-test or repeated-measures analysis of variance (ANOVA), depending on the count of measurements. With the Wilcoxon signed-rank test or Friedman's ANOVA by ranks, non-normally distributed repeated-measurements were analyzed. $P<0.05$ was accepted as a statistically significant level.

Results

The mean age of the 26 patients in the study was 18.85 (11.12) years. The demographic and clinical characteristics of the participants in the study groups are presented in Table 1. Fifteen (57.69%) and eleven (42.31%) patients with esodeviation and exodeviation underwent MR and LR recessions, respectively. Slit-lamp and fundus examination were normal in all eyes. None of the patients had an abnormal head position or extraocular muscle overaction. Eye movements in nine cardinal positions showed no limitation in all participants.

Table 1: Demographic and clinical characteristics of the patients

Parameter	n=26
Age (years)	15 (7–45)
Gender	
Male	10 (38.46%)
Female	16 (61.54%)
Diagnosis	
Esotropia	15 (57.69%)
Exotropia	11 (42.31%)
Preoperative angle of deviation (PD)	40.5 (30–50)
Amount of recession (mm)	6 (5–9)

PD: prism dioptres

No major complications (e.g., scleral perforation, ocular hemorrhage, or fat prolapse) were observed in any patients during or after surgery. All patients received satisfactory results in terms of deviation, and all of them were within 10 PD of deviation in the first month. None of the patients showed any major changes in cycloplegic refraction. No significant difference was noted in postoperative SE ($P=0.845$). Compared to preoperative values, no change in postoperative UCVA and BCVA was also noted.

The OCT scans were qualitatively and quantitatively assessed. Moreover, postoperative morphological abnormalities were not detected in OCT scans. No significant differences in CST and MV values were observed 1 week and 1 month after surgery ($P=0.472$ and $P=0.182$, respectively; Table 2). Similarly, no significant difference was noted in postoperative AL ($P=0.637$).

In the preoperative and postoperative comparison, subfoveal CT and ART showed a statistically significant decrease 1 week after surgery ($P=0.012$ and $P=0.046$, respectively). No significant differences in measurement exist between the preoperative, postoperative first week and first month in terms of nasal ($P=0.494$, $P=0.590$ and $P=0.446$, respectively) and temporal ($P=0.815$, $P=0.868$ and $P=0.506$, respectively) CT values (Table 1).

Table 2: Summary of preoperative and postoperative measurements of the patients

Parameter	Preoperative	Postoperative		*P*-value	*P*-value Preoperative vs. 1st week	*P*-value Preoperative vs. 1st month
		1st week	1st month			
AL (mm)	22.33 (20.36-24.83)	22.34 (20.45–24.80)	22.46 (20.36–24.76)	0.637[a]	0.354[c]	0.588[c]
SE (diopter)	2.13 (−0.63–6.38)	1.94 (−0.63–7.63)	2.00 (−0.75–6.38)	0.845[a]	0.943[c]	0.552[c]
CST (µm)	243.85 (19.79)	243.92 (20.15)	245.50 (20.08)	0.472[b]	0.964[d]	0.261[d]
ART (µm)	279.12 (19.91)	277.08 (20.04)	279.19 (19.59)	0.098[b]	**0.046**[d]	0.953[d]
MV (mm^3)	10.05 (0.72)	9.99 (0.72)	10.6 (0.72)	0.182[b]	0.083[d]	0.807[d]
Subfoveal CT	354 (274-529)	352 (273-520)	354.50 (287-509)	0.062[a]	**0.012**[c]	0.264[c]
Nasal CT						
500 µm	332.96 (53.42)	329.27 (48.32)	328.50 (49.05)	0.494[b]	0.341[d]	0.315[d]
1000 µm	319 (242-448)	319.50 (240-448)	311.50 (227-480)	0.590[a]	0.577[c]	0.899[c]
1500 µm	283.50 (205-420)	282 (227-420)	281 (215-438)	0.446[a]	0.289[c]	0.199[c]
Temporal CT						
500 µm	340 (267-546)	338.50 (265-546)	329.50 (253-515)	0.815[a]	0.331[c]	0.576[c]
1000 µm	333 (237-519)	335 (260-519)	335 (256-508)	0.868[a]	0.764[c]	0.830[c]
1500 µm	320 (217-511)	307 (242-511)	315 (229-485)	0.506[a]	0.721[c]	0.360[c]

AL: axial length, SE: spherical equivalent, CST: central subfield thickness, ART: average retinal thickness, MV: macular volume, CT: choroidal thickness, [a] Friedman's analysis of variance by ranks, [b] Repeated measures analysis of variance, [c] Wilcoxon Test, [d] Paired-Samples T Test

Discussion

Advances in OCT technology, allow detailed analysis of the retinal and choroidal structures and understanding of the pathophysiology of many diseases. In the literature, the relationship between retinal/CT and strabismus, anisometropic amblyopia, and strabismic amblyopia were investigated [14-17]. Studies investigating the retinal structures and choroidal thickness in patients who underwent strabismus surgery are limited. In this study, the morphological effects of extraocular muscle surgery on posterior segment structures were evaluated.

Yetkin and Simsek [11] evaluated CT at seven points and found a significant decrease at all points in the first week and the first month after double horizontal muscle surgery. Consequently, it returned to normal in the third postoperative month. In contrast, no significant differences were noted in our study between the preoperative, postoperative first week, and first month measurements in the nasal and temporal CT. A possible explanation for this discrepancy is that our study included only patients with single muscle recession. Furthermore, Inan and Niyaz [13] showed a significant decrease in CT in all areas in the first postoperative day and 2 weeks after single muscle surgery. Similarly, a significant decrease was noted in only the subfoveal CT in the first month but returned to preoperative values at the end of the third month. The subfoveal CT in our study showed a significant decrease in the first week, but returned to preoperative values 1 month after surgery. Contrary to these results, Atalay et al [18] reported a temporary increase in subfoveal CT in the first postoperative day following single muscle surgery, but a return to preoperative values in the first postoperative week. The disruption of anterior ciliary arteries and anterior ciliary circulation, venous drainage obstruction (due to recession/resection of rectus muscle), and periocular inflammation may be responsible for the temporary increase in subfoveal CT [18].

Inan and Niyaz [13] also examined the effect of different strabismus surgeries on CT at five points and found that a decrease in CT was lower in multiple muscle surgeries compared with single muscle surgery. They suggested that multiple muscle surgeries may cause choroidal vasoconstriction, ischemia, and inflammation resulting in increased choroidal blood flow. Studies investigating CT in inflammatory diseases showed choroidal thickening in the active phases of diseases related to the corresponding vascular involvement [19]. In the present study, nasal and temporal CT may not have changed due to single muscle recession surgery resulting in less choroidal microcirculatory dysfunction, less mechanical traction, and less surgical trauma. Although inflammation following strabismus surgery is an expected condition, vasoconstriction in the dense vascular structures of the choroid may cause a decrease in CT [13]. Postoperative steroid therapy may also affect the extent of the inflammation and thus choroidal thickness. In studies evaluating the effect of strabismus surgeries on CT, there was no significant difference between the postoperative steroid treatment regimen [11,13]. In our study, postoperative steroid treatment was applied similarly to previous studies.

All surgeries were performed with a limbal conjunctival incision in previous studies evaluating the effect of different strabismus surgeries on CT or macular changes. In this study, the fornix-based conjunctival incision was used in all patients. Atalay et al [18] commented that using a limbal incision instead of a fornix-based incision and applying more mechanical traction to muscles during surgery may cause greater inflammation. Consequently, the American Association for Pediatric Ophthalmology and Strabismus members thought that fornix-based incisions result in less postoperative inflammation and faster soft-tissue healing [20]. Furthermore, no significant decreases were observed in nasal and temporal CT values in this study, although subfoveal CT and ART showed statistically significant decreases in only the first postoperative week. In addition, any significant differences in CST and MV values and morphological abnormalities in OCT scans could not be found. The use of fornix-based conjunctival incision resulting in less inflammation in the patients of the current study may cause unchanged CT, CST, ART, and MV values at month 1. Moreover, retinal thickness could be expected to not be different because CT did not change. Subfoveal CT is the highest in this study, followed by temporal CT. Moreover, nasal CT is the thinnest. The results of this study are consistent with previous studies suggesting a radial distribution of choroidal vessels from the peripapillary region and progressive increase of choriocapillaris vessel size, increased density of vascular structures in the foveal area due to increased metabolic activity, and finally optic nerve passage through the lamina cribrosa [21, 22].

Zhou et al [23] demonstrated an increase in central retinal arteriolar equivalent and central retinal venular equivalent on the first day following strabismus surgery and reported that both double and single muscle surgeries may increase retinal blood flow in the early postoperative period but will return to normal later. Additionally, they detected retinal hemodynamic changes in the eyes undergoing only MR muscle surgery and argued that the main cause of these changes compared to inflammation was the number of transected ACAs, and at least two ACAs injuries were required to change retinal blood flow. Unfortunately, the correlation between retinal/CT and retinal blood flow was not evaluated in that study.

In addition to unchanging AL, retinal, and CT, none of the patients in this study developed a significant change in SE, UCVA, and BCVA. Visual function was reported to remain unaffected, even if changes were detected in CT following strabismus surgery [11]. No change in visual function can be expected because a significant difference in CT was not determined.

Limitations

The small number of cases and the relatively short-term follow-up were the limitations of this study. All examinations including posterior ocular parameters were evaluated 1 week and 1 month after surgery. However, AL, retinal and choroidal thickness could not be measured on the first postoperative day due to the patients' discomfort. This is also a limitation. Despite these limitations, the current study will contribute to the literature because it is the first to evaluate the posterior ocular parameters including CST, ART, CT, MV, and also AL and SE following single horizontal rectus muscle recession surgery performed with the fornix-based conjunctival incision.

Conclusion

Extraocular muscle surgery performed with the fornix-based conjunctival incision is a safe procedure in terms of posterior ocular parameters including CST, ART, CT, and MV. Thus, further studies comparing the effect of recession and resection surgeries performed with a limbal or fornix-based conjunctival incision on posterior ocular parameters with a larger number of subjects are needed.

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Relationship between voice handicap index and reflux symptom index in patients with laryngopharyngeal reflux with dysphonia: A cross-sectional study

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Ethics Committee Approval
The ethics committee approval (Date:04/02/2021-No:114) was obtained from the Ethics Committee for Non-Interventional Clinical Research, Dicle University Faculty of Medicine, for this study. 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: Laryngopharyngeal reflux (LFR) occurs due to the backward traveling of gastric contents through the esophagus, resulting in their contact with the upper respiratory tract and laryngopharynx. It has been determined that more than 50% of patients presenting with voice hoarseness may have a pathology associated with such reflux. Symptoms including hoarseness, difficulty in making high-pitched sounds, and a tired and cracked voice may occur due to changes in the vocal cord mucosa induced by the reflux. The present study investigated the relationship between the Reflux Symptom Index (RSI) and Voice Handicap Index-10 (VHI-10) evaluations of patients with significant findings for LFR.
Methods: Patients with an RSI score of 13 and above and RFS of 7 and above, considered significant for LFR, and patients aged between 18 and 65 years, who met the mandatory requirements, were included in the study. The patients included in the study were divided into three groups, mildly impaired (MII), moderately impaired (MOI), and severely impaired (SEI) based on their response to the question, "How do you feel about your voice?'' VHI-10 was also applied to the patients included in the study. The RSI and VHI-10 scores of the patients were separately recorded and compared using various parameters.
Results: Of the 38 patients included in the study, 18 (47.4%) were female and 20 (52.6%) were male. It was observed that RSI and VHI-10 scores increased significantly as the patients' level of voice disorder increased ($P<0.001$, $P<0.001$). A statistically significant positive correlation was found between the RSI and VHI-10 scores of the patients ($r=0.749$, $P<0.001$).
Conclusion: The high level of significant positive correlation between VHI-10 and RSI scores suggested that VHI-10 could serve as a valuable supportive tool in the evaluation of dysphonia in patients with LFR. RSI and VHI-10 can further play an important role in the initiation of appropriate treatment on diagnosis of LFR.

Keywords: Dysphonia, Laryngopharyngeal reflux, Reflux symptom index, Voice handicap index

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Introduction

The backward traveling of gastric contents via the esophagus causes contact with the upper respiratory tract and laryngopharynx, leading to laryngopharyngeal reflux (LFR). More than 10% of the patients presented to otorhinolaryngology outpatient clinics are considered to have LFR. More than 50% of patients with voice hoarseness are determined to have a pathology associated with such reflux [1]. LFR diagnosis can be overlooked by clinicians as several characteristic symptoms of classical reflux, including indigestion and pyrosis, are not prevalent in LFR [2]. The most common symptoms of LFR include voice disorders, cough, dysphagia, frequent throat clearing, and globus pharyngeus [3]. No gold standard diagnostic test solely intended for this clinical pathology exists; nevertheless, the Reflux Symptom Index (RSI) and Reflux Finding Score (RFS), the validity and reliability of which was demonstrated by Belafsky et al. [4, 5], have been used for the evaluation of patients with LFR symptoms.

Gastric content reflux that reaches the upper levels of the throat frequently affects vocal cords and consequently phonation. Symptoms, such as hoarseness, a tired and cracked voice, and difficulty in making high-pitched sounds may occur due to changes in the vocal cord mucosa. Failure to diagnose LFR for an extended period and the resultant delay in treatment may cause permanent deterioration in the vocal cord mucosa and lasting voice disorders, whereas timely diagnosis based on associated symptoms and appropriate treatment implementation may prevent permanent damage and lead to recovery [6].

In this study, the literature-recommended RSI and RFS values were applied to patients with voice disorders persisting for more than three months and/or accompanying symptoms, such as cough, dysphagia, frequent throat clearing, globus sensation in the throat, etc. We investigated the relationship between RSI and Voice Handicap Index-10 (VHI-10) by applying it to patients, resulting in significant findings for LFR.

Materials and methods

This study was carried out in Mardin State Hospital Otorhinolaryngology Outpatient Clinic between March and August of 2021. Of the 152 patients who applied to the otolaryngology outpatient clinic with the complaint of dysphonia in a six-month period, 38 patients who had significant findings in terms of LFR and agreed to participate were included in the study. The required ethics committee approval (Date:04/02/2021-No:114) was obtained from the Ethics Committee for Non-Interventional Clinical Research, Dicle University Faculty of Medicine, for this study. The patients included in the study underwent physician examinations at the Otorhinolaryngology Outpatient Clinic. Patients with LFR-related symptoms received complete ear, nose, and throat (including larynx) examinations. Akbulut et al. [7] performed the Turkish validity and reliability study of RSI and RFS, which was utilized in this study only for patients presenting with voice hoarseness as a symptom suggesting LFR. The inclusion criteria of the study were as follows: patients with an RSI score of 13 and above and RFS of 7 and above, which were considered significant for LFR, and patients between the ages of 18 and 65 years, who met the mandatory requirements. The patients included in the study were divided into three groups, mildly impaired (MII), moderately impaired (MOI), and severely impaired (SEI) based on their response to the question, “How do you feel about your voice?” All the patients, regardless of their participation in the study, were recommended dietary and lifestyle changes and prescribed proton pump inhibitors. VHI-10 was also administered to the patients included in the study. The RSI and VHI-10 scores of the patients were separately recorded and compared by various parameters.

Study inclusion criteria

The presence of voice disorders, such as hoarseness and a cracked voice, for at least three months and the absence of previous vocal cord surgery, neck radiotherapy, known allergic history, tobacco use, psychiatric and mental health disorders hindering communication were considered inclusion criteria. In addition, a healthy assessment, recent proton pump inhibitor or other antireflux drug use as well as the presence of symptoms suggesting LFR upon examinations and assessments were considered for inclusion in this study.

Exclusion criteria

Presence of any organic laryngeal pathology apart from the findings specified in the RFS, neurological clinical condition that might cause abnormalities in phonation, upper respiratory tract infection in the last three weeks, untreated thyroid gland-related diseases, and chronic exposure to chemical agents were considered as the exclusion criteria of this study.

Data collection tools

VHI-10

Adapted to the Turkish population by Kılıç et al. [8], VHI-10 is a 5-point Likert scale that consists of 30 items scored between 0 and 4 points, where a higher score indicates more severe voice disorder, which is associated with deteriorated daily life quality.

RSI

The RSI is a 6-point Likert scale consisting of nine items, each rated between 0 and 5. The minimum and maximum scores of RSI are 0 and 45, respectively. An RSI score of 13 or above is considered significant for LFR [4].

RFS

The RFS scores eight common symptoms of LFR by the degree of their severity. The minimum and maximum scores of RFS are 0 and 26, respectively. Belafsky et al. [5] suggested a 95% likelihood of LFR in a patient with a total RFS score of 7 or above.

Statistical analysis

IBM SPSS Version 21.0 for Windows software program was used for statistical assessment of the data. The measured variables were presented as mean (standard deviation (SD)) and median, whereas categorical variables were presented as numbers and percentages. Distribution normality hypothesis was tested for the data. The independent t test was used for the comparison of two independent groups with normal distribution. The Kruskal–Wallis H test was used to compare groups without normal distribution, with more than two options. The Mann–Whitney U test was used after Bonferroni correction for post hoc analysis in the binary comparison of the groups. Spearman’s correlation test and simple linear regression analysis were

performed to evaluate the relationship between the continuous variables. The hypotheses were dual and a *P*-value of ≤0.05 was considered as statistically significant.

Results

Of the 38 patients included in the study, 18 (47.4%) were female and 20 (52.6%) were male. No statistically significant difference was observed between the sexes by age and RSI and VHI-10 scores (Table 1).

Table 1: Comparison of age, total RSI score, and total VHI-10 score parameters by sex

Sex	Parameter	N (%)	x̄	SD	DF	*t*	*P*-value
Female	Age (years)	20(52.6)	35.75	9.96	37	0.238	0.814
Male		18(47.4)	34.72	15.73			
Female	RSI	20(52.6)	28.95	9.34	37	1.351	0.185
Male		18(47.4)	24.78	9.69			
Female	VHI	20(52.6)	29.65	10.57	37	1.656	0.106
Male		18(47.4)	23,11	13.71			

N: Number, x̄: Mean, SD: Standard deviation, DF: Degree of freedom, *t*: Independent t test value, RSI: Reflux Symptom Index, VHI-10: Voice Handicap Index-10

The patients were divided into three groups based on their responses to the question, "How do you feel about your voice?" Fourteen patients (36.8%) responded indicating mildly impaired (MII), 10 (26.3%) as moderately impaired (MOI), and 14 (36.8%) as severely impaired (SEI). There was a significant difference in the RSI scores among the three groups (MII median: 20.50; MEI median: 23.50; SEI median: 33.00; $P<0.001$). Upon paired intergroup comparisons, statistically significant differences in RSE scores between SEI and MOI ($P=0.011$) and between SEI and MII ($P=0.001$) were observed, whereas no statistically significant difference between RSE scores of MII and MOI was found (Table 2).

Table 2: Evaluation of the RSI scores based on the patients' responses to the question "How do you feel about your voice?"

Group	N (%)	Median	x̄ (SD)	*H*	*P*-value*
(MII)[1]	14(36.8)	20.50	19.21 (4.49)		<0.001*
(MOI)[2]	10(26.3)	23.50	25.90 (8.14)	21,684	P^{1-3}<0.001
(SEI)[3]	14(36.8)	33.00	35.50 (7.26)		P^{2-3}=0.011, P^{1-2}=0.048

MII: Mildly impaired, MOI: Moderately Impaired, SEI: Severely Impaired, N: number, x̃: mean, SD: standard deviation, *H*: Kruskal–Wallis H test value, *P**: Kruskal–Wallis H test statistical significance value, Mann–Whitney U test used in binary comparisons. Bonferroni correction used ($P<0.016$).

The intergroup comparisons of VHI-10 scores indicated a significant difference among the three groups (MII median: 11.00; MEI median: 32.00; SEI median: 41.00, $P<0.001$). Upon paired intergroup comparisons, statistically significant differences in VHI-10 scores between MII and MOI ($P=0.002$) and between SEI and MII ($P=0.001$) were found, whereas no statistically significant difference between RSE scores of SEI and MOI was observed (Table 3).

Table 3: Evaluation of the VHI-10 scores based on the patients' responses to the question "How do you feel about your voice?"

Group	N (%)	Median	x̄ (SD)	*H*	*P*-value*
(MII)[1]	14(36.8)	11.00	14.93 (9.42)		<0.001*
(MOI)[2]	10(26.3)	32.00	30.30 (7.20)	20,000	P^{1-2}=0.002
(SEI)[3]	14(36.8)	41.00	35.50 (8.56)		P^{1-3}<0.001
					P^{2-3}=0.086

MII: Mildly Impaired, MOI: Moderately Impaired, SEI: Severely Impaired, N: number, x̃: mean, SD: standard deviation, *H*: Kruskal–Wallis H test value, *P**: Kruskal–Wallis test statistical significance value, Mann–Whitney U test used in pair comparisons. Bonferroni correction used ($P<0.016$).

A statistically significant positive correlation was observed between the RSI and VHI-10 scores of the patients ($r=0.749$, $P<0.001$; Table 4, Figure 1).

Simple linear regression analysis found the RSI scores to be a significant predictor of the VHI-10 scores ($F=47.114$, $P<0.001$). The RSI scores predicted 56% of the VHI-10 score variances. A one-unit increase in the RSI scores of the patients led to a 0.974 unit increase in their VHI-10 scores. The equation for predicting the VHI-10 scores was as follows: VHI score= −75.667 + 0.974 × RSI score (Table 5).

Table 4: Result of the Spearman's correlation test evaluating the relationship between the total RSI and VHI-10 scores

	n	*r*	*P*-value
RSI	38	0.749	<0.001
VHI			

RSI: Reflux Symptom Index, VHI-10: Voice Handicap Index-10, N: number, *r*: correlation coefficient, The Spearman's correlation test found a significant positive relationship between total RSI and VHI-10 scores of the patients ($r=0.749$, $P<0.001$).

Figure 1: Correlation between the total RSI and VHI scores

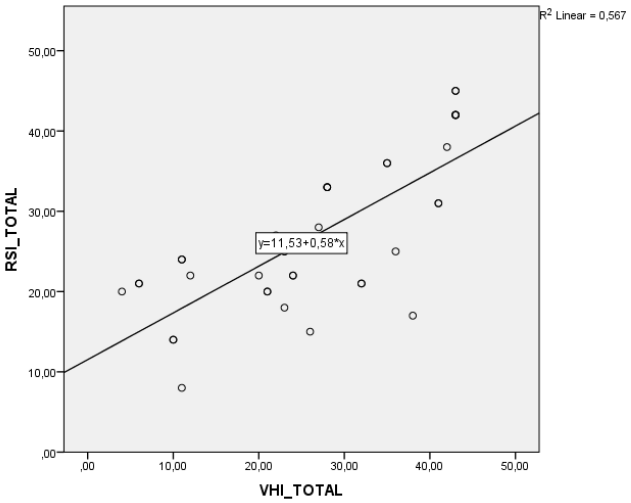

Table 5: Simple linear regression analysis to predict the VHI-10 scores by the RSI scores

	R	R^2	*F*	*P*-value	*B*
RSI	0.753	0.567	47.114	<0.001	0.974

RSI: Reflux Symptom Index, Simple linear regression analysis was performed to predict the VHI-10 scores by the total RSI scores. The RSI scores were a significant predictor of the VHI-10 scores ($F=47.114$, $P<0.001$). The RSI scores predicted 56% of the VHI-10 score variances. A one-unit increase in the RSI score increased the VHI-10 scores by 0.974 units. The equation that predicted the VHI-10 score was as follows: VHI score=−75.667 + 0.974 × RSI score.

Discussion

LFR presentation is quite prevalent in the otorhinolaryngology practice and induces dysphonia in patients [9]. The results of this study suggested a strong and positive relationship between RSI, intended for evaluating LFR, and VHI-10, which is used to investigate the effect of dysphonia on the quality of life. Despite the high prevalence of LFR, no gold standard test or diagnostic method has been developed yet, and research on its pathophysiology, diagnosis, and treatment continues [2]. Although there is no consensus on the standardization of LFR diagnostic criteria, the multichannel intraluminal impedance-pH monitoring can be used in the diagnosis process [10]. However, RSI and RFS are more commonly used in practice due to difficulties with ambulatory pH monitoring [5, 11]. A number of studies in the relevant literature suggest hoarseness as one the most common symptoms associated with LFR [2, 12, 13]. Although the pathophysiology of LFR-related hoarseness is not well-established, the contact of pepsin and acid with the vocal cord surface during reflux was one suggested mechanism of this condition; 55%–79% of the patients with hoarseness persisting for more than three months had LFR [14, 15].

VHI is a tool that investigates the effect of voice disorders on the patient's quality of life [16, 17]. It is one of the most widely used surveys worldwide in the evaluation of voice disorders. The original 30-point VHI (VHI-30) was translated into several languages [17, 18]. Over time, a simplified 10-point version (VHI-10) was developed, reducing the time spent on the

procedure and making it easily implementable in a clinical environment while maintaining statistical significance [16]. In this study, VHI-10 adapted to the Turkish language was used for LFR patients presenting with hoarseness [8].

The VHI-10 scores were suggested to be higher in patients with LFR than in the healthy control group [19]. Lechien et al. [9] reported that VHI could be employed to identify, follow-up, and assess voice disorders in patients with LFR.

A number of studies on the relationship between LFR and RSI and VHI have been adapted to several languages [9, 15, 20-22]. A study investigating the RSI and VHI-30 indexes in patients with LFR, adapted to Arabic, reported a statistically significant correlation between RSI and VHI-30 [23]. Another study by Alanazi et al. [15] suggested that there was a significant relationship between RSI and VHI-10 scores, and thus, these indexes could prove to be valuable tools for monitoring patients with LFR.

Upon evaluating the relationship between the VHI-10 and RSI scores and the responses of the patients to the question, “How do you feel about your voice?” the patients’ perceived severity of their voice impairment and index scores were observed to be significantly affected by their voice disorders. Spearman’s correlation analysis of VHI-10 and RSI scores indicated a strong positive correlation between them. This supports the suggestion that index scores could serve as important tools for the initial evaluation, follow-up, and detection of dysphonic severity in LFR-related dysphonia.

Limitations

The limitations of the study included the restricted number of patients, diagnoses not confirmed by pH monitoring, and the lack of certain measurements, such as acoustic analyses, of patients with dysphonia. Therefore, further multicenter studies with larger samples accommodating objective diagnostic methods would contribute to the ongoing research.

Conclusion

The high level of significant correlation between VHI-10 and RSI scores suggested that VHI-10 could serve as a valuable supportive tool in the evaluation of dysphonia in patients with LFR. Since multichannel intraluminal impedance-pH monitoring technology is currently in limited use due to issues associated with availability, applicability, and cost, RSI and VHI-10 can play an important role in the initiation of appropriate treatment following diagnosis. Furthermore, they can also play an important role as prognostic indicators of LFR. The symptoms of laryngopharyngeal reflux may differ from the symptoms of classical gastroesophageal reflux. Therefore, this should be kept in mind in the differential diagnosis of patients who come to the outpatient clinic with dysphonia. Finally, we recommend long-term studies with larger samples to explore the role of RSI.

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Research article

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Do women living in northeast Anatolia get mammography screening? A hospital-focused cross-sectional study

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Ethics Committee Approval
Research data were collected after ethical approval (15.04.2021 / 4-60) from the Ethics Committee of Kafkas University Faculty of Medicine.
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: In Turkey, women between 40–69 years of age are routinely subjected to mammography screening for breast cancer. Despite this, the mammography rate is only 28.9% in women aged 15 years and above. This is an indication that women in Turkey are not sufficiently interested in mammography screenings. This study aimed to determine the factors that affect the decision to not have mammography screening for women aged 40 and above.

Methods: The study was designed as a hospital-focused cross-sectional study. The population of the study comprised 7,239 women aged 40 years and above. The sample size that would represent the population was calculated as 365 women with 50% prevalence, 95% confidence interval, and 5% deviation in the Epi Info program. A Chi-square test used in the binary analysis ($P<0.05$ was considered statistically significant); and backward LR logistic regression analysis was used in multiple analyses.

Results: Based on the findings of the study, 57.0% of women did not have mammography screening. This was 2.047 times (CI: 2.341–5.841) higher among those living in rural areas when compared with women living in the city/district center, 2.639 times (CI: 1.291–3.247) higher in women with eight years or less of education as compared with those who had nine or more years of education, and 1.9 times (CI: 1.172–3.081) higher in women not informed by family doctor/family health staff (AH/ASE) when compared with women receiving information.

Conclusion: The percentage of mammography screening is low in women over the age of 40. The risk factors were determined to be low education, rural areas of residence, and a lack of information provided by the family doctor.

Keywords: Mammography, Breast, Breast cancer, Risk factor

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Introduction

Breast cancer is the most prevalent type of cancer in women in Turkey as well as throughout the world. The level of incidence of 46.0 per hundred thousand worldwide is similar to the incidence in Turkey (45.6 per hundred thousand); whereas, in developed countries, the incidence rises to 79.0 per hundred thousand [1]. The survival rate in developed countries is higher than that of developing countries. It has been suggested that the reason for higher survival rate is due to the extensive use of mammograms in developed countries [2].

Breast self-examination, clinical breast examination, and mammography have been recommended as the main early diagnosis methods for breast cancer. Among these methods, mammography is known to be a powerful screening method and used in routine breast cancer screening in a number of countries [3].

In Turkey, women between 40–69 years of age are routinely subjected to mammograms in screening for breast cancer [4]. Despite this, the rate of mammography is only 28.9% in women aged 15 years and above [1]. This is an indication of the fact that women in Turkey are not sufficiently interested in mammography screenings. This study aims to determine the contributing factors to this phenomenon.

Materials and methods

Type of study: Hospital-focused cross-sectional study

Research population: In 2020, 7,239 women aged 40 and above were examined in the general surgery outpatient clinic . It was assumed that the same number of women would apply for examination in 2021. Thus, the research population was determined to be 7,239 women.

Research sample: The sample size that would represent the population was calculated as 365 women with 50% prevalence, 95% confidence interval, and 5% deviation in the Epi Info program.

Research variables

Dependent variable: Women's status of having a mammogram at any point in time

Independent variables: Sociodemographic, socioeconomic, and bio-demographic characteristics

Data collection form: The data form of the research was prepared by the researchers.

Ethics committee approval and verbal consent: The research data were collected upon obtaining ethical approval (15.04.2021 / 4-60) and verbal consent.

Preliminary trial of the study: Conducted with nine women who presented to the outpatient clinic. After the preliminary trial, the issues related to the data collection form were corrected.

Selection of subjects in the study and collection of data: Data from female patients age 40 and above who presented to the outpatient clinic were collected using a face-to-face interview technique until the sample size was reached.

Statistical Analysis

SPSS version 20 for Windows was used for data analysis. Chi-square test in paired analysis (P<0.05 was considered statistically significant); backward LR logistic regression analysis was used in multiple analyses.

Results

In this study, 57.0% of women did not undergo mammography screening.

A review of Table 1 shows that there was a statistically significant difference between the place of residence (P=0.001), educational background (P=0.001), and information provided by family physicians and/or family health staff (AH/ASE) in regard to mammography (P=0.003). It also indicates whether the total income of the family was significant (P=0.044) in having mammography screening. There was no statistically significant difference between the age of the women (P=0.114), type of family (P=0.112), health insurance (P=0.209), family history of cancer (P=0.564), profession of women (P=0.835), and the total number of pregnancies (P=0.081).

Table 1: Distribution of the demographic characteristics of women aged 40 years and above on the status of not having mammography

Independent variables		Dependent variable: mammography		Total	X^2	*P*-value
		Yes	No			
		n (%)*	n (%)*	n (%)**		
Residing at	Village/town	43 (25.9)	123 (74.1)	166 (45.5)	36.364	0.001
	City/district center	114 (57.3)	85 (42.7)	199 (54.5)		
Age	40–49	71 (48.0)	77 (52.0)	148 (40.5)	2.498	0.114
	≥50	86 (39.6)	131 (60.4)	217 (59.5)		
Educational status	8≤	84 (36.4)	147 (63.6)	231 (63.3)	11.352	0.001
	9≥	73 (54.5)	61 (45.5)	134 (36.7)		
Family type	Nucleus	134 (45.0)	164 (55.0)	298 (81.6)	2.526	0.112
	Large	23 (34.3)	44 (65.7)	67 (18.4)		
Did AH/ASE provide information?	No	39 (32.0)	83 (68.0)	113 (33.4)	9.123	0.003
	Yes	118 (48.6)	135 (51.4)	252 (66.6)		
Health assurance	Yes	136 (44.4)	170 (55.6)	306 (83.8)	1.581	0.209
	No	21 (35.6)	38 (64.4)	59 (16.2)		
Family history of cancer	Yes	11 (37.9)	18 (62.1)	29 (7.9)	0.332	0.564
	No	146 (43.5)	190 (56.5)	336 (92.1)		
Woman's profession	Unemployed	117 (43.3)	153 (56.7)	270 (74.0)	0.043	0.835
	Employed	40 (42.1)	55 (57.9)	95 (26.0)		
Total income	Sufficient	46 (52.3)	42 (47.7)	88 (24.1)	4.056	0.044
	Insufficient	111 (40.1)	166 (59.9)	277 (75.9)		
Total no. of pregnancy	3 and less	119 (40.8)	173 (59,2)	292 (80.0)	3.043	0.081
	4 and more	38 (52.1)	35 (47.9)	73 (20.0)		
Total*		157 (43.0)	208 (57.0)	365 (100.0)		

* row percentage, ** column percentage, *** AH/ASE = Family Doctor, Family Health Staff

Table 2 shows the results of logistic regression analyses. The number of women not having mammograms was 2.047 times (CI: 2.341–5.841) higher in women living in rural areas when compared with those living in the city/district center, 2.639 times (CI: 1.291–3.247) higher in women with eight years or less of education when compared with those with those who had nine or more years of education, and 1.9 times (CI: 1.172–3.081) higher in women not informed by family doctor/family health staff (AH/ASE) when compared with those who received information.

Table 2: Results of logistic regression analyses

Independent variables		B	SE.	Wald	Odds Ratio	95% CI (Minimum-Maximum value)
Residing at	Rural Areas	1.308	0.233	31.449	3.698	2.341–5.841
	Urban Areas				Reference	1
Educational status of woman (years in education)	8≤	0.717	0.235	9.275	2.047	1.291–3.247
	9≥				Reference	1
Family doctor information	No	0.642	0.247	6.782	1.900	1.172–3.081
	Yes				Reference	1

Dependent variable: Mammography

Discussion

Determination of risk factors for breast cancer and the possibility of early diagnosis is of great importance. Nevertheless, there is an insufficient number of studies that aim to determine the factors that have an impact on breast cancer early diagnosis behaviors in women, both on a local level and throughout Turkey. In this context, our research provides health administrators with guidance in developing health policies that aim at to increase the level of having mammograms at a local level.

In the study, 57.0% of the women had never had a mammogram. According to data provided by Turkey Statistical Institute, in Turkey approximately 65.1% of women aged 15 years and above never had mammography as of 2019 [5]. However, this level varies in localized studies conducted in different regions of Turkey. Two field studies conducted with rural women aged 40 years and above determined that 76.9% [6] and 74.7% [7] of women had not undergone mammography screening. Studies conducted in an urban setting reported that 44.1% [8] and 34.5% [9] of women did not undergo mammography exams. Another study found that 52.8% of women never had mammography [10]. In general it may be suggested that the level of having mammography is quite low in Turkey.

The number of women who did not have a mammogram was 2.047 times (CI: 2.341–5.841) higher in women living in rural areas when compared with those living in the city/district center. As a matter of fact, as mentioned in the above paragraph, the rate of not having mammography in rural women was 74.7%–76.9%, while the same rate in urban residents varied between 34.5%–52.8% [6-10]. It may be inferred that the reason for this situation includes inadequate access to health services and the patriarchal relationship in rural life. A previous study reported that patriarchal relations were important in regard to utilizing the public space related to health, even for people who have migrated from rural areas to urban centers [11].

In our study, the number of women who did not have mammography screening was 2.639 times (CI: 1.291–3.247) higher among those who had an educational background of eight years or less, when compared with women who had nine or more years of education. Relevant studies have also emphasized that women with a lower educational level also had lower levels of mammography screening [10, 12]. In many studies, the educational level of the mother has been associated various health behaviors. This is explained by the fact that educated women have increased knowledge about healthcare issues, are more effective in domestic decision-making mechanisms, have a job, and thus have health insurance [11, 13, 14].

The number of women who did not have a mammogram was 1.9 times (CI: 1.172–3.081) higher among those who were not provided information by AH/ASE, compared to women who received such information. According to the findings of a study held in the Aegean region, the number of women who had mammography was 3.923 times (2.248–6.848) higher when they were provided information by doctors as compared with women who did not receive information [15]. Another study emphasized that the source of information for 45.6% of women who had mammograms was the physician [16]. In a field study conducted in western Turkey, 43.5% of women stated that they had mammography screening upon recommendations of a physician [10]. In a study conducted in Istanbul, 60.4% of women underlined that they received relevant information about mammography from doctors [9]. As a result, it may be suggested that information provided by the physicians to their patients or by family physicians to the women in the registered population increases the level of those obtaining mammograms.

Limitation of the study

The most important limitation of the study is that the research was hospital-oriented; in other words, it created a limitation with regard to generalization.

Conclusion

This study indicated that the having mammography screening was low in women 40 years and over in the research area. Risk factors that affected whether mammograms were obtained included the place of residence, the educational background, and whether women were provided relevant information by the family doctor.

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Research article

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Comparison of the use of graft augmented tubularized split (GATS) and tubularized incised plate urethroplasty (TIPU) techniques for hypospadias repair in patients with narrow plate and small glans

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Ethics Committee Approval
The study has been approved by Marmara University Faculty of Medicine Clinical Research Ethics Committee on 04.12.2020 with protocol number 09.2020.1333.
Informed consent for both participation and publication was obtained from parents of the patients who included this study.
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: Hundreds of repair techniques were described for hypospadias repair. It is still a problem to choose the right technique in hypospadias repair for patients with narrow plate and small glans, because the patients with narrow urethral plate and small glans usually suffer from complications. GATS (Glans Augmented Tubularized Split) is an alternative technique with different details from grafted TIPU (Tubularized Incised Plate Urethroplasty). The aim of this study is to compare the outcomes of TIPU and GATS procedures on these difficult cases.

Methods: This retrospective cohort study consists of the analysis of patients who underwent GATS and TIPU procedures in our department between January 2017 and January 2020. Patients with distal and midpenile hypospadias and with shallow groove, glans smaller than 17 mm, and plate narrower than 8mm were included the study. Patient with follow-up shorter than 1 year or incomplete data and secondary cases were excluded. Patients were divided into two groups according to the technique performed, as 25 patients in TIPU group and 20 patients in GATS group.

Results: The mean diameter of glans were 15.3 mm and 14.5 mm, mean width of plate were 5.2 mm and 4.1 mm in TIPU and GATS groups respectively. Complications were observed in 7 (28%) patients of TIPU group and in 2 (10%) patients of GATS group (P>0.05). Urethral stenosis in one patient, urethral fistula in two patients, urethral dehiscence in two and urethral stenosis and diverticula in one patient, urethral stenosis and fistula in one patient were detected in TIPU group. Urethral fistula in one patient and urethral dehiscence in one patient were observed in GATS group.

Conclusion: GATS procedure is an alternative method for difficult cases with narrow urethral plate and small glans with less complications than TIPU technique.

Keywords: Hypospadias, Narrow urethral plate, Small glans, Shallow groove, Grafting, Complication

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Introduction

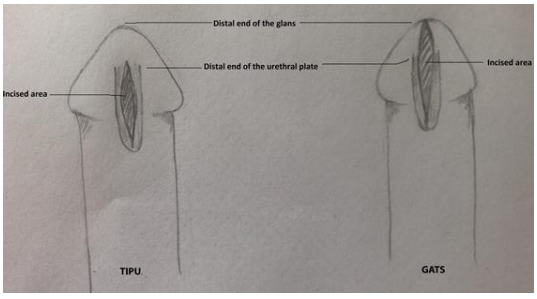
Hypospadias repair is one of the most common surgeries in pediatric urology. In this context, more than one hundred surgical techniques have been described in the literature for hypospadias repair, yet there is still no consensus on the technique that can serve as the gold standard technique.

Tubularized incised plate urethroplasty (TIPU) technique was first described by Snodgrass in 1994 [1] and has become the most commonly used technique for hypospadias repair since then. The rates of complications reported to have been associated with TIPU vary between 0% and 60% [2, 3]. The patients with narrow plate, small glans and shallow groove generally bear higher complication risks, and are thus commonly considered as difficult hypospadias cases [3, 4].

TIPU generally results in narrow neourethra in hypospadias cases with narrow plate, and subsequently in inelastic narrow urethra [5].

Surgeons attempted to solve the mentioned complications observed in hypospadias cases considered as difficult through the augmentation of the plate with graft [6]. Additionally, Snodgraft or inlay tubularized plate urethroplasty techniques were described and performed with less or similar complications [6-9]. In these techniques, plate is incised deeply, graft is applied inside the plate and tubularization is performed on a urethral stent. Grafts should be inlayed to increase the width of the plate, improve re-epithelialization, and prevent scar formation [10, 11]. In both of these techniques, the final meatus position is mostly glanular, yet not at the top of the glans, which is thus not an optimal position. On the other hand, in graft augmented tubularized split (GATS) [12] technique, plate and also glans are incised till the top of the glans deeply, and in this way the meatus is moved to the distal end of the glans (Figure 1). The defect is augmented with graft and the procedure is completed with tubularization of the neourethra. GATS technique provides a wider neourethral plate, a neomeatus that is positioned at the distal end of the glans, which is the optimum position, and also a slit-like meatus. Therefore, use of GATS procedure in hypospadias cases may lead to lower complication rates, although it is considered as a difficult procedure. But the debate in this issue for difficult cases with narrow and shallow plate and small glans still continues, whether TIPU is sufficient or a graft should be placed on the incised area. In our report, we compare the outcomes of the TIPU and GATS techniques in these difficult hypospadias cases with narrow plate, small glans and shallow groove and tried to determine whether the grafting of narrow urethra and deepen the shallow groove decreases the complications after GATS procedure.

Figure 1: Differences between the TIPU (on the left) and the GATS (on the right) techniques in terms of incised area



Materials and methods

The study has been conducted upon the required ethics committee approval has been obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee on 04.12.2020 with protocol number 09.2020.1333. The clinical data of the patients with hypospadias, who underwent either TIPU or GATS procedures, between January 2017 and January 2020, in the clinic, where the study was conducted, were reviewed retrospectively. The clinical data of the patients, which were recorded to be analyzed within the scope of this study, included all penile anatomical details, i.e. diameter of the glans, width of the plate and length of penis in both stretched and normal positions, and classification of the groove of the glans as shallow (flat), mild (intermediate) or deep (like a cleft). Patients with distal and mid-penile hypospadias, shallow groove, glans diameter less than 17 mm, and plate width smaller than 8 mm, were included in the study; whereas patients, who were followed up clinically for less than 1 year as well as the patients, who require secondary surgery or were circumcised, were excluded from the study. Consequentially, a total of 45 patients were included in the study. These 45 patients were divided into two groups based on the hypospadias repair technique they underwent, as the TIPU group, which included 25 patients and as the GATS group, which included 20 patients.

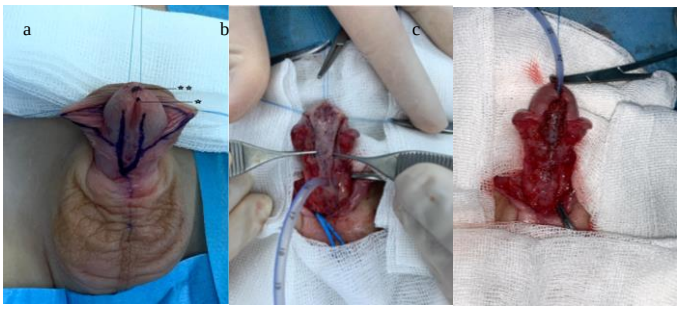
Patients' age at the time they underwent the surgery, diameter of glans, width of plate, the type of hypospadias and the complications they had, and their follow up times were compared.

Surgical procedure

All procedures were performed under general anesthesia and penile block was performed at the beginning of the procedure. Antibiotic prophylaxis was administered one hour prior the surgery. The procedures started with U incision around the hypospadiac meatus ending on both sides of the plate (Figure 2a). Degloving and dissection of the glanular wings were performed in case of both TIPU and GATS techniques. A deep midline incision that is limited to inside the urethral plate was performed in TIPU technique. A deep midline incision was also performed in GATS technique, yet the incision was extended distally to the top of the glans, that is, a few millimeter further to the point the urethral plate ends. In the GATS technique, the graft was harvested from the inner prepuce and placed in the incised plate and also in the incised area on the glans (Figure 2b). 7/0 PDS (polydioxanone suture) was used to fix the graft inner border of the plate. In addition, a few fixation sutures were placed between graft and base, in the midline in particular. Subsequently, the urethral plate was tubularized over 6 or 8 Fr (French) urethral catheter in two layers in both techniques; first layer with continuous subcuticular 7/0 Vicryl sutures and second layer with interrupted subcuticular 7/0 Vicryl sutures (Figure 2c). A pedicle flap from dartos fascia was prepared and placed on the neourethra as a cover. Glanuloplasty was performed with 6/0 PDS sutures. Urethral catheter was left in place for seven days postoperatively. Patients were followed up during the second week, first month and third month after the surgery. Thereafter, the follow up of patients were conducted by means of patient visits made to the outpatient clinic every 3 months until the end of the first year from the surgery, and annually thereafter. During

these follow visits, patients were evaluated for penile cosmetics, meatal and urethral stenosis, urethrocutaneous fistula by means of physical examination, and their neourethras were calibrated by means of 6-8 Fr catheter and video voiding device.

Figure 2: GATS procedure. 2a: U incision around the narrow urethral plate. *Distal end of the urethral plate. **Top of the glans. 2b: Grafting the incised area. 2c: Tubularization of the grafted neo-urethral plate.



Statistical analysis

SPSS 21.0 (IBM Statistical Package for Social Sciences version 21.0) software package was used to conduct the statistical analyses of the research data. Quantitative variables were expressed as numbers, mean or median values. Probability (*P*) values of <0.05 were deemed to indicate statistical significance. Mann-Whitney U test was used to compare information such as age, diameter of glans, width of plate and follow-up time, whereas Pearson's Chi-squared test was used to compare the categorical variables between the groups.

Results

There was no statistically significant difference between the groups in terms of age, hypospadias type and glans diameter (*P*>0.05 for each) (Table 1). Additionally, all patients had shallow groove. The mean width of plate values were 5.2 mm and 4.15 mm in TIPU and GATS groups, respectively (*P*=0.045). The mean width of the plate in GATS group was narrower than the width in TIPU group. Complications were observed in 7 patients in the TIPU group, and in 2 patients in the GATS group (Table 1). Of the patients, who developed a complication in the TIPU group, two patients had urethral fistula, two patients had urethral dehiscence, one patient had urethral stenosis, one patient had urethral stenosis and diverticula, and one patient had urethral stenosis and fistula. On the other hand, of the patients, who developed a complication in the GATS group, one patient had urethral fistula and another patient had urethral dehiscence. The complication rates and severity of the cases were higher in TIPU group (28%) than in the GATS group (10%), albeit not statistically significantly (*P*=0.134). None of the patients had hormonal therapy or underwent plication for chordee. The median follow up times were 19 and 28.5 months in TIPU and GATS groups, respectively.

Table 1: Demographic and clinical characteristics of the patients included in the study

	TIPU Group	GATS Group	Total	*P*-value
Mean age (months) mean (SD) (min-max)	33.6 (20.2) (10-84)	34.35 (22.2) (6-81)	(6-84)	0.917*
Hypospadias type				0.651**
Distal	6	6	12	
Midpenile	19	14	33	
Mean width of the plate (mm) (min-max)	5.2 (3-8)	4.15 (2-8)		0.045***
Diameter of the glans (mm) (min-max)	15.32 (12-17)	14.55 (10-17)		0.141***
Number of patients with a complication	7 (28%)	2 (10%)	9 (20%)	0.134**
Median follow-up time (months)	19 (13-26)	28.5 (12-55)	19 (12-55)	0.108***

SD: Standard deviation, * t-test, **Pearson's Chi-Squared test, *** Mann-Whitney U Test

Discussion

More than one hundred surgical techniques have been described in the literature for hypospadias repair in order to have better cosmetic and functional outcomes. Most common complications are urethrocutaneous fistula, meatal stenosis and the stricture of neourethra, dehiscence and diverticulum. These complications are seen more frequently in patients with narrow plate, shallow groove and small glans [4, 13]. Narrow urethral plate of less than 8 mm wide is associated with higher complication rates in the postoperative period. 40% of patients with shallow groove, 15% of patients with moderate groove, yet none with deep groove, develop narrow neourethra following the surgery [4]. It was reported in a prospective randomized study conducted by Sarhan et al. that urethral plate width affects the outcome of the surgery and that the plate width should be 8 mm or more for tubularization [14]. Accordingly, the major challenge is to repair the hypospadias in cases with narrow plate and shallow groove. In this context, only the patients with urethral plate width less than 8 mm, glans smaller than 17 mm, and shallow groove, were included in this study.

Tubularized incised plate urethroplasty (TIPU) technique is the most commonly used hypospadias repair technique both in the world and in the clinic, where this study was conducted. Braga et al. reported that the complication rates associated with TIPU ranged between 0% and 50%, with a median value of 7.3% [2]. This huge variation in the complication rates associated with TIPU can be attributed to the anatomy of the hypospadias and level of experience of the surgeon. Accordingly, only the patients, who were operated by the same experienced pediatric urologists, were included in this study. The main anatomic features of the hypospadiac penis that affect the surgical outcome are the location of the meatus, chordee, width of the plate, diameter of the glans, and depth of the groove. Tugtepe et al. [13] presented a scoring system to predict the complications that may arise following the hypospadias surgery. They demonstrated in the study they conducted with 394 patients who underwent TIPU that the complications were higher in those with narrow plate, shallow groove, chordee, and small glans [13, 15]. On the other hand, Bush and Snodgrass reported short term outcomes of TIPU in 224 cases, 80% of whom had narrow urethral plate (< 8 mm), and concluded that width of the urethral plate does not affect the outcome of TIPU [16]. Some authors suggest that the incision of the plate may provide enough width for tubularization of the urethra, and some surgeons suggest that the area without epitelle tissue may heal with scar tissue later and the caliber of the neourethra may reduce in long term. Leslie et al. performed an experimental animal study to assess the status of the urethra at 4 to 8 weeks-time following urethroplasty without incision, TIPU, or grafted TIPU [17]. The tubularized incised plate defect was bridged by urothelium, while the preputial graft in the incised plate kept its original histological characteristics. However, simple tubularization of the narrow urethra led to significant decrease in flow. TIPU and grafted TIPU resulted in similar urethral flow dynamics [17]. In another study conducted in 2000, Holland and Smith reported that the incision of the plate is similar to urethrotomy and that it heals with scar tissue instead of epithelization. They concluded that the depth of the urethral

groove and width of the plate affect the caliber of the neourethra, and that shallow groove and narrow plate were associated with narrow neourethra and urethrocutaneous fistula following TIPU [4].

TIPU vs grafted TIPU

In another study conducted in 2000, Kolon and Gonzales [7] described a new technique involving inner preputial free graft to augment urethral plate in TIPU. They reported to have performed the incision on the plate as described in the Snodgrass technique without extension from the end of the plate to the top of the glans and grafting the plate before tubularization. Consequentially, they reported a complication rate of 6% in 32 patients, also taking complications such as glans dehiscence and ventral skin breakdown into consideration, but they did not have any patient that had meatal stenosis, neo-urethral stricture, urethrocutaneous fistula or diverticulum, during the 21-month follow up period. Gundetti et al. [8] reported that they did not observe any meatal stenosis but only one recessed meatus associated with the use of grafted TIPU technique. In their prospective study, Silay et al. [9] reported to have performed the grafted TIPU procedure with a 9.8% urethrocutaneous fistula rate. Shuzhu [6], Eldeeb [10] and Helmy [11] et al. compared the outcomes of TIPU and grafted TIPU procedures, and did not find any significant difference between the two procedures. The authors of the aforementioned studies indicated that the graft was placed on the incised area, limited with the plate and not extended to the tip of the glans. To the contrary of the findings reported in those studies, Mouravas et al. [18] reported complication rates of 30.4% and 8.3% associated with the use of TIPU and grafted TIPU, respectively.

TIPU vs GATS

The meatal position of the neourethra following TIPU or grafted TIPU procedure is generally not located at the top of the glans. Instead, the end of the neourethra lies in glanular position in most cases due to the distal end of the urethral plate. GATS is a procedure performed with a very deep incision on the urethral plate that extends to the top of the glans and which provides a good deep groove and a wide plate. The graft is used to augment the neo-plate or neo-groove and neo-slit in the glans tip. In comparison, Ahmed and Alsaid reported as a result of the study they conducted using a similar technique, that is, preputial inlay graft with TIPU procedure without a control group, that they have achieved excellent (96.09%) cosmetic and functional results regardless of the width and depth of plate or size of the glans, and that urethrocutaneous fistula was developed in only 3.91% of the patients [19]. Similarly, Asanuma reported a urethrocutaneous fistula rate of 3.6% in the study conducted in 2007 with 28 patients, who underwent dorsal inlay graft urethroplasty [20], whereas Nerli et al. [21] reported a urethrocutaneous fistula rate of 0% in the study they conducted with 12 patients with proximal hypospadias, who underwent dorsal inlay graft urethroplasty. Urethroplasty was performed using a technique similar to GATS in all these studies, in which no meatal or neo-urethral stenosis was observed and wide slit-like meatus was achieved at optimum position. However, the width of the urethral plate was not indicated in these studies, which constitutes a limitation of these studies, since no solution was suggested as to the choice of the most appropriate technique for hypospadias repair in patients with narrow plate, shallow groove and small glans.

Making a direct comparison of the success and complication rates of the techniques used for hypospadias repair using the research data available in the literature is difficult, due to reasons such as varying patient selection criteria or patient selection bias and varying types of hypospadias in these researches. Despite the fact that the features of urethral plate are deemed to be an important risk factor affecting the outcomes of hypospadias repair techniques, the results of the studies conducted to assess the urethral plate are highly subjective [22]. In comparison, only patients with shallow groove, urethral plates less than 8 mm wide and glans diameter smaller than 17 mm, were included in this study. Consequentially, the complication rates were determined as 28% and 13% in the TIPU and GATS groups, respectively. Urethrocutaneous fistula was observed in 3 patients in the TIPU group and only in 1 patient in the GATS group. There was no case of meatal or urethral stenosis in the GATS group. Nevertheless, the difference between the groups in terms of complications was not found to be statistically significant. The complication rates found in this study may appear to be higher than those reported in the literature. However, this should not come as a surprise, since all the cases included in this study were cases that are considered as difficult hypospadias cases, contrary to the cases reported in the studies available in the literature, most of which neither mentioned width of the plate nor diameter of the glans.

We usually select the GATS technique for difficult cases with narrow plate, shallow groove and small glans. We did not compare all patients who underwent GATS with patients who underwent TIPU. To eliminate selection bias we compare the patients with similar difficulty by excluding patients with glans bigger than 17 mm, and plate wider than 8 mm and patients without shallow groove.

The mean follow up time reported in the literature for hypospadias cases is longer than 12 months in most studies [6, 7, 10, 19-21]. Even though a decrease is observed in the rate of complications by the 6th month after the surgery, there remains a risk up until the 12th month from the time of the surgery. Therefore, the patients with follow-up times longer than 12 months were included in this study. The median follow-up time of the patients included in this study was 20 months (min.12 and max. 55) months.

Limitation

There were some limitations of this study. First, it was carried out as a retrospective cohort study. Secondly, the study group consisted of relatively a small number of patients. Lastly, the quality of spongiosum was not recorded in patients' data. Therefore, prospective, randomized, double-blind studies with larger populations are needed to corroborate the findings of this study.

Conclusion

The findings of this study suggest that grafting the deeply incised plate and split glans may reduce the fistula rate and prevent meatal or neo-urethral stenosis. Additionally, even though the difference was not statistically significant, lower complication rates achieved with GATS technique as compared to the TIPU technique. In conclusion, GATS technique stands

out as a good alternative to TIPU technique, particularly for use in difficult hypospadias cases with narrow plate and small glans.

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Research article

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Effects of vitamin D treatment on the heart tissue and adropin levels in thyrotoxicosis rats

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Ethics Committee Approval
Adiyaman University Animal Experiments Local Ethics Committee, protocol no.2020/062 Experiments were conducted on animals according to the recommended ethical rules (the National Institutes of Health guide for the care and use of Laboratory animals, NIH Publications No 8023, revised 1978) for the care of laboratory animals.

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

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Abstract

Background/Aim: Thyrotoxicosis is a hypermetabolic disease, common in people with iodine deficiency. Cardiac pathologies can be seen in untreated cases. Vitamin D is a supportive therapy for thyrotoxicosis and its deficiency also plays an important role in pathologies including cardiac diseases. Adropin is a peptide hormone regulating the energy homeostasis, and its levels in blood change in cardiac pathologies. Our purpose is to reveal the effects of vitamin D treatment on the heart tissue of rats with thyrotoxicosis and on the adropin levels.

Methods: Our study was designed as 25 days. 28 Sprague-Dawley female rats were divided into 4 groups; Control (3ml of distilled water), Thyrotoxicosis (100µg/day L-thyroxine) Treatment (100µg/day L-thyroxine+200IU /day Vit. D), Vit D (200IU/day Vit. D). Firstly, heart tissues were stained with Masson trichrome method. The preparations were examined under the microscope and evaluated semi-quantitatively. After that, serum adropin levels were measured with ELISA method. Malondialdehyde level of heart tissue was evaluated by spectrophotometry. Heart tissue was evaluated in aspects of fibrosis, congestion, edema and impairment of tissue integrity.

Results: All of the evaluation parameters of the heart tissue were found highly significantly increased in thyrotoxicosis group, in contrast to the control and vitamin D group. Despite a decrease in the treatment group, there was no significant difference in the thyrotoxicosis group ($P<0.001$). Serum adropin levels of all groups were found to be decreased in contrast to the thyrotoxicosis group. Similarly, tissue MDA levels were significantly higher in the thyrotoxicosis group compared to the other groups.

Conclusion: Consequently, heart tissue damage and differences in adropin levels were found in rats with thyrotoxicosis. It was observed that supportive vitamin D treatment helps to regulate these effects.

Keywords: Thyrotoxicosis, Vitamin D, Adropin, L-thyroxine, Heart

How to cite: Aydin H, Türk A, Karadağ A. Effects of vitamin D treatment on the heart tissue and adropin levels in thyrotoxicosis rats. J Surg Med. 2022;6(3):382-385.

Introduction

Thyrotoxicosis is a hypermetabolic process that results from the release of large amounts of thyroid hormone into the circulatory system. The most common cause of thyrotoxicosis is Graves' disease followed by multinodular goiter or toxic adenoma. All forms of thyroid pathologies are frequently seen in women, besides iodine deficiency is another major parameter [1]. Thyrotoxicosis syndrome also affects the heart tissue. While rhythm problems and coronary diseases are more common in elderly, tachycardia is more defined in young people [2].

Supportive therapy is one of the treatment strategies in thyrotoxicosis. Vitamin D (Vit D) is a steroid molecule regulate bone metabolism besides calcium and phosphorus levels. Additionally, Vit D deficiency is common worldwide and plays an important role in pathologies including cardiac disease [3]. Vit D has strong antiproliferative, prodifferentiative, and immunomodulatory properties, and also increases the expression of glucose-6-phosphate-dehydrogenase which is protective against oxidative stress [4].

Adropin is a peptide hormone expressed in many tissues including heart [5], and regulates energy homeostasis. Recent data suggests that it has protective effect for endothelial cells, impacts angiogenesis, accelerates blood flow, and intensifies capillarities [6]. Yu et all. showed that adropin levels decreased in acute myocardial infarction [7]. In another study, adropin plasma levels are found to be significantly increased than control group according to the severity of heart failure [8]. These findings revealed the association between adropin and the heart, by making it remarkable target for research.

In this study, we aimed to examine the effects of Vitamin D on heart tissue of experimental thyrotoxicosis rat model, to reveal its relationship with adropin.

Materials and methods

Animals

After smear tests were performed, 28 Sprague-Dawley female rats were divided into 4 groups with 7 animals in each group. The animals were maintained on commercial rat diet that contained 5% fat, 21% protein, 55% nitrogen free extract, and 4% fiber (wt/wt) with adequate mineral and vitamin contents. Each had ad libitum access to food and water. They were kept under a photoperiod of 12 hours of light and 12 hours of darkness in controlled temperature conditions of (20-24ºC). No procedure was performed for 7 days to ensure in-group adaptation of rats. After that, the experimental phase was started, and the experimental period was design as 25 days.

Groups

Control: Each rat was given 3ml of distilled water by oral gavage during the experiment period.

Thyrotoxicosis group: Each rat was given 100μg / day L-thyroxine dissolved in 3ml distilled water by oral gavage during the period [9].

Treatment group: Each rat was given 100μg / day L-thyroxine dissolved in 3ml distilled water, followed by 200IU / day Vitamin D, by oral administration via a dropper during the study period.

Vit D group: Vitamin D was administered orally to rats via the dropper for the duration of the study [10].

24 hours after the last application, experimental animals were anesthetized. Then blood was transcardiacly collected from all rats under anesthesia, and tissue samples were stored under suitable conditions for histological and biochemical studies. Blood samples were centrifuged at 1500 rpm for 15 minutes to separate the sera. Serum samples were stored at -80 ° C until the end of the study.

Ethical committee approval

Experiments were conducted on animals according to the recommended ethical rules (the National Institutes of Health guide for the care and use of Laboratory animals, NIH Publications No. 8023, revised 1978) for the care of laboratory animals (Adiyaman University Animal Experiments Local Ethics Committee, protocol no.2020/062).

Histology

Heart tissues fixed with 10% neutral formaldehyde were embedded in paraffin blocks after a routine tissue follow-up procedure. 4-6 μm sections taken from paraffin blocks were stained with Masson trichome staining method. The prepared specimens were examined under Leica DM500 microscope, evaluated semi-quantitatively and photographed under the light microscope [11]

Serum adropin levels

For the analysis of rat serum adropin levels, ELISA method was used. ELISA kits were commercially obtained from Bio assay technology laboratory Co., Ltd, Shanghai, CHINA (Rat Adropin Catalog no: Cat. No E1069Ra YL). All analyses were performed in accordance with the instructions of the manufacturer, and protein expression levels were calculated by Curve Expert 1.4 (Hyams Development).

MDA levels

Heart tissue samples were homogenized for analysis of the Malondialdehyde (MDA) level. A buffer containing 14.5 mmol Tris base, 36.5 mmol Tris-HCl, 161 mmol KCl and 2% Tween 20 was used for tissue homogenization. 5 ml buffer was added to the weighed samples and homogenized at 16000 rpm for 3 minutes using the homogenizer (Ultra Turrax Type T25-B, IKA Labortechnic, Germany). Homogenates were centrifuged (5000 rpm for 5 minutes) and mixed with 1 ml supernatant, 1 ml 10% (w / v) trichloroacetic acid (TCA), 1 ml 0.6% (w / v) thiobarbituric acid (TBA) and 1 ml distilled water. After 120 minutes incubation at 95 ° C, the mixture was cooled to room temperature. 3 ml butanol was added to each tube after that straightened and centrifuged for 5 minutes at 5000 rpm. The butanol phase was removed and read blank against butanol at a wavelength of 532 nm [12]. Results are given in nmol/g.

Statistical analysis

GraphPad® software program was used for statistical analysis. One-way ANOVA test was used for comparison between more than two groups. Tukey test was used for parametric data and Kruskal-Wallis test for nonparametric data. The statistical significance (*P*-value) level was taken as 0.050 in all tests.

Results

Histology

Heart tissue of rats was performed Masson trichrome staining method (Figure 1). After that, tissues were analyzed in aspects of the fibrosis, congestion, edema and impairment of tissue integrity by histoscoring (Figure 2). All groups were analyzed according to thyrotoxicosis group**.** Similar results were obtained for all aspects. A high increase was seen in the thyrotoxicosis group in contrast to the control and Vit D group (P<0.001). Despite a decrease was shown in the treatment group, significant difference was not revealed (P>0.05).

Figure 1: Masson' trichrome staining results of heart tissue. Scala bar, 200 µm. (a) Control Group: and (b) Vitamin D Group: normal histological view of heart tissue. (c) Thyrotoxicosis Group: Effect of Thyrotoxicosis on heart histopathology in rats remarkable increments of fibrosis, (black arrows), congestion (red arrows); edema and disruption of tissue integrity (black stars). (d) Treatment Group: it was observed that Vit D treatment reduced the heart tissue damage.

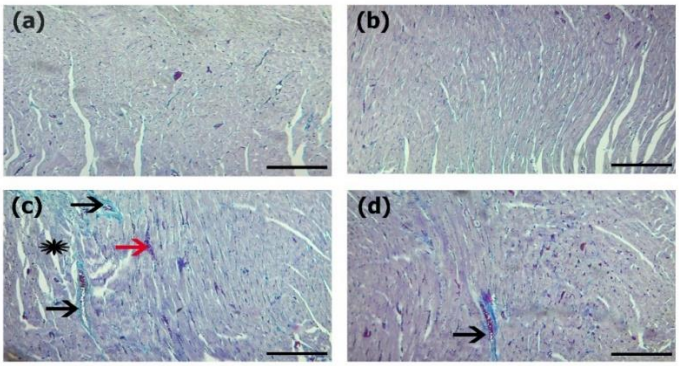
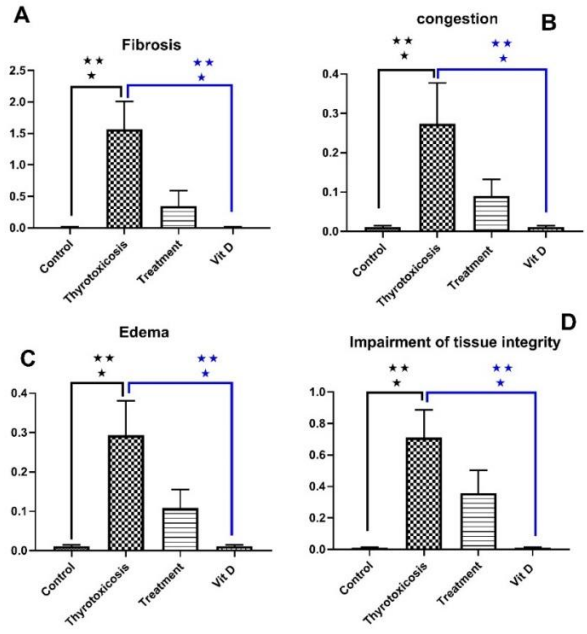


Figure 2: All groups were analyzed according to thyrotoxicosis group. After histoscoring, all groups were evaluated aspects of fibrosis (A), congestion (B), edema (C) and impairment of tissue integrity (D). It was found highly significant increase in thyrotoxicosis group in contrast to the control and Vit D group. Despite a decrease in the treatment group, there was no significant difference.



Serum adropin levels

All groups were compared with the thyrotoxicosis group. Highly significant decrease was found in control group (P=0.005), Vit D group (P<0.001) and treatment group (P<0.001) (Figure 3).

MDA levels

There were seen very high significant decrease in tissue MDA levels in whole groups according to the thyrotoxicosis group (P<0.001) (Figure 4).

Figure 3: All groups were analyzed according to thyrotoxicosis group. Serum adropin levels were found highly significantly reduced in Vit D and treatment group.

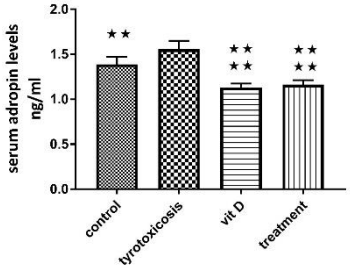
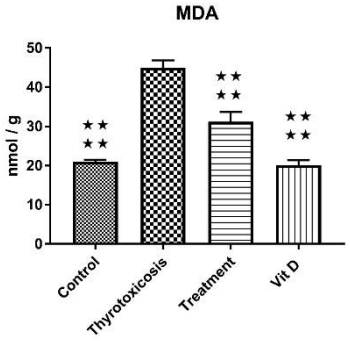


Figure 4: All groups were analyzed according to thyrotoxicosis group. Heart tissue MDA concentrations in all groups were found highly reduced (P<0.001).



Discussion

Thyrotoxicosis is a syndrome characterized by highly increased basal metabolic rate and can cause serious cardiovascular disorders leading to death, if left untreated. The increased metabolic state leads to consumption of oxygen, elevated reactive oxygen radicals, increased metabolic products and acceleration in heartbeat [1]. In addition to the lack of correlation between circulating hormone levels and clinical symptoms, the frequency of symptoms is higher in younger patients [13].

Our results show that patients with thyrotoxicosis have increased fibrosis and impaired tissue integrity in the heart tissue, coherent by the tissue damage effect of thyrotoxicosis. The increased edema and congestion seen in these patients indicate the impairment in the venous return, and thus resulting cardiac problems. All these effects decrease after Vit D treatment, closer levels to the control group. It has been reported that Vit D deficiency is more common in thyroid pathologies [14-16]. These data support that Vit D levels should be measured together with thyroid hormones in thyroid patients, and it makes more important to apply the Vit D supportive treatment.

Lipids in the cell membrane undergo peroxidation by free radicals. The formed products as a result of the reaction join the membrane structure and cause irreversible damage [17]. Measurement of MDA levels, which is an indicator of lipid peroxidation, is one of the methods used to determine the damage. In our study, it was observed that Vit D treatment reduced lipid peroxidation. Another study showed that Vit D support decreased the level of damage in DNA, especially in type 2 diabetes mellitus patients [18]. These results show that Vit D reduces the oxidative damage.

Our findings show that adropin levels increase in patients with thyrotoxicosis, and decrease with Vit D treatment. Previous studies suggested that decreased adropin level is a risk factor for the development of coronary heart disease, but

increased levels are associated with severe heart failure [6]. Kalkan et al. [19] defined that serum adropin and irisin levels were significantly increased in patient with cardiac cachexia. Kumar et al. showed that adropin gene expression decreased in obese mice and administration of adropin reduced the liver steatosis and insulin resistance [20]. Another study emphasized that plasma adropin levels of older rats were lower than younger rats. Besides that, Enho (Energy homeostasis) mRNA and adropin protein levels were decreased in older rat brains [21]. These data suggest that the elevation of adropin in patients with thyrotoxicosis may be the result of increased sympathetic activity and/or tissue damage. From this point of view, adropin levels seem to be more suitable as a prognostic marker rather than treatment.

Limitations

In our study, the number of experimental animals are kept low due to ethical problems. Further studies can be conducted on different antioxidant enzymes and mechanisms that are effective in apoptosis.

Conclusion

In conclusion, tissue damage occurs in the heart tissues of patients with thyrotoxicosis and their adropin levels change. Supportive Vit D treatment has positive effect in both circumstances. We support that Vit D levels should be measured regularly in patients with thyrotoxicosis.

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Research article

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Association between SYNTAX II score and Index of electrophysiological balance in patients with stable angina pectoris

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Ethics Committee Approval
All patients gave their informed consent in accordance with a protocol approved by the Ethics Committee of Necmettin Erbakan University, Meram Medical Faculty (date/decision number: 14.04.2021, 2021/3189).
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: Syntax II scoring system has been established by integrating anatomical features and clinical characteristics of patients in order to achieve better prediction of post-procedural outcomes. On the other hand, its predictive value for the occurrence of life-threatening arrhythmias is inconclusive. Index of cardio electrophysiological balance (iCEB) serve as an ECG based derivative of cardiac wave length and associated with torsades de pointes (TdP) and nontorsadogenic ventricular tachycardia (VT) or ventricular fibrillation (VF). In this study we aimed to investigate the prognostic value of SYNTAX II scoring system for predicting malignant ventricular arrhythmias by using iCEB.
Methods: 297 patients undergoing coronary angiography (CAG) were included in the retrospective cohort study. Patients were divided into two groups based on their calculated SYNTAX Score II. For each group, ECG parameters including heart rate (b.p.m.), QRS interval (ms), QT interval (ms), corrected QT (QT_C) interval (ms), QTc difference (V1-V6), QT/QRS ratio (iCEB) and QT_C/QRS ratio (iCEBc) were analyzed.
Results: According to our study estimated QRS, QT and QTc intervals were signifciantly higher in patients with calculated SYNTAX S II >26 as compared to patients with calculated SYNTAX S II ≤26 (respectively; P=0.001, P=0.014 and P=0.001). In addition, estimated QT/QRS (iECB) and QTc/QRS (iECBc) ratio were significantly lower in patients with calculated SYNTAX S II >26 as compared to those with calculated SYNTAX S II ≤26 (respectively; P=0.002 and P=0.005).
Conclusion: Our data showed that, there was a strong association between QT_C, iECB, iECBc and SYNTAX Score II. Therefore, the SYNTAX Score II might be considered as an important tool to predict malignant ventricular arrhythmias.

Keywords: SYNTAX Score II, Index of cardio electrophysiological balance, Electrocardiography

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Introduction

As a result of the Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery (SYNTAX) study, researchers aiming to determine whether the percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was more suitable in patients with coronary artery disease (CAD) requiring revascularization designed a new scoring system [1]. Recent research has shown that patients with left main and multivessel coronary artery diseases who underwent PCI can be evaluated with the SYNTAX scoring system in terms of not only the lesion complexity but also the probability of major cardiovascular events [2]. However, the SYNTAX scoring system is based entirely on the anatomical features of coronary vasculature and lesion properties without putting into consideration clinical variables, making it inefficient [3]. The SYNTAX II scoring system was developed by combining anatomical properties and clinical data of patients to improve the prediction of post-procedural outcomes [4]. Despite the fact that the Syntax II scoring system yields a more accurate and personalized prediction of post-procedural outcomes, its predictive efficacy for life-threatening arrhythmias is unproved.

Recently, a novel noninvasive marker has been introduced that shows the balance between repolarization and cardiac depolarization. The index of cardioelectrophysiological balance (iCEB), which is determined by dividing the QT interval by the QRS duration, is an ECG-based derivative of cardiac wavelength and is linked to torsades de pointes (TdP) and nontorsadogenic ventricular tachycardia (VT) or ventricular fibrillation (VF) [5, 6].

Hence, this retrospective study aimed to research the prognostic importance of the SYNTAX II scoring system in estimating malignant ventricular arrhythmias (VAs) by employing iCEB in stable patients with coronary artery disease.

Materials and methods

Study design

A total of 297 consecutive patients who underwent elective coronary angiography between April and December 2020 at Necmettien Erbakan University Meram Medical Faculty were enrolled in the retrospective study. Chest pain was noted in all patients, and coronary angiography (CAG) was recommended because of objective pieces of evidence of ischemia, such as a positive exercise stress test or radionuclide study positive noninvasive test. We retrospectively analyzed the patients' demographic and clinical data, as well as the indication for the procedure. We excluded the patients with a history of valvular heart disease, hypertrophic, restrictive, and dilated cardiomyopathy, congestive heart failure, left ventricular hypertrophy, vasculitis, history of end-stage renal failure, liver failure, coagulopathy, malignancy, inflammatory disease, pregnancy, use of medications known to have an effect on cardiac conduction (any kind of therapy for chronic obstructive pulmonary disease, antiarrhythmic drugs, non-dihydropyridine calcium channel blockers medication, digitalis, or β-blocker) and the patients with permanent cardiac pacemaker implantation, documented atrial fibrillation (AF), any kind of bundle branch blocks, pre-excitation syndromes, sick sinus syndrome, or atrioventricular block.

Before performing coronary angiography, blood samples were taken from the patients' forearm veins following 12-hour fasting. Full blood count, liver and kidney functions, and lipid profile were all evaluated using routine blood testing. The Cockcroft-Gault formula was employed to calculate the glomerular filtration rate (GFR).

Before the intended procedure, a GE Vingmed Vivid 5 echocardiography device (GE Vingmed Ultrasound, Horten, Norway) was used to perform a comprehensive transthoracic echocardiographic examination in all patients. During the echocardiographic investigation, we took apical 4- and 2-chamber and parasternal long and short-axis images and used continuous-wave, pulsed-wave, and tissue Doppler, M-mode, and 2-D techniques.

An online calculating tool (www.syntaxscore.com) was used to determine the SYNTAX Score II. In a nutshell, this calculation method incorporated anatomical-based Syntax Score I and baseline clinical data (such as age, sex, left ventricle ejection fraction, creatinine clearance, peripheral vascular disease, left main disease, and chronic obstructive pulmonary disease) [4]. Related variables were evaluated and calculated by two blind expert cardiologists who had experience with the website. In this study, patients were split into two groups based on their determined median SYNTAX Score II: Group 1 (patients with a SYNTAX Score II $\leq$ 26) and Group 2 (patients with a SYNTAX Score II >26). All patients gave their informed consent in accordance with a protocol approved by the Ethics Committee of Necmettin Erbakan University, Meram Medical Faculty (date/decision number: 14.04.2021, 2021/3189).

ECG interpretation

The guidelines of the American Heart Association and the Heart Rhythm Society were used when standardizing and interpreting the ECG parameters [7]. When the patients were lying with the face and torso facing up (supine position), their 12-lead ECGs were recorded at a gain of 10mm/mV and a paper speed of 25mm/s (Nihon Kohden, Tokyo, Japan). In order to diminish the margin of error during the assessment, all ECG recordings were transferred to a digital platform. Subsequently, software (Adobe Photoshop) was used for magnification. For the needed calculations, a suitable ECG was considered at least 10 analyzable leads. Or else, the ECG was seen as inadequate. We analyzed standard ECG parameters such as heart rate (b.p.m.), P wave, QRS interval (ms), QT interval (ms), corrected QT (QTC) interval (ms), QT/QRS ratio (iCEB) and QTC/QRS ratio (iCEBc). A blinded cardiologist performed the ECG measurements. To prevent errors in measurements, the measurements were also confirmed by a second physician. For each lead, a mean value of three measurements was determined. We measured the QT interval from the beginning of the QRS complex to the point at which the tangent of the maximal downslope of the descending limb of the T wave crossed the isoelectric baseline. Later, the Bazett formula: $cQT=QT\sqrt{(R–R}$ interval) was used to correct the QT interval for heart rate. The QTc in lead V6 was subtracted from the QTc in lead V1 to determine the QTc difference (V1-V6). Also, these intervals should be validated as the mean value from at least three to five

cardiac cycles [8]. These readings were then used to calculate the iCEB and iCEBc. The intra- and inter-observer coefficients of variation (the SD of differences between two observations divided by the mean value and reported as a percentage) were calculated as 1.0% and 1.6%, respectively.

Statistical analysis

Data analysis was performed using the SPSS software version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). The continuous variables are expressed as mean (SD) while categorical variables as counts and percentages. The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov Test and Shapiro–Wilk tests. The categorical variables were analyzed with the $\chi 2$ test and Fisher's exact test. Normally distributed variables were examined with the student's t-test, whose results were expressed as mean (SD). On the other hand, intergroup comparison of non-normally distributed variables was conducted using the Mann-Whitney U-test. Statistical significance was set at $P<0.05$.

Results

Of a total of 297 patients examined in the first phase, 153 (33% women; mean age: 66.13 (9.76) years) were included in Group 1 (SYNTAX S II ≤ 26) and 144 (44% women; mean age: 68.5 (10.91) years in Group 2 (SYNTAX S II > 26). Table 1 shows the demographic characteristics of the patients. Accordingly, demographic characteristics and baseline laboratory values were similar in both groups. However, Group 2 had more patients with a history of hypertension (HT), peripheral artery disease (PAD), and chronic obstructive pulmonary disease (COPD) (P=0.001). Also, serum creatinine concentrations were significantly higher, and the estimated glomerular filtration rate (eGFR) was lower in Group 2 (P=0.001 for both). As regards the echocardiographic calculations, Group 2 had a significantly lower estimated left ventricular ejection fraction (LVEF) but a significantly higher estimated posterior wall and septum thickness (P=0.001 for both).

Table 1: Demographical characteristic and comparison of parameters between groups

Variables	Study population (n=297)	SYNTAX S II ≤26 group (n=153)	SYNTAX S II >26 group (n=144)	*P*-value
Age, years	65.17 (12)	66.13 (9.76)	68.5 (10.91)	0.459
Men (n, %)	184 (62)	103 (67)	81 (56)	0.063
Hypertension (n, %	200 (67)	86 (52)	114 (79)	0.001
Diabetes mellitus (n, %)	102 (34)	50 (33)	52 (36)	0.535
Smoking (n, %)	174 (59)	102 (67)	72 (50)	0.003
Prior coronary artery disease (n,%)	125 (42)	64 (42)	61 (41)	0.898
COPD, (n, %)	81 (27)	26 (17)	55 (38)	0.019
PAD, (n, %)	31 (10)	11 (7)	20 (13)	0.043
Ejection Fraction, % (n,%)	54.31 (8.5)	57.27 (4.98)	51.17 (10.22)	0.001
Posterior wall thickness (mm)	1.1 (0.11)	1.05 (0.11)	1.14 (0.15)	0.001
Septum wall thickness (mm)	1.13 (0.28)	1.02 (0.12)	1.12 (0.12)	0.001
Hb (g/dL)	13.29 (1.93)	13.65 (1.95)	12.91 (1.85)	0.001
PLT count (×10^{3}cells/dL)	252 (70.91)	253 (65.84)	252 (76.39)	0.865
WBC	8.58 (2.81)	8.57 (2.5)	8.59 (3.11)	0.962
Creatinine (mg/dl)	1.18 (1.29)	0.82 (0.19)	1.56 (1.78)	0.001
GFR (mL/min/1.73 m2)	74.58 (17.75)	82.58 (26.58)	52.16 (14.56)	0.001
Potassium	4.42 (0.51)	4.32 (0.36)	4.52 (0.62)	0.059
SGOT	20.61 (14.97)	19.68 (8.91)	21.59 (19.39)	0.277
SGPT	22.42 (18.44)	22.14 (15.21)	22.72 (21.37)	0.787
Albumine	4.11 (0.44)	4.23 (0.35)	4 (0.48)	0.001
CRP	13.57 (0.2-275)	12.66 (0.2-194)	14.43 (0.8-275)	0.605
LDL (mg/dL	95 (41-327)	100 (44-327)	89 (41-195)	0.027
HDL (mg/dL)	40.81 (11.66)	40.77 (11.81)	40.85 (11.54)	0.954
Triglycerides (mg/dL)	167 (44-1429)	181 (59-1429)	151 (44-685)	0.032
Syntax Score I	7.24 (7.27)	5.66 (6.54)	8.46 (8.75)	0.002
Syntax Score II	27.5 (3.9-71)	20.22 (4.26)	35.19 (7.84)	0.001

Table 2 presents the ECG measurement results. Accordingly, Group 2 had significantly higher QRS, QT, and QTc intervals (respectively; P=0.001, P=0.014 and P=0.001). Besides, Group 2 had significantly lower QT/QRS (iCEB) and QTc/QRS (iCEBc) ratios (respectively; P=0.002 and P=0.005). The difference in QT and QTc between leads V1 and V6 was similar in both groups (respectively; P=0.614 and P=0.989. Finally, there was a statistically significant negative relationship between SYNTAX Score II and ECG parameters of iCEB and iCEBc (respectively, r = -0.235, r=-0.222, and P=0.01) (Table 3).

Table 2: Electrocardiographical parameters and comparing of variables between groups

Variables	Study population	SYNTAX Score II ≤26 group	SYNTAX Score II >26 group	*P*-value
Heart rate, bpm	75.07 (13.95)	73.08 (14.12)	76.41 (13.71)	0.111
QT interval	362.82 (40.71)	357.17 (38.79)	368.78 (41.95)	0.014
QTc interval	389.14 (37.97)	381.17 (33.67)	397.49 (40.41)	0.001
QRS interval	79.28 (24.29)	72.96 (21.08)	85.94 (25.71)	0.001
İCEB (QT/QRS ratio)	5.05 (1.88)	5.38 (1.99)	4.71 (1.71)	0.002
İCEBc (QTc/QRS ratio)	5.39 (1.91)	5.71 (1.99)	5.07 (1.77)	0.005
QT in V1, ms	359.73 (40.74)	354.61 (39.33)	365.17 (41.65)	0.026
QTc in V1, ms	385.99 (38.58)	378.56 (34.87)	393.81 (40.83)	0.001
QT in V6, ms	367.20 (41.23)	362.06 (35.94)	372.66 (45.69)	0.027
QTc in V6, ms	393.42 (38.29)	385.96 (31.77)	401.29 (42.85)	0.001
QT difference (V1-V6), ms (median, IQR)	-7 (-20-0)	-7 (-20-0)	-8 (-20-0)	0.614
QTc difference (V1-V6), ms (median, IQR)	-8 (-20-0)	-7 (-20-0)	-7 (-20-0)	0.989
QT ratio in V1/V6	0.98 (0.04)	0.97 (0.04)	0.98 (0.05)	0.614
QTc ratio in V1/V6	0.99 (0.04)	0.98 (0.04)	0.99 (0.04)	0.733

Table 3: Correlation analysis of SYNTAX II score and electrocardiographical variables

Variables	R value	*P*-value
QTc interval	0.192	0.001
iCEB (QT/QRS ratio)	-0.235	0.001
iCEBc (QTc/QRS ratio)	-0.222	0.001
QTc in V1, ms	0.187	0.001
QTc in V6, ms	0.198	0.001
QT difference (V1-V6), ms	-0.018	0.762
QTc difference (V1-V6), ms	-0.021	0.732

Discussion

According to our results, a lower iCEB value correlates with a higher SYNTAX II score. This, therefore, may suggest that in patients with stable coronary artery disease, the high SYNTAX score indicates a risk of non-TDP-related VT or fibrillation.

The SYNTAX score system was used with respect to the SYNTAX study, which compared the best revascularization option and predicted long-term mortality in patients with left main and multivessel CADs [1]. This scoring method, despite its clinical value in interventional cardiology, relies nearly entirely on the anatomical and lesion properties of the diseased coronary arteries and disregards the clinical data of patients [3]. Hence, the previous SYNTAX score was replaced by the SYNTAX Score II that combined patients' clinical data (such as age, sex, creatinine clearance, left main CAD, left ventricular ejection fraction, peripheral vascular disease, and chronic obstructive pulmonary disease) with the anatomical features of the coronary arteries (anatomical SYNTAX score) [4]. This scoring technique was incorporated into the clinical practice by some studies such as Evaluation of the Xience Everolimus-Eluting Stent versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL), which put forward more accurate

results than those given by the SYNTAX Score method [9]. A meta-analysis by Chen J et al. [10] showed that SYNTAX Score II, having a significant impact in forecasting negative clinical results in patients who underwent a percutaneous coronary intervention, was more effective than SYNTAX Score.

As regards real-life practice, Song et al. [11] verified the value of SYNTAX Score II in predicting negative outcomes with their observational study, where they divided estimated SYNTAX Score II scores of a total of 4,398 patients into tertiles (with cut-off points at 20 and 26) to analyze their outcomes after three-vessel and/or unprotected LMCA-PCI. The authors found that during the 2-year follow-up period, the upper tertile had a significantly higher mortality rate than the intermediate or lower tertiles (2.7% vs 1.7% vs 0.5%, respectively; $P<0.001$). Also, the results of their multivariate analysis demonstrated that SYNTAX Score II independently predicted 2-year mortality (hazard ratio, 1.66 [95% CI, 1.03-2.68]; $P=0.04$). Furthermore, Rencuzogullari et al. [12] found a strong relationship between the SYNTAX Score II and the development of the first detectable episode of AF in patients with known CAD. The authors noted that in long-term follow-up, the higher the SYNTAX Score II, the worse the prognosis is.

Despite the fact that a lot of research has been put into determining the relationship between adverse cardiac events and SYNTAX Score II, no study has been conducted to examine the relationship between VAs and SYNTAX Score II. Therefore, the present study sought to investigate the clinical importance of SYNTAX Score II in predicting the development of malignant VAs by employing cardiac depolarization and repolarization indices. As far as we know, this study is the first to use iCEB and V1-V6 QT differences to evaluate the relationship between the SYNTAX II scoring system and the development of malignant VAs. We found that SYNTAX Score II statistically significantly correlated with SYNTAX Score II and ECG parameters of QTC, iECB, and iECBc.

iCEB (QT/QRS), which is equivalent to the cardiac wavelength λ (λ=effective refractory period (ERP) x conduction velocity), is a well-known indicator of altered cardiac depolarization and repolarization. It has recently been demonstrated that proarrhythmic risk can better be predicted by this parameter than other ECG parameters including Tp-e, Tp-e/QT, Tp-e/QTc. Studies have associated high iCEB values with Torsades de Pointes (TdP) and low values with non-TdP mediated VT and VF [5,6]. Indeed, Yumurtaci et al. [13] also reported consistent findings, showing that patients with acute myocarditis had higher iCEB and iCEBc values than healthy controls. The authors suggested that higher iCEB and iCEBc values may be the reason why patients with acute myocarditis had an increased frequency of malignant VAs. A strong correlation between iCEB values and increased pericardial fat volume was also reported by Nafakhi et al. [14]. Increased amounts of pericardial fat, because of well-known pro-inflammatory features and anatomical proximity to the cardiac myocytes, results in structural and electrical remodeling of the myocardium and promotes arrhythmogenesis [15-17]. As a consequence, greater iCEB values were correlated with an increase in pericardial fat volume, confirming the findings of prior research that studied the relationship between pericardial fat thickness and arrhythmogenesis.

Limitation

The current research had certain limitations, including being a retrospective, single-center study and having a relatively small size of cases. Therefore, future studies may be recommended to include a larger sample size to verify this study's findings. Although the study sought to explore the association between the SYNTAX Score II and cardiac depolarization and repolarization values, further follow-up of the patients in terms of the development of malignant VAs and sudden cardiac death was not performed. Also, the study excluded the patients who had a QRS duration ≥120 ms, complete bundle branch block, intraventricular conduction delay, and history of permanent pacemaker implantation, making our findings inapplicable to these patient groups.

Conclusion

Our findings point to a strong correlation between QTC, iCEB, iCEBc, and SYNTAX Score II. Hence, malignant VAs can be effectively predicted with the SYNTAX Score II. In terms of exploring the association between SYNTAX Score II and cardiac depolarization and repolarization parameters, this study may offer a clinically helpful method, which can be used in clinical practice because of its ease of use and accessibility.

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Overweight and obese adolescents: A risk group for vitamin B12 deficiency and anemia?

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Ethics Committee Approval
The study was approved by the Ethics Committee of Ankara Education and Research Hospital (Approval number: E-19-195).
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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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Obesity is a major clinical and public health problem for adolescents. It leads to various nutritional problems as well as adult diseases such as cancer, cardiovascular diseases, and diabetes. Some studies have found that dietary intakes of some micronutrients were inadequate among adolescents. The aim of this study was to investigate anemia and vitamin B12 deficiency in obese children and adolescents and to determine whether obesity has a role in vitamin B12 deficiency. Additionally, we aimed to assess ferritin levels and their relationship with body mass index in obese children and adolescents.

Methods: This retrospective cross-sectional study group consisted of 1574 patients between 10 and 18 years old who were admitted to the pediatrics department of the hospital, some for a weight problem and some, who constitute a control group, for other issues. Those excluded included patients with missing data, those with co-morbidities situations, patients taking vitamin supplements, children whose obesity was the result of a syndromic condition, and those whose obesity had endocrinal causes. Finally, 436 patients remained in the study. Vitamin B12 deficiency was defined as a serum level <200 ng/L. We defined anemia as a hemoglobin concentration under 12.5g/dl in males or 12g/dl in females according to depleted iron store, which is defined as a plasma ferritin level <12ug/L.

Results: 252 (57.8%) of 436 patients were normal weight, 51 (11.7%) were overweight, and 133 (30.5%) were obese. The overweight/obesity group had a significantly higher level of plasma ferritin compared to the normal group. No relationship was found between weight and anemia (P=0.95). Vitamin B12 levels negatively correlated with increasing age (P<0.001, Spearman's rho = -0,185). Obese and overweight adolescents had lower vitamin B12 concentrations than normal weight adolescents (P=0.01).

Conclusion: Serum ferritin concentrations are higher in obese and overweight adolescents than in those with normal weight. Obese and overweight adolescents are at high risk for low serum vitamin B12 concentrations, but not for anemia.

Keywords: Vitamin B12, Obesity, Adolescent, Anemia, Ferritin

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Introduction

Children's nutrition has a remarkable impact on lifelong health [1]. Adolescence is an intense growth period, second only to infancy. Therefore, as in infancy, general nutritional needs to support optimal growth and development are high in adolescence [2]. Food habits of adolescents are usually characterized by an irregular meal pattern with skipped meals [3]. In some studies, dietary intakes of certain micronutrients were found to be inadequate among adolescents [4, 5].

Iron deficiency is one of the micronutrient deficiencies for obese children and adolescents [6, 7], and it may lead to adverse effects, including lower cognitive or behavioral function, delayed mental and physical development, impaired sensorimotor function, and decreased work capacity [8].

Vitamin B12 is an essential vitamin found in foods of animal origin [3, 9]. Hematologic, psychiatric, and neurologic manifestations are seen because of vitamin B12 deficiency, which can cause irreversible neurological damage despite treatment [10]. In some studies, obesity in children and adolescents has been associated with an increased risk of low vitamin B12 concentrations [3, 9]. On the other hand, Gunanti et al. [11] reported that higher serum concentrations of vitamin B12 were associated with a reduced risk of obesity.

Our study aimed to assess whether obese children and adolescents are at increased risk for anemia and vitamin B12 deficiency.

Materials and methods

Study design and participants

This retrospective cross-sectional study was carried out by examining the data of 1574 patients between 10 and 18 years old who were admitted to the pediatrics department of the hospital between December 2018 and February 2019 for weight problems or who served as part of a control group. Patients whose serum vitamin B12, hemoglobin concentration, and plasma ferritin had been measured were included. Patients with missing data, having co-morbid situations, or using vitamin supplements were omitted. Also excluded were children whose obesity was the result of syndromic conditions and those whose obesity had endocrinal causes. Finally, 436 (27.7%) adolescent patients (268 female), 252 (57.8%) with normal weight, 51 (11.7%) overweight, and 133 (30.5%) obese remained in the study. The study proposal was approved by the Ethics Committee of Ankara Education and Research Hospital (approval number: E-19-195). There are no conflicts of interest; thus, the researchers do not have biases.

Anthropometry and body composition

Weight (measured by a digital electronic scale) and height (measured by a portable stadiometer) were recorded in digital patient files. Nutritional status was assessed using the body mass index (BMI)—the ratio of body weight (kg) and the square of the height (m^2)—according to World Health Organization recommendations. BMI categories were classified as obese (>95th percentile), overweight (85–95th percentile), and normal weight (<85th percentile), considering age and specific to gender [12].

Biochemical and clinical assessment

All blood analyses were performed at the Ankara Education and Research Hospital biochemical laboratory. The serum vitamin B12 levels were determined using the electro-chemiluminescence immunoassay method. Vitamin B12 deficiency was defined as a serum level <200 ng/L [13]. We defined anemia as a hemoglobin concentration under 12.5g/dl in males or 12g/dl in females, according to depleted iron store, which is defined as a plasma ferritin level <12ug/L [14, 15].

Statistical analysis

Statistical analyses were performed using SPSS version 15.0. Mean, standard deviation, median, range, and minimum and maximum values were shown as the descriptive statistics for age, BMI, hemoglobin, plasma ferritin, and vitamin B12. Percentages were given for groups of categorical variables. Differences between the groups for categorical data were analyzed using Pearson's chi-square or Fisher's exact test, as appropriate. The Shapiro-Wilk test was used for the test of normality. Continuous variables were compared using the Mann-Whitney U test. The relationship between age and B12 was evaluated using Spearman's rho correlation coefficient. A *P*-value <0.05 was considered statistically significant.

Results

In the study, the average age of patients was 13.7 (1.34) years. Laboratory characteristics of the patients are presented in Table 1.

Table 1: Laboratory characteristics of study population

	N	Minimum	Maximum	Mean	SD
Age (years)	436	10	18	13.7	1.34
BMI	436	13.6	44.4	23.4	5.82
Hemoglobin (g/dL)	434	7.9	17.6	13.8	1.34
Plasma Ferritin (ug/L)	427	0.9	166.3	39.7	26.71
Vitamin B12 (ng/L)	428	111.5	830.8	302.2	117.81

SD: Standard deviation, BMI: Body Mass Index

Normal weight and overweight/obesity groups, hemoglobin, and plasma ferritin levels are presented in Table 2 for both female and male adolescent participants. There was no gender difference between weight groups. Adolescent girls had significantly higher prevalence of anemia and lower plasma ferritin than boys (P<0.001 for each). The normal weight group had a significantly lower level of plasma ferritin compared to the overweight/obesity group (P=0.005) (Table 3). No relationship was found between weight and anemia (P=0.483).

Table 2: Distributions of adolescents according to weight groups, the hemoglobin level, anemia presence and plasma ferritin levels in both genders

	Female	Male	P-value
Weight group			
Normal weight	155 (57.7%)	97 (57.7%)	0.984
Overweight/Obesity	113 (42.2%)	71 (42.3%)	
Hemoglobin level (g/dL) Mean+ SD	13.31+1.15	14.49+1.39	0.483
Anemia			
No	241 (90.6%)	160 (95.2%)	<0.001
Yes	25 (9.4%)	8 (4.8%)	
Plasma ferritin level			
≤12 (ug/L)	50 (18.9%)	1 (0.6%)	<0.001
>12 (ug/L)	215 (81.1%)	161 (99.4%)	

SD: Standard deviation

Table 3: Anemia and plasma ferritin level according to weight status

		Normal weight	Overweight/ Obesity	Total	*P*-value
Anemia	No	230 (91.6)	171 (93.4)	401 (92.4)	0.483
n (%)	Yes	21 (8.4)	12 (6.6)	33 (7.6)	
Plasma ferritin level	Normal	210 (84.3)	166 (93.3)	376 (88.1)	0.005
n (%)	Low	39 (15.7)	12 (6.7)	51 (11.9)	

Vitamin B12 deficiency was seen in 68 of 428 (15.8%) patients. Also, 19% of male patients and 13.5% of female patients had a vitamin B12 deficiency. This difference was statistically insignificant (P=0.28). There was a correlation between age and vitamin B12 deficiency (P<0.001, Spearman's rho = -0,185). Vitamin B12 levels decreased with increasing age.

Obese and overweight adolescents had lower vitamin B12 concentrations than normal weight adolescents (P=0.019) (Table 4).

Table 4: Relationship between BMIP and Vitamin B12

		Vitamin B12		Total
		Deficiency n (%)	Normal n (%)	
BMIP	<85	31 (12.4)	219 (87.6)	250
	>85	37 (20.8)	141 (79.2)	178
Total		68 (15.9)	360 (87.6)	428

BMIP: Body Mass Index Percentile

Discussion

The prevalence of anemia in Turkey is 1.5–12.5%, and adolescence is considered as a risky age group for anemia [16]. In this study, the prevalence of anemia was found to be 7.6%. That broke down to 9.4% of girls and 4.8% of boys. A study by Huang et al. [8] compared 2099 adolescents and found that adolescent girls had significantly lower plasma ferritin and hemoglobin concentrations and a greater prevalence of anemia compared with boys. As seen in other studies, in our study, too, iron deficiency was higher in girls than in boys [8, 16–18]. Adolescent girls are vulnerable to anemia because their overall iron requirement increases two to three times during adolescence due to high growth and 12.5–15 mg iron loss in each menstrual cycle [2, 19].

Although some studies have found iron deficiency anemia to be more common in obese adolescents [7, 20], we couldn't find any significant relationship between BMI and anemia. Huang et al. [8] found a positive correlation between BMI and hemoglobin. Scheer and Guthrie [21], investigating whether hemoglobin criteria should be adjusted according to weight status, observed iron deficiency but no anemia, as in our study. Again, a study by Simsek et al. [22] in Turkey showed that hemoglobin levels were similar in both obese and control groups; in addition, ferritin levels were higher in the obese than in the control group.

We found that plasma ferritin levels increased as children's BMIs increased from normal weight to obesity. In this study, as in previous studies [8, 22, 23], higher ferritin levels were observed in children with overweight and obesity. These findings are consistent with the observation that obesity is an inflammatory condition that increases acute phase reactants [23, 24]. Ferritin functions not only as a parameter of iron storage but also as an acute phase protein; hence, its level in plasma increases in response to inflammation due to obesity [6, 23, 25]. However, in a study done in the Iranian population by Ghadiri et al. [6, 26], there was no difference in serum iron and ferritin among normal weight, overweight, and obese people. In several studies, children with higher BMIs had lower serum iron levels; however, ferritin concentrations were similar in both normal weight and obese children [6, 27].

Our study indicates that 20.8% of overweight and obese adolescents had B12 deficiency, while 12.4% of normal weight adolescents had B12 deficiency. In a study by Ho et al. [9] in Australia, the rate of obese adolescents with a serum vitamin B12 concentration ≤221pmol/L was reported to be 32.1%. In a study by MacFarlane et al. [28], this percentage was 20.4% in obese children and adolescents in Canada.

Our results show that obese and overweight adolescents had significantly lower vitamin B12 concentrations than normal weight adolescents. Pinhas-Hamiel and his colleagues [3] reported that obesity was associated with a greater than four times risk for low vitamin B12 concentrations. Gunanti et al. [11] also supported our results, finding that normal weight children's vitamin B12 mean serum concentrations were higher than those of overweight and obese children. In contrast, in a case control study in Brazil by Brasileiro et al. [3, 11], lower serum concentrations were detected in overweight adolescents compared with normal weight adolescents, but no significant difference was shown. Also, no significant difference was found in another study in adults [29]. Vitamin B12 deficiency is caused by decreased intake, abnormal nutrient absorption, or a rare congenital defect of vitamin B12 metabolism [3, 30]. Because obese children gain weight easily, there is no reason to suspect they have a problem with absorption [3]. Nutrition of obese and overweight children may consist of foods low in vitamin B12. In addition, it is also possible that obese children may have increased need for vitamin B12 compared to non-obese children due to increased growth and body surface area [3].

We found that the frequency of vitamin B12 deficiency increases with increasing age. A study evaluating the serum B12 levels of 3766 children (aged 4 to 19 years) in the USA found that the greatest proportion of children with levels <200 pg/mL was in the 12- to 19- year age category, with a rate of one in 112 [30]. Additionally, Pinhas-Hamiel et al. [3] reported that each increase of one year of age decreased vitamin B12 concentration by 22pg/mL.

There was no relationship between gender and vitamin B12 level. Pinhas-Hamiel et al. [3] also supported this finding. In contrast to our study, Gunanti et al. [11] observed higher mean concentrations of serum vitamin B12 among girls.

Limitations

We conducted a retrospective cross-sectional study, and the data were obtained by scanning patient files. Since only patients with complete data were included in the study, the number of patients included was limited.

In future studies, vitamin B12 levels can be measured in obese and normal weight adolescents, and their response to treatment can be evaluated prospectively by administering B12 therapy to those with low vitamin B12 levels.

Conclusion

Our findings show that serum ferritin concentrations were higher in obese and overweight adolescents due to the inflammatory state caused by obesity. Obese and overweight adolescents are at high risk for low serum vitamin B12 concentrations but not for anemia. We recommend including vitamin B12 intake in the dietary evaluation of obese and overweight adolescents. Clinicians should be careful about this.

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Journal of Surgery and Medicine

Cutaneous manifestations of COVID-19 in children: Four case presentations

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The authors stated that the written consent was obtained from the parents of the patients presented with images in the study.

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Abstract

The dermatological signs of Coronavirus disease 2019 (COVID19) in children are uncommon and different from adults. The majority of infected children were asymptomatic, and cutaneous symptoms of infection in children usually appear several weeks after the disease. This article describes four different cutaneous manifestations of COVID-19 in children, including chilblains, erythema multiforme-like lesions (EM), urticaria, and vesicular rash in terms of recalling to mind COVID-19 infection.

Keywords: COVID-19 in children, Chilblains, Covid-toe, Erythema multiforme, Urticaria

Introduction

Dermatological symptoms of Coronavirus disease 2019 (COVID-19) in children are uncommon (0.25 to 3 percent) [1, 2]. Unlike adults, the majority of children with COVID-19 infection are asymptomatic. The skin lesions caused by COVID-19 in children differ from adults. The urticaria, maculopapular and vesicular rash may be seen in people of all ages while chilblains, erythema multiforme-like lesions (EM), and cutaneous manifestations of pediatric inflammatory multisystem syndrome are more frequently seen in children [1]. The latency time between the appearance of general symptoms and the appearance of cutaneous symptoms in symptomatic cases ranges from a day to weeks. As a result, cutaneous symptoms of COVID-19 in children are typically late indicators of infection, appearing after several weeks [3]. In this article, four different cutaneous manifestations of COVID-19, including chilblains, EM, urticaria, and vesicular rash are described.

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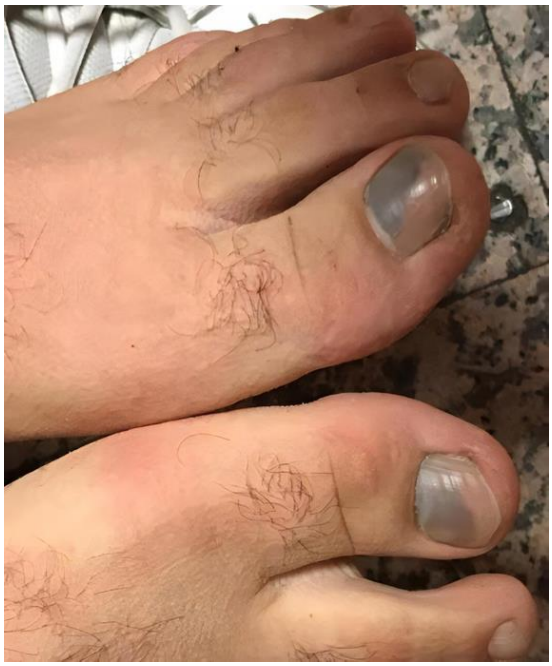
Case presentation

Written informed consent was acquired from the patient's parents. This study was prepared in accordance with CARE standards.

Case 1

In the absence of any systemic symptoms, a 15-year-old male patient presented with chilblain-like erythema (Figure 1), swelling and pain in toes, and ecchymotic lesions in the toenails. There were no vesicles or pustules. The drug history was unfavorable. He was not exposed to any exanthematous diseases. Except for muscle soreness and cough, clinical signs of bacterial or viral illness were not observed. The blood tests were normal, except an elevated D-dimer level. His PCR for SARS-CoV-2 was positive four weeks ago following family interaction. The medication was generic, consisting of paracetamol. Without therapy, the lesions vanished within 15 days.

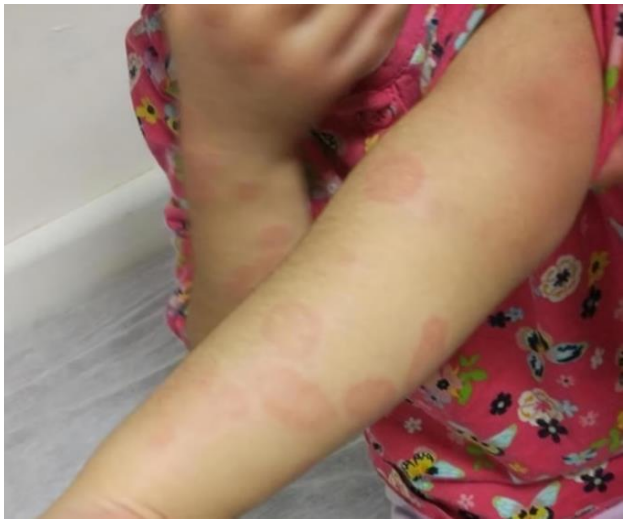
Figure 1: Chilblain like erythema accompanied by swelling and pain in the toes and ecchymotic lesions in toenails.



Case 2

A four year-old girl patient presented with erythema multiforme like lesions accompanied by swelling in her arms and legs (Figure 2). Lesions consisted of confluent macules and plaques of different sizes, some with hemorrhagic or a small central crust. She had no previous history of erythema multiform, no recent lip sores, no new medications, and no vaccinations before the onset of the skin lesions. Solely, her asymptomatic father was in treatment of COVID-19 infection because of being PCR positive for SARS-CoV-2. Her PCR for SARS-CoV-2 was negative and immunoglobulin (Ig) G and IgM antibodies against SARS-CoV-2 were resulted as negative. There was no serological evidence of other viral infections. Significantly elevated interleukin-6 (IL-6), D-dimer, lactate dehydrogenase (LDH), C-reactive protein(C-RP) levels and lymphocytopenia were the signs of COVID-19 disease in blood tests. The patient received only symptomatic treatment. Lesions were resolved within two days.

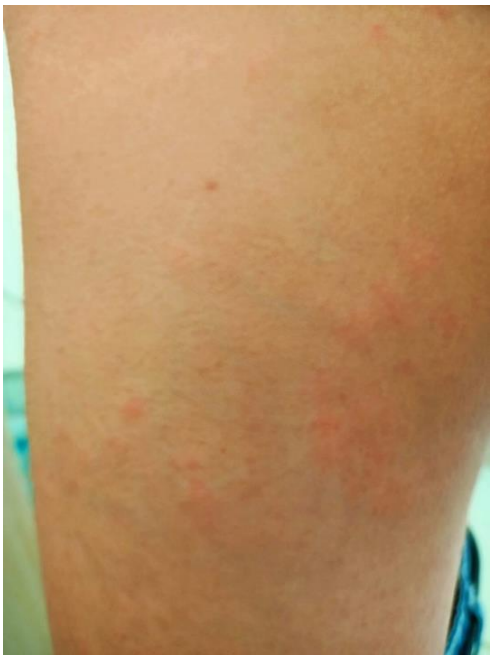
Figure 2: Erythema multiforme like lesions accompanied by swelling in arms. Lesions consisted of confluent macules and plaques of different sizes, some with hemorrhagic or a small central crust



Case 3

A 17-year-old girl was presented with erythematous, swollen, irregular shaped urticaria on the skin of the thigh and lower leg (Figure 3). Five weeks ago, his PCR was positive for SARS-CoV-2 due to family interaction. The patient did not have a history of drug use, allergy, or chronic disease. Except for an elevated D-dimer level, the general blood test was normal. There was no evidence of other viral infections at laboratory investigation. The patient received only oral antihistamine because of pruritus. Lesions resolved within seven days.

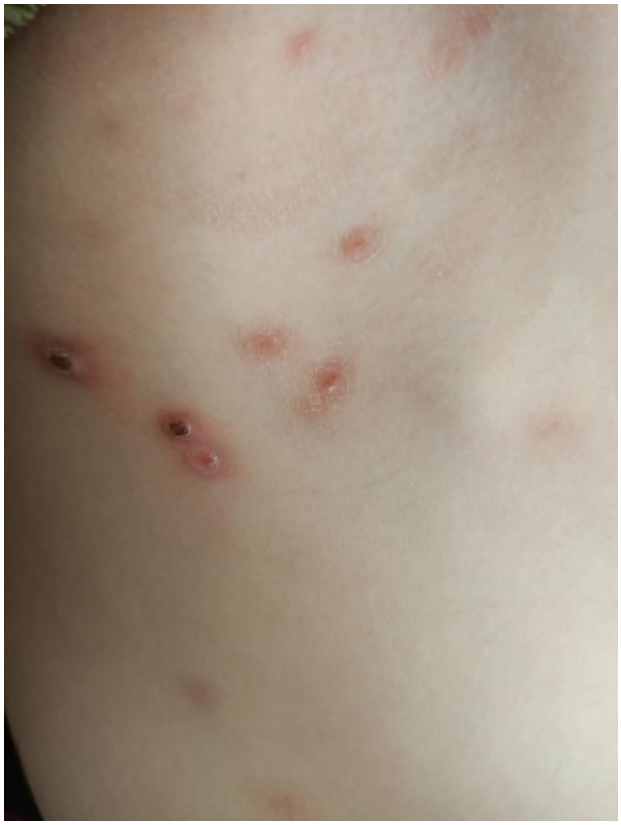
Figure 3: Erythematous, irregular, swollen urticaria on the skin of the thigh and lower leg



Case 4

A 12-year-old boy was presented with disaggregated vesicular eruptions in some areas and persisted for nearly one week. Lesions were formed on his trunk and arms (Figure 4). He recovered from COVID-19 infection seven weeks ago. Except for an elevated D-dimer, the general blood test was normal. There was no evidence of other viral infections at laboratory investigation. The patient received only symptomatic treatment for lesions and all of them disappeared within ten days.

Figure 4: Disaggregated vesicular eruptions in some areas, generally in trunk and arms



Discussion

During the COVID-19 outbreak, there have been reports of chilblains (COVID toe) as acral ischemic lesions [4]. Patients are mainly isolated at home, and interestingly, the first patient has no previous pernio history. Lesions in children under the age of ten are uncommon [4, 5]. Children are normally asymptomatic, however they may have local pain and itching. Chilblains were usually seen in the feet, but also reported as erythematous swelling in fingers, as seen in our patient. Splinter hemorrhages were found in our patient's nails. Chilblains were commonly seen in the feet, but also documented in fingers. The lesions on our patient's feet were erythematous, with increased edema and nail splinter hemorrhages. PCR for COVID-19 was frequently negative in children with COVID-associated chilblains, and immunoglobulin (Ig) G and IgM antibodies against SARS-CoV-2 were detected in a very restricted number of patients [4, 5]. Our patient's COVID-19 PCR test was positive four weeks ago due to familial interactions. As it appeared in our patient, all children have a favorable prognosis, with spontaneous regression of the lesions without complications [4].

Erythema multiforme is a self-limiting hypersensitivity reaction that manifests as a skin eruption with symmetrical erythematous lesions known as iris or target lesions. Systemic infection is the most common cause of EM [6]. *Herpes simplex virus (HSV)* and *Mycoplasma pneumonia* are the two pathogens most commonly related in children with EM. SARS-CoV-2 infection has been associated with an EM-like eruption both in adults and children [6, 7]. Children with EM were generally reported with asymptomatic infection. PCR for SARS-CoV-2 is generally negative and skin biopsies demonstrated endothelial immunohistochemistry stain positivity to SARS-CoV-2 spike protein [8]. While the clinical signs of COVID-19 were not seen in our patient except fever, significantly high levels of interleukin-6, procalcitonin, D-dimer, C-reactive protein suggested infection. Family interaction played the main role in this.

Urticaria presents with pruritic, circular, swollen lesions which persisted 24 hours. It was formed on the trunk [6]. The most common causes of urticaria are infections (parvovirus, rhinovirus, rotavirus, *Epstein–Barr virus* allergens, hepatitis, *Streptococcus*, *Mycoplasma*, *Helicobacter pylori*), allergens, insects and drugs [6, 9]. In addition to these, urticaria represents about 10%–20% of the cutaneous manifestations in patients with COVID-19. Most reported cases of children with urticarial rash appeared in asymptomatic cases [6, 9]. Generally, patients were not tested but had household contact with confirmed cases of COVID-19, as similar to our patient. The urticaria in COVID-19 is likely to be associated with systemic eosinophilia, which in turn leads to better outcomes of COVID-19 infection according to some studies [10], whereas eosinopenia is more frequently observed and may have a prognostic value in more severe cases of infection. Eosinophilia was not seen in our patient and no evidence of other viral infections were found in blood tests.

The vesicular eruption reported in COVID-19 was a varicella-like papulovesicular rash that was mostly on the trunk and rarely on the limbs [6, 11]. The vesicular exanthema was reported in 4% -15% of confirmed or suspected COVID-19 cases [6]. Vesicular lesions are thought to appear in early stages of COVID-19 disease compared with other skin manifestations occurring later [12]. Our patient's lesions appeared in the late stage of infection disparately from the literature.

Because there are no particular biomarkers or laboratory tests for COVID-19 diagnosis, patients have high CRP and LDH levels, low albumin levels and lymphopenia. Except significantly elevated D-dimer levels in most cases, various coagulation markers were found to be within the normal range in youngsters [13]. Our findings show that PCR may be positive when cutaneous symptoms coexist with clinical illness, but sensitivity is relatively low. The lesions occur several days after, and PCR is usually negative. The presence of IgM and IgG by immunoassay has very little diagnostic relevance to cutaneous symptoms of COVID-19 in children. According to the findings, when cutaneous symptoms coexist with symptomatic illness, PCR may be positive, but sensitivity is quite low. Testing is frequently negative when the lesions occur much later. The detection of IgM and IgG by immunoassay has very little diagnostic value in children with cutaneous symptoms of COVID-19 [13]. All patients showed elevated D-dimer levels in coagulation tests, while one patient also had elevated IL-6, CRP and LDH levels with lymphocytopenia. After family interaction, three of them had a positive PCR test for COVID-19 in bygone four and a half weeks.

Conclusion

Children with COVID-19 have an asymptomatic course and usually discovered through contact. Emerging skin lesions may hold a hint for COVID-19. Chilblains, EM, urticaria, and vesicular eruption are the most commonly reported skin pathologies in children, and they are significant in terms of recalling COVID-19.

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Choledochoduodenal fistula: A rare cause of upper gastrointestinal bleeding in a child

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Informed Consent
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Abstract

Spontaneous choledochoduodenal fistula (CDF) is a rare form of biliary enteric fistula. A child with CDF who had a motor vehicle collision as a pedestrian at the age of 2 years is presented in this article. Since the accident, recurrent abdominal pain and black-colored stools were noted thrice a year. As a 13- year-old, the patient was admitted with vomiting of blood and melena. He was hospitalized with gastrointestinal bleeding. Endoscopy is performed because of bleeding and a fistula was detected incidentally. Barium swallow series and magnetic resonance cholangiopancreatography showed a fistula tract. Endoscopic retrograde cholangiopancreatography (ERCP) confirmed the definitive diagnosis and guided treatment. In our case, we emphasize the importance of ERCP in facilitating the diagnosis of CDF. Barium swallow radiography detects the passage of barium to the biliary system in only half of the CDF patients diagnosed via ERCP. In summary, we reported the youngest case of CDF with a large fistula orifice managed by endoscopic sphincterotomy.

Keywords: Children, Choledochoduodenal fistula, Endoscopy, Endoscopic retrograde cholangiopancreatography (ERCP)

Introduction

The first biliary fistula was described in 1654 by Bartholini, and it was observed between the gallbladder and intestine. Various types of biliary fistulas have since been described between the biliary and respiratory systems, skin, and vessels. Most biliary fistulas originate from the gallbladder and end up in the digestive tract. Spontaneous biliary fistulas between the common bile duct and the duodenum are rare [1]. All of the reported choledochoduodenal fistula (CDF) cases consisted of adult patients except one patient as 15 years old [2 - 4].

Herein, we report a rare form of biliary fistula. To our knowledge, this case of CDF of a 13-year-old is the youngest reported case.

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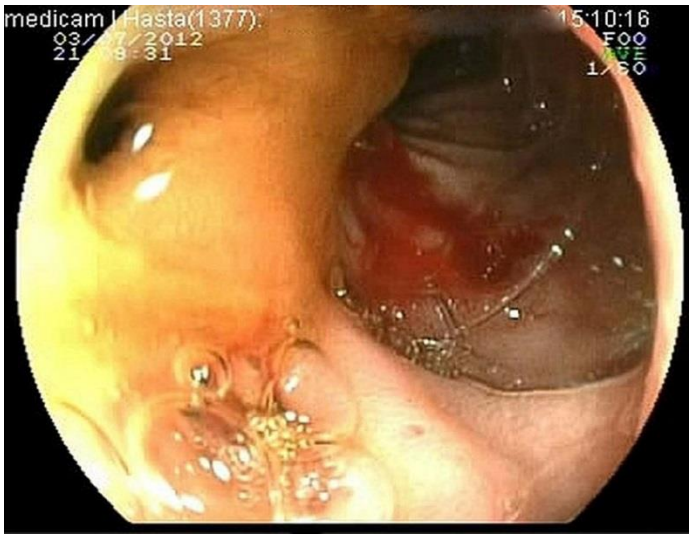
Case presentation

A thirteen-year-old male was admitted with the complaint of blood vomiting. The blood had an appearance similar to that of ground coffee. He had been suffering from epigastric pain for one month. The patient had a motor vehicle collision as a pedestrian when he was two-years old. Two months after the accident, abdominal pain and black-colored stools were noted and these recurred two to three times a year. The patient appeared ill and pale, without jaundice or fever. Abdominal examination revealed epigastric tenderness without muscular defence, and melena was present. Other physical examination findings were unremarkable. Laboratory analysis revealed anemia, with hemoglobin and hematocrit levels as 10 g/dL [normal: 13- 14.5] and 30 % [normal: 36-43], respectively. Liver function tests, serum amylase levels, and coagulation test results were within normal ranges. Neither an abdominal X-ray nor abdominal ultrasonography demonstrated any pathologies. The patient was hospitalized with a diagnosis of gastrointestinal bleeding and intravenous fluids were commenced. The informed consent was taken from the parents.

Endoscopy was performed after the restoration of intravascular volume. The endoscopy revealed a duodenal ulcer, measuring 1.5 cm, located on the posterior wall of the bulbus. The major duodenal papilla had a normal appearance and was located in the medial wall of the second part of the duodenum. There was a 1.5 cm fistula orifice proximal to the ampulla of Vater (Figure 1).

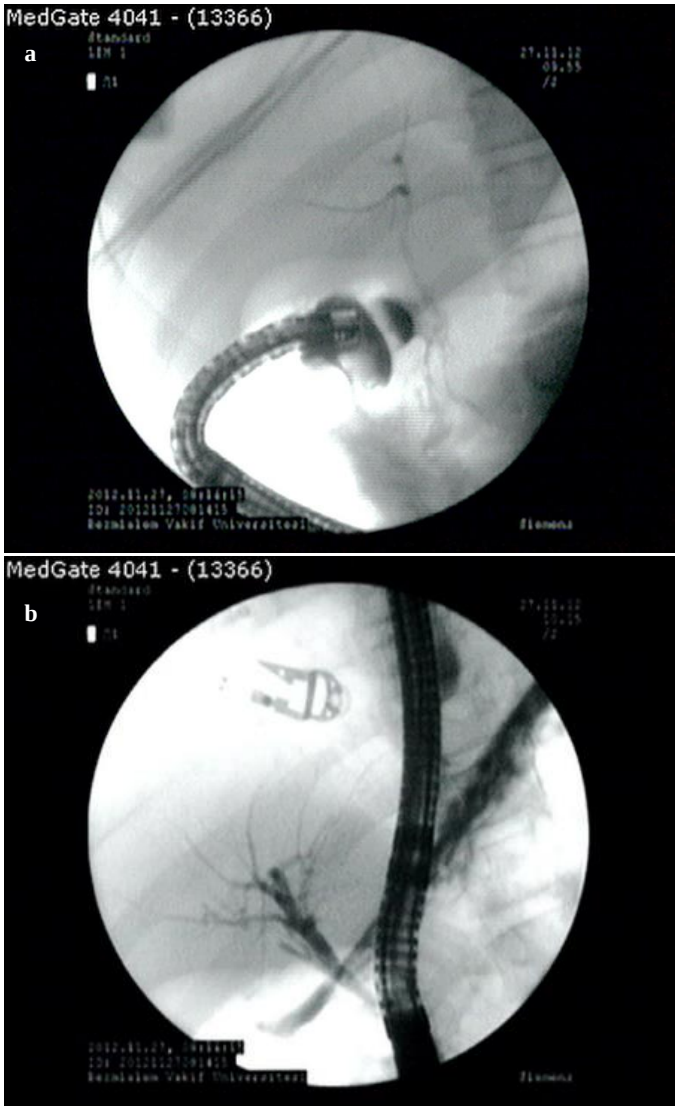
Figure 1: Endoscopic appearance of the fistula orifice



In this case, we were able to observe active bile flow to the duodenum. The upper gastrointestinal system barium swallow series showed a fistula orifice and ulcer niche in the duodenum, as well as barium reflux to the biliary system.

Magnetic resonance cholangiopancreatography (MRCP) also revealed a fistula between the duodenum and middle-to-distal common bile duct. Duodenal ulcer and gastroesophageal reflux were treated with three months of lansoprazole and domperidone. The symptoms subsequently resolved. Control endoscopy showed complete regression of the ulcer, but the fistula orifice size remained. Endoscopic retrograde cholangiopancreatography (ERCP) revealed that the biliary tree was filled through both the fistula and papilla of Vater (Figure 2a and 2b).

Figure 2: a: Endoscopic retrograde cholangiopancreatography. Biliary tree filling through the fistula, b: Endoscopic retrograde cholangiopancreatography. Biliary tree filling through the papilla of Vater



We were also concerned about the future consequences of bile ponding in a segment of the common bile duct, especially in the segment between the fistula and papilla of Vater. Sphincterotomy was performed both to provide the union from the papilla extending to the fistula and to divert the bile flow distally, because bile reflux from the large fistula orifice may have caused recurrent ulcers and cholangitis. The patients follow-up was done periodically after the procedure, there were no recurrent bleeding or any symptoms related with the fistula.

Discussion

Choledochoduodenal fistula cases constitute less than 5 % of all biliary fistulas especially before 1980 in literature [1]. With frequent use of ERCP, published cases of CDF were also increased. In 1997, Yamashita et al. [3] reported that 62 % of biliary fistulas in their study were CDF cases. Endoscopic retrograde cholangiopancreatography facilitated the diagnosis of CDFs. Barium swallow detects the passage of barium to the biliary system in only half of the CDF patients diagnosed via ERCP [3]. Air in the biliary system is another indirect fistula sign that can be detected with X-ray or computed tomography, but it is only seen in 25%–40% of patients with CDF [4, 5]. In our patient, the abdominal X-ray was normal, but endoscopy revealed a fistula orifice, and barium swallow series and MRCP

confirmed the fistula tract. Finally, ERCP provided a definite diagnosis.

Endoscopic retrograde cholangiopancreatography is useful for diagnosing CDF but may be complicated by pancreatitis, cholangitis, hemorrhage, and perforation, particularly after sphincterotomy. Our patient did not have any complaints after ERCP. Choledochoduodenal fistulas are classified according to the opening level of the fistula to the common bile duct as either peripapillary or proximal. The proximal fistulas are detected less frequently and are thought to be caused by the perforation of ulcers located in the bulbus, to the common bile duct [6]. Peripapillary fistulas originate from the distal 2 cm of CBD. Spontaneous peripapillary fistulas are associated with biliary stones in more than 95% of patients [5, 7]. They are supposed to be formed by common bile duct stones fistulizing to the duodenum due to associated infection and pressure. In addition to biliary stones, papillary cancers [8] or blunt abdominal trauma [2] may result in spontaneous peripapillary fistulas. Our patient had no history of biliary surgery or intervention, and we did not detect any biliary stones. The fistula orifice and ulcer did not overlap in terms of localization. Complaints in our patient started after a traffic accident. Chao et al. [2] reported a similar CDF case due to blunt abdominal trauma. The trauma resulted in papillary edema, biliary flow obstruction, pancreatitis, and fistula in a 15-year-old patient. The mean age of patients with CDF is reported as 60 years in previous studies [3-8].

Here, we present the youngest case. Symptoms of CDF are usually associated with underlying diseases. In proximal fistulas, ulcer symptoms [6] are common, whereas biliary stones and cholangitis symptoms [5, 7] are predominant in peripapillary fistulas. Studies concerning peripapillary fistulas [3-5] reported biliary and pancreatic complaints. In our case, we performed an endoscopy because of bleeding, and a fistula was detected incidentally. Unlike the major duodenal papilla, the fistula orifice does not have a sphincter, so the intestinal flora may reflux into the biliary system. Li et al. [4] reported that cholangitis attacks become more frequent when the size of the fistula orifice is increased. In a third of patients, food particles were present in the biliary system if the fistula orifice was larger than 1 cm [4]. Our patient did not have symptoms of cholangitis on admission. His course after the sphincterotomy procedure was uneventful.

Conclusion

In summary, we reported the youngest case of CDF resulting from a duodenal ulcer that was managed by endoscopic sphincterotomy. Because of high suspicion, radiologic procedures were followed for the definitive diagnosis, although the abdominal X-ray was normal. Barium swallow series and MRCP showed fistula tract. Finally, ERCP provided a definite diagnosis. Endoscopic retrograde cholangiopancreatography is a useful diagnostic procedure for CDF.

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Journal of Surgery and Medicine

A novel percutaneous intrafocal reduction technique for brachialis penetrating irreducible type 4 supracondylar humerus fracture

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Abstract

Type 4 supracondylar fractures are challenging to treat. Closed reduction may become impossible due to brachialis muscle penetration and devastating results like a neurovascular injury that may occur during recurrent manipulations. We here report an intra-focal percutaneous reduction technique for maintaining closed reduction. An extensively posterior displaced type 4 supracondylar fracture with a dimple at the antecubital fossa and an extensive ecchymosis is presented. During surgery, we could not obtain closed reduction with the milking maneuver. We inserted an intrafocal K-Wire from the posterior side into the fracture site. With the levering of the wire, the dimple disappeared, after which we maintained the anatomical reduction and fixed the fracture with two lateral K-wires. Neither complication nor residual deformity was observed during postoperative follow-up. To show the exact long-term effects and the safety of this procedure, we need more fractures with brachialis penetration operated on by the described technique.

Keywords: Brachialis penetration, Supracondylar, Humeral fracture, Closed reduction, Intrafocal reduction

Introduction

Multidirectional unstable supracondylar fractures are challenging for the treating orthopedic surgeons. Especially displacement through the brachialis muscle makes the treatment even harder [1]. Penetration of the muscle has a high incidence of neurovascular injury. The traditional technique to overcome the penetration is the milking maneuver. If this is not successful, open reduction with an anterior approach is considered to visualize the integrity of neurovascular structures and obtain anatomical reduction [2]. Type 4 supracondylar fractures are associated with longer surgical times, utilization of medial pin and increased levels of technical difficulty [3]. We here report a technical report to achieve closed reduction with minimal invasion to soft tissues.

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Informed Consent
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Case presentation

A five-year-old female patient was admitted to our Emergency Department by her parents after falling from a bicycle. Physical examination showed a gross deformity and ecchymosis at the antecubital fossa with a dimple in the skin. Due to brachialis muscle penetration, she had numbness in first and second digits. We applied an arm cast before any reduction and obtained roentgenograms (Figure 1). We decided on an urgent surgical intervention due to excess displacement and likelihood of neurovascular compromise. In the operation room, we attempted a gentle milking maneuver to obtain closed reduction but failed to pull the proximal diaphyseal fragment out from the brachialis muscle. Then we inserted a 2.00 mm Kirschner wire from the posterior side inside the triceps muscle towards the proximal fragment, directly into the fracture site. We attempted a leverage maneuver to overcome the penetration. As the dimple disappeared, we achieved an anatomical reduction and fixated the fracture with two lateral Kirschner wires in the traditional Jones position. The reduction and fixation were confirmed by the fluoroscopy (Figure 2). We applied a long arm cast for covering the fixation. The total surgery time was 10 minutes. The patient was discharged one day later as the swelling resolved and followed up postoperatively. Union was achieved in the 3rd week, at which point we took off the cast. The patient was started on gentle elbow range of motion exercises. In the fourth week, we removed the wires at the office then initiated stretching exercises. No residual deformity was seen postoperatively (Figure 3). The patient and her parents were content with the healing process. Informed consent was obtained from the patient's parents for the publication of this case report.

Figure 1: Preoperative clinical image of Pucker Sign and X-ray that demonstrates severely displaced type 4 supracondylar humerus fracture

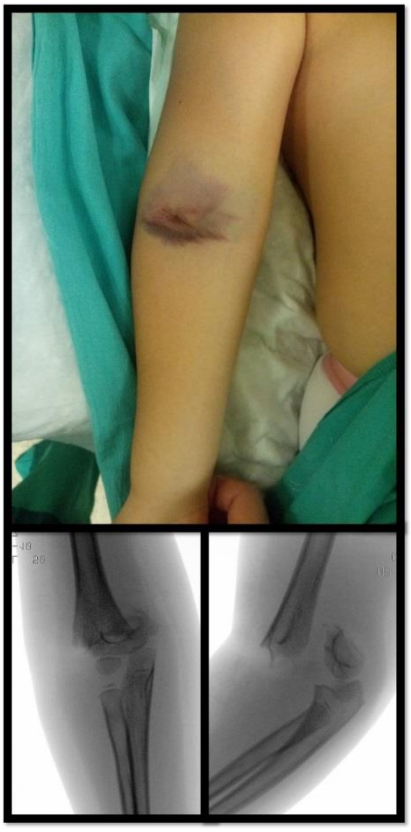


Figure 2: Peroperative x-rays, The application of the intrafocal pinning and fixation with 2 lateral K-Wires.

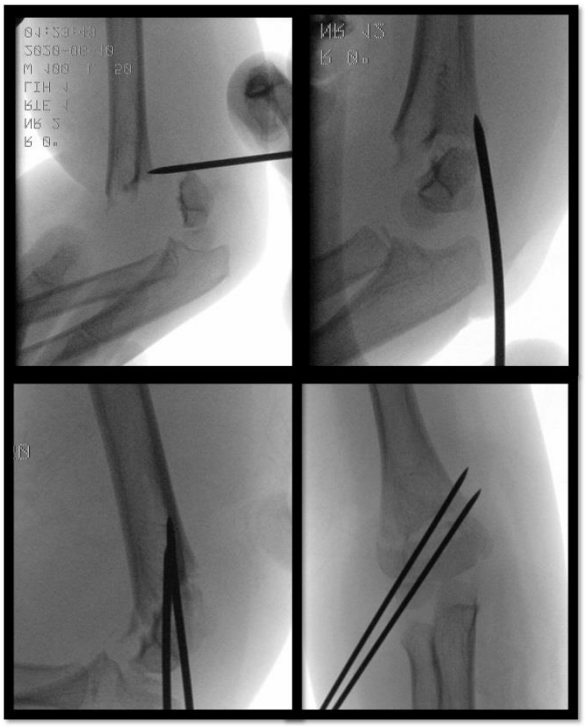
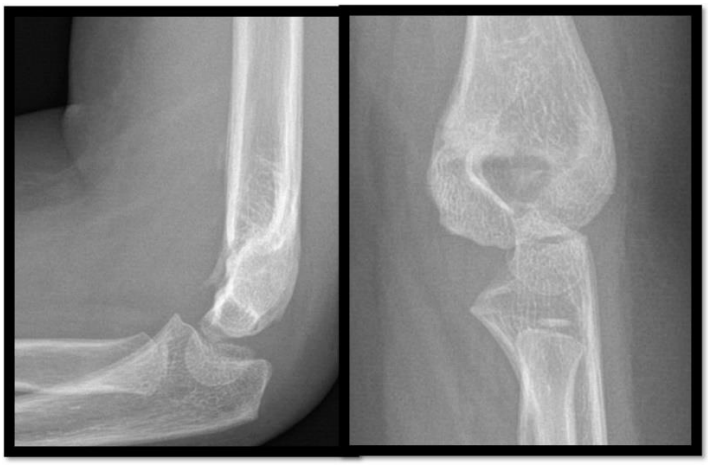


Figure 3: Postoperative late (6th week) X-ray



Discussion

Type 4 supracondylar fractures are challenging to treat, and they are associated with a longer operative time, and a higher likelihood of open reduction [4]. Joystick maneuver is the generally preferred technique for reduction of the distal fragment [1, 2, 5]. With this technique, if lateral views are obtained by rotating the C-arm (instead of rotating the arm), the loss of reduction can be avoided [1, 5]. Silva et al. have described similar results with the same technique by rotating the arm with less effort [2]. When the brachialis muscle is penetrated, the proximal fragment may become entrapped in the antecubital fossa. There is also a high incidence of brachial artery and median nerve injury due to entrapping [6]. The well-known traditional technique, the "Milking maneuver," was described by Peters et al [3]. They attempted the technique in eight patients and achieved successful closed reduction in all without any complications. Archibeck et al. [7] used this method in 16 patients but they could not obtain closed reduction in one patient. Closed reduction may become impossible due to the penetration and devastating results may occur during recurrent

manipulations. It is not recommended to attempt manipulations more than twice [6]. Open reduction with the anterior approach is utilized to get rid of the interposing brachialis muscle directly and to confirm the continuity of neurovascular structures if closed reduction could not achieved [8].

There are different suggestions in the current literature regarding the number and placement of wires applied after closed reduction. Crossed pin constructs had shown superior fracture stability than the divergent lateral pin fixation in biomechanical studies. However, there was no difference between these techniques in terms of loss of fracture reduction. Guven et al. [9] retrospectively evaluated pediatric lateral condylar fractures with divergent and parallel pins. They concluded that there was no difference in the radiologic results between these methods. We tend to perform divergent Kirschner wires, as in our case, the reduction was secured by two divergent wires with less than 60-degree angles to each other.

The ratio of closed reduction was very low in the previous reports when pucker sign (buttonholing of proximal fragment through brachialis muscle) was present [2, 4, 5]. With our described technique, we could still obtain the closed reduction and reduce the need for the open reduction to avoid complications even if the milking maneuver was not successful. We need more patients with pucker sign to document the safety and efficacy of this method.

Conclusion

The described technique may become a primary alternative to the milking maneuver to obtain closed reduction of pediatric supracondylar humerus fractures and reduce the open reduction rates as well as complications due to the open approach.

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Approach to paracetamol intoxication in intensive care: 2 pregnant cases

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Abstract

Acetaminophen (paracetamol) is a commonly used drug during pregnancy and is considered safe. However, it is among the most frequent agents of which overdoses are reported during pregnancy. The most important result of overdose use is hepatotoxicity, which can cause death. We herein present our approach to two pregnant cases we followed up in the intensive care unit due to acetaminophen intoxication.

Keywords: Acetaminophen, Pregnancy, Intoxication, Unit care

Introduction

N-acetyl-para-aminophenol (paracetamol) was discovered in 1889 and entered clinical use in 1955 [1, 2]. Paracetamol is an active metabolite of phenacetin and is used for its analgesic and antipyretic effects [3]. It is among the most used drugs in pregnancy and generally considered safe [4]. However, its overdose is commonly reported during pregnancy [5]. Hepatotoxicity is the most important consequence of paracetamol overdose [7], which may also have renal effects, albeit less frequently [8]. We herein present our clinical approach to two pregnant patients who were followed up in the intensive care unit due to paracetamol intoxication.

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Case presentation

Case 1

A 23-year-old pregnant patient was admitted to the emergency department after ingestion of 30 tablets of paracetamol (500mg.tb^{-1}), 7 drugs containing iron and folic acid, 24 drugs containing ibuprofen, and 21 drugs containing cyproterone acetate and ethinylestradiol 8 hours ago. On admission to the emergency department, the patient was conscious with a Glasgow coma scale (GCS) of 15 and her vitals were stable. Gastric lavage and activated charcoal were not recommended for the patient who was consulted with the poison counseling hotline. The consultation of the obstetrician was requested due to the pregnancy of the patient and fetal vitality was detected. The patient, who was hospitalized to the intensive care unit for close follow-up, was conscious at the time of admission with stable vital findings. N-Acetyl Cysteine (NAC) treatment was initiated. Daily laboratory values and fetal heart rate were followed and recommendations of the obstetrician were obtained. After 5 days of intensive care follow-up, psychiatry recommendations were received, and she was transferred to the ward uneventfully.

Case 2

An 18-year-old pregnant patient was admitted to the emergency department after ingestion of 20 tablets containing paracetamol. She was conscious with a GCS score of 15 and her vitals were stable. After consultation with the poisoning hotline, gastric lavage and activated charcoal were administered. The consultation of the obstetrician was requested due to the pregnancy of the patient and fetal vitality was detected. The patient, who was taken to intensive care for close follow-up, was conscious at the time of admission with a GCS of 15 and stable vitals. NAC treatment was administered. The suggestions of the obstetrician were obtained by following the daily laboratory values and fetal heart rate. After 3 days of intensive care follow-up, she was transferred to the ward with the recommendations of the psychiatrist uneventfully.

Discussion

Paracetamol is the most common drug that is overdosed during pregnancy [5]. The vast majority of cases of paracetamol toxicity reported during pregnancy involve a large amount of use at one time [9].

N-acetyl-p-benzoquinonimine (NAB), the toxic metabolite of paracetamol, is responsible for the liver toxicity of paracetamol overdose.

N-Acetyl Cysteine (NAC) is an antidote to acetaminophen poisoning. It has been reported that NAC treatment administered in the first eight hours following acute paracetamol intake prevents the development of this liver toxicity to a great extent [6, 7, 10, 11]. NAC, which crosses the placenta, adheres to toxic metabolites formed in both the mother and the fetus and reduces toxicity, can be safely administered to pregnant women [11].

A 17-year-old, 21 weeks pregnant patient used 25 g of paracetamol in two doses of 10 and 15 g 18 and 8 hours before hospitalization, and hepatotoxicity developed. However, a normal pregnancy was achieved with NAC treatment [12]. Another 24-year-old, 27-28 weeks pregnant case used 29 g of paracetamol in less than 24 hours, after which hepatotoxicity and fetal death occurred. However, it has been reported that maternal recovery occurs with NAC treatment [13]. NAC treatment was started immediately in both of our pregnant cases and hepatotoxicity did not occur.

Hepatotoxicity developed in a case in which repeated use of paracetamol in supratherapeutic amounts during pregnancy was reported and subsequently occurred with liver transplantation. Intrauterine fetal death occurred 2 weeks after the operation [14]. This case shows that repeated supratherapeutic intake of paracetamol also has serious morbidity potential.

In order for paracetamol to cause toxicity, the amount of acute overdose should be 150 mg/kg^{-1} (approximately 7.5 g in adults) within 24 hours [11]. However, it should be taken into account that the pharmacokinetics and pharmacodynamics of drugs differ from other patients due to physiological changes in pregnant women [15].

Clinical findings in paracetamol poisoning can be examined in 4 stages:

Stage 1 (30 min-24 hours): Nausea, vomiting, pallor, sweating, lethargy, weakness

Stage 2 (24-72 hours): Increase begins in liver aminotransferase enzymes [16]. Right upper quadrant pain and hepatomegaly can be seen. Increase in prothrombin time (PT) and total bilirubin, oliguria and renal dysfunction can be seen.

Stage 3 (72-96 hours): In addition to the return of clinical symptoms seen in stage 1, signs of jaundice, confusion, hepatic encephalopathy can be seen. Significant increase in liver enzymes and bleeding diathesis may develop. Acute kidney failure and pancreatitis can be seen.

Stage 4 (4 days-2 weeks): Recovery of hepatotoxicity or multiple organ failure (sometimes fatal) may develop [11, 17]. Clinical and laboratory deterioration was not observed in both pregnant patients we followed up, and their fetal vitality continued.

The treatment in paracetamol intoxication includes supportive therapy to prevent the absorption of the drug, antidote therapy and increasing the elimination of the drug. Gastric lavage can be performed to those who are admitted within the first 2 hours of taking the drug and activated charcoal should be administered to those who are admitted in the first 4 hours [18].

NAC, the antidote of paracetamol, can be administered intravenously or orally and is equally effective. Intravenously, 150 mg.kg^{-1} NAC is administered in 200 ml of 5% dextrose, with a 15 minute-loading dose. Subsequently, 50 mg.kg^{-1} NAC in 500 ml 5% dextrose is administered for up to 4 hours, and then 100 mg.kg^{-1} NAC in 1000 ml 5% dextrose is given in 16 hours. The oral loading dose is 140 mg.kg^{-1}. Following this dose, 17 additional doses are administered every 4 hours (70 mg.kg^{-1}) [11].

Anaphylactoid reactions, nausea and vomiting are the reported side effects of NAC treatment [2, 11, 19, 20]. A study conducted in Australia recommends one infusion dose instead of others for simple use [21]. We administered 150mg/kg loading dose of intravenous NAC treatment in 1 hour to two patients. There were no side effects due to NAC in our patients.

Conclusion

NAC treatment is considered safe in the treatment of paracetamol poisoning, which is common in pregnant women. However, large-scale studies are required to support this result.

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A rare pathology of syncope: A dilemma for hypertrophic cardiomyopathy or right atrial huge thrombosis

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Abstract

The complications associated with central venous catheters for hemodialysis access are well known. A rare complication is the development of right-sided intracardiac thrombus, which typically occurs in the right atrium. The location of the permanent catheter tip is associated with the development of thrombi. In this case report, we describe a patient with hypertrophic cardiomyopathy diagnosed with chronic kidney failure 2 years before contrast examination. The patient presented syncope during his last routine hemodialysis, and echocardiography imaging showed a hyperechogenic mass at the tip of the catheter.

Keywords: Syncope, Hypertrophic cardiomyopathy, Thrombus

Introduction

The complications associated with central venous catheters (CVCs) for hemodialysis access are well known. A rare complication is the development of right-sided intracardiac thrombus, especially in the right atrium [1]. The location of the permanent catheter tip is associated with the development of thrombi. According to Hickman et al. [2], the optimal location for the catheter tip is at the junction of the superior vena cava and right atrium but not within the atrium itself.

Catheter-related right atrial thrombus (CRAT) is often asymptomatic, and hence the true incidence is unknown, though it has been reported as anywhere from 5.4% to 46.2% [3]. CRAT is a rare complication of dialysis catheter placement that can lead to pulmonary thromboembolism, bacteremia, endocarditis, tricuspid regurgitation, right heart failure, or cardiac arrest if left untreated.

In this case report, we present a patient who presented to the hospital with syncope during hemodialysis and was determined to have a massive thrombus in the right atrium.

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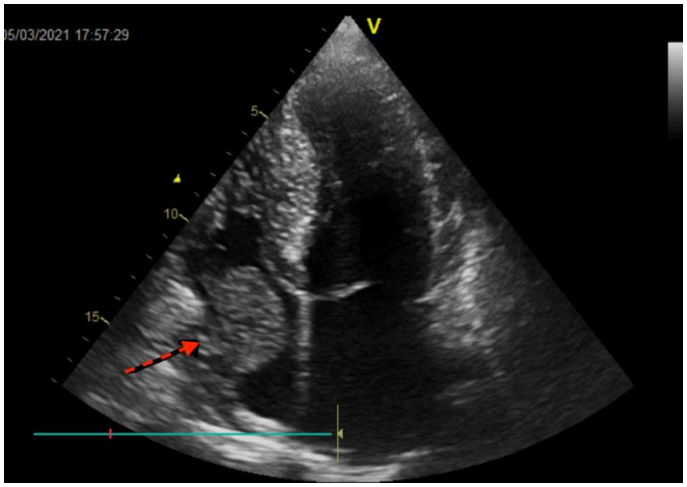
Case presentation

A 48-year-old male follow-up patient with hypertrophic cardiomyopathy (HCM) was diagnosed with chronic kidney failure 2 years after contrast examination. The patient presented with syncope that occurred during his last routine hemodialysis. The patient experienced recurrent fever over the past year and received antibiotics and anticoagulant medication. Echocardiography imaging showed a 30 × 17 mm hyperechogenic mass at the tip of the catheter. The patient's medical history included two episodes of cardiac arrest due to hyperkalemia in the past year. Before admission to our clinic, the patient's central venous catheter was removed at the nephrology department after the last hemodialysis.

The patient's complaints consisted of a 2 month history of weakness and palpitations induced by minimal effort and dizziness after standing up. Physical examination displayed no pathological signs except a 3/6 systolic murmur at the tricuspid auscultation site. Echocardiography imaging revealed left ventricular hypertrophy and a 40 × 35 mm well-circumscribed pedicled hyperechogenic mass at the right atrium attached to the inferior vena cava orifice, which advances from the tricuspid valve into the right ventricle during diastole and occludes the tricuspid annulus (Figure 1). The image showed tricuspid regurgitation of moderate severity induced by the mass.

The patient was admitted to the intensive care unit and put under hemodynamic monitoring. Following further evaluation, the heart team chose surgical thrombectomy as the initial method of approach. The patient later refused treatment and was discharged. We believe that our patient's presyncope and syncope attacks developed due to the relative decrease in right atrium size secondary to hypovolemia, especially following hemodialysis, which led to decreased right atrium and right ventricle filling and a rapid reduction in cardiac output. Due to the large size of the mass, lytic therapy was not considered applicable as the mass could detach during treatment and completely obstruct the tricuspid annulus or the right ventricular outlet, potentially leading to death. The patient's consent was obtained for the clinical presentation.

Figure 1. Echocardiography imaging revealed left ventricular hypertrophy and a 40 × 35 mm well-circumscribed pedicled hyperechogenic mass at the right atrium.



Discussion

The complications associated with central venous catheters are divided into two categories: infectious and non-infectious. Thrombi formation is the most common non-infectious complication. Echocardiographic documentation of right heart thrombi has poor prognostic implications. Pulmonary embolism occurs in 67% of cases, and the early mortality rate is 42% in such patients [4]. There are two major types of thrombi. Type A thrombi are large, mobile and serpiginous; they usually originate outside the heart within the venous structures and are quite lethal. Type B are laminated thrombi related to blood stasis in dilated dysfunctional right heart structures; they are associated with a very low mortality rate [5]. The optimal management of patients with catheter-related atrial thrombi is still uncertain.

Reported treatment options for catheter-induced thrombosis include removal of the catheter, very-low-dose-warfarin (1 mg daily, in a mixed oncological population) [6], fibrinolytic therapy [7], low-molecular-weight heparin [8], observation, catheter-directed thrombolysis, percutaneous retrieval of thrombi with basket versus vacuum-assisted thrombectomy [4], and surgical thrombectomy. Surgery should be considered in the beginning if the thrombus is infected [9]. Given the symptoms and the size of the thrombi, the patient was thought to be at high risk of embolization and tricuspid valve obstruction with anticoagulant medication alone. Therefore, surgical thrombectomy was preferred by the heart team.

Conclusion

In hemodialysis patients, especially those with a central venous catheter who experience presyncope-syncope attacks during hemodialysis, clinicians should consider the possibility of a massive thrombus in the right atrium or catheter tip.

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A complex case of retropharyngeal and mediastinal abscess during the Covid-19 pandemic: Lemierre's syndrome

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

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Abstract

Lemierre’s syndrome, which is commonly observed in healthy adolescents and young adults, is characterized by septic thrombophlebitis of the internal jugular vein and is usually observed after an oropharyngeal infection. At the time of the pandemic, as a result of so many patients COVID-19, similar symptoms were initially diagnosed as a possible coronavirus case and followed up with a possible diagnosis of COVID-19 before being consulted. We present the case of a 23-year-old male patient, who was referred to our clinic with complaints of fever, sore throat, dysphagia, shortness of breath, and chest pain. A retropharyngeal and mediastinal abscess occurred after these symptoms were successfully treated with surgical and medical interventions. The patient was initially considered a potential case of COVID-19 and followed as such. COVID-19 was then excluded, and the patient was reported to have an abscess extending from the retropharyngeal area to the mediastinum. We aim to present the diagnosis and treatment of Lemierre’s syndrome based on a literature review.

Keywords: Lemierre’s syndrome, Internal jugular vein, Retropharyngeal abscess, COVID-19

Introduction

In the early 21st century, a new member of the human RNA coronavirus affecting the entire world was identified in Wuhan, China. International committees referred to it as severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) [1]. The most common COVID-19 symptoms are fever, cough, fatigue, shortness of breath, myalgia, arthralgia, dysphagia headache, sore throat, and loss of smell and taste [2]. Lemierre’s syndrome (LS) is a clinical presentation of human necrobacillosis or postanginal sepsis that develops after an acute anaerobic oropharyngeal infection, which is a rare condition with a potentially fatal course. Fusobacterium necrophorum, an obligate anaerobe, non-spore-forming and gram-negative bacillus, can cause severe infections [3, 4]. In its primary stage, this infection is characterized by persistent fever and widespread metastatic abscesses that originate from the head and neck of healthy and young adults (15–30 years old) [5]. In this study, we present the case of LS in a young adult patient with retropharyngeal and mediastinal abscess who initially presented symptoms of sore throat, dysphagia, shortness of breath, chest pain and persistent fever. The diagnosis was made during an early stage of COVID-19 in Turkey. The clinical results included sepsis, septic thrombophlebitis in the internal jugular vein (IJV) and pericardial abscess. Thus, we reviewed the clinical features, treatment, and complications associated with LS.

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Case presentation

In April 2020, a dark-skinned 23-year-old male of Asian origin and no specific occupation was admitted to our hospital's pulmonology clinic with complaints of shortness of breath, fever, sore throat, and chest pain. There was poor oral and dental hygiene and a smoking habit. He had no systemic disease. Because of a persistent fever on the first day of his follow-up and suspected COVID-19, a nasopharyngeal and oropharyngeal swab sample was obtained. SARS-CoV-2 was determined by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) and SARS-CoV-2 IgG/IgM antibody tests were conducted.

The patient was provided detailed information about the study and an informed consent form was obtained. PCR and antibody results yielded negative results. Thorax computed tomography (CT) showed ground-glass appearance and focal consolidation zones in both lungs as well as minimal pericardial effusion. Because of a recent history of dental infection, the cardiology department verified the patient for infective endocarditis and excluded it. Despite the piperacillin/tazobactam + moxifloxacin treatment, the fever did not decrease, and there was no bacterial growth in the blood, urine, stool, or sputum cultures; therefore, the treatment was changed with meropenem + ciprofloxacin. During follow-up, the patient developed thrombocytosis (platelet count >820 x 10^3/µL) and no atypical cells were observed in the peripheral smear examination. Brucella serology and sputum acid-fast bacilli smear tested negative.

Because of the accompanying sore throat symptoms, the presence of persistent fever and constant high C-reactive protein, a neck ultrasonography (USG) was performed on the 14th day of the treatment, thus showing echogenic appearances that suggested diffuse air in the posterior proximity of the thyroid gland and a suspicious area of ~7 × 6 cm with indistinct borders. Subsequently, contrast-enhanced neck and thorax CT scans were performed, revealing fluid collection and free air density in the retropharyngeal space. The abscess started from the retropharyngeal region and extended from the posterior of the trachea to the thoracic inlet and carina (Figure 1). It was a retropharyngeal abscess consistent with fluid loculation with dense contents extending from the mediastinum, compressing the esophagus from the posterior, with local air foci. There was thrombus in the left IJV and thickening around the vessel, consistent with thrombophlebitis (Figure 2). Fluid loculations with similar dense content and peripheral contrast enhancement were observed in the arcus aorta and anterior areas of the heart. There was pericardial and bilateral pleural effusion measuring 3 cm in its widest part. Consolidations were then observed in the medial segment of the right lung middle lobe and in the left lung inferior lingula (Figure 3).

The patient, referred to us for consultation, was then taken in for an emergency operation simultaneously with chest–cardiovascular surgery. Abscesses in the mediastinum and pericardial regions were drained with median sternotomy. Moreover, there was multioculated pus in the anterior mediastinum; moreover, abscess and necrotic foci in the upper lobe of the right lung were removed. Granulated necrotic tissues around the pericardium were excised, and specimens were collected. Bilateral pleural effusion was drained. A total of three tube thoracostomies were applied; one each to the right and left thorax and the mediastinum. Subsequently, neck exploration and tracheotomy surgeries were performed in the neck region. An abscess focus was located in the posterior part of the trachea, medial to the carotid; it was highly purulent and a penrose drain was placed in the surgical area. There was no growth in abscess cultures obtained from either the mediastinum or neck during surgery.

Figures 1: In the axial (a) and sagittal (b) sections of the neck, an abscess cavity is seen in the retropharyngeal region, enhanced from the periphery and air densities in the superior.

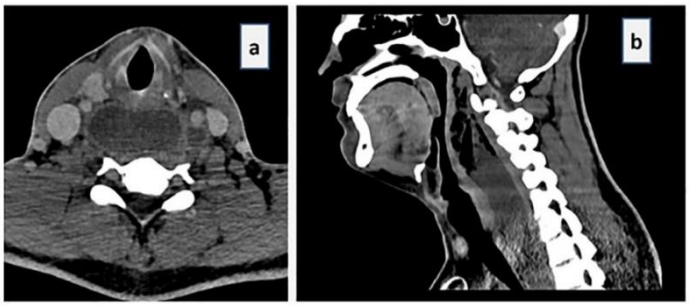


Figure 2: In consecutive axial sections, the left internal jugular vein is not filled with contrast and thickening is seen in the vessel wall (red arrow). Findings are consistent with jugular vein thrombophlebitis.

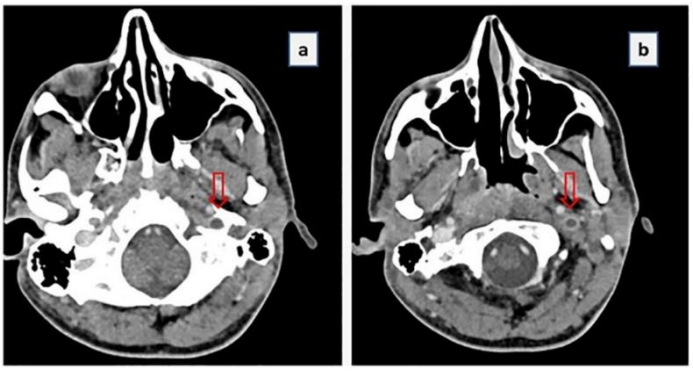
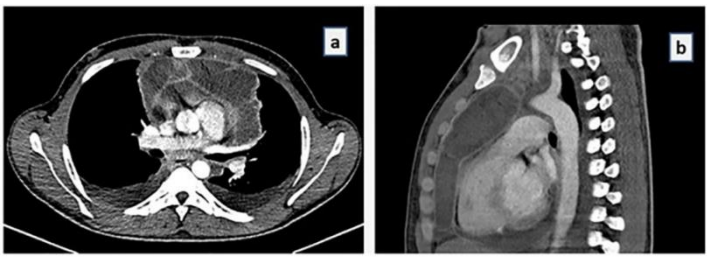
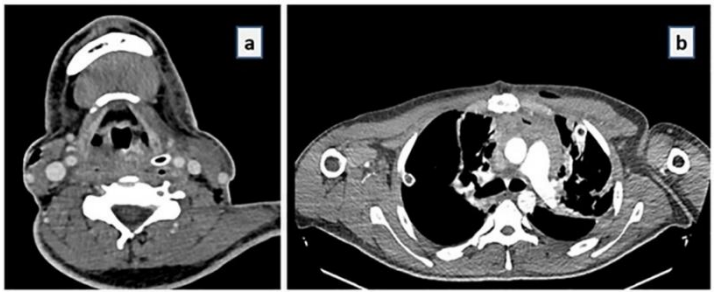


Figure 3: In the thoracic sections in the axial plane (a), a fluid is observed in the prevascular area in the multiloculated character, which is enhanced from the periphery, and pleural fluid is observed in both hemithoraces. In sagittal sections (b), a loculated fluid cavity is observed, which is compatible with an abscess enhancing from its periphery, which extends from the superior mediastinum to the anterior mediastinum.



On the first postoperative day, control contrast-enhanced thorax/neck CT showed that abscesses in both the neck and mediastinum were completely drained (Figure 4). The pathology was reported as chronic active pericarditis and debridement material in the mediastinum as abscess formation. The patient was followed up in the intensive care unit for ten days with meropenem + tigecycline + enoxaparin sodium 6000 anti-Xa IU/0.6 ml treatment, and followed for eight days in patient service. On improvement of the clinical picture, the patient was discharged with oral dual antibiotherapy and anticoagulant treatment with tracheostomy stoma closed. Antibiotherapy was continued for six weeks in total, and no additional problems developed in the four-month follow-up of the patient.

Figure 4: Postoperative changes in axial neck (a) and axial thorax (b) sections and total regression of the mentioned loculated fluid collections.



Discussion

LS, a rare clinical condition, occurs after an oropharyngeal infection in adolescents and young adults between the ages of 10 and 35 and causes potentially fatal complications, such as septic thrombophlebitis in IJV. To prevent this life-threatening situation, action must be taken very quickly [6-7].

The diagnosis of LS includes anamnesis, laboratory tests, blood cultures, and neck CT scan. Although F. necrophorum is the most common pathogen isolated in the blood cultures of patients, Streptococcus, Bacteroides, and Lactobacillus species play a role in the LS pathogenesis, which is determined by selective culture analysis. The treatment is initially medical, after which antibiotherapy is provided. Indications for surgical intervention are a failure of medical treatment, as well as abscesses and septic embolisms in the neck and other areas. Surgical options include the drainage of abscesses and IJV ligation and resection [8].

Although some studies oppose anticoagulant therapy, additional studies recommend it to prevent the spread of metastatic embolism and the existing thrombus in the LS clinic [9, 10]. Because our case had initial findings of COVID-19 disease, coinciding with the COVID-19 pandemic, this patient was followed up with a pre-diagnosis of COVID-19 in the clinic. However, because the clinical situation of the patient did not improve, despite the broad spectrum of antibiotherapy treatment, imaging techniques were used on the neck 14 days later, thus revealing deep neck infection and mediastinal abscess. The antibiotherapy treatment given at the beginning of the treatment did not provide a complete cure. Although it seemed to slow down the patient's clinical course, it did cause thrombophlebitis in the left IJV and an abscess extending to the mediastinum and pericardium in terms of radiological results.

The reason for the absence of any pathogen growth in the blood cultures of this case and from the abscess samples obtained during surgery could be attributed to the lack of selective culture media for F. necrophorum in our laboratory. However, the onset of complaints after dental infection in the anamnesis of the patient, the development of neck and medistinal abscesses in the follow-up, and the presence of a thrombus in the left IJV suggest the prevalence of LS.

Conclusions

- Despite delayed diagnosis due to COVID-19-like symptomatology and potentially fatal complications secondary to infection, timely acute interventions have saved lives.

- If clinical improvement is not observed despite medical treatment, the initial diagnoses should be reviewed.

- We recommend advanced imaging (USG, CT) for a definitive diagnosis without delay in patients with complaints, such as fever, sore throat, and dysphagia, when no obvious findings are seen in ear, nose, and throat examinations and no improvements are observed despite empirical treatments.

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