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Clinical and functional outcomes of pediatric elbow dislocations: Level 1 tertiary trauma center experience

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The study was approved by the Health Science University Istanbul Mehmet Akif Ersoy Chest an Cardiovascular Surgery Training and Research Hospital ethic committee (approval number 2020-084).
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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Traumatic elbow dislocations have been reported as uncommon in pediatric population. Because of low frequency, there are not many studies on the subject in the literature. The aim of this study was to retrospectively evaluate the radiological and functional results of pediatric patients treated for elbow dislocations in a level-1 tertiary trauma center and to compare the results of simple and fractured dislocations.

Methods: This is a retrospective cohort study of a single center experience diagnosed with pediatric elbow dislocations between 2015 and 2019. The cases were evaluated by dividing them into two groups as simple dislocations and fracture dislocations. Demographic features, injury mechanism, treatment, complications and Mayo elbow performance score (MEPS) were evaluated.

Results: Fifty-seven patients, (46 male/ 11 female), were included in the study, with a mean age of 11.1 (3-15) years. Mean follow up time was 27.2 (12-51) months. While 30 patients had fracture dislocations, 27 patients had simple dislocations. Of 30 patients with fracture dislocations, 19 were operated. Nonunion in the medial epicondyle in five patients, AVN (avascular necrosis) in radial head in two patients, heterotrophic ossification in one triceps, and recurrent dislocation in one patient were detected. According to MEPS, 42 (73%) of 57 patients were excellent, 12 (21%) good, one (2%) moderate, and two (4%) poor. According to MEPS, functional results of simple dislocations were found to be better than those of fracture-dislocations, and this result was statistically significant ($P<0.05$).

Conclusion: Elbow dislocations in children can be treated with good results if they are accurately diagnosed and if concentric stable reduction of the elbow as well as stable osteosynthesis of displaced fractures can be achieved. Simple dislocations are easier to manage and functional results are better, whereas the treatment of fractured dislocations is more complex and complications are more common in follow-up.

Keywords: Pediatric elbow dislocation, Simple dislocation, Fracture dislocation, Complication, MEPS

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Introduction

Traumatic elbow dislocations have been reported as uncommon in skeletally immature patients, with an incidence of 3–6% of all elbow injuries [1, 2]. Pediatric elbow dislocations are usually observed in the second decade when the epiphysis is beginning to close [1, 3].

Elbow dislocations are classified according to displacement of the distal structures, with the most prevalent displacement being posterior or posterolateral. These injuries are often in the form of complex injuries that may be associated with fractures or avulsions, with medial epicondyle avulsions having been reported as the most common concomitant fracture [4]. Coronoid process, radial head, olecranon, trochlea and lateral condyle fractures are observed less frequently [3, 5, 6]. Due to the complex nature of the elbow and to prevent future complications, early diagnosis and effective treatment are required. Therefore, it is extremely important to diagnose and treat pediatric elbow injuries correctly at the time of the initial injury to optimize treatment outcomes. Associated fractures are likely to occur when the physes are still open; when they are closed, collateral ligaments might be ruptured [1]. Pediatric elbow dislocations can be divided into fracture dislocations and simple dislocations without fracture. Although simple dislocation of the elbow in children is usually considered to be a benign injury, which can be treated conservatively with only closed reduction without any sequelae during follow-up, surgical treatment is an option for patients with concomitant fractures. Only a few studies described this injury in children [3-7].

The aim of this study was to retrospectively evaluate the radiological and functional results of pediatric patients treated for elbow dislocations in a level-1 tertiary trauma center.

Materials and methods

The medical records of pediatric patients with elbow trauma who were admitted to the Emergency Department between January 2015 and January 2019 were reviewed. The study inclusion criteria were patient age less than 15 years at the time of dislocation, isolated elbow dislocation or fracture-dislocation, adequate follow-up of at least 12 months and written informed consent provided by the parents for the use of clinical data. Patients with pathological fracture-dislocation, previous surgery of the relevant joint, inappropriate radiological evaluations or missing follow-up data were excluded from the study.

Medical charts were reviewed for the following demographic and presenting variables: trauma mechanism (fall, sports injury, fall from height, or motor vehicle accident) and associated neural and / or vascular injuries. Charts were also examined for length of immobilization (cast) and time from injury to final follow-up visit. Outcomes were assessed with range of motion (ROM) parameters at the final follow-up examination, and the functional outcome was measured using the Mayo Elbow Performance Score (MEPS) [7]. Complications were also recorded (Table 1).

Table 1: Fracture types and complications of the patients

	n	Complications	n
Simple dislocation	27	Valgus deformity	2
		Recurrent dislocation	1
Fracture dislocation			
Medial epicondyle	20	Medial epicondyle nonunion	5
Radius neck	3	Radius head avn	2
Olecranon	2	Heterotropic ossification	1
Medial condyle	1	Varus deformity	2
Lateral condyle	4	Valgus deformity	4
Total	57		17

Treatment protocol

For all dislocations, elbow anteroposterior / lateral radiographs were taken and all reductions were performed under sedation (propofol 1–1.5 mg/kg) in the emergency. Accompanying fractures were treated based on the amount of residual displacement of the fracture. Patients with medial epicondyle fractures with less than 8 mm of displacement after reduction and a negative valgus stress test were treated conservatively, while patients with displacement greater than 8 mm and a positive valgus stress test were treated surgically [8, 9]. Medial and lateral condyle fractures with displacement greater than 2 mm were treated with open reduction and internal fixation (ORIF). Kirschner wires (K-wires) (0.062-inch diameter) were used in all cases. Fracture fixation was performed with two K-wires. In olecranon fractures, patients with more than 2 mm of displacement were operated on using the tension band technique. In patients with radial neck fractures, the surgical procedure was performed as follows: if the reduction was successful after closed reduction, closed pinning was applied; if successful reduction was not achieved (radial neck angle >60°), ORIF was applied. One patient with a radial neck fracture with an angulation of less than 30° was followed up conservatively. Closed reduction and percutaneous pinning with K-wires (K-wire joystick technique) was applied to one patient with an angulation between 30° and 60°, and the open reduction internal fixation (ORIF) with K-wire method was used for two patients with an angulation of more than 60° [10].

Postoperative management

A long-arm splint was initially applied to patients with simple dislocations and fracture-dislocations which were treated conservatively. The splints are removed in two weeks in simple dislocation group and four weeks in the fracture-dislocation group. For operated cases, the K-wires were removed six weeks postoperatively. For olecranon fractures, the K-wires and tension band wires were removed under sedation in six months postoperatively.

Follow-up Assessments

At the final follow-up examinations of the patients, elbow flexion / extension and varus / valgus angle were measured using a goniometer by a physiotherapist who was double blind of the study design. The MEPS form was completed to evaluate elbow function [11]. The MEPS is based on an observer-derived assessment of a variety of clinical criteria (pain, motion, stability and function), which are scored in four subscales separately and then aggregated. The total MEPS score ranges from 5 to 100 points and is considered excellent when the total score is between 90 and 100 points, good between 75 and 89 points, fair between 60 and 74 points and poor below 60 points.

Statistical analysis

Data were analyzed using SPSS for Windows version 23.0 software (SPSS Inc., Chicago, IL, USA). Median with range was used to describe continuous data, whereas absolute count with percentage was used for categorical data. Univariate analysis was performed for demographic and clinical characteristics of patients to predict our two primary outcomes. Student's t-test, the chi-square test and Fisher's exact test were used as appropriate for individual variables. $P<0.05$ was considered statistically significant.

Results

Among 57 patients included in the study, 46 (81%) were male and 11 (19%) were female. The average age was 11.1 (3-15) years, and 42 patients were aged ≥10 years. Dislocation in left and right extremity was seen in 31 (54%) and 26 patients (46%), respectively. The mean follow-up period was 27.2 (12-51) months.

According to the injury mechanism, 46 were because of simple falls. There were four falls from height, four sports injuries and three traffic accidents. All patients in this study had posterior / posterolateral dislocation. As an additional orthopedic injury, distal radius fracture (opposite extremity) was detected in two patients, femur diaphysis fracture in one patient and tibial diaphysis fracture in one patient.

Twenty-seven patients (47%) had only a simple dislocation without an additional fracture (Figure 1), while other 30 patients had an additional fracture. 19 patients with a concomitant fracture were operated.

Figure 1: Simple posterior elbow dislocation

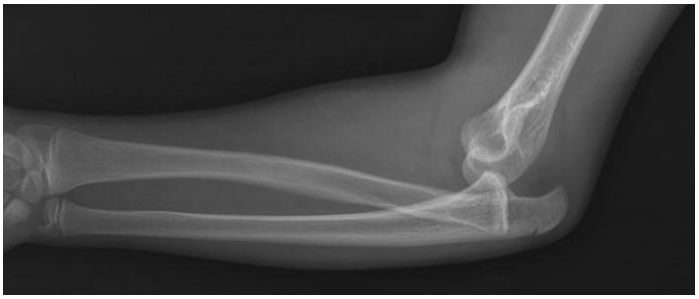
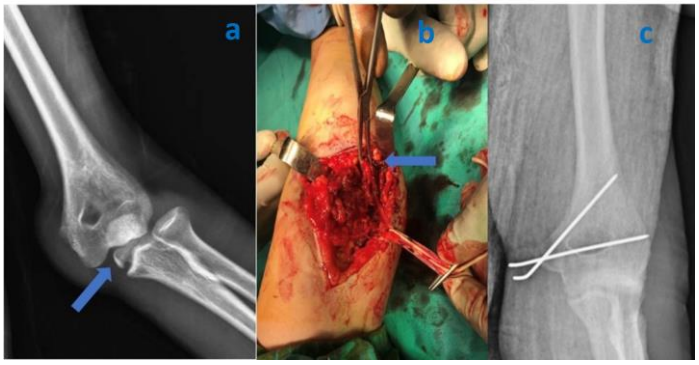


Figure 2: a. Preoperative X-ray of the incarcerated medial epicondyle. b. Intraoperative view of the incarcerated medial epicondyle after reduction. c. Postoperative X-ray of the incarcerated medial epicondyle.



As an early complication in the follow-up of the fracture-dislocation group, the pulse could not be palpated before reduction in two patients (dislocated medial epicondyle fracture), but circulation was improved after reduction. Three patients (posterolateral dislocation / medial epicondyle fracture) developed ulnar neuropraxia that recovered in 4–6 weeks without sequelae. Early complications were not detected in the simple dislocation group.

In five patients, fibrous nonunion was detected in the medial epicondyle, but there were no functional complaints. Medial epicondyle nonunion was observed in four conservatively followed patients and one patient underwent surgery.

Avascular necrosis developed in the radius head in two patients who underwent open surgery for radial neck fractures. No additional treatment was performed in these two patients, and the pronation loss was measured as 25º (range: 20º–30º). These patients were functionally good, although they were evaluated radiologically as having complications.

Six (four fracture-dislocations and two simple dislocations) patients had valgus deformity in the follow-up examinations. In these patients whose elbows had cubitus valgus deformities compared to the opposite elbow, the mean valgus angle was 7.8° (5°–10°) in the four fracture-dislocation patients and 7.5° (5°–10°) in the two simple dislocation patients

The MEPS score was fair or poor in three patients. The first patient, whose medial condyle fracture was planned to be followed up conservatively, ignored the routine follow-up procedures, and developed varus deformity (17.7º) with nonunion in the last follow-up. In the second patient operated due to dislocation / olecranon fracture, calcification was detected in the triceps muscle and cubitus varus deformity (22º) was identified, but no additional treatment was performed. The third patient, who was in the simple dislocation group, had more than 10 recurrent dislocations, and although surgery was recommended, the patient continued with physical therapy in another hospital.

The functional results of simple dislocations and fracture-dislocations were significantly different ($P<0.05$) (Table 2).

Table 2: Comparison of simple and fracture-dislocation

	Simple Dislocation	Fracture Dislocation	*P*-value
Age (year)	10.8(3.1)	11.3(2.9)	0.555
Follow-up (month)	37.8(8.5)	27.2(10.1)	0.001
Immobilization (week)	2(0)	3.76(0.5)	0.001
MAYO	95.1(10.6)	90(11.8)	0.046
Excellent	22	20	
Good	4	8	
Fair	0	1	
Poor	1	1	
ROM	138.7(2.9)	132.6(13.5)	0.023
Extension Loss	0.5(1.6)	4.6(10.4)	0.04

Discussion

Pediatric elbow dislocations are generally seen in the second decade of life. In a study by Murphy, the average age was reported to be 11 years old [7]. Most pediatric injuries are more common in males [12]. In the present study, the mean age was 11.1 years old, and the proportion of male was significantly higher than female. In the literature, it has been reported that 95% of the dislocations are posterior dislocations, of which 70% are the posterolateral type [5]. In the present study, all patients had posterior dislocations, and 40 (70.2%) were the posterolateral type. These results are consistent with the literature.

Elbow dislocations can be in the form of simple dislocations without a fracture, but they may also be seen with additional fractures. It has been reported that there are concomitant fractures with posterior elbow dislocations in more

than 50% of cases [13]. In the present study, additional fractures were seen in 53% of the patients. In the literature, the most common fracture concomitant with elbow dislocation has been reported to be the medial epicondyle at a rate of 60% [4, 6, 13]. Treatment of medial epicondyle fractures remains a matter of debate. Fracture with displacement <8 mm usually heals conservatively with plaster cast treatment [14]. According to Lieber, even minimally displaced fractures should be treated surgically to ensure the integrity, to prevent the elbow instability and to reduce the occurrence of valgus deformity [4]. In the present study, 20 medial epicondyle fractures were detected. While the partially healed fractures after elbow reduction were treated conservatively, seven patients were treated surgically. The current standard treatment for patients with more than 5 mm of displacement and positive valgus stress test is surgery [15]. In our department, medial epicondyle fractures with a displacement of more than 8 mm and a positive valgus stress test are routinely operated. Therefore, we may have encountered non-union in our four conservatively treated patients.

Incarceration of the intra-articular medial epicondyle is seen in 5–18% of medial epicondyle fractures and may cause irreducible dislocations [16]. In the present study, five of the 20 medial epicondyle fractures were of the incarcerated medial epicondyle type. Patrick stated that the ulnar nerve could be damaged with repetitive manipulations, and therefore fragments could not be removed by manipulation, so surgical removal was recommended [17]. In the present study, reduction was achieved after manipulation in one of the five incarcerated cases, while the other four patients were treated surgically and fixed without attempting a second reduction (Figure 2).

Fractures of the lateral condyle are the second most commonly associated injury following posterolateral elbow dislocation according to Lieber's series [4] and others [13], but some authors describe this injury as very rare [18, 19]. All displaced intra-articular fractures, such as fractures of the lateral condyle, with a gap of more than 2 mm of the articular surface require accurate reconstruction to prevent lack of extension as well as growth disturbances [6, 20]. Similarly, screw fixation allows early mobilization and also yields high fragment compression compared with K-wire fixation. In our department, these operations are performed with K-wires. Screws are not preferred because a second operation would be required to remove the screw.

Radial head and neck fractures may be seen with elbow dislocations. Although closed reduction and pinning are recommended in pediatric radius neck fractures, open reduction and pinning can be performed in cases that cannot be reduced as closed. Concomitant radius neck fractures cause proximal radioulnar synostosis or radial neck pseudoarthrosis, both of which severely limit elbow movements [1, 21]. Major risk factors are open reduction maneuver, severe trauma, subtotal periosteal disruption and complete dislocation of the radius head [22]. In the study by Lieber [4], three of the four cases were fixed using closed reduction with a K-wire, and one patient was operated on with open reduction. Pseudoarthrosis developed in one patient during follow-up, which was attributed to total dislocation, open surgery, inadequate reduction and early removal of the implant. In the present study, four radius neck fractures accompanied the dislocation. One of the patients was treated with closed reduction and K-wires, fixation was obtained with ORIF + K-wires in two patients, and one patient was followed up conservatively. Despite the union in the two patients who underwent open surgery, they developed avascular necrosis in the radius head. Although these two patients had pronation loss, they did not describe any problems in daily life.

Olecranon fractures usually occur in anterior dislocations in the form of avulsions. In a study by Rasool [5], five olecranon fractures were reported. In the current study, two patients had olecranon fractures, and surgical treatment was performed with the tension band method. In one patient in the current study who was operated on for an olecranon fracture, cubitus varus deformity developed with calcification in the triceps.

Medial condyle fractures occur as a result of high-energy trauma and therefore can be observed with other injuries around the elbow, especially elbow dislocation and radial head dislocation [2, 3]. Nonunions, particularly when left untreated, have been reported by different authors in 7.4–33.3% of patients [4, 5, 12]. The medial condyle fracture in the present study was followed conservatively due to the displacement being <2 mm, but nonunion and cubitus varus deformity developed due to the fact that the patient did not come to the outpatient clinic regularly and the plaster treatment was terminated by his family.

In a study by Sofu et al. [23] in which 12 patients with simple elbow dislocations were evaluated, ROM was 119.5 ± 17.8, and the mean MEPS value was 91.6. In the present study, patients with simple dislocation had higher ROM (138.7 ± 2.9) and MEPS values (95.1 ± 10).

Recurrent dislocation is rare in children and is caused by the capsule and ligament structures not healing sufficiently after traumatic dislocation [24, 25]. Only two recurrent dislocations have been reported as case reports [26, 27]. In recurrent dislocations in adults, hinged fixators are applied after soft tissue relaxation, but the results are unknown [28]. In one patient in the present study with no additional fracture, reduction was performed due to recurrent dislocation. This recurrent dislocation was thought to be due to ligamentous instability, and although surgical treatment was recommended, it was refused, and the patient continued treatment with physical therapy at another centre.

Early complications in dislocations are neural and vascular problems [5]. Vascular injuries are rare [29]. Vascular injuries can be intimal damage, thrombosis or direct injuries [24]. Rasool et al. reported that one brachial artery injury occurred, and vascular repair was performed [5]. In the present study, in two patients in the fracture-dislocation group, the pulse could not be palpated before reduction, but circulation returned to normal after reduction. Nerve injury is rare after elbow dislocations, although ulnar nerve injury is often seen in medial epicondyle fractures with dislocations [30]. There were three cases of ulnar nerve paraesthesia in the present study in the fracture-dislocation group, all of which fully recovered within four to six weeks.

Loss of elbow range of motion is the most commonly reported complication in elbow dislocations. Extension defects in particular are the most prominent sequelae of elbow dislocations.

In a series of pediatric elbow dislocations, Di Gennaro reported that 37% of the study group had extension loss [31]. In the follow-up of patients with pediatric elbow dislocations, Murphy found the mean flexion to be 126° ± 14°, and the average terminal extension loss was 5° ± 7°. No significant correlation was determined between age, gender, mechanism of injury, presence of a related fracture, type of fracture, need for open reduction and measurement of flexion or extension [7]. In the present study, there was no loss of extension in the simple dislocation patients, but there was 4.5° ± 12° loss of extension in the fracture-dislocation patients. There was a significant difference according to ROM between simple dislocations and fracture-dislocations, which is consistent with the findings in the literature.

For patients who developed valgus deformity of the elbow, like all other patients, the mechanism of trauma was falling on an open hand and valgus strain. Elbow valgus deformity was determined in an average of one year of follow-up. Cubitus valgus is the most frequently observed complication after elbow dislocation. It is more often seen in dislocations associated with other injuries and leads to growth disturbance around the elbow [32]. Since there is a natural valgus angle present in the elbow, cubitus valgus deformity can be cosmetically tolerated. Most cubitus valgus deformities are not clinically problematic. However, the increase in elbow carrying angle seems to be an independent factor of ulnar neuropathy that develops in the absence of trauma [33]. Our patients who developed valgus deformity had no complaints other than cosmetic appearance.

Different rates of functional results after elbow dislocations have been published. Murphy et al. [7] reported outcomes according to the MEPS as 72% excellent, 18% good, 9% moderate and only one patient with poor results. Lieber et al. [4] reported 100% excellent / good results in simple dislocations and 96% excellent / good results in fracture-dislocations. Rasool et al. [5] found 67% excellent / good and 30% moderate / poor results. In the present study, when the patients were evaluated radiologically, the complication rates seemed to be high, but since these complications did not cause functional limitations, the MEPS values were found to be high. The comparison of the current study with similar studies in the literature is given in table 3.

The limitations of the present study are its retrospective design, follow-up of some of the patients was less than two years, and there was incomplete evaluation of chondral and ligamentous injuries or coronoid avulsions since magnetic resonance imaging was not performed. The strength of the study is having more patients compared to similar studies. In addition, prospective studies to be performed on more patients are needed to reach more definite conclusions.

Table 3: Elbow fracture dislocations in children, literature review

	n	Associated fractures	n	Complications	n	Results% (excellent and good)
Murphy[7]	145	Medial epicondyle	80	A symptomatic heterotopic ossification	2	
		Lateral condyle	17	Ulnar neuritis	2	
		Olecranon	3	Subjective instability	1	90%
		Radial head/neck	12	Fracture nonunion fixation	3	
		Other upper extremity fracture	16	Instability reconstruction	4	
				Neural decompression	2	
				Infection	2	
				Compartment syndrome	1	
				Contracture release	3	
				Osteochondritis dissecans lesion	1	
Lieber [4]	56	Medial epicondyle	10	Ulnar nerve	3	48%
		Lateral condyle	5	Median nerve	1	
		Lateral epicondyle	1	Brachial artery injury	1	
		Radial neck	4	Cubitus recurvatum	2	
		Transcondylar fracture	1			
		Processus coronoideus	2			
		Collateral ligament (isolated)	3			
		Collateral ligament (and fracture)	7			
Carlioz [13]	58	Medial epicondyle	24	Pulse deficit	4	90%
		Olecranon	1	Ulnar nerve	2	
		Lateral flakes of bone	5	Osteochondral flap (ulna)	2	
		Coronoid	2	Radioulnar synostosis	2	
		Combined	2			
Present study	57	Medial epicondyle	20	Pulse deficit	2	94%
		Radius neck	3	Ulnar nerve	3	
		Olecranon	2	Medial epicondyle nonunion	5	
		Medial condyle	1	Heterotrophic ossification	1	
		Lateral condyle	4	Recurrent dislocation	1	
				Radius head avn	2	
				Medial condyle malunion	1	

Conclusion

Elbow dislocations are rare injuries. A dislocation of the elbow in a child may be associated with an unrecognized additional fracture. There should be a high index of suspicion, with good clinical examination and meticulous assessment of the radiographs and systematic examination of the medial (medial epicondyle, olecranon, coronoid, medial condyle) and lateral compartments (radial head, lateral condyle) for associated fractures or avulsions. Simple dislocations are easier to manage and functional results are better, whereas treatment is more complicated and complications may develop in patients with concomitant fractures. Elbow dislocations in children can be treated with good results if they are accurately diagnosed and when concentric stable reduction of the elbow as well as stable osteosynthesis of displaced fractures can be achieved. In addition, families should be informed about possible complications, and it should not be forgotten that patients may require effective physical therapy during follow-up.

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Does perioperative fluid management affect the development of postoperative complications in major gastrointestinal tract surgery? A retrospective cohort study

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The study was approved by the local Ethics Committee of Istanbul Kartal Dr. Lutfi Kirdar City Hospital (514/194/30-27.01.2021)
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Abstract

Background/Aim: In major abdominal surgeries, maintenance of electrolyte homeostasis and euvolemia is crucial. However there is still no consensus on the most effective intraoperative fluid regimen. Our primary aim in this study was to investigate the impact of colloid infusion given in addition to perioperative fluid replacement on the development of postoperative complications in patients undergoing major gastrointestinal tract surgery.

Methods: Patients who underwent major abdominal surgery in our hospital due to gastrointestinal tract malignancy between January 2015 and January 2020 were enrolled in this retrospective cohort study. We recorded data regarding the volume of perioperative fluid replacement, the amount of crystalloid and colloid administered, postoperative complications, length of hospital stay, frequency of follow-up in the intensive care unit and length of stay.

Results: A total of 326 patients, who underwent gastrointestinal tract surgery, were included in the study. Postoperative pulmonary complications (24.2%), wound infection (20.6%), and anastomotic leakage (3.1%) were the most-observed three complications in the study cohort. Among 163 patients who required postoperative ICU follow-up, 84 (25.7%) patients received colloid infusion, whereas 79 (24.2%) patients did not receive (P=0.181). However, the incidence of other complications in the group with a crystalloid intake of ≤2 L was found to be significantly higher compared to the group receiving >2 L of crystalloids (P=0.038).

Conclusion: We found no association between the administration of colloids along with crystalloid infusion and the incidence of postoperative complications. Besides there was no relation with the adverse effects in terms of the length of hospital stay and the frequency of admission to the intensive care unit.

Keywords: Crystalloid, Colloid, Surgery, Fluid replacement

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Introduction

Perioperative fluid management in major surgeries aims to optimize intravascular fluid balance to maintain adequate tissue perfusion. Fluids administered with this purpose directly impacts patient outcome [1]. Both the volume of fluids administered and the decision of using colloids or crystalloids have been topics of discussion for years [2]. Colloid fluids provide the continuity of oncotic pressure, providing a decrease in the total amount of perioperative fluid required [3]. Hydroxyethyl starch (HES) and gelatin solutions are the two colloid fluids easily accessible and most commonly used. These fluids are used for volume replacement in hemorrhagic surgeries to compensate the period up to blood transfusion. Modern starches are considered safe for use in surgery [4]. However, the use of colloids is not complication-free. Serious side effects such as acute kidney injury, bleeding, and death are reported following the use of HES [5, 6]. Similarly, gelatins are reported to have adverse effects on renal functions and coagulation parameters [7, 8].

In major abdominal surgeries, the goal is to maintain electrolyte homeostasis while attempting to achieve euvolemia. In the majority of surgeries, intraoperative bleeding and third space losses accompany the condition of hypovolemia [9]. As a result of increased microvascular permeability, capillary leaks and hemostatic disorders can develop [10]. There is still no consensus on the most effective intraoperative fluid regimen [11].

Our primary aim in this study was to investigate the impact of colloid fluid infusion given in perioperative fluid replacement on the development of postoperative complications in patients undergoing major gastrointestinal tract surgery. Our secondary aim was to investigate the effect of colloid use on the incidence of intensive care unit admission and the length of hospital stay.

Materials and methods

Following the approval of the local Ethics Committee (514/194/30-27.01.2021), patients who underwent major abdominal surgery at our hospital due to gastrointestinal tract malignancy between January 2015 and January 2020 were enrolled in this retrospective study. Data regarding the volume of perioperative fluid replacement, the amount of crystalloid and colloid fluids administered, postoperative complications, length of hospital stay, frequency of admission to the intensive care unit are recorded.

All patients were given 10 -12 mL/kg/h intravenous (IV) crystalloid infusion in the perioperative period to meet their requirements [12]. The central venous pressure was monitored with a 7F catheter. Patients with CVP <8 mmHg and/or a 20% change in hemodynamics compared to baseline values were determined to have a fluid deficit and colloid fluid replacement is started [12]. HES and gelatin were used as colloid fluids, whereas Ringer's lactate and 0.9% saline were the crystalloid solutions used. Patients were given colloid infusion in addition to crystalloids until blood and blood products became available for replacement. Patients who required crystalloid fluid more or less than 2 L were recorded. In patients who received a high volume of crystalloid and/or colloid fluid replacement, the association of fluid replacement with postoperative complications, frequency of ICU admission, and length of hospital stay was examined.

Patients with incomplete data, and patients who required vasopressors in the intraoperative period were excluded from the study.

Statistical analysis

We used descriptive statistics of mean, standard deviation, median, minimum, maximum, frequency, and ratio. The Kolmogorov Smirnov test was used to measure the distribution of the variables. Quantitative independent data were analyzed by Mann-Whitney U test. Quantitative independent data were analyzed by the Chi-square test, but when the conditions for the Chi-square test were not met, Fisher test is used. SPSS 27.0 program was used for the analyses.

Results

For five years, a total of 18,986 patient files were scanned who underwent operations in general surgery. Of those, 585 patients which had gastrointestinal tract surgery were enrolled in the study. However, 259 patients were excluded from the study because of missing data. We analyzed the data of 326 patients in total. The mean age of patients was 61.3 (46-74) years. The most commonly performed gastrointestinal surgical procedures were total gastrectomy (25.2%), low anterior resection (LAR) (24.8%), and anterior resection (14.4%). The mean length of hospital stay was 7.5 (5-14) days. On average, 2572.4 (750-4500) mL crystalloids were used. Colloid fluids were administered to 55.2% of the patients. The average of colloid fluids used was 727.8 (300-1200) mL (Table 1).

Table 1: Comparison of patients in terms of demographic characteristics, surgical details, amount of crystalloid and colloid given, and length of hospital stay

		Mean (SD) /n-%	
Age (year)		61.3	(46-74)
Gender	Female	197	60.4%
	Male	129	39.6%
Tumor size (cm)		49.1	(29.6)
Number of positive lymph nodes		3.6	(7.0)
Hb (g/dL)		11.6	(2.3)
Received colloids	No	146	44.8%
	Yes	180	55.2%
Amount of colloids (mL)		727.8	(300-1200)
Amount of crystalloids (ml)	>2000	192	58.9%
	<2000	134	41.1%
Total amount of crystalloids (mL)		2572.4	(750-4500)
Surgical procedure	Anterior resection	47	14.4%
	LAR	81	24.8%
	Miles	6	1.8%
	Right hemicolectomy	41	12.6%
	Segmental resection	1	0.3%
	Sleeve gastrectomy	6	1.8%
	Left hemicolectomy	12	3.7%
	Subtotal gastrectomy	45	13.8%
	Subtotal esophagectomy	4	1.2%
	Total gastrectomy	82	25.2%
	Total colectomy	1	0.3%
Postoperative admission to ICU	(-)	163	50.0%
	(+)	163	50.0%
Length of hospital stay (days)		7.5	(5-14)
Discharge status	Transferred to another hospital with the same scope of practice	3	0.9%
	Transferred to another hospital with broader scope of practice	2	0.6%
	Transferred to another department within the same hospital	73	22.4%
	Discharged in stable condition	156	47.9%
	Discharged with healing	88	27.0%
	Exitus	4	1.2%

Postoperative pulmonary complications (24.2%), wound infection (20.6%), and anastomotic leakage (3.1%) were the mostly observed three complications in our patient population. Postoperative pulmonary complications include atelectasis, laryngospasm, bronchospasm, pulmonary embolism, and pneumothorax. Pulmonary embolism developed in one patient (14.3%) who did not receive colloids, and pneumothorax developed in one patient (14.3%) who received colloids. The distribution of complications did not significantly differ between the groups with and without colloid infusion. Postoperative pulmonary complications were observed in 46 (14.1%) patients who were given colloid fluid and in 33 (10.1%) patients who did not receive colloids (P=0.536).

Even though 84 (25.7%) patients who received colloid infusion required postoperative ICU follow-up, 79 (24.2%) patients without any colloids given were admitted to ICU (P=0.181). There was no significant difference between these two groups in terms of patients' discharge status and length of hospital stay (P>0.05 and P=0.971, respectively) (Table 2).

Table 2: Comparison of patients that received colloid and that did not receive, in terms of postoperative complications, ICU admission rates, length of hospital stay, and discharge status.

	Received colloids (-) Mean (SD)/n-%		Received colloids (+) Mean (SD)/n-%		*P*-value	
Complications						
Postoperative pulmonary complication	33	22.6%	46	25.6%	0.536	X^2
Wound site infection	31	21.2%	36	20.0%	0.784	X^2
Anastomotic leakage	3	2.1%	7	3.9%	0.340	X^2
Other complications	7	4.8%	11	6.1%	0.605	X^2
Hemorrhagic drainage	2	28.6%	2	18.2%		
Ureteral injury	0	0.0%	2	18.2%		
Subcutaneous hematoma	1	14.3%	0	0.0%		
Evisceration	0	0.0%	1	9.1%		
Ischemic hepatitis	1	14.3%	0	0.0%		
Delayed oral intake tolerance	1	14.3%	0	0.0%		
Stricture at the opening of the stoma	0	0.0%	1	9.1%		
Stoma retraction	1	14.3%	0	0.0%		
Stoma retraction, fasciitis	0	0.0%	1	9.1%		
Stomal ischemia	0	0.0%	1	9.1%		
Repair of ureter and bladder	0	0.0%	1	9.1%		
Vocal cord edema	0	0.0%	1	9.1%		
Postoperative ICU (-)	67	45.9%	96	53.3%	0.181	X^2
(+)	79	54.1%	84	46.7%		
Number of inpatient days	7.4	(7.1)	7.5	(5.3)	0.329	m
Discharge status						
Transferred to another hospital	2	1.4%	3	1.7%	1.000	X^2
Transferred to another department within the same hospital	27	18.5%	46	25.6%	0.128	X^2
Discharged in stable condition	74	50.7%	82	45.6%	0.357	X^2
Discharged with healing	42	28.8%	46	25.6%	0.516	X^2
Exitus	1	0.7%	3	1.7%	0.631	X^2

m: Mann-Whitney u test, X^2: Chi-square test (Fischer test)

The rates of postoperative pulmonary complications, wound infection and anastomotic leakage did not differ significantly between patients with a crystalloid infusion of ≤2 L or >2 L (P>0.05). However, the incidence of other types of complications in the group with a crystalloid infusion of ≤2 L was found to be significantly higher compared to the group receiving >2 L of crystalloids (P=0.038). Nevertheless, there was no significant difference between the amount of crystalloid infusion and the rate of admission to ICU in the postoperative period, the length of hospital stay, and patients' discharge status (P>0.05, Table 3).

Table 3: Comparison of patients that received more than 2 L crystalloid solution and those that received less than 2 L, in terms of postoperative complications, ICU admission rates, length of hospital stay, and discharge status.

	Crystalloid ≤2000 Mean (SD) /n-%		Crystalloid >2000 Mean (SD)/n-%		*P*-value	
Complications						
Postoperative pulmonary complication	44	22.9%	27	24.1%	0.813	X^2
Wound site infection	36	18.8%	25	22.3%	0.453	X^2
Anastomotic leakage	6	3.1%	2	1.8%	0.482	X^2
Other complications	14	7.3%	2	1.8%	0.038	X^2
Hemorrhagic drainage	3	21.4%	0	0.0%		
Ureteral injury	2	14.3%	0	0.0%		
Subcutaneous hematoma	1	7.1%	0	0.0%		
Evisceration	1	7.1%	0	0.0%		
Ischemic hepatitis	1	7.1%	0	0.0%		
Delayed oral intake tolerance	1	7.1%	0	0.0%		
Stricture at the opening of the stoma	0	0.0%	1	50.0%		
Stoma retraction	1	7.1%	0	0.0%		
Stoma retraction, fasciitis	0	0.0%	1	50.0%		
Stomal ischemia	1	7.1%	0	0.0%		
Repair of ureter and bladder	1	7.1%	0	0.0%		
Need for postoperative admission (-)	94	49.0%	55	49.1%	0.980	X^2
to ICU (+)	98	51.0%	57	50.9%		
Number of inpatient days	7.2	(5.0)	7.9	(7.8)	0.971	m
Discharge status						
Transferred to another hospital	2	1.0%	1	0.9%	1.000	X^2
Transferred to another department within the same hospital	40	20.8%	25	22.3%	0.760	X^2
Discharged in stable condition	97	50.5%	54	48.2%	0.698	X^2
Discharged with healing	50	26.0%	32	28.6%	0.632	X^2
Exitus	3	1.6%	0	0.0%	0.300	X^2

m: Mann-Whitney u test, X^2: Chi-square test (Fischer test)

Discussion

This retrospective study investigated patients who underwent major abdominal surgery due to gastrointestinal system malignancy. It was demonstrated that the risk of developing complications did not increase in patients when the volume of crystalloid fluid replacement was increased or colloid fluid infusion was added in the intraoperative period. There was no significant difference in the need for postoperative intensive care or the length of hospital stay in patients receiving colloids.

There is still controversy on the intraoperative fluid regimen and the types and amount of fluids used. Conflicting results have been reported in studies addressing this matter. In a study evaluating the adequacy of tissue perfusion through measurement of subcutaneous oxygen tension, the fluid requirements of patients undergoing elective open abdominal surgery were met with boluses of Ringer's lactate or HES [13]. Postoperative surgical site infection or subcutaneous partial oxygen pressure did not differ significantly in the colloid-administered group. In this study, Ringer's lactate and 0.9% saline solution was compared with colloids. Apart from HES, the effectiveness of gelatins was also evaluated and it was revealed that colloids added to crystalloids did not have a significant negative effect on patient outcomes.

In abdominal surgeries, the amount of fluid administered in the perioperative period may vary in different operations and hospitals. In one study, the total amount of crystalloid fluid given in abdominal surgeries was calculated [14]. It was demonstrated that the amount highly differ depending on the anesthesiologists. The total amount of crystalloids infused to provide 1 mL/kg/h urine output in a 4-hour surgery has been reported to vary from 700 to 5400 mL. On the other hand, Kim et al. [15] reported that 90% of the differences in the amount of fluid administered are due to factors related to the patients, emphasizing that the role of care providers in this difference is as low as 10%. Many factors including the size of the surgical incision, patients' oncotic pressure, third

space losses, and the amount of hemorrhage can affect this. Besides the effects of colloids, the results of the amount of crystalloids given to the patients were also investigated in this study, and the cut-off value was determined as 2 L. Nevertheless, there was no significant increase in the incidence of postoperative complications in patients given cristalloid infusions below or above this value. The three most common complications observed were postoperative pulmonary complications, wound site infection, and anastomotic leakage, respectively. Moreover, the rate of complications developing other than these was found to be higher in patients who had fluid infusion less than 2 L which shows the importance of achieving euvolemia and applying an optimal fluid regimen for patients.

Also, the necessity of avoiding colloidal overload is clear. As with all replacement fluids, some complications have been reported during the use of colloid fluids. A study including 1041 patients revealed that postoperative delirium developed in 22.7% of patients who were given HES during esophagectomy [16]. In another study, HES and Ringer's lactate were compared regarding their effects on perioperative fibrinogen thromboelastometry (FIBTEM) and maximum clot firmness (MCF) values [17]. A dose-dependent deterioration impairment in fibrin polymerization was observed in patients who received HES. However, it was reported that the results returned to normal on the first postoperative day without the need for procoagulant agents, and there was no difference in blood loss of the patients. Colloids used for the treatment of patients in intensive care unit have been reported to have iatrogenic side effects and have been associated with acute kidney injury and mortality [18]. However, it was emphasized that damage to the endothelial glycocalyx layer of critically ill patients may also have a role in that result. In our study, the data of patients were examined in terms of complications that may develop during the hospitalization (for an average of 1 week). It was found that the use of colloids did not pose any additional risk within the specific time. Therefore, it was concluded that the use of colloids is safe unless there is an overdose in the operating rooms.

Limitations

The most significant limitation of this study is that the goal-directed hemodynamic strategy was not used in the perioperative period. Transesophageal Doppler evaluation or non-invasive monitoring of cardiac output and stroke volume were not performed to determine the patients' response to fluid therapy. The response to fluid therapy was only evaluated through CVP and hemodynamic data. Another limitation to note is the retrospective design and the sample size of the study. It is obvious that there is a need for further clinical trials with larger series of patients to decrease the controversies on this subject.

Conclusion

In patients undergoing major abdominal cancer surgery, administering colloids along with the crystalloid infusion is not associated with the incidence of postoperative complications, the length of hospital stay and the frequency of admission to the intensive care unit.

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Research article

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The effect of national restrictions on computed tomography severity score and the prognosis of COVID-19

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Ethics Committee Approval
The study was approved by Giresun University Clinical Studies Ethics Committee (Approval number: 2020/11-191).
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Abstract

Background/Aim: The SARS-CoV-2 pandemic is spreading rapidly all over the world and has high mortality rates. Governments implement quarantine or restrictions to prevent the virus from getting out of control. Computed Tomography (CT) has an important place in the diagnosis of COVID-19 and patient management. This study aimed to evaluate the changes in chest CT findings and the disease prognosis of COVID-19 pneumonia during the restriction and post-restriction periods.

Methods: A total of 1150 patients whose COVID-19 disease was confirmed by a reverse transcriptase-polymerase chain reaction and who underwent chest CT examination between April 1-September 30, 2020 were included in this retrospective cohort study. The participants were categorized into two groups according to CT examination dates, as during (April 1-May 31), and after the restriction periods (June 1-September 30). Each patient's CT severity score (CTSS) was calculated, and the need for admission to the intensive care unit (ICU) and mortality related to COVID-19 were noted for statistical analysis.

Results: Of the 1150 cases, 213 were in the restriction period group (RPG), while 937 were in the post-restriction period group (PRPG). The median value of CTSS was 5 in the RPG, and 6 in the PRPG (P=0.095). In the RPG and PRPG, the number of patients who needed ICU admission were 20 (9.4%), and 50 (5.3%), respectively, while 12 (7%) and 39 (4.2%) patients, respectively, died from COVID-19. Both parameters were comparable between the two groups (P=0.073, P=0.060 respectively).

Conclusion: The restrictions did not change the severity of the COVID-19 disease, ICU hospitalization rate, and death rate.

Keywords: COVID-19, Computed tomography, Restriction period, Post-restriction period

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Introduction

The first novel coronavirus SARS-CoV-2 outbreak was reported to WHO on December 31 2019 from the Hubei Province of the People's Republic of China [1, 2]. On January 30, 2020, the WHO declared COVID-19 as an international emergency that threatened public health, as a pandemic on March 11, 2020 [3]. COVID-19 may be asymptomatic or mild or may have a clinical course that may cause severe pneumonia requiring hospitalization and even intensive care [4]. The disease is associated with high mortality rates [5, 6]. Computed Tomography (CT) is a well-known modality to show the parenchymal changes associated with viral pneumonia in COVID-19 cases and helps patient management [7].

As COVID-19 has rapidly spread around the world, governments in many countries have implemented quarantine rules on an unprecedented scale. The first restrictions were imposed in China, where the epidemic started, and entry and exit bans were imposed on all cities [8]. Turkey also imposed restrictions. Shortly after the disease emerged, a curfew was imposed for people over 65 and under 18 years of age. Partial quarantine rules were gradually enacted as of April 1, 2020, and the restrictions were over as of June 1. Since the onset of the infection, community-based preventive rules such as the use of masks, social distancing, and personal hygiene continued. To the best of our knowledge, no studies determined the temporal changes in the prognosis of the disease and compared the CT severity scores (CTSS) in COVID-19 pneumonia between the restriction and post-restriction periods (i.e., when only personal protection strategies such as mask use, social distancing, and personal hygiene are implemented).

This study aimed to comparatively evaluate the changes in chest CT findings and the prognosis of COVID-19 pneumonia between the restriction and the post-restriction periods.

Materials and methods

Study design

This retrospective study was approved by the Ethics Committee for Clinical Studies, Giresun University (Approval number: 2020/11-191) and adhered to the principles of the Helsinki Declaration. Adult patients over 18 years of age who had received a chest CT scan for the initial diagnosis of COVID-19 pneumonia between April 1 and September 30, 2020, and confirmed to have COVID-19 disease by reverse transcriptase-polymerase chain reaction (rT-PCR) were included. Sixteen patients' CT images were excluded due to movement artifacts and a study group consisting of 1150 patients was formed. The patients' demographic features including gender, age, and comorbidities (chronic heart disease, chronic lung disease, diabetes, cerebrovascular disease, anxiety) were noted. To analyze the differences in the severity of lung involvement in chest CTs and the prognosis of COVID-19, the patients were grouped into two, as during (April, 1 – May, 30) and after the restriction period (June, 1 – September, 30).

Image acquisition

All CT examinations were performed with a 16-slice spiral CT scanner (Emotion 16, Siemens Healthineers) from the apex to the base of the lung, during deep inspiration and breath-hold, without contrast administration. We used the following parameters: Tube voltage: 80 kVp, tube current: 35–50 mA, rotation time: 0.75 s, pitch: 1.5, slice thickness: 3 mm, and detector width: 1.5 mm.

CT image analysis

The images were analyzed by two radiologists with experiences of 10 and 11 years, who were blinded to the study and clinical data. All discrepancies were resolved by consensus. CTSS, which is a semi-quantitative scoring suggested by Pan et al., was used to predict the severity of pulmonary parenchymal involvement (7). Each of the five lung lobes were visually scored between 0 and 5, as follows: 0) No involvement; 1) <5% involvement, 2) 5-25% involvement, 3) 26-49% involvement, 4) 50-75% involvement, and 5) >75% involvement. Total CTSS was the sum of the individual lobar scores, and it ranged from 0 (no involvement) to 25 (maximum involvement). The following features of CT findings were also recorded: (a) Lesion characteristics- ground-glass opacity (GGO), consolidation, mixed GGO (GGO and consolidation) crazy paving, reticular pattern, (b) lesion location- peripheral, central, mixed, (c) extrapulmonary findings- lymph node enlargement (short-axis diameter 10 mm) and pleural effusion.

The regions with increased lung parenchymal density were defined as GGO if the veins and bronchial walls under the density were distinguished, and as consolidation if not. Crazy paving indicated the appearance of ground-glass opacity with superimposed inter-and intralobular septal thickening. The reticular pattern was characterized by the appearance of ground-glass opacity with superimposed intralobular septal thickening.

Comparison between groups

Restriction period group (RPG) and post-restriction period group (PRPG) were compared in terms of the presence and severity of pulmonary involvement, CT features of the lesions, intensive care unit (ICU) need, and mortality.

Statistical analysis

Statistical analyses were performed with IBM SPSS V23. Normality distributions of quantitative data were assessed with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare the abnormal distribution of quantitative data. Pearson Chi-square test was used to compare qualitative data. The data were presented as n (%), mean (standard deviation), median (minimum-maximum), and median (interquartile range). $P<0.05$ was considered statistically significant.

Results

Demographic features

Among 1150 cases, 213 (18.5%) were in the RPG, and 937 (81.5%) were in the PRPG. Table 1 shows the demographic features of both groups. The mean age of the study group was 56 (18-95) years. The most frequent comorbid diseases were chronic heart disease, chronic pulmonary disease, and diabetes mellitus in both groups. No significant differences were found between the groups in terms of age, gender, and frequency of comorbid diseases ($P>0.05$).

Table 1: Demographic and prognosis features in the restriction and post-restriction period

		Restriction period	Post-restriction period	*P*-value
Age, y, mean(SD)		54 (19.2)	56 (17.2)	0.836
		n%	n%	
Gender*	Male	94 (44.1)	445 (47.5)	0.375
	Female	119 (55.9)	492 (52.5)	
Comorbidities*				
	Chronic heart disease	94 (44.2)	381 (40.7)	0.610
	Chronic lung disease	45 (20.9)	158 (16.9)	0.130
	Diabetes	30 (14.0)	80 (8.5)	0.378
	Cerebro-vascular disease	20 (9.3)	96 (10.2)	0.884
	Anxiety	15 (7)	80 (8.5)	0.781
Prognosis*				
	Survive	198 (93)	898 (95.8)	0.073
	Exitus	15 (7)	39 (4.2)	
ICU*				
	None	193 (90.6)	887 (94.7)	0.060
	Yes	20 (9.4)	50 (5.3)	

* n (%)

CT findings

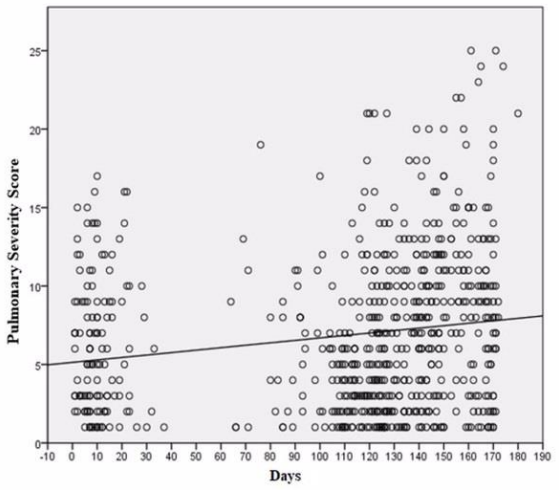
Among all patients, 673 (58.9%) had CT findings of pneumonia, 61.1% (130/213) of the RPG patients, and 58% (543/937) of the PRPG patients (*P*>0.05). Table 2 shows the extent of lung involvement in terms of the lobe, segment, CTSS, and lesion distribution. The median (IQR) CTSS values were 5 (7) in the RPG and 6 (7) in the PRPG (Figure 1) (*P*=0.095). The most common CT lesion in both groups was GGO (Figure 2). GGO was significantly more common in the PRPG, while consolidation and reticular patterns were more common in the RPG (*P*=0.009). The lesions were mostly peripheral in both groups (Figure 3). Central and mix distribution were significantly more common in the PRPG (*P*=0.038).

Table 2: CT features in the restriction period and post-restriction period

	Restriction period	Post-restriction period	*P*-value
CT positive findings*	130 (61)	543 (58)	0.410
Number of Lobes Held**	3 (1 - 5)	4 (1 - 5)	0.045
Number of Segment Held **	6 (1 - 17)	7 (1 - 18)	0.050
CTSS***	5 (7)	6 (7)	0.095
Ground glass opacity (GGO)	98 (64.5)	418 (77.6)	<0.001
Consolidation*	24 (15.8)	25 (4.6)	0.001
Mixed (GGO+Consolidation) *	30 (19.7)	96 (17.8)	0.561
Reticular Pattern*	13 (10)	23 (4.3)	0.009
Crazy Paving*	15 (11.5)	47 (8.7)	0.317
Effusion*	13 (10.8)	11 (2)	<0.001
Lymphadenopathy*	2 (1.5)	5 (0.9)	0.537

* n (%),** Median (minimum-maximum), *** median (IQR)

Figure 1: Scatter diagram showing pulmonary severity score on patients' CT scans throughout the 180 days of study. (CT: computed tomography)



The number of patients with lymph node enlargement was comparable between the two groups (*P*=0.537). Effusion was significantly more common in the RPG (*P*<0.001).

Figure 2: Axial CT image of a 48-year-old man in the restriction period group shows bilateral ground-glass opacities with a peripheral distribution. The pulmonary severity score was 12.

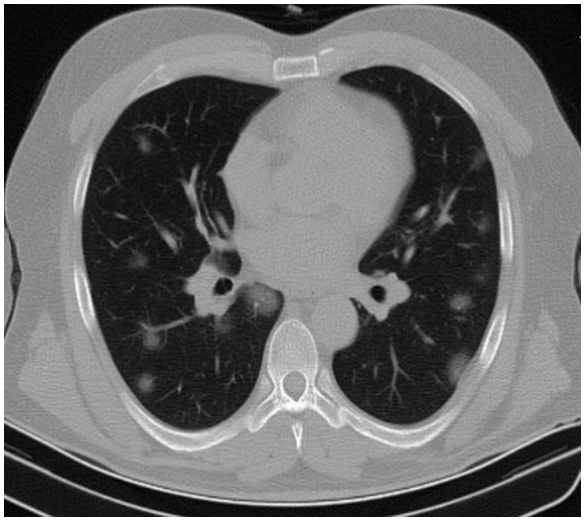
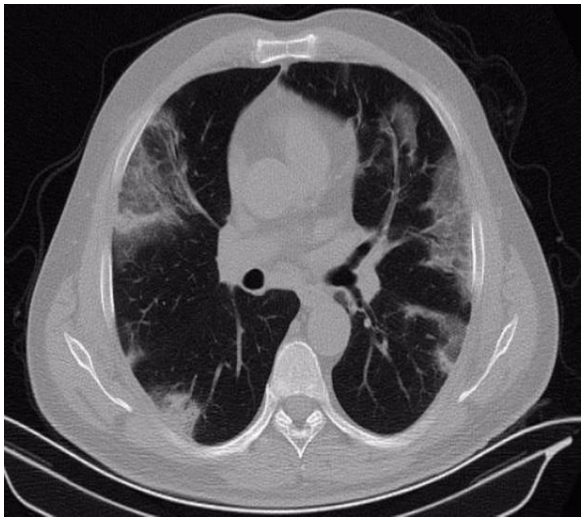


Figure 3: Axial CT image of a 62-year-old man in the post-restriction period group shows bilateral mixed pattern (ground-glass opacities and consolidation) with a peripheral distribution. The pulmonary severity score was 13.



Disease prognosis

Seventy (6%) patients needed admission to the ICU and 54 (4.6%) patients died. In the RPG, 20 (9.4%) patients needed admission to the ICU and 15 (7%) died, while in the PRPG, 50 (5.3%) needed admission to the ICU and 39 (4.2%) died. Both parameters were comparable between the groups (*P*=0.073, *P*=0.060 respectively).

Discussion

In our research, although there was an increase in the number of patients in the PRPG, no significant difference was found between RPG and PRPG in terms of ICU need, death rates, and CTSS.

COVID 19, which is transmitted by inhalation of SARS-CoV-2, is an airborne disease [9]. However, there is no consensus about whether the virus is transmitted through droplets or aerosol [10-12]. In China, cases related to air conditioning in a restaurant in Guangzhou and a bus trip in Hubei strengthened the thesis that the disease is transmitted through aerosols [13, 14]. Aerosol particles are smaller than droplets (<5 μm), and they can circulate in air-conditioning and ventilation systems and migrate through human airways to penetrate the alveolar space [15]. Human coronaviruses can survive on surfaces between 2 hours-9 days, and people who touch such fomites are at risk of becoming infected if they then touch their eyes, noses, or mouths [16]. Due

to the fast transmission of SARS-CoV-2, crowded and closed spaces, as well as lack of hygiene, present a favorable environment for the virus to spread faster [15]. In addition, people are exposed to the viral pathogen for longer in such spaces, which may increase the viral load [17]. Studies show that the SARS-CoV-2 viral load is associated with disease severity and prognosis [18-21].

Mainly, the use of a mask, social distancing, and personal hygiene practices are recommended to reduce the spread of the virus [22, 23]. Personal protective rules can reduce its spread to a certain extent. Experts argue that community-based public guidelines such as social distancing, contact tracing, and isolation are equally successful and that such rules will be less effective than movement restriction [24]. Governments need to implement quarantine and restriction rules to prevent the virus from getting out of control and the health system from collapsing [8].

As a result of the removal of restrictions and the increase of density in crowded and closed environments, individuals are exposed to the virus longer. In parallel with this view, in our study, there was an increase in the number of cases in the PRPG. However, no significant difference was found between the two groups in terms of CTSS score, the need for ICU admission, and death rates. One of the possible reasons for this may be the decrease in the virulence of SARS-CoV-2. It is known that the genetic material of viruses can mutate in a way that makes them more or less lethal [25, 26]. Since there are six months between the RPG and PRPG, the mutation of the virus during this time is one of the possible reasons, although the probability is low.

It is possible these results may be associated with the effect of society-based preventive rules, such as mask use, social distancing, and personal hygiene, encouraged since the infection started in Turkey. It has been shown that the transmission of viruses, including SARS-CoV-2, is reduced by protective rules, such as social measures and the use of face masks [27]. Such personal protective habits can decrease viral load and thus cause a decreased rate of disease transmission and clinical severity.

Another reason could be the fact that people spend less time indoors in the summer months, and infected people are exposed to less viral load. Another factor may be the progress in treatment strategies due to clinical management of cases and accumulated experience related to the disease. For example, studies show that systemic corticosteroids improve the outcome in COVID-19 patients [28].

No studies compared the changes in disease prognosis and CT findings between RPG and PRPG. In the United Kingdom, the fatality rate (death rate per positive test) was lower in May and June when compared with March and April, with a steady decline through July and August [29]. Burgess et al. [30] reported that although there was a sharp increase in the number of SARS-CoV-2 positive tests during the summer months in many European countries, the rates of hospital admission and mortality from COVID-19 were not as high as those in March and April. They stated that the possible causes may include public health measures taken to prevent the spread of SARS-CoV-2, the decrease in the number of cases in the elderly population and the resulting decrease in mortality, and advances in treatment methods and protective rules – such as masks and social distancing – causing a decrease in viral load and therefore decreasing disease severity.

The limitations of our study include the fact that the seasonal effect on the cases in both study groups was not ruled out and that the full compliance of individuals within the restriction period was fully known.

Conclusion

Since there is no significant difference in the CTSS scores, death rates, and ICU need in individuals who had COVID-19 disease before and after the restriction, it can be stated that restrictions do not affect these parameters. However, it should be kept in mind that the lack of restrictions may increase the patient number and collapse the health system.

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Comparison of manual and automatic cell count methods for synovial fluid: A prospective study

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Ethics Committee Approval
Ethics committee permission for this study was granted by Hitit University Faculty of Medicine Clinical Research Ethics Committee on 19.12.2017, with the decision number 2017-199. 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: Cell count measurement methods in the synovial fluid are still a current problem in orthopedic practice. Knowing the cell count in the synovial fluid is important for the assessment of a variety of orthopedic and rheumatologic diseases. We aimed to assess the correlation of WBC and RBC results obtained with a complete blood count analyzer with that obtained by a manual cell count.
Methods: The WBC and RBC count in the synovial fluid of 43 patients undergoing gonarthrosis surgery were determined by a Mindray BC-6800 hematology analyzer. The study groups were defined as manual cell count (MC), hemogram mode (HM), and body fluid mode (BFM). All samples were analyzed twice consecutively, and the mean results were calculated. Cell counting was performed using different methods in the same samples and compared statistically.
Results: The mean age of the patients was 60.9 years, and there were 17 males (39.5%) and 26 females (60.5%). The WBC and RBC counts in the synovial fluid samples were determined using manual cell count, and the HM and BFM on a Mindray BC-6800 automatic hematology analyzer. WBC counts significantly differed between MC and BFM, and RBC counts significantly differed between HM-MC and HM-BFM (P=0.001, P=0.001, P=0.001, respectively). There was a significant positive correlation between BFM and MC in WBC counts (r=0.633, P<0.001), with no statistically significant correlations identified between other methods. For RBC counts, there was a significant positive correlation between BFM and MC results (r=0.363, P=0.032).
Conclusion: While the body fluid mode in hematology analyzers can be recommended for obtaining an RBC count in the synovial fluid, the hemogram mode may be recommended for the WBC count.

Keywords: Synovial fluid, Hematology analyzer, Cell count, WBC, RBC

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Introduction

Synovial fluid cell analysis is important to assess a variety of diseases, such as inflammatory disorders, infection, hemorrhage, and malignancy and may be used for differential diagnosis and treatment monitoring [1-6]. The manual cell count is the gold standard method for the assessment of cell counts in body fluids [7]. Cell counts in the synovial fluid show the degree of inflammation in the joint [8, 9]. Hematology analyzers provide accurate results in the synovial fluid, though the results are better for other body fluids [10]. However, the use of hematology analyzers for synovial fluids is not common [1, 11]. Additionally, recently developed hematology analyzers have the potential to take the place of the manual cell count [12].

The gold standard method for cell count, manual cell counting, is time-consuming and not common due to the lack of qualified personnel trained in the field. Additionally, the repeatability between the analyzers is low. For this reason, automated methods were developed [13]. However, problems are encountered during the analysis of synovial fluid with automated methods due to high viscosity linked to hyaluronic acid [1, 2, 14, 15].

Different analyzers and automated methods were trialed for cell counts in body fluids. The Mindray BC-6800 used in this study is an automatic hematology analyzer equipped with a special module [1, 15]. This study aimed to use the Mindray BC-6800 hematology analyzer in the hemogram and body fluid modes for obtained synovial fluid cell count and perform manual cell counts to determine compatibility.

Materials and methods

Study design

Ethics committee permission was granted by Hitit University Faculty of Medicine, Clinical Research Ethics Committee, dated 19.12.2017, with the decision number 2017-199. This study included 52 voluntary patients who underwent gonarthrosis surgery in the orthopedics and traumatology clinic from January 2019-December 2019. The synovial fluid samples of the patients who provided informed consent were used.

The samples were collected in tubes containing K_3EDTA, inverted gently 6-8 times, and did not undergo any preliminary processing. Every sample reaching the laboratory was analyzed within one hour. Bloody or cloudy samples were diluted 1/10 before manual and automatic analysis due to high concentrations of RBC and/or WBC. Each sample was analyzed twice consecutively, first with a manual count, then in the BFM and HM modes of the Mindray BC-6800, automated hematology analyzer, and the mean results were obtained.

Cell count with Neubauer slide

A Neubauer slide was used for manual cell counts. Two count areas are determined on the Neubauer slide and separated from each other with a hollow. Each count area contains four sections of 16 squares with 1 mm^2 in the corners for leukocyte count and a section of 25 squares with 1 mm^2 in the central section for erythrocyte count.

In our study, all manual cell counts were performed by the same researcher. A clean coverslip was placed on the Neubauer slide, 10 µL of the synovial fluid sample was taken with calibration-certified automatic pipettes and pipetted onto the Neubauer slide under the coverslip without any air bubbles. Synovial fluid rapidly filled the area between the coverslip and the gridded area on the Neubauer slide. The cells were left for five minutes to settle onto the slide. With a microscope, the homogeneous distribution of cells was checked at 100X magnification, and the microscope was set to 400X for the count. Leukocytes were counted in one of the 4 sections with 16 squares at the edges of the Neubauer slide. Erythrocytes were counted from the section comprising 25 squares in the center of the slide. At the end of counts, cell numbers were multiplied by 10 and the cell numbers in 1 mm^3 volume were calculated (cells/mm^3). Mesothelial cells were not included in WBC counts. The macroscopic images of samples and microscopic leukocyte morphologies and aggregation were assessed.

Cell count with Mindray BC-6800 automated hematology analyzer

After the targeted blood cells enter the reaction, scattered laser light coming from two angles and fluorescent signals are used for three-dimensional counting. The three-dimensional scatter diagram is especially important to better identify and differentiate blood cell populations and can determine abnormal cell populations that are not identified with other techniques. The Mindray BC-6800 analyzer uses BFM-SF cube technology and assesses WBC count, as well as the distribution of cells and nucleated cells. The targeted cells undergo 3D analysis with the information from the fluorescence flow cytometry signals and from a laser scanner that is illuminated at two angles. BFM can directly perform WBC and total nuclear cell counts from the DIFF channel. After studying each blood sample with the hematology analyzer, a blank sample is studied to minimize the carry-over effect. The study was performed according to the CLSI document numbered H56-A6 and International Council for Standardization in Hematology (ICSH) recommendations and abided by the Helsinki Declaration [1, 16].

Statistical analysis

Statistical analysis was completed using the SPSS IBM Version 23.0 (SPSS Inc Chicago, IL, USA). The normal distribution of the data was assessed with the Shapiro Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation, while non-normal data were presented as median (25^{th}-75^{th} percentile). Descriptive statistics for the categorical data are given in number and percentage. Inter-group comparisons were performed with the Wilcoxon signed-rank test. The correlation between measurement methods was researched with Spearman's correlation coefficient. $P<0.05$ was accepted as the level of statistical significance. A power analysis yielded the minimum sample size as 34.

Results

Of the patients, 17 were males (39.5%) and 26 were females (60.5%). The median values of WBC and RBC count in the synovial fluid, detected with the hemogram and body fluid modes of the Mindray BC-6800 automatic hematology analyzer, and the manual cell counts are shown in Table 1.

For WBC counts in synovial fluid, the results obtained from MC are nearly twice that obtained from HM, while BFM

counts are nearly half. For RBC counts, HM was thirteen times more than the manual count; however, MC and BFM results were close (Table 1).

Table 1: Comparison of the hemogram mode, body fluid mode, and manual cell count results

	WBC		RBC	
	Median (Q1-Q3)	*P*-value	Median (Q1-Q3)	*P*-value
HM (1)	100 (50-400)	1-2: 0.957	20,000 (10,000-30,000)	1-2: <0.001
MC (2)	175 (100-366)	1-3: 0.077	1,540 (340-4,000)	1-3: <0.001
BFM (3)	275 (136-450)	2-3: 0.001	2,000 (1,000-4,000)	2-3: 0.734

HM: Hemogram Mode, MC: Manual count, BFM: Body fluid mode, WBC: White Blood Cell, RBC: Red Blood Cell

According to two-way group comparisons with the Wilcoxon signed-rank test, there were significant differences between MC and BFM in terms of WBC counts (P=0.001) and between MC-HM and HM-BFM for RBC counts (P<0.001 and P<0.001, respectively, Table 1).

According to Spearman's correlation analysis, the BFM and MC results of the WBC counts were significantly correlated (r=0.633, P<0.001), while the results of the other methods were not. For RBC counts, there was a significant correlation between BFM and MC counts (r=0.363, P=0.032), but no significant correlation between HM and MC and between BFM and HM results (Table 2).

Table 2: The correlation of WBC and RBC values with the three methods

	WBC		RBC	
	r	*P*-value	r	*P*-value
HM-MC	0.083	0.595	0.171	0.395
BFM-MC	0.633	<0.001	0.363	0.032
BFM-HM	0.009	0.956	0.297	0.132

HM: Hemogram Mode, MC: Manual count, BFM: Body fluid mode, WBC: White Blood Cell, RBC: Red Blood Cell

Discussion

Limited studies are comparing the gold standard for cell count in the synovial fluid with the performance of automatic analyzers. In this study, a BC-6800 Mindray (Mindray, Shenzhen, China) automated hematology analyzer was used to determine the cell counts in the synovial fluid with cell counts performed in hemogram and body fluid modes. Considering the manual count results as a reference, the compatibility between the two automatic cell counts with the manual cell count was researched. The body fluid mode of the hematology analyzer was significantly correlated with the manual method results in terms of WBC and RBC count. However, the hemogram mode on the hematology was not.

Cell counts in the synovial fluid still pose a significant problem for clinical laboratories because manual assessment is difficult and time-consuming. Additionally, there may be intra- and inter-observer variability, and repeatability is low. This problem increased the need for automatic analyzers. Despite the increased sensitivity and accuracy of automatic analyzers, reduced variability between the observers, getting the results within a short time and a good correlation with manual counts, debates about whether automatic cellular analyzers can be used instead of a manual cell count continue [3, 17-19]. Most automated hematology analyzers have a body fluid mode. Nearly all cell count studies performed with different hematology analyzers use the body fluid mode for different body fluids [1, 3, 7, 10, 12, 13, 16, 18-21]. However, some hematology analyzers in clinical laboratories only have a hemogram mode. This means that the analysis of body fluids is performed in the hemogram mode. Additionally, different cell counts are obtained with the use of automatic analyzers in different modes. For this reason, it is very important to determine the correlation of different cell count methods with the manual count and find a standard cell count method.

Cho et al. assessed RBC, WBC, neutrophil, eosinophil, basophil, and polymorphonuclear cell counts using the manual method and three different automatic analyzers (Beckman Coulter UniCel DxH 800, Sysmex XN-350, and Sysmex UF-5000) for five synovial fluids and different body fluid samples. They identified a significant correlation between all cell counts with the UniCel DxH 800, except for the RBC count in cerebrospinal fluid samples [3]. Lim et al. counted WBC, RBC, mononuclear, polymorphonuclear cells, and differentiated cells in full blood mode and high-fluorescence body fluid (HF-BF) mode with a Sysmex XN-350 device. They concluded that the HF-BF mode will be beneficial for screening abnormal cells in body fluids [22].

Jiwon et al. [23] counted total cells, WBC, RBC, polymorphonuclear leukocytes (PMN), mononuclear leukocytes (MN), neutrophils, lymphocytes, monocytes, and eosinophils in body fluids using an XN-350 hematology analyzer. Their results very strongly correlated with the manual count of total cells, WBC, RBC, PMN, and MN, strongly correlated in terms of neutrophil and lymphocyte percentages, and weakly correlated in terms of eosinophil percentages.

As hematology analyzers normally study blood samples with much higher cell densities, acceptable cell density is important. According to published data, counts are not reliable in body fluids with the available automatic analyzers below 3 cell/μL for WBC and 1,000 cell/μL for RBC. Additionally, manual counts may not be definite for low cell densities. Due to the high inconsistency in low cell counts, cell numbers above 50 cell/μL for WBC and 3,000 cell/μL for RBC are recommended [13].

In synovial fluid samples obtained from healthy individuals, the WBC count is less than 200 per mm³. A WBC threshold of 2000 cell/mm³ is needed to differentiate inflammatory and non-inflammatory diseases [11]. In our study, synovial fluids which are considered normal were used, so the WBC count cut-off was determined as 200 cell/mm³, and we could not identify a suitable cut-off value for RBC.

Fuster et al. [7] reported no significant difference between the median WBC counts in the three fluids analyzed with the BC-6800 body fluid mode and a manual count, and there was a good correlation between them in a study assessing peritoneal dialysis fluid, ascites, and pleural fluids. A correlation between results obtained with automated methods and manual cell counts in these fluids are expected, as pleura and peritoneal fluid are non-viscous body fluids. However, synovial fluid has high viscosity due to hyaluronic acid. The increase in viscosity may be another cause of the false low values for WBC and RBC counts with both the automatic and manual methods. Samples may be treated with hyaluronidase to prevent these erroneous values and reduce viscosity. Hyaluronidase prevents the reduction in cell flow in automatic analyzers [1, 15]. A study by Kerolus et al. [24] performing manual cell counts did not use hyaluronidase; however, samples were only diluted with 3% saline solution, and they reported that the low cell counts were not due to dilution but due to the slow investigation.

A study by Buoro et al. [1] stated that the body fluid mode in the BC-6800 device may provide a rapid and accurate assessment of WBC and PNL counts in synovial fluid. They identified a high correlation between samples undergoing pretreatment with hyaluronidase during analyses of synovial fluid cell counts in samples treated and not treated with hyaluronidase.

The Sysmex XE-2100 has two different WBC count modes. The first is the WBC/BASO channel, which performs total WBC count and selective basophil count. The second is the DIFF channel and is used to count neutrophils, lymphocytes, monocytes, and eosinophils. In terms of WBC counts, there is a weak correlation between WBC/BASO channel and manual counts. Contrarily, the DIFF channel and manual reference method are highly correlated in WBC counts. In this study, there was a high correlation between WBC counts in diluted and undiluted synovial fluid samples analyzed with the DIFF channel on the hematology analyzer. For this reason, the dilution procedure is not necessary to investigate synovial fluid samples in the DIFF channel. The reason for obtaining false low WBC counts with the WBC/BASO channel is the mucin clotting and hyaluronate polymerization linked to the low pH (pH=3.4) of the inorganic surfactant used in the WBC/BASO channel. When the WBC/BASO channel sample is treated with hyaluronidase, the WBC count significantly increases and equalizes with the WBC count in the DIFF channel. As the surfactant used in the DIFF channel is not acidic (pH=7.3), mucin clotting does not occur, and the WBC count is accurate [20]. The BF mode of the BC-6800 Mindray automatic hematology analyzer used in our study uses the DIFF channel, so we did not consider it necessary to process with hyaluronidase. We concluded that the body fluid mode and manual count were not affected for WBC and RBC. However, we think false low WBC and RBC values were obtained because of hemolysis and disrupted cell flow, because of high viscosity. Under these circumstances, low WBC and RBC counts were encountered on automatic counts. However, the manual counts of samples with hemolysis yielded much better cell counts and differentiation. Additionally, the human eye can differentiate new and old cells with clinical significance. These features are the superior aspects of manual count compared to automatic devices. Though there are studies performed with RBC, WBC, and other cell counts in different body fluids in the literature, there does not appear to be any study with RBC counts in synovial fluid. For this reason, we think it is important to detect RBC values in synovial fluids.

Limitations

Limitations of our study include the lack of the use of different automatic analyzers and counts for leukocyte subclasses, as well as the manual counts not being performed by several individuals and the lack of use of staining techniques.

Conclusion

Body fluid mode in hematology analyzers may be recommended as a cell count method for synovial fluid as results show a high correlation with manual cell counts. The development of a standardized method for cell counts in the synovial fluid is an open issue. The selection of hematology analyzers with a BF mode by the laboratories may contribute to the diagnostic power of the test by increasing awareness about BF mode among laboratory personnel.

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The role of ultrasound in the diagnosis of vesicoureteral reflux disease

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Ethics Committee Approval
The study was approved by the local Ethics Committee of University of Health Sciences, Inonu University (approval number: 2021/1807, data: 23.03.2021).
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 gold standard in the diagnosis of VUR (vesicoureteral reflux) is voiding cystouretrography (VCUG), but it is an invasive test with risk of radiation. The aim of the study was to determine the sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) of ultrasound (US) in the diagnosis of VUR.

Methods: 760 kidneys of 380 patients were examined in this cohort study. The patients were grouped by three age groups; 0-2, 3-5 and 6-17 years old. US reports included the data of anteroposterior renal pelvic diameter (APRPD), kidney parenchyma, kidney size, and the size of ureters. For all age groups, the sensitivity, specificity, PPV and NPV were evaluated separately in two circumstances; APRPD is accepted pathologic when >5 mm and >10 mm.

Results: A correlation was found between VCUG and US results in all age groups (P<0.001). When pathologic APRPD was accepted as >5 mm, sensitivity, specifity and NPV of US were 86.99%, 60.26% and 88.13% respectively, regardless of age. In contrast, when pathologic APRPD was >10 mm, sensitivity, specifity and NPV were 79.45%, 79.91% and 71.17%, respectively. Sensitivity and NPV of US were found highest in group of 0-2 age.

Conclusion: If US are performed by radiologists experienced in the pediatric urinary system US and if it includes other parameters with APRPD, it will guide for VCUG in the diagnosis of VUR. Thus, radiation exposure can be minimalized in clinical practice.

Keywords: Ultrasonography, Voiding cystourethrography, Vesicoureteral reflux

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Introduction

The vesicoureteral reflux (VUR) disease is present in the etiology of urinary tract infections in children with a rate of 30-40% [1]. VUR is also responsible for 25% of end-stage renal disease [2]. In 90% of VUR in pediatric patients, there is a congenital problem in the vesicoureteral junction [2]. The gold standard in the diagnosis of VUR is voiding cystouretrography (VCUG), which is an invasive diagnostic test with a risk of radiation exposure. The children are more sensitive to radiation, and the application of VCUG is difficult for children. Therefore, application of VCUG examination should be meticulously decided for children with accurate indications. In the last guideline, VCUG is not recommended in children < 2 years of age, if the ultrasound is normal in the first urinary tract infection [3]. This has increased the importance of ultrasound (US) for the decision of VCUG indication. US is noninvasive, radiationless, and easy to apply.

Urinary tract dilatation (UTD) is one of the most common indications of VCUG in children, as well as recurrent urinary tract infections. Various classification systems have been developed to categorize UTDs [4, 5]. In these multiparametric systems, anteroposterior renal pelvic diameter (APRPD) is also used as a quantitative value. However, a consensus cannot be established within definitions of different threshold values for APRPD.

The aim of the study was to determine the sensitivity, specificity, positive and negative predictive values (PPV and NPV) of US in the diagnosis of VUR and to determine the role of US in performing VCUG with absolute indications. In addition, we aimed to show the effect of differentiation in pathologically accepted APRPD values on the sensitivity, specificity, PPD and NPV of US examinations done for detection of VUR.

Materials and methods

All procedures were followed in accordance with the Helsinki Declaration, all parents of patients have been informed and have been approved to participate in this study. This study was approved by the Inonu University Ethical Committee with number 2021/1807 at 23-03-2021.

Patients between ages of 0-17, who were referred to our department from the pediatric nephrology department for VCUG imaging due to urinary tract infection and hydronephrosis between January 1, 2017 and December 31, 2017 were included in our study.

Children with a history of neurogenic bladder, congenital and acquired urogenital anomalies were excluded from the study. All VCUGs and USs were analyzed retrospectively through the PACS system of our hospital. A total 760 kidneys of 380 patients were evaluated in our study. The patients were grouped by three, according to their ages. Group 1, 2 and 3 includes patients with ages 0-2, 3-5, and >5, respectively.

US findings

US of all patients were performed by the same pediatric radiologist, who had 2 years experience in pediatric radiology with GE LOGIC S8, USA. All USs were performed at least one week before VCUG. For the evaluation of hydronephrosis, SFU classification system was used in our department in 2017 [6]. In addition, all US reports written by the pediatric radiologist included findings related to the kidney parenchyma, kidney size, and the size of ureters (Figure 1). Children, whose US examinations are not performed by a pediatric radiologist or US reports contain missing information, were excluded from the study. Pathologies in US reports were also grouped in 3 among themselves. Patients with pathological APRPD were in group 1, patients with small kidney size, increased renal parenchyma echogenicity, increased ureter diameters, thick ureter wall were classified as group 2, patients with pathological APRPD and small kidney size, increased renal parenchyma echogenicity, increased ureter diameters, thick ureter wall were classified as group 3. Hydronephrosis and prominent renal pelvis were defined by APRPD ≥10 mm and ≥ 5 mm in the supine position, respectively [7].

VCUG findings

Reflux evaluation was done by 2 pediatric radiologists, A.S had 12 years and G.M.D. had 2 years experience in pediatric radiology. VUR was classified 0 to 5 according to the International Reflux Study Classification [8]. Grade 1, 2, and 3 VUR were accepted as low-grade reflux (Figure 2), whereas Grade 4 and 5 VUR were accepted as high-grade reflux.

Sensitivity, specificity, PPV and NPV of US were calculated for reflux detection, by comparing VCUG as a reference method.

Figure 1: Imaging in the sagittal plane US. The parenchyma of the left kidney was abnormal, but APRPD was normal.

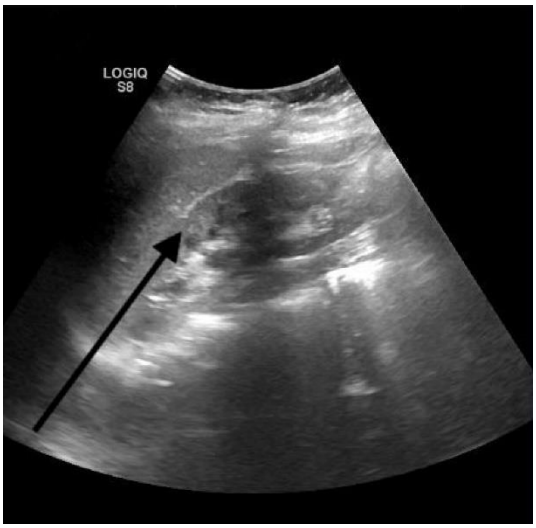
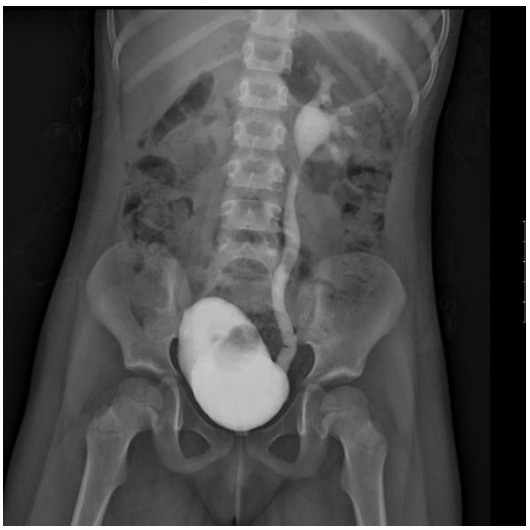


Figure 2: VCUG. There was a grade 3 reflux (low-grade reflux) to the left kidney.



Statistical analysis

SPSS version 22 (IBM, Armonk, NY, United States) was used to evaluate the data. Categorical data were expressed as count and percentage. Pearson's chi-square test and ROC analysis were used for comparisons based on independent groups. Sensitivity and specificity comparisons were performed by McNemar test. *P*-values <0.05 were considered statistically significant.

Results

The male and female ratios in our study were 53.4% (n=203) and 46.6% (n=177), respectively. 33.5% (n=127) of patients were 0-2 years old, 25.5% (n=97) were 3-5 years old, whereas 41% (n=156) were 6-17 ages, and the average was 5.8.

Reflux was observed in 216 (28.4%) of 760 kidneys with VCUG . While 98 (45.3%) of these were high grade, 118 (54.7%) were low grade. If APRPD >5mm was considered as pathological, 57.9% (n=122) of urinary USs were pathological. Of these 122 US examinations, 93 (42.2%) did not show reflux on VCUG (false positive), and the pathology was related to APRPD in 67 (72%). Among the pathologies causing false positivity, the number of those related to APRPD was statistically significantly higher than the other groups (P<0.001).

If APRPD >10 mm (hydronephrosis) was considered as pathologic; 44.8% (n=170) of urinary USs were pathological. 44 (25.8%) USs were pathological without reflux on VCUG (false positive). The pathology was related to APRPD in 26 (59%) of these USs. Among the pathologies that cause false positivity, the number of those related to the APRPD was higher than the other groups, but it was not statistically significant (P=0.08).

Aside from VCUG being the gold standard, sensitivity, specificity, PPV and NPV of US, AUC (area under the curve) and *P*-values according to age ranges were given in detail in Tables 1 and 2 (Figure 3, 4). A correlation was found between VCUG and US results in all age groups (P<0.001).

Table 1: Results of the ROC analysis for APRD >10 mm

Age	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P*-value	AUC
0-17	79.45	79.91	71.17	86.18	<0.001	0.797
0-2	84.78	69.14	60.94	88.89	<0.001	0.770
3-5	82.86	83.87	74.36	89.66	<0.001	0.834
>5	73.85	86.81	80.00	82.29	<0.001	0.803

APRPD: anteroposterior renal pelvic diameter. PPV: positive predictive values, NPV: negative predictive values VCUG: voiding cystouretrography, AUC: Area under curve. The results APRPD >10mm in determination of the necessity of VCUG is summarized.

Figure 3: ROC curve for APRPD >10 mm for determination of the indication of VCUG

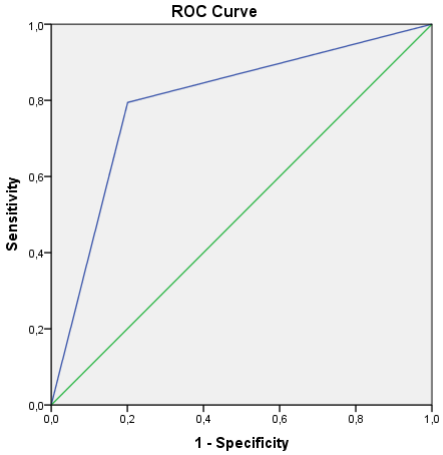
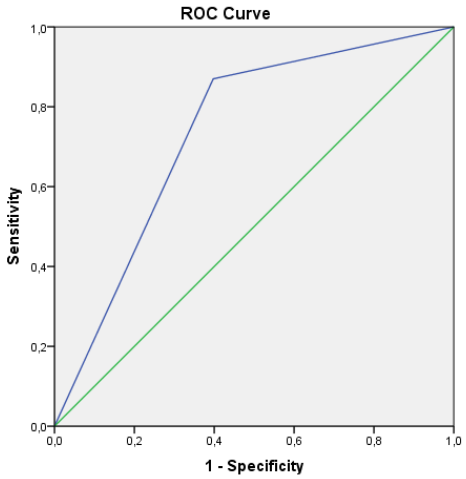


Table 2: Results of the ROC analysis for APRD >5 mm

Age	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*P*-value	AUC
0-17	86.99	60.26	57.73	88.13	<0.001	0.736
0-2	95.65	37.04	46.32	93.75	0.002	0.663
3-5	88.57	72.58	64.58	91.84	<0.001	0.806
>5	80	72.53	67.53	83.54	<0.001	0.763

APRPD: anteroposterior renal pelvic diameter. PPV: positive predictive values, NPV: negative predictive values VCUG: voiding cystouretrography, AUC: Area under curve. The results APRPD >5 mm in determination of the necessity of VCUG is summarized.

Figure 4: ROC curve for APRPD >5mm for determination of the indication of VCUG



Discussion

VUR is an important health problem that is seen in 0.5-1.5% of the children [9]. High-grade VUR is more likely to develop injuries in kidney. Therefore, antibiotic prophylaxis is not recommended in patients with low-grade VUR in the last guidelines, although these children need antibiotic prophylaxis and / or surgical treatment [10]. VCUG, which is used for diagnosis of VUR as the gold standard, is not an appropriate diagnostic method in the screening and follow-up of patients due to its high radiation risk and being invasive [9]. US is a non-invasive examination that is easy to perform and has no radiation, and it is used as a screening method in many centers, especially in the follow-up of urinary tract infection and hydronephrosis. US is recommended by the American Academy of Pediatrics (AAP) as a screening method for predicting the presence of VUR in patients with urinary tract infections [3].

In our study, the sensitivity and NPV of US for reflux were found to be 79.45% and 86.18%, respectively. In the literature, the sensitivity and NPV of US is reported in a wide range between 16-40% and 25-86% for VUR [11], respectively. Preda et al. [12] reported the sensitivity of US for reflux to be %63, whereas Massanyi et al. [11] reported 42% and 86% for low and high grade reflux, respectively. There were 98 kidneys with high grade reflux in our study cohort and only 6 (6.1%) of these kidneys were not pathological in US. This supports that US can be a guide for VCUG examination. In previous studies, the number of patients with high grade reflux were quite low compared to our numbers [13-15]. Our study group included patients of a university hospital with pediatric surgery, a pediatric radiology, and a pediatric nephrology departments, where complicated cases were referred from other hospitals. That revealed the difference in our patient population.

Although there are studies favoring US [15], there are also studies emphasizing the possibility of diagnostic delay of grade 4-5 reflux with a normal US which points out not to use US as a screening test for VUR [13]. Just like Massanyi et al. [11],

Nelson et al. [16] claims that US cannot be used as a screening test for VUR alone due to its low sensitivity and NPV. Compared to the literature, our results were better explained. We expressed the reasons for these results; all of US examinations were performed by the same pediatric radiologist in the study, the status of bladder and ureters, kidney size, and parenchymal features were described in detail in our reports, and non-detailed US examinations were excluded from the study. In most of the previous studies, none of these parameters were not evaluated in US [13, 17, 18]. In some studies emphasizing the importance of US parameters other than APRPD (such as decreased renal size, increased renal parenchymal echogenicity and ureteral dilation), decreased renal size and ureter dilatation were found to be the most important parameters [19, 20].

Most of the studies for US sensitivity for VUR are reported in 0-2 age group in the literature. There are only a few studies comparing the sensitivity of different age groups [21, 22]. Otukesh et al. [21] compared colored doppler voiding urosonography with radionuclide voiding cystography, found that US of young children were more sensitive for reflux, and claimed that the reason for this was the increased sonographic resolution in young children. Ilikan et al. [22] showed a correlation between US and VCUG results in the 0-6 age group, while no correlation was found for >6 years old. In this study, sensitivity and NPV for 0-6 years were 89.76% and 81.2%, whereas for >6 years, sensitivity and NPV were 50.49% and 65.8%, respectively [22]. US results were consistent with VCUG results across all age groups in our study, while 0-2 age group had the highest sensitivity and NPV (84.78% and 88.89%, respectively).

On the other hand, Ilikan et al. [22] found the specificity lower in the 0-6 age group than in the >6 age group. Despite the high sensitivity and NPV in the 0-2 age group, the specificity was as low as 37.04% in our study. The lowest specifity between the groups in our study was in the 0-2 age group, whereas 0-6 age group in the study of Ilikan et al. [22].

The screening with US should reduce the risk of excessive radiation exposure with VCUG imaging as much as possible. When US reports with APRPD >10 mm are considered as pathological, the specificity was 79.91% for all age groups and 69.14% for 0-2 age group. Also, the sensitivity and NPV were still quite high when compared with the literature. In addition, the number of kidneys that caused false positive decreased from 93 to 44. US results causing false positive were clearly related to pathologically accepted APRPD value. In the last guidelines, APRPD 10 mm and above, together with other parameters, was considered pathological [4]. Excessive false positives and low specificity in the 0-2 age group were an expected result depending on the APRPD. One of the most common reasons for performing urinary US in radiology departments for 0-2 age group is the follow-up of hydronephrosis detected in the antenatal period. Most of the dilatations in the pelvicalyceal system are transient in these patients. If there are not any additional findings such as ureter dilatation, and calyceal, parenchymal or clinically severe urinary tract anomaly, surgical treatment is less required in patients with APRPD <10 mm [23]. Also prominent renal pelvis can be detected incidentally in children and it is not related to VUR [24].

Limitations

The most important limitation of our study was being retrospective. Secondly, US is a method that gives subjective, user-dependent results.

Conclusion

We agree with the recent trend in reducing radiation exposure in the radiology community. If US is performed by an experienced radiologist and includes other parameters with APRPD, it will guide for the indication of VCUG in the diagnosis of VUR. By that, some children can be saved from unnecessary radiation exposure.

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Can vitamin D level be a marker for predicting risk in pulmonary thromboembolism? Comparative evaluation with pulmonary embolism severity index and CT angiography obstruction index

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Abstract

Background/Aim: Venous thromboembolism is a pathological process that is among the leading causes of hospital mortality, and many studies showed that vitamin D receptors have a role in thrombosis. This study aimed to investigate the effect of 25(OH)D deficiency on pulmonary thromboembolism and evaluate the pulmonary embolism severity index (PESI).

Methods: Eighty-one patients over 18 years of age who underwent CT angiography with a pre-diagnosis of pulmonary embolism were included in this case-control study. Groups 1 and 2 consisted of 45 patients with pulmonary embolism (PE), and 36 patients without pulmonary embolism, respectively. The PE patients were divided into five groups in terms of age, gender, fever, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, history of chronic lung disease and heart failure, mental status, and malignancy to calculate the PESI score. Classes 1 and 2 were classified as low-risk, and Classes 3, 4, and 5 as high-risk. The CT obstruction index (CTOI) was calculated in patients with pulmonary embolism. Vitamin D levels were noted.

Results: No significant difference was observed between the groups in terms of age, gender, and body mass index values ($P>0.05$). 25(OH)D level was significantly lower in the pulmonary embolism group (7.2(3.3) vs. 8.7(7.0), $P=0.028$). The CTOI was significantly higher in the high-risk patient group ($P=0.019$).

Conclusions: The evaluation of 25(OH)D levels may be beneficial in determining the risk of thromboembolism.

Keywords: CT obstruction index, PESI score, Pulmonary embolism, 25(OH)D

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Introduction

Vitamin D is essential for maintaining health [1]. In addition to the calcium-phosphorus metabolism, it also affects the immune system, inflammation, anti-oxidation, and anti-fibrosis [2, 3]. Recent studies revealed that chronic diseases, including cardiovascular diseases, diabetes, cancers, autoimmune, and infectious diseases are associated with vitamin D [4-6]. 25(OH)D deficiency is thought to increase inflammation, insulin resistance, pancreatic beta-cell dysfunction, and renin-angiotensin-aldosterone system dysfunction, leading to atherosclerotic and cardiovascular diseases [7]. Numerous studies showed that 25(OH)D receptors have a role in thrombosis and increased 25(OH)D levels reduce the venous thromboembolism (VTE) risk [8, 9].

VTE is a pathological process that includes pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT). The current clinical classification used to predict the prognosis in PTE is PESI [10, 11]. CT angiography (CTA) helps to evaluate the presence of thrombus up to the distal segmental branches, and calculate the CTOI, which reveals the extent of the thrombus and the arterial occlusion's degree [12, 13]. Many studies compared the efficiency of PESI and CTOI in evaluating the prognosis [14, 15].

Our study aims to examine the effect of 25(OH)D deficiency on PTE and evaluate the PESI, which helps to predict prognosis, and CTOI findings with 25(OH)D levels comparatively.

Materials and methods

Our study was designed retrospectively and approved by the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (2020/331). Eighty-one patients over 18 years of age who underwent CTA with a pre-diagnosis of pulmonary embolism and signed the consent form between 01.08.2019-01.02.2020 were included in the study. Our study comprised patients who visited the radiology department between these periods and did not match the exclusion criteria. The G*Power 3.1 tool was used to calculate the number of patients to be included in each group, with a confidence interval of 95% and a power of 80%. To avoid bias, the patients who met the inclusion criteria were consecutively grouped. Patients with autoimmune and inflammatory diseases, hypercalcemia, renal failure, sarcoidosis, malignancy, hypophosphatemic rickets, enzyme deficiency, and receptor defects, and patients with suboptimal CTA were excluded from the study. The patients' demographic data, history of ischemic heart disease, diabetes, and hypertension (HT), and laboratory results were recorded.

The patients underwent a CTA examination with a 64-slice CT device (General Electric Revolution EVO, 64-slices). The scan parameters were as follows: 0.6 mm collimation, 1.5 mm slice thickness, 1.4 mm increment, 100kV, 135 mAs, a pitch of 0.9, and a gantry rotation time of 0.33s. According to the results of CT angiography, 45 patients diagnosed with pulmonary embolism constituted Group 1, and 36 patients without pulmonary embolism constituted group 2. The CTOI was calculated in PE patients with the consensus of two radiologists based on the formula used by Qanadli et al. [13]. Pulmonary trunk diameter and the ratio of right ventricle (RV) diameter to the left ventricle (LV) were noted in 45 patients with embolism and 36 patients without embolism, apart from the calculation of vascular obstruction percentage.

No consensus exists about the optimum serum 25(OH)D level. 25(OH)D deficiency indicates 25(OH)D levels<20ng/ml (50nmol/l) in many studies, and insufficiency indicates levels between 21-29 ng/ml. The optimal 25(OH)D concentration is at least 30ng/ml [16]. These reference values were used in our study, as well.

The patients with pulmonary embolism were divided into five groups based on age, gender, fever, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, history of chronic lung disease and heart failure, mental status, and malignancy to calculate the PESI score. Classes 1 and 2 were classified as low-risk, and Classes 3, 4, and 5 as high-risk [17].

Statistical analysis

The analysis was performed with SPSS 20.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA). The normality of the variables was tested with the Kolmogorov-Smirnov method. Quantitative variables were presented as mean (standard deviation) (SD) and median (interquartile range (IQR)) values, while qualitative variables as numbers and percentages. Differences between independent groups were evaluated by *t*-tests and ANOVA for quantitative data and Mann-Whitney U and Kruskal Wallis tests for non-normal variables. A two-tailed *P*-value of <0.05 indicated significance.

Results

Forty-five patients with PE and 36 patients without PE were included in our study. No significant difference was observed between the groups in terms of age, gender, and body mass index values ($P>0.05$). The patients were evaluated in terms of ischemic heart disease, diabetes, HT, hyperlipidemia, and smoking. The mean 25(OH)D level was 7.2(3.3) ng/ml in the PE group with embolism and 8.7(7) ng/ml in the control group ($P=0.028$). In the PE group, 25(OH)D levels were 10ng/ml or less in all patients (severe deficiency), significantly lower than that in the control group (Table 1).

Table 1: Demographic and clinical data and vitamin D level of pulmonary embolism (+) and (-) patients (n=81)

Demographic/Clinical date	Pulmonary embolism (+) (n=45)	Pulmonary embolism (-) (n=36)	*P*-value
Age, (years)	67.4 (16.3)	66.8 (13.4)	0.185
Gender, male (%)	53.3(24)	75(27)	0.045
Body mass index (Kg/m^2)	28.2 (4.8)	26.4 (4.2)	0.427
Ischemic heart disease, n (%)	10(22.2)	1(2.7)	0.011
Diabetes, n (%)	1(2.2)	0	0.368
Hypertension, n (%)	18(40)	12(33.3)	0.537
Hyperlipidemia, n (%)	5(11.1)	0	0.039
History of smoking, n (%)	15(33)	21(58)	0.024
25-Hydroxy Vitamin D (ng/mL)	7.2(3.3)	8.7(7)	0.028

Data are presented as mean (SD) or n (%). 25-hydroxy vitamin D (ng/mL) level is presented median (IR)

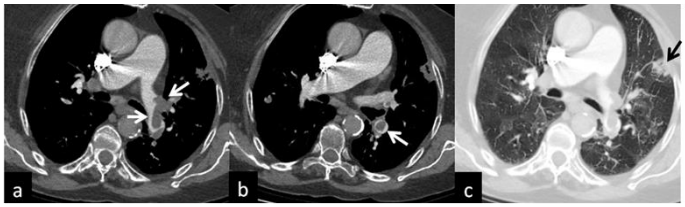
In the PE group, the PESI score was correlated with the CTOI. According to the PESI score, 71% and 29% of the PE patients were in the high and low-risk groups, respectively. The mean CTOI was 36.1 (19.7) in the high-risk group (Figure 1) and 20.8 (17.4) in the low-risk group ($P=0.019$). The mean 25(OH)D levels were 6.84 (2) and 7.19 (1.7) ng/ml in the high and low-risk groups, respectively ($P=0.598$). The data of the PE group are summarized in Table 2.

Table 2: The patient groups with pulmonary embolism (n=45)

	High risk patients (n=32)	Low risk patients (n=13)	*P*-value
CT Obstruction Index	36.1 (19.7)	20.8 (17.4)	0.019
25-Hydroxy Vitamin D (ng/mL)	6.84 (2)	7.19 (1.7)	0.598

Data are presented as mean (SD) or n (%).

Figure 1: 78-year-old patient's CT angiography examination with a massive pulmonary embolism (a, b) (white arrow) and parenchymal infarction (c) (black arrow) In the high-risk group patient, the CT obstruction index was 27 and serum vitamin D level was 3.49 ng/ml.



In both groups, besides the evaluation of CTA in terms of embolism, the diameter of the main pulmonary artery, RV/LV, and superior vena cava (SVC) diameters were also measured. The pulmonary trunk diameters were 29.3 (4.2) mm and 30.1 (3.7) in the PE and control groups, respectively (P=0.049). The ventricular diameter ratio was 1.3 (1.05) in the PE group and 0.95 (0.2) in the control group (P<0.001), and the RV diameter was significantly higher in the PE group.

Discussion

Venous thromboembolism is one of the most critical causes of preventable mortality, especially in the elderly and patients confined to bed, and the relationship between 25(OH)D level and thrombosis was shown in many studies [18]. 25(OH)D level was significantly lower among the PE patients in our study. Besides, our study made a comparative evaluation between 25(OH)D levels and embolism burden as well as the relationship between 25(OH)D and thromboembolism, and it is the first in the literature, as per our research. For this purpose, the PESI score and CTOI, which are related to 25(OH)D levels and embolism burden, were evaluated comparatively. Although mean levels of 25(OH)D were lower in the high-risk group, no significant difference was found. However, 25(OH)D levels were below 10ng/ml (severe deficiency) in all patients with embolism. 25(OH)D deficiency and thromboembolism etiology are multifactorial [1]. Nonetheless, existing studies and ours support that a low 25(OH)D level is associated with thromboembolism. We think that evaluating 25(OH)D levels in patients who constitute the risk group for thromboembolism and who are planned to be hospitalized, and vitamin D addition to the treatment in patients with a deficiency may contribute to reducing the risk of thromboembolism.

Another significant result of our study was the correlation between the PESI score and CTOI in PE patients. The CTOI was significantly higher in the high-risk patient group than in the control group. In contrast to the advancements in prophylaxis, diagnostic methods, and therapeutic options, venous thromboembolism is still a major health problem. Since death usually occurs in the first hours after hospitalization, rapid and specific diagnosis is critical [19]. In addition to detecting the embolism, the ability of CT examination to provide information about the embolic burden and RV load is very valuable for a rapid pre-evaluation. For this reason, the correlation between the PESI score, which contributes to the assessment of the prognosis, but takes time due to the number of parameters, and the CTOI, which provides information about the embolism burden, and the inclusion of the ventricle diameter ratio, can provide a quick and objective assessment of the patient prognosis.

Thromboembolism patients were shown to have low 25(OH)D levels in many studies, as in ours. In a cohort study conducted by Lindqvist et al. [9] on 40,000 women followed for 11 years based on the "Does active sun exposure habit reduce the risk of venous thrombotic events?" question, they found that the risk of venous thromboembolism was 30% lower in Swedish women who sunbathed or used solarium during summer-winter holidays or abroad, compared to those who were not exposed to the sun. Khademvatani et al. [7] investigated the relationship between idiopathic lower extremity DVT and 25(OH)D, and a significantly lower 25(OH)D level was observed in the DVT group compared to the control group.

Although numerous studies [20] and ours support the relationship between 25(OH)D and thromboembolism, studies with larger participants and a longer follow-up are needed.

The correlation between the PESI score and the CTOI, and significantly higher CTOI in the high-risk patient group, were also in line with the literature. In the study of Wu et al. [12], there was a correlation between PE indices, PE volume, and survival, and preliminary evidence showed that clot quantity is a significant predictor of patient death in PE. Qanadli et al. [13] concluded that CTOI and Miller index showed a good correlation. In our study, the calculation method of Qanadli et al. [13] was used as a reference in the calculation of the CTOI. Nural et al. [14] found that CTOI, RV and SVC diameters, RV/LV short-axis ratio, ventricular septum shape, and contrast reflux to the inferior vena cava were useful in distinguishing hemodynamically stable and unstable patients in the patient group with embolism. In our study, the main pulmonary artery diameter, RV/LV, and SVC diameters were measured to predict right ventricular load. Ventricular diameter ratios were 1.3 (1.05) in the embolism group and 0.95 (0.2) in the control group, and the RV diameter was significantly higher in the embolism group.

Limitations

Our study's most significant limitation was the small number of patients. Many studies also showed that 25(OH)D levels were lower in the winter compared to in the summer [9], and that the incidence of thromboembolism increased during the winter [20]. Our study was conducted between August and February, and we could not evaluate the relationship between 25(OH)D, embolism, and seasonal effects. Also, 25(OH)D levels were measured in patients hospitalized due to embolism, but control values were not measured before and after hospitalization. More extensive clinical studies and meta-analyses are needed to demonstrate the effect of vitamin D supplements on thrombosis, since many factors affect 25(OH)D levels, such as genetics, inflammatory causes, and seasonal changes.

Conclusion

25(OH)D levels were significantly lower among patients with thromboembolism in our study, and evaluation and supplementation of 25(OH)D levels in patients at risk for thromboembolism may be beneficial in reducing its risk. Our study suggested that the 25(OH)D level, which is routinely checked in clinical practice, can be used as a marker for pulmonary thromboembolism. Besides, we think that evaluating

the embolism burden as well as the presence of embolism may help objectively predict the prognosis and affect treatment planning in this disease with remarkably high mortality.

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Covid-19 and maxillo-facial fractures: A comprehensive retrospective cohort study on the analysis of costs in COVID-19 era

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Ethics Committee Approval
The research protocol of this study was approved by the Ege University local clinical research ethics committee (EgeTAEK) on 10/31/2020 and with approval number 20-11T/23.
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: Maxillofacial trauma management has also undergone a change starting from December 2019 due to the emergence of a new viral infection, later called COVID-19, and then a pandemic mandating new medical protocols. This retrospective cohort study aimed to explain the changes in medical costs and underlying causes of cases with maxillofacial bone fractures during the COVID-19 period, based on the lack of focus on cost analyses on this subject in previous studies.
Methods: Patients who were operated on for maxillofacial trauma in our clinic before and during the COVID-19 outbreak were retrospectively analyzed in terms of sex, age, etiology, personal protective equipment (PPE) usage, treatment methods, and total costs. Statistical analyses were carried out for any significant changes.
Results: A total of 78 patients of which 38 were operated on before whereas 40 were operated on during the COVID-19 outbreak, were included in this study. Accordingly, 24 patients of the pre-COVID-19 group and 37 patients of the post-COVID-19 group were admitted from Emergency Department (ED), which included all the first wave patients (*n*=21). In the pre-COVID-19 group, a total of 220 screws and 58 plates were used for 22 IRFs. The total LoH of the patients was 180 days. In the post-COVID-19 group, 274 screws and 70 plates were used for 24 IRFs. The total LoH of the patients was 185 days. A total of 156 PPE including N95 masks and extra operation shirts were used. The pre-COVID-19 group's treatment costs were calculated as USD 320.3 per patient. Post-COVID-19 group's treatment costs were calculated as USD 496.68 per patient.
Conclusion: The statistical evaluations revealed that the COVID-19 pandemic resulted in differences due to the introduction of PCR tests applied for each patient and the PPE used for the precautions taken for the COVID-19 infections. On the other hand, there were no changes in the number of the use of plates, screws, and in the length of hospitalization. It can be argued that this outcome has led to no necessary changes in the treatment protocols in terms of costs.

Keywords: Maxillo-Facial fractures, COVID-19, Closed fractures, Medical costs, Multiple fractures, Cost analysis

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Introduction

In December 2019, a novel pneumonia epidemic hit Wuhan and then became a pandemic in only 3 months [1]. Daily life and the burden of daily stresses changed to lockdown and pandemic stress that caused different morbidities [2]. In this era, traumatic patients with maxillofacial (MF) fractures were expected to have operated in facilities with adequate manpower and COVID-19-segregated services [3]. Some of the departments in our hospital which were organized to serve in several buildings in a complex, like the burn center allocated under service of infectious disease, pulmonology, and anesthesiology departments to isolate and treat COVID-19-patients. Inherently, as clinicians of a tertiary hospital, we are obliged to treat emergency patients such as traumatic maxillofacial fractures and tumor patients with bone/soft tissue defects, too, as usual. However, we observed alterations in types of admissions and clinical features of patients with maxillofacial area problems in our center.

Before the COVID-19 pandemic hit the world, only surgical masks, caps, shirts, and gloves were used for most of the operations. Literature had argued and settled most of the issues about postoperative complications, costs, and hospitalization lengths. Conversely, we were introduced to a novel status with alterations which cannot be foreseen. Precautions were taken and changed by governments, as recent data accumulated. Like many countries that halted the routine normal life, Turkey had curfew periods during the pandemic term, similarly, to limit the spread of the disease. Therefore, in the past year, medical professionals encountered many different situations.

Medical practice costs a lot according to the amounts mentioned in the literature. However, costs and prices of medical supplies and services per country may change. In this study, we aim to find out if characteristic features like etiology, admission rates, or costs of maxillofacial patients changed in a tertiary trauma center during the pandemic.

Materials and methods

This study was designed as a single-center, retrospective study in Ege University Hospital, Plastic Surgery, and Emergency Medicine Clinics. The research unit is a tertiary reference health center, and about 190,000 patients were cared for annually before the COVID-19 era. The research protocol of this study was approved by the Ege University local clinical research ethics committee (EgeTAEK) on 10/31/2020 and with approval number 20-11T/23. After the approval of the committee, adult patients with Maxillofacial Fractures (MF FX) of which the International Statistical Classification of Diseases and Related Health Problems (ICD) code is S02, who were operated in our clinic between 07/21/2019 and10/31/2020 were retrospectively evaluated. This date range was determined by the beginning of lockdowns and hospital arrangements for the COVID-19 pandemic in our center (03/11/2020, named as "COVID-19 -deadline"). Prior to this date, patients who were treated with routine algorithms formed the pre-COVID-19 group, whereas the patients who were operated on after this date with necessary COVID-19 precautions formed the post-COVID-19 group. Exactly 234 days were set for both pre-and post-event to build the control and study groups. Additionally, the COVID-19 group was further divided into three groups, including the first lockdown period (11.02.2020 – 01.07.2020), the summer period without lockdowns (01.07.2020 – 15.09.2020) and the second lockdown period (15.09.2020 - 31.10.2020). A retrospective search was conducted to obtain data about epidemiology, admission methods (Emergency Department (ED) or Plastic Surgery outpatient clinic), etiologies, operations, lengths of hospitalization (LoH), precautions are taken per operatively, and treatment costs were recorded. Etiologies were further divided for traffic accidents (TA), falls; assaults, home (or sport) accidents, and gun wound (or crush) injuries. Costs of the treatments were calculated as the total of multiple admissions and screening tests for COVID and PPEs that had been used were included. All costs were calculated as US dollars (USD) per exchange rate of Turkish Lira (TL) as of January 2021 (7.35TL/USD).

Statistical analysis

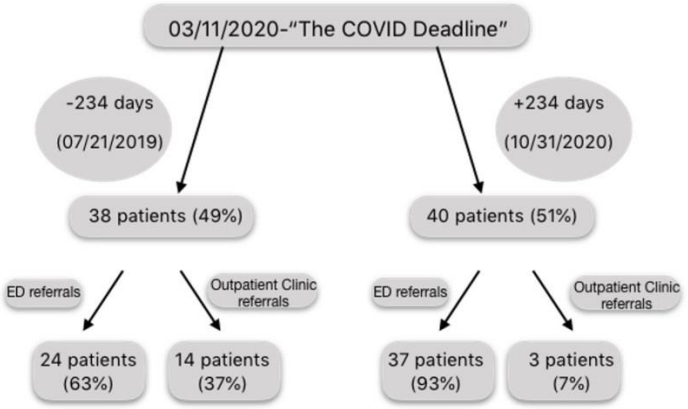
Statistical analysis was done to reveal any significant changes between pre-and post- COVID-19 groups. As the first step of the statistical evaluations, to validate the sample size, the G*Power computer software was utilized for Power Analysis, with medium effect size (d=0.66), 80% power, and 5% type I error level, for the Independent Sample T-test to be performed within the framework of the above-mentioned purposes [4, 5]. Accordingly, a minimum of 38 participants were required in each group.

The IBM SPSS 25.0 software was used for the statistical evaluations. Descriptive statistics in the analyses were presented as frequency (n), mean, standard deviation (SD), minimum (Min), and maximum (Max) values. The independent sample t-test was used to compare the two-group comparisons of costs, the number of plates, screws, and the length of hospitalization before and during the COVID-19 pandemic. The level of significance was set as $P<0.05$.

Results

A total of 78 patients were operated on in our clinic for fractures during this timeline. Of these patients, 38 were operated on before, and 40 were operated on after the COVID-19 -deadline. Also, 22 of the patients were females while 56 were male. Of the patients, 39 of the patients were aged 20 or lower whereas the remaining 39 were aged 30 or higher. A group of 24 patients of the pre- COVID-19 group was admitted from ED, while 37 patients of the post- COVID-19 group were referred from ED. The ED referrals in the post-COVID-19 group comprised all the first wave patients (n=21), 6 of the summer patients (n=8), and 8 of the second wave patients (n=10) (Figure 1). Three patients from the pre-Covid-19 group and five patients from and the post-COVID-19 group had two admittances to the PS ward, due to intermaxillary fixation (IMF) extraction or postoperative follow-ups, respectively.

Figure 1: Flowchart of building the patient population



Treated bone fractures were 20 mandible fractures, including four cases of other concomitant MF FXs, 15 zygomatic fractures (ten tripods and five isolated arches), one nasal fracture, four blow-out fractures, and three Le Fort III fractures that two tripod zygomatic and one mandible fractures were associated with. Seven mandible fractures were treated with IMF only, while 13 were treated with IRF with or without IMF. All tripod fractures were treated with IRF, as all zygomatic arch fractures were treated with Gillies Operation. All the blow-out fractures were treated with cartilage grafting. In total, 220 screws and 58 plates were used for 22 IRFs (avg. 10 screws/patient and 2.63 plates/patient). The total LoH of the patients was 180 days (avg. 4.74 days/patient) (Table 1).

Table 1: Cases of pre- and post-COVID groups

	Pre-COVID	Post-COVID
Mandible FX	26	38
Zygomatic FX	17	7
Frontal FX		3
Blow-out	4	3
Nasal FX	1	
LeFort II		1
LeFort III	3	
IRF	26	27
Plate	60	75
Screw	226	291
PPE	0	192
LoH*	4.33	4

LoH: Length of hospitalization, *: Is given as average days per patient.

All the patients were tested for COVID-19, and negative results were obtained for all patients. Treated bone fractures were 31 mandible fractures, of which three were with other MF FXs concomitantly, seven zygomatic fractures (five tripods and two isolated arches), two frontal bone fractures, one inferior orbital rim fracture, one blow-out fracture, and one Le Fort II fracture. 12 mandible fractures were treated with IMF only, while 19 mandible fractures were treated with IRF. Two zygomatic arch fractures and one of the zygomatic tripod fractures were treated with Gillies operation. Four tripods, two frontal bone fractures, and the blow-out fracture were treated with IRF. In total, 274 screws and 70 plates were used for 24 IRFs (avg. 11.42 screws/patient and 2.92 plates/patient). The total LoH of the patients was 185 days (avg. 5 days per patient). A total of 156 PPE including disposable gowns and sheets were used (3.9/patient).

The etiology of pre-COVID-19 group comprised 16 TAs (42%), three home accident injuries (8%), nine falls (24%), nine assault-related injuries (24%), and one gun wound injury (2%). The post-COVID-19 group comprised 16 assault injuries (40%), 10 fall injuries (25%), 10 TA (25%), three home accidents (8%), and one crush injury (2%) due to the Izmir earthquake in October 2020. Eight patients (20%) were operated on during the first wave whereas 22 (55%) were operated on during summer and ten patients (25%) during the second wave.

The treatment costs of the pre-COVID-19 group were calculated as USD 12,171.78 in total. The Average cost per patient was USD 320.31 (min. USD 10.42-max. USD 1.208,40). The lowest cost of USD 10.42 was for a nasal fracture patient, which was treated with only closed reduction. The treatment costs of the post-COVID-19 group were calculated as USD 18,712.40 in total. The average cost per patient was USD 496.68 (min. USD 20.00, max. USD 2515.30) (Table 2) (Figure 2, 3).

Table 2: The values and changes in parameters before and after the COVID-19 pandemic

Variables	Group	f	min	max	$\bar{X}$	SD	*t*	*P*-value
Total Costs including PCR tests (in the post-COVID-19 group)	Pre-COVID-19 Group	38	10.42	1208.40	320.31	244.46	-2.131	0.036
	Post-COVID-19 group	40	20.00	2515.30	496.68	450.97		
Plate	Pre-COVID-19 Group	38	0	7	1.53	1.62	-0.546	0.578
	Post-COVID-19 group	40	0	9	1.75	1.97		
Screw	Pre-COVID-19 Group	38	0	30	5.79	6.69	-0.689	0.493
	Post-COVID-19 group	40	0	25	6.85	6.89		
Length of Hospitilization	Pre-COVID-19 Group	38	1	17	4.74	4.76	0.115	0.908
	Post-COVID-19 group	40	1	16	4.63	3.77		

Figure 2: Distributions (left) histogram and (right) plot charts of logarithmic derivatives of the costs.

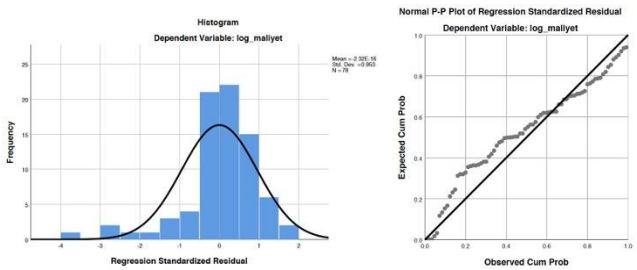
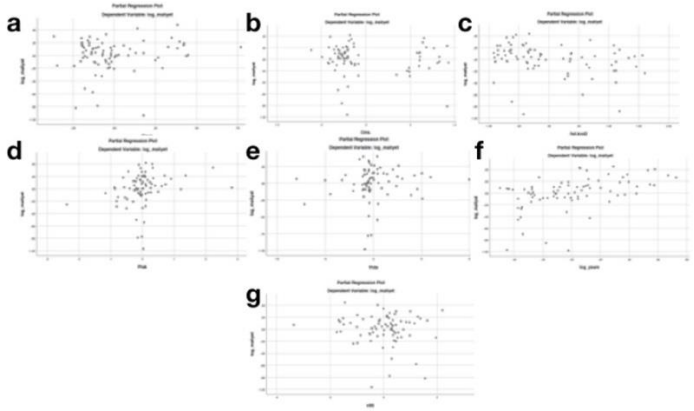


Figure 3: Plot charts of the variables and logarithmic derivative of the costs. Variables: a>Group, b>Sex, c>Fractured bone, d>Plate count, e>Screw count, f>hospitalization length, g>PPE



Discussion

When the COVID-19 pandemic hit, the threshold for interventions was raised to assure fewer transfections of COV-SARS-2 virus between hospital environments and patients [2].

Early suggestions for elective MF surgery were to be deferred as orthognathic surgery [6]. This was logical and strictly followed, like lockdowns. However, besides social and psychological ones, there was also an economic impact of the pandemic. From macro - to micro -, all the parts of the economic systems of the world adapted to a "new normal", which necessitates a different income-expenditure balance, assuring older entries of expenditures to change [7]. For this instance, as we examine in this study, patient-care costs for trauma surgery in maxillofacial area have changed.

After the COVID-19 outbreak, most of the people got scared and obeyed the restrictions. As a result of their fear of the disease, they got out of their homes only for mandatory needs. We expected to see the same effect in our patients. Our patient profile which showed a relative rise in ED admissions in the post-COVID-19 era satisfied this expectation, indicating a higher tendency of the patients to refer to the ED only in the case of unbearable discomfort. We believe that this can be interpreted as a social expression of the human behavior of which life is at stake under the COVID-19 threat.

The etiology of MF bone fractures has been extensively studied in previous studies. It was thought that the changes in the circumstances due to the COVID-19 outbreak might have caused the etiological distribution and ranking of the cases. For example, trauma due to firearm injuries or domestic violence was shown to increase in the USA [5]. In our study, we conversely found less assault and even no firearm injuries. Surprisingly, MF traumas were more frequently encountered than the same length of time before the COVID-19 -deadline. Most of the patients were encountered during summer. This can be accounted to loosened lockdown restrictions, allowing the population to interact more. Nevertheless, we encountered no gunshot wounds or sports injuries during this whole term. This may be caused by the reason that; team sports were restricted during this time interval. Moreover, maxillofacial gunshot injuries probably caused a higher and faster mortality rate, making them less encountered by us.

In different studies, zygomatic fractures were shown to be the most injured bone in MF trauma, while some others indicate the mandible. Also, literature mentions a male predominance in MF fractures [8,11]. When the most common etiologies were taken into account (TA and assaults), male predominance is not sound overwhelming as the cause [11]. However, during the COVID-19 pandemic, due to lockdowns around the globe, this etiological ranking might have changed, also affecting sexual predominance. Yet, in our study, male predominance continues, while rankings of etiologies changed only during the first wave.

COVID-19 also changed protocols for the patient approach. For instance, it is known when an asymptomatic patient is encountered, a high risk of COVID-19 transfection is possible in the MF-area surgeries, due to close interaction of the operative team with the oro-nasal area [8]. Therefore, in our algorithm, we prefer preoperative PCR tests to minimize the risk of operating a COVID-19 (+) patient, which has a higher risk of postoperative pulmonary complications. This algorithm also minimizes the surgical team's exposure risk, while adding to total costs [2]. On the other hand, unlike our previous algorithm, patients sometimes wait in the ward, occupying a room isolated until the PCR test result is obtained, adding extra time to LoH. Nevertheless, as LoH values were shown to differ statistically insignificant in this rise, the PCR tests seem to be a major reason. In the future, the development of cheap testing kits may reduce the costs, maybe even to a level that may not give statistically significant differences in costs.

Costs for maxillofacial fracture treatments have been examined many times in previous studies. A Turkish study by Altıparmak et al. [8] has reported a median of USD 114 in their MF FX cost-analysis study. In a US-based study, treatment costs for mandible and zygomaticomaxillary fractures were given as high as between USD 5.620,61 and USD 9.051,94 [9]. As the study by Altıparmak et al. was also conducted in Turkey, it grants a more accurate estimation of the pre-COVID-19 period. However, our results revealed higher costs than those reported by Altıparmak et al., showing a 2.5- COVID-19 increase in costs of such patients of the pre- COVID-19 era. Furthermore, our statistics showed that COVID-19 has added an extra 1-fold of increase to the average values of costs when compared with Altiparmak et al.'s study. Their study compared different hole counts referring screw counts in IRF, but without taking the plate counts into account [8]. However, although our costs were found to be strongly correlated with plate usage, LoH, and fractured bone types (but not screw usage), none of these parameters were found to be statistically significant between pre-and post-COVID-19 groups. Therefore, it would not be wrong to say that we did not change our treatment protocols, but COVID-19 precautions increased the costs by addition of some expenses. The increase in the total costs was directly related to the use of PCR tests for the detection of the disease and the PPE used for the precautions taken for the COVID-19 infections. On the other hand, there were no changes in the number of the use of plates, screws, and also in the length of hospitalization.

With this study, we aimed to reveal if COVID-19 pandemic conditions affect the etiology of MF fractures, treatments, and costs of MF traumas. Eventually, our population's characteristics were found to be similar in the COVID-19 era, with higher costs of total treatments.

The small size of the patient population can be regarded as one of the limitations of the present study. However, the power analysis carried out prior to the Sample t-test to analyze the significance of the differences between the groups yielded that sample size is adequate to carry on with the current data. Also, our comparison does not focus on different bone fractures' treatment costs. To overwhelm these problems, larger populations, even enough counts of patients that may allow specific bone fracture comparisons, can be used in future studies.

Conclusion

The present study revealed that the circumstances that emerged with the onset of the COVID-19 outbreak yield differences in terms of the total costs of treatment of MF fracture surgeries. Accordingly, the onset of the use of PCR tests for the detection of the disease and the PPE used for the precautions taken for the COVID-19 infections. On the other hand, there were no changes in the number of the use of plates, screws, and in the length of hospitalization. It can be argued that this outcome has led to no necessary changes in the treatment

protocols in terms of costs and the procedures were carried out in their normal routine.

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Evaluation of LIPI and mGPS as prognostic factors in extensive-stage small-cell lung cancer

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Ethics Committee Approval
The study was performed according to the institutional ethical standards (University of Health Sciences, Umraniye Training and Research Hospital, Number: B.10.1.TKH.4.34.H.GP.0.01/367).
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: There is an unmet need for effective prognostic models in small cell lung cancer. Lung immune prognostic index (LIPI) and Modified Glasgow Prognostic Score (mGPS) markers are prognostic in various cancers. We aimed to examine LIPI and GPS markers' prognostic effects on overall survival (OS) in extensive-stage small-cell lung cancer (SCLC) patients.

Methods: Patients who were 18 years of age or older, diagnosed with extensive-stage small cell lung carcinoma who received platinum-based chemotherapy as first-line treatment were included in this retrospective observational study. Having concurrent or sequential radiotherapy to the thorax and receiving non-platinum-based chemotherapy as first-line treatment were the criteria for exclusion. We measured their pretreatment LIPI and mGPS markers and performed multivariate Cox regression analyses of progression-free survival (PFS) or OS in extensive stage-SCLC patients.

Results: A total of 129 patients were included in the study. Twenty-eight patients (21.7%) were mGPS 0, 65 patients (50.4%) were mGPS 1, and 36 (27.9%) were mGPS 2. Fourteen percent of the patients were LIPI 0 (n=18), %38 were LIPI 1 (n=49), and %48 were LIPI 2 (n=62). The OS of the mGPS 0, mGPS 1, and mGPS 2 patients were 19.0 months (95% CI, 16.3-21.7), 8.4 months (95% CI, 7.1-9.8), and 6.4 months (95% CI, 3.1-9.6) respectively, and those of LIPI 0, LIPI 1, and LIPI 2 patients were 18.3 months (95% CI, 9.9-26.7), 11.7 months (95% CI, 5.3-18.1), and eight months (95% CI, 6.6-9.5), respectively. In the multivariate analysis, ECOG PS 0-1 and LIPI score 0-1 were associated with better PFS (P=0.035 and P=0.03 respectively) and OS (P=0.003 and P=0.036 respectively).

Conclusions: LIPI score predicted an unfavorable prognosis, whereas mGPS was not associated with survival. It would be better to consider the use of the LIPI score when managing extensive-stage small cell lung cancer.

Keywords: Lung immune index, Small cell, Prognostic factor, Extensive stage, Survival

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 13% -15% of all lung cancers. One-third of the cases are diagnosed with limited disease (LD) and two-thirds, with extensive disease (ED) [1, 2]. Small cell lung cancer is a very chemosensitive tumor, however, the median overall survival (OS) of ED-SCLC is around 10 months. Although extended survival is attempted with various chemotherapeutic agents, the advantage remains limited [3,4]. Studies found that patients' performance status (PS), age, smoking status, and disease stage are prognostic factors [5, 6]. Inflammation and immunity play an essential role in tumor formation, progression, invasion, metastasis, and response to treatment [7]. The survival effect of systemic inflammatory response has rarely been studied in these patients [8].

Lung immune prognostic index (LIPI) is a marker that combines the derived neutrophil-lymphocyte (dNLR) ratio and serum lactate dehydrogenase (LDH) level. Recent studies reported it as a prognostic factor, especially in patients with non-small lung cancer. LIPI was categorized into 3 groups in the studies: Group 0 (favorable) indicates a dNLR of <3 and a normal LDH, group 1 (intermediate) indicates a dNLR of <3 but high LDH and group 2 (poor) indicates a dNLR >3 and a high LDH level [9].

Serum albumin and C-reactive protein (CRP) are routinely examined during SCLC diagnosis. Modified Glasgow Prognostic Score (mGPS) includes the serum albumin and CRP values. Sonehara et al. [10] reported that mGPS had a prognostic effect on SCLC patients' overall survival.

mGPS was categorized into 3 groups, as follows: mGPS group 0: Patients with normal albumin levels (>3.5 g/dl) and CRP (<1.0 mg/dl), mGPS group 1: Patients with normal albumin levels (>3.5 g/dl) and an elevated CRP (>1.0 mg/dl) or a normal CRP (<1.0 mg/dl) with low albumin levels (<3.5 g/dl), and mGPS group 2: Patients with low albumin levels (<3.5 g/dl) and a high CRP (> 1.0 mg/dl).

Our study aimed to examine the prognostic effect of LIPI and GPS markers on overall survival.

Materials and methods

The Ethics Committee approved the study protocol at the University of Health Sciences, Ümraniye Education and Research Hospital, (Date: 22.11.2020, Number: B.10.1.TKH.4.34.H.GP.0.01/367). Eligible patients were aged 18 years of age or older, histopathologically diagnosed with extensive-stage small-cell lung carcinoma, received platinum-based chemotherapy as first-line treatment, and had adequate liver and kidney function. Exclusion criteria were having concurrent or sequential radiotherapy to the thorax and receiving non- platinum-based first-line treatment.

Between 2012 and 2020, a total of 129 patients were recruited from four different institutions.

The baseline characteristics of the patients, namely, age, gender, smoking, performance scores (PS) according to Eastern Cooperative Oncology Group (ECOG), were evaluated. The laboratory values obtained one week before the treatment were as follows: A complete blood count, serum albumin, serum lactate dehydrogenase, serum C-reactive protein, serum creatinine, serum aspartate aminotransferase, and alanine aminotransferase. LIPI and mGPS groups were categorized as previously described. The radiological response to chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Objective response rate (ORR), complete response (CR) + partial response (PR) (ORR: CR + PR) and disease control rate (DCR), ORR + stable disease (SD) (DCR: CR + PR + SD) were calculated. Progression-free survival (PFS) was considered as the time from the date of first chemotherapy initiation to the date of progressive disease documented or death, and overall survival (OS), as the time from the start of the first chemotherapy to death or last follow-up date. OS and PFS were compared between both the LIPI and mGPS groups.

Statistical analysis

The PFS and OS analyses of all SCLC patients were evaluated with the Kaplan-Meier method. Significance tests for PFS and OS were compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazard model to determine the independent prognostic factors. The last follow-up date in the present study was 30 September 2020, and a *P*-value of <0.05 indicated statistical significance. Statistical analysis was performed using IBM SPSS Statistics, version 26.

Results

mGPS

A total of 129 patients were included in the study. Twenty-eight patients (21.7%) were mGPS 0, 65 patients (50.4%) were mGPS 1, and 36 (27.9%) were mGPS 2. There were 108 (83.7%) males. One hundred and twenty-six patients (97.7%) smoked. Among mGPS 0 patients, 19 (67.9%) were ECOG PS 0, 8 (28.5%) were ECOG PS 1 and 1 (3.6%) was ECOG PS 2. Among mGPS 1 patients, 15 (23.1%) were ECOG PS 0, 24 (36.9%) were ECOG PS 1, 24 (36.9%) were ECOG PS 2, and 2 (3.1%) were ECOG PS 3. Among mGPS 2 patients, 6 (16.7%) were ECOG PS 0, 9 (25%) were ECOG PS 1, 20 (55.5%) were ECOG PS 2, and 1 (2.8%) was ECOG PS 3 (Table 1).

Table 1: Demographics, and clinical characteristics of mGPS

Characteristic	All patients, n (%)	mGPS		
		0	1	2
Patients	129	28 (21.7)	65 (50.4)	36 (27.9)
Age, years, median (range)	62 (42-82)	61 (42-77)	64 (43-79)	63 (42-82)
Gender				
Male	108 (83.7)	22 (78.6)	59 (90.8)	27 (75)
Female	21 (16.3)	6 (21.4)	6 (9.2)	9 (25)
ECOG PS				
0	40 (31)	19 (67.9)	15 (23.1)	6 (16.7)
1	41 (31.8)	18 (28.5)	24 (36.9)	9 (25)
2	45 (34.9)	1 (3.6)	24 (36.9)	20 (55.5)
3	3 (2.3)	0	2 (3.1)	1 (2.8)
Smoking history				
Current+former	126 (97.7)	28 (100)	62 (95.4)	36 (100)
Never	3 (2.3)	0	3 (4.6)	0
Metastasis				
Brain	18 (14)	4 (14.3)	10 (15.4)	4 (11.1)
Bone	37 (28.7)	14 (50)	14 (21.5)	9 (25)
Liver	42 (32.6)	6 (21.4)	20 (30.8)	16 (44.4)
Pleural	9 (7)	1 (3.6)	2 (3.1)	6 (16.7)
Lymph nodes	24 (18.6)	4 (14.3)	10 (15.4)	10 (27.8)
Adrenal gland	25 (19.4)	3 (10.7)	17 (26.2)	5 (13.9)

While all patients received first-line chemotherapy, second-line chemotherapeutics were administered to 60.7% of the patients in mGPS 0, 30.8% in mGPS 1, and 22.2% in mGPS

2. Third-line chemotherapeutics were administered to 21.4% of patients in mGPS 0, 3.1% in mGPS 1, and 5.6% in mGPS 2 (Table 2). In the first-line chemotherapy response evaluation, ORR was 92.9% in mGPS 0, 52.4% in mGPS 1 and 44.5% in mGPS 2, while DCR was 92.9% in mGPS 0, 55.5% in mGPS 1 and 52.8% in mGPS 2 (Table 3).

Table 2: Treatment content according to mGPS and LIPI

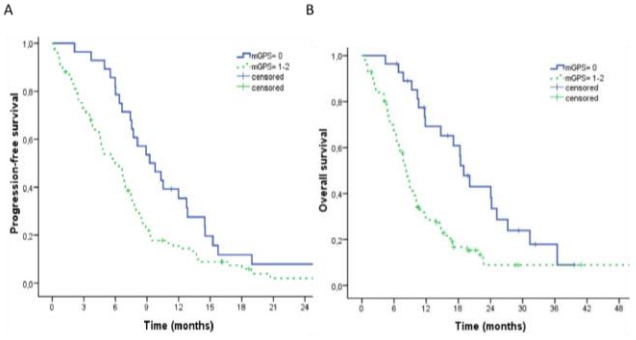
Treatment	All patients	mGPS 0	mGPS 1	mGPS 2	LIPI 0	LIPI 1	LIPI 2
n	129	28	65	36	18	49	62
First-line treatment, n	129	28	65	36	18	49	62
Treatment administration, %	100	100	100	100	100	100	100
Second-line treatment, n	45	17	20	8	10	14	21
Treatment administration, %	34.9	60.7	30.8	22.2	55.6	28.6	33.9
Third-line treatment, n	10	6	2	2	3	3	4
Treatment administration, %	7.8	21.4	3.1	5.6	16.7	6.1	6.5

Table 3: The efficacy of first-line chemotherapy according to mGPS and LIPI

Category	All patients (n=129)	mGPS 0 (n=28)	mGPS 1 (n=65)	mGPS 2 (n=36)	LIPI 0 (n=18)	LIPI 1 (n=49)	LIPI 2 (n=62)
Best overall response, n (%)							
CR	14 (10.9)	8 (28.6)	4 (6.2)	2 (5.6)	1 (5.6)	9 (18.4)	4 (6.5)
PR	62 (48.1)	18 (64.3)	30 (46.2)	14 (38.9)	11 (66.1)	25 (51)	26 (41.9)
SD	5 (3.8)	0	2 (3.1)	3 (8.3)	1 (5.6)	1 (2)	3 (4.8)
PD	48 (37.2)	2 (7.1)	29 (44.5)	17 (47.2)	5 (27.7)	14 (28.6)	29 (46.8)
ORR, %	59	92.9	52.4	44.5	66.7	69.4	48.4
DCR, %	62.8	92.9	55.5	52.8	72.3	71.4	53.2
PFS,months	6.8	9.2	6.3	4.4	7.5	7.5	4.9
(95% CI)	(5.9-7.7)	(6.4-12.1)	(4.9-7.8)	(2.1-6.8)	(5.4-9.6)	(6.1-8.9)	(2.6-7.2)

The PFS of the mGPS 0, mGPS 1, and mGPS 2 patients were 9.2 months (95% CI 6.4-12.1 months), 6.3 months (95% CI 4.9-7.8 months), and 4.4 months (95% CI 2.1-6.8 months), respectively. The median PFS of mGPS 2 patients was not significantly different from those of the mGPS 0 and mGPS 1 patients (4.4 months vs. 9.2 months, P=0.024 and 4.4 months vs. 6.3 months, P=0.967, respectively), but that of the mGPS 0 patients significantly differed from that of the mGPS 1 patients (9.2 months vs. 6.3 months, P=0.006) (Figure 1).

Figure 1: Kaplan-Meier curves according to the modified Glasgow prognostic score (mGPS) in small cell lung cancer (SCLC) patients. (A) The median progression-free survival (PFS) of the mGPS 0 group was significantly longer than those of the mGPS 1 and mGPS 2 groups (9.2 months vs. 6.0 months, respectively, P=0.006). (B) The median overall survival (OS) of the mGPS 0 group was significantly longer than those of the mGPS 1 and mGPS 2 groups (19.0 months vs. 8.3 months, respectively, P<0.001).



The overall OS was 9.6 months (95% CI, 8.3-10.8). The OS of the mGPS 0, mGPS 1, and mGPS 2 patients were 19.0 months (95% CI, 16.3-21.7), 8.4 months (95% CI, 7.1-9.8), and 6.4 months (95% CI, 3.1-9.6) respectively. The median OS of the mGPS 0 patients was significantly different from those of the mGPS 1 and mGPS 2 patients (19.0 months vs. 8.4 months, P<0.001 and 19.0 months vs. 6.4 months, P=0.001, respectively), while that of the mGPS 1 patients was comparable to that of the mGPS 2 patients (8.4 months vs. 6.4 months, P=0.526) (Figure 1).

In the multivariate analyses, the PFS of mGPS 0 patients did not significantly differ from those of mGPS 1 and mGPS2 patients (HR 1.42, 95% CI 0.87-2.31, P= 0.161). mGPS was not an independent prognostic factor for OS (Tables 4, 5).

Table 4: Univariate and multivariate Cox hazard analysis of potential factors associated with PFS

Category		Univariate			Multivariate		
	PFS (months)	HR	95% CI	*P*-value	HR	95% CI	*P*-value
ECOG PS							
0-1/2-3	7.5 vs. 4.4	1.71	1.17-2.49	0.005	1.54	1.03-2.30	0.035
LIPI							
0-1/2	7.5 vs. 4.9	1.64	1.13-2.37	0.008	1.53	1.04-2.24	0.030
mGPS							
0/1-2	9.2 vs. 6.0	1.85	1.18-2.89	0.006	1.42	0.87-2.31	0.161

Table 5: Univariate and multivariate Cox hazard analysis of potential factors associated with OS

Category		Univariate			Multivariate		
	OS (months)	HR	95% CI	*P*-value	HR	95% CI	*P*-value
ECOG PS							
0-1/2-3	11.8 vs. 6.4	2.40	1.61-3.59	< 0.001	1.92	1.25-2.93	0.003
LIPI							
0-1/2	14.5 vs. 8.0	1.54	1.16-2.05	0.002	1.54	1.03-2.31	0.036
mGPS							
0/1-2	19.0 vs. 8.3	1.55	1.20-2.01	< 0.001	1.71	0.99-2.95	0.053

LIPI

Fourteen percent of patients were LIPI 0 (n=18), 38% were LIPI 1 (n=49), and 48% were LIPI 2 (n=62). Among LIPI 0 patients, 11 (61.1%) were ECOG PS 0, 5 (27.8%) were ECOG PS 1, 1 (5.6%) was ECOG PS 2, and 1 (5.6%) was ECOG PS 3. Among LIPI 1 patients, 14 (28.6%) were ECOG PS 0, 18 (36.7%) were ECOG PS 1, and 17 (34.7%) were ECOG PS 2. Of the LIPI 2 patients, 15 (24.2%) were ECOG PS 0, 18 (29%) were ECOG PS 1, 27 (43.5%) were ECOG PS 2, and 2 (3.2%) were ECOG PS 3 (Table 6).

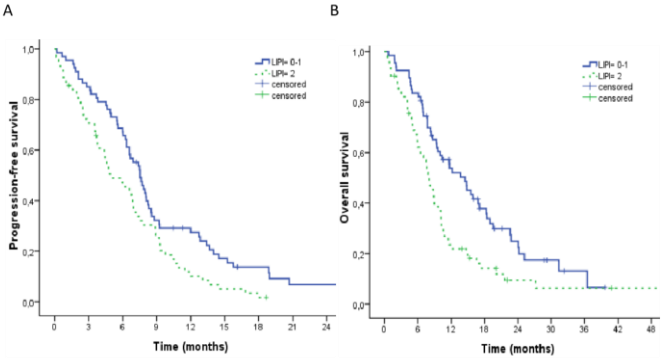
Table 6: Demographics, and clinical characteristics of patients in LIPI groups

Characteristic	LIPI, n (%)		
	0	1	2
Patients	18 (14.0)	49 (38.0)	62 (48.0)
Age, years, median (range)	62 (42-77)	62 (43-79)	63 (42-82)
Gender			
Male	15 (83.3)	40 (81.6)	53 (85.5)
Female	3 (16.7)	9 (18.4)	9 (14.5)
ECOG PS			
0	11 (61.1)	14 (28.6)	15 (24.2)
1	5 (27.8)	18 (36.7)	18 (29.0)
2	1 (5.6)	17 (34.7)	27 (43.5)
3	1 (5.6)	0	2 (3.2)
Smoking history			
Current + former	17 (94.4)	48 (98.0)	61 (98.4)
Never	1 (5.6)	1 (2.0)	1 (1.6)
Metastasis			
Brain	0	7 (14.3)	11 (17.7)
Bone	8 (44.4)	10 (20.4)	19 (30.6)
Liver	5 (27.8)	16 (32.7)	21 (33.9)
Pleural	1 (5.6)	4 (8.2)	4 (6.5)
Lymph nodes	2 (11.1)	8 (16.3)	14 (22.6)
Adrenal gland	3 (16.7)	8 (16.3)	14 (22.6)

While all patients received first-line chemotherapy, second-line chemotherapeutics were administered to 55.6% of the patients in LIPI 0, 28.6% in LIPI 1, and 33.9% in LIPI 2. Third-line chemotherapeutics were given to 16.7% of patients in LIPI 0, 6.1% in LIPI 1, and 6.5% in LIPI 2 (Table 2). In first-line treatment response assessment, the ORR was 66.7% in LIPI 0, 69.4% in LIPI 1, and 48.4% in LIPI 2, while the DCR was 72.3% in LIPI 0, 71.4% in LIPI 1, and 53.2% in LIPI 2 (Table 3).

The PFS of LIPI 0, LIPI 1, and LIPI 2 patients were 7.5 months (95% CI 5.4-9.6 months), 7.5 months (95% CI 6.1-8.9 months), and 4.9 months (95% CI 2.6-7.2 months), respectively. The LIPI 0 group's median PFS was not significantly different from those of the LIPI 1 and LIPI 2 groups (7.5 months vs. 7.5 months, P=0.575 and 7.5 months vs. 4.9 months, P=0.078, respectively). The LIPI 2 group's median PFS significantly differed from that of the LIPI 1 group (4.9 months vs. 7.5 months, P=0.015) (Figure 2).

Figure 2: Kaplan-Meier curves according to the lung immune prognostic index (LIPI) in small cell lung cancer (SCLC) patients. (A) The median progression-free survival (PFS) of the LIPI 0 and LIPI 1 groups were significantly longer than that of the LIPI 2 group (7.5 months vs. 4.9 months, respectively, *P*=0.008). (B) The median overall survival (OS) of the LIPI 0 and LIPI 1 group was significantly longer than that of the LIPI 2 group (14.5 months vs. 8.0 months, respectively, *P*=0.002).



The OS of LIPI 0, LIPI 1, and LIPI 2 patients were 18.3 months (95% CI, 9.9-26.7), 11.7 months (95% CI, 5.3-18.1), and 8 months (95% CI, 6.6-9.5) respectively. The LIPI 2 group's median OS was significantly different from those of the LIPI 0 and LIPI 1 groups (8.0 months vs. 18.3 months, *P*=0.011 and 8.0 months vs. 11.7 months, *P*=0.015, respectively), while that of the LIPI 0 group was comparable to that of the LIPI 1 group (18.3 months vs. 11.7 months, *P*=0.441) (Figure 2).

In the multivariate analysis, ECOG PS 0-1 and LIPI score 0-1 were correlated with better PFS (*P*=0.035 and *P*=0.03 respectively) and OS (*P*=0.003, and *P*=0.036 respectively) (Tables 4, 5).

Discussion

In our study, while the LIPI score was an independent prognostic factor in both PFS and OS in extensive-stage small cell lung cancer, mGPS was not a significant independent prognostic factor of survival.

In their study, Sonehara et al. [10] evaluated whether high mGPS predicts poor survival and reported that mGPS was not prognostic in limited-stage small-cell lung cancer. Similarly, in the research conducted by Fan et al. [11] on operable and inoperable NSCLC patients, although mGPS was significant in the univariate analysis, it proved otherwise in the multivariate analysis.

Zhou et al. [12] investigated the effect of systemic inflammation markers (such as mGPS, CRP/albumin, albumin/globulin, and prognostic nutritional index) on small cell lung cancer prognosis. They stated that all markers were independent risk factors in patients with extensive-stage disease, but this effect was not observed in limited-stage disease. Similarly, mGPS was prognostic in the study performed by Zhou et al. [8]. Minami et al. [13] examined the prognostic effect of pretreatment GPS and the prognostic nutritional index (PNI) markers on OS and PFS in small cell lung cancer patients. GPS and PNI markers were not significant in terms of PFS in the multivariate analysis. To the best of our knowledge, the mGPS has not been investigated in terms of chemotherapy effect (PFS) in small cell lung cancer, except for Minami et al.'s study.

In our study, although mGPS significantly affected both PFS and OS in univariate analysis, multivariate analysis did not yield significant results in terms of OS. However, the p score was remarkably close to significance**.** The lack of homogeneity due to the small number of patients in the groups may be responsible for this finding. Similar to the literature, ECOG PS was a poor prognostic factor in our multivariate analysis.

Studies evaluating the LIPI were generally conducted on non-small cell lung cancer. In these studies, the LIPI score was a significant prognostic factor in terms of OS [9, 14]. In the study conducted by Minami et al. [14], LIPI was assessed in patients with metastatic lung adenocarcinoma. It was an independent prognostic factor in patients who received tyrosine kinase therapy and systemic chemotherapy. In this study, LIPI was of no significance in the group with squamous histology.

There is no sufficient data on the LIPI marker in extensive-stage small-cell lung cancer in the literature. In the first study conducted by Sonehara et al. [10], in which the LIPI score was evaluated, LIPI was an independent risk factor for both PFS and OS in extensive-stage disease. The second study, conducted by Galvano et al. [15], evaluated LIPI and other immune markers in patients with extensive-stage lung neuroendocrine carcinoma. Although the LIPI was numerically different between the groups in terms of its effect on OS, the prognostic effect was not significant.

Similar to the literature, LIPI was a prognostic factor for both OS and PFS in our study.

Inflammation and immunity play an essential role in tumor formation, progression, spread, metastasis, and response to systemic treatment [7]. In recent years, especially in lung cancer, immune checkpoint inhibitors gained an essential role in treatment.

In the IMpower-133 study, both PFS and OS were lengthened with the addition of atezolumab to systemic chemotherapy (carboplatin + etoposide) in the first series in extensive-stage small cell lung cancer [16].

It can be predicted that markers such as LIPI may help predict response to treatment with immune checkpoint inhibitors, where immune markers are essential.

Limitations

Selection bias was inevitable given the retrospective nature of the work. Additionally, the size of the patient population was relatively small.

Conclusion

In our study involving extensive-stage small cell lung cancer patients, LIPI and mGPS were both assessed for their prognostic effects. LIPI score predicted an unfavorable prognosis. It would be better to consider using the LIPI score in managing extensive-stage small cell lung cancer.

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The effects of ilioinguinal nerve block on acute and chronic neuropathic pain in patients following inguinal hernia repair with spinal anesthesia: A prospective cohort study

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Ethics Committee Approval
Uludag University Clinical Research Ethics Committee with approval number of 2017-17/24
Clinical Trials Number: NCT04295629
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: Post-surgical pain is a major factor affecting the quality of life of patients. This study aims to investigate the effectiveness of ilioinguinal block on acute and chronic neuropathic pain after inguinal hernia surgery with spinal anesthesia.

Methods: This prospective cohort study included sixty ASA I-III patients aged 18-65 years, who underwent a unilateral inguinal hernia operation. The patients were divided into two groups: Those who received spinal block only (Group 1, n=30), and those who received spinal and ultrasound-guided ilioinguinal nerve block (Group 2, n=30). The perioperative and postoperative complications, Visual Analogue Scale (VAS) scores on rest and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scores at the postoperative 2nd, 6th, 12th, and 24th hours, and in the 3rd and 6th months were noted.

Results: No significant difference was observed in the time of first analgesic administration among the groups, but tramadol use significantly reduced in Group 2 (P=0.019). Time until mobilization and discharge was significantly shorter among the Group 2 patients (P<0.001, P=0.021, respectively). Visual Analogue Scale scores at rest at the 12th and 24th hours, and in the 3rd and 6th months were significantly less in Group 2 (P=0.032, P=0.005, P=0.022, P=0.008, respectively). Leeds Assessment of Neuropathic Symptoms and Signs scores of the patients at the 24th hour, 3^{rd,} and 6th months were significantly lower in Group 2 (P<0.001, P<0.001, P=0.012, respectively).

Conclusion: We think that ilioinguinal nerve block with spinal anesthesia is a successful and reliable technique for acute postoperative and chronic neuropathic pain management in unilateral inguinal hernia repair.

Keywords: Inguinal hernia, Spinal anesthesia, Ilioinguinal nerve block, Chronic pain, Neuropathic pain

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Introduction

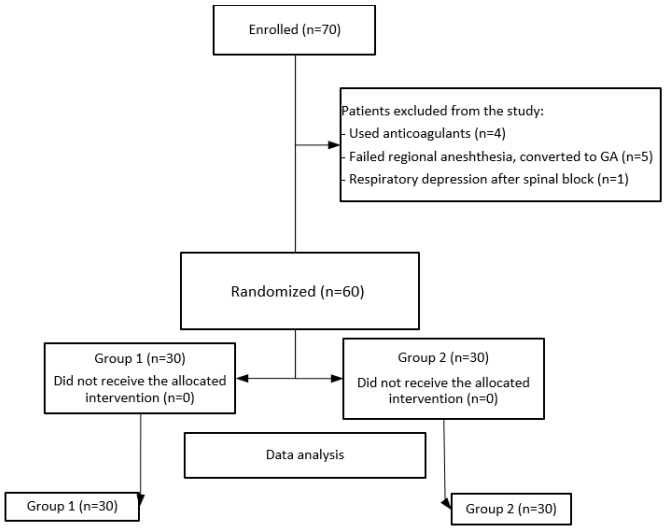
One of the most popular outpatient procedures is inguinal hernia repair. Chronic pain is a frequent complication of this procedure that places a significant financial strain on medical care and health services, causes depression and anxiety, limits daily activities, and increases painkiller use. Postoperative chronic pain incidence varies between 6-54% in numerous studies [1]. After inguinal herniorrhaphy, 5-10% of patients experience pain which makes it difficult to perform daily tasks [2]. While the actual source of this persistent discomfort is unknown, ilioinguinal nerve entrapment or trauma could be the leading reasons [3]. According to research, postoperative and preoperative pain, weight, age, anesthetic method, recurrence, and surgical approach are among the risk factors for postoperative pain [4]. Chronic postoperative pain indicates neuropathic pain that lasts for at least 3 months after the surgery, despite the healing of the surgical site [5]. Although many oral opioids and/or non-steroid agents can be utilized in the cure of chronic pain, regional anesthesia approaches have become popular due to increased systemic side effects. Regional nerve blocks are becoming increasingly common for postoperative pain management, allowing faster ambulation and discharge. Blocks of the iliohypogastric and ilioinguinal nerves (IHN/IIN) are two of the most often utilized regional blocks for analgesia after an inguinal hernia operation. Moreover, they are proven to considerably decrease discomfort related to herniorrhaphy [6]. Ultrasound-guided (USG) nerve block allows for precise needle placement, which may minimize the risk of drug toxicity and overdose, and block failure. This research aimed to explore the effects of ilioinguinal nerve block in addition to spinal anesthesia on postoperative chronic and acute neuropathic pain.

Materials and methods

Study design

Sixty ASA I-III patients aged 18-65 years, who underwent unilateral inguinal hernia surgery and gave consent were included in this prospective cohort study, which was approved by the Clinical Research Ethics Committee of Uludag University (approval number: 2017-17/24). The Clinical Trials number of the study is NCT04295629. Open anterior surgical treatment was performed on all patients with the Lichtenstein method. All patients received spinal anesthesia in the sitting position. With the closed envelope technique, the patients were split into two groups randomly: Thirty patients received spinal anesthesia only with 15 mg 0.5% hyperbaric bupivacaine (Group 1) to the subarachnoid gap, and the other thirty were administered 10 ml 5% bupivacaine during ultrasound-guided ilioinguinal block after the surgery in the reanimation unit, in addition to the prior spinal anesthesia (Group 2). Patients undergoing recurrent inguinal hernia surgery, those with failed spinal anesthesia or ilioinguinal block, those who had an infection at the site of intervention, patients with dysregulated hyperglycemia, bleeding diathesis, and history of neuropathic pain were excluded from the study. Permission forms were signed by 70 informed patients, who were originally recruited in the research after the exclusion criteria were implemented. Nevertheless, for a variety of reasons, such as switching to general anesthesia when spinal anesthesia failed (n=5), use of anticoagulants (n=4), and the development of respiratory depression after spinal block (n=1), ten patients were omitted from the research (Figure 1). Mean Arterial Pressure (MAP), Saturation of Peripheral Oxygen (SpO2), perioperative and postoperative complications, and Heart rate (HR) were recorded for both groups. The patients were interviewed at the postoperative 2nd, 6th, 12th, and 24th hours at the bedside and the 3rd and 6th-month follow-ups. The Visual Analog Scale (VAS) at rest was used to investigate chronic pain and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) tests were utilized to determine the neuropathic character of pain. A standard postoperative analgesia regimen was used within the first 24 hours. Patients who had a VAS score of ≥4 within the first 24 hours following the surgery were given tramadol (1 mg/kg) intravenously. The Visual Analog Scale scores at rest, the dose of tramadol, hospitalization duration, the first mobilization time, and postoperative complications were recorded. A VAS score of ≥ 4 at least three months following the operation was considered chronic pain and a LANSS score of ≥12 indicated that the pain was likely neuropathic.

Figure 1: Flow chart of the study



Spinal anesthesia technique

After routine monitoring, spinal anesthesia was performed with 15 mg 0.5% hyperbaric bupivacaine injection by a pen-tipped (M. Schilling) 25 G needle from the L3-4 subarachnoid space under sterile conditions and a proper body position in all patients. After achieving sensory blockage at the T10 level, surgery began. The sensory blockade was determined with the pin-prick test.

Ilioinguinal Nerve Block Technique (IINB)

The ilioinguinal block was performed using a high frequency, linear 10 MHz or greater ultrasound probe (GE Healthcare Logiq P5, USA) while the patient is lying down in the supine position. The probe was obliquely positioned along the line connecting the umbilicus and the anterior superior iliac spine. Ten milliliters of 5% bupivacaine were administered by a needle to patients in Group 2 postoperatively, after locating the region between the transversus abdominis and internal oblique muscles, towards the iliohypogastric and ilioinguinal nerves, which were observed as two circular hypoechoic structures near one another.

Visual Analog Scale (VAS)

The VAS is a commonly used pain severity outcome measure that is responsive, valid, and reliable [7]. It includes a ten cm bidirectional straight bar with two tags at either end, namely, "worst possible agony" and "no pain." Patients are encouraged to make a sign on the bar to indicate the level of their pain [8].

Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

LANSS is one of the neuropathic pain assessment scales. The LANSS is a seven-item pain scale with a simple scoring procedure that comprises a grouped sensory assessment and sensory description. The first section consists of five questions: Skin color changes (pink, mottled, or red), the existence of troublesome skin sensations such as prickling and needles or pins, pain bursts for no apparent cause, and heightened skin sensitivity to touch. An altered pinprick threshold and the existence of allodynia are assessed in the second phase by comparing non-painful and painful areas. Scores of ≥12 almost certainly indicate neuropathic pain. The LANSS has a specificity and sensitivity of 80% and 85%, respectively [9].

Statistical analysis

The results were analyzed with IBM SPSS 23.0 statistics package program. The power analysis of 60 patients, with $\alpha = 0.05$, and an effect size of 0.6 yielded a power of $(1-\beta) = 0.80$. The data were evaluated with descriptive methods (mean, frequency, standard deviation, percentage, min-max, median). The student t-test and Chi-Square (2) test were used in the comparison of qualitative data. $P<0.05$ was considered significant.

Results

The demographic and hemodynamic data of 60 patients were similar (Tables 1 and 2).

Table 1: Demographic data

	Group 1	Group 2	*P*-value
Age (years)	62.96 (7.25)	59.76 (11.08)	0.19
Gender (M/F)	24/6	26/4	0.11
BMI (kg/m^2)	28.23 (2.58)	27.20 (2.76)	0.13
ASA I/II	9/21	10/20	0.78

BMI: Body Mass Index, ASA: American Society of Anesthesiology

Table 2: Comparison of the groups' hemodynamic parameters

	Group 1	Group 2	*P*-value
HR			
0 hours	77.96 (12.78)	83.13 (13.48)	0.113
1 hour	81.50 (11.02)	82.23 (11.69)	0.802
2 hours	64.33 (16.13)	64.26 (15.78)	0.236
MAP			
0 hours	94.10 (11.66)	91.43 (6.17)	0.273
1 hour	90.64 (9.40)	89.03 (6.77)	0.443
2 hours	81.06 (22.49)	88.26 (17.47)	0.711
SpO_2			
0 hours	98.26 (0.73)	98.46 (0.86)	0.330
1 hour	98.10 (0.72)	98.13 (1.04)	0.882
2 hours	97.90 (1.32)	98.23 (1.35)	0.342

HR: Heart Rate, MAP: Mean Arterial Pressure, SpO_2: Peripheral Oxygen Saturation, *$P<0.05$, ** $P<0.001$, Student t-test

While there was no significant difference in the time of the first analgesic administration among the groups, tramadol dose used was significantly less in Group 2 ($P=0.019$) (Table 3). Time until mobilization and discharge was significantly shorter among the Group 2 patients ($P<0.001$, $P=0.021$, respectively) (Table 3). Visual Analogue Scale scores at rest at the 12th and 24th hours, and in the 3rd and 6th months were significantly less in Group 2 ($P=0.032$, $P=0.005$, $P=0.022$, $P=0.008$, respectively) (Table 4). Leeds Assessment of Neuropathic Symptoms and Signs scores of the patients at the 24th hour, 3^{rd,} and 6th months were significantly lower in Group 2 ($P<0.001$, $P<0.001$, $P=0.012$, respectively) (Table 4). No complications were observed perioperatively or postoperatively.

Table 3: Comparison of groups first analgesic times, tramadol dose, mobilization, and hospitalization durations

	Group 1	Group 2	*P*-value
First analgesic time (h)	5.33 (1.68)	5.23 (0.93)	0.772
Tramadol dose (mg)	140.0 (62.14)	103.33 (55.60)	0.019*
Mobilization (h)	5.83 (1.08)	4.80 (0.76)	<0.001
Hospitalization (h)	22.70 (5.46)	19.33 (5.56)	0.021*

*$P<0.05$ Student t-test, h: Hour, mg: Milligram

Table 4: Comparison of VAS on rest and LANSS values of the groups

	Group 1	Group 2	*P*-value
VAS			
2(h)	0.00 (0.00)	0.26 (1.01)	1.153
6(h)	4.46 (1.36)	4.00 (1.36)	0.620
12(h)	5.90 (1.24)	4.90 (1.14)	0.032*
24(h)	3.46 (1.22)	3.63 (0.99)	0.005*
3(m)	1.20 (1.29)	0.53 (0.86)	0.022*
6(m)	0.86 (1.04)	0.23 (0.72)	0.008*
LANSS			
2(h)	0.00 (0.00)	0.16 (0.91)	0.322
6(h)	4.83 (2.93)	3.60 (2.09)	0.062
12(h)	7.80 (3.38)	5.90 (2.69)	0.196
24(h)	9.73 (3.85)	5.56 (4.62)	<0.001
3(m)	9.03 (4.20)	5.46 (5.66)	<0.001 0.012*
6(m)	8.38 (3.93)	5.03 (5.69)	

VAS: Visual Analog Scale, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, h: hour, m: month, *$P<0.05$ Student t-test

Discussion

In this study, significantly lower doses of tramadol, earlier mobilization, short hospitalization time were observed in patients who received IINB in addition to spinal anesthesia. VAS scores at rest at the 12th and 24th hours, and in the 3rd and 6th months, as well as LANSS scores at the 24th hour, 3rd and 6th months, were lower in Group 2.

Open inguinal hernia surgery is among the most performed surgeries throughout the world, with general or regional anesthesia approaches. Postoperative pain may be related to surgical technique, the psychosocial structure, and the physiology of the patient [10]. The distribution of the iliohypogastric and ilioinguinal nerves causes parietal discomfort after hernia surgery. Studies on the localization and character of chronic pain after herniotomy indicate that this pain is a neuropathic pain syndrome related to sensorial disorder symptoms [11]. However, whether the underlying physiopathological process is a consequence of an intraoperative direct nerve injury or an indirect nerve injury related to the inflammatory response to mesh, is yet unknown. IL/IH or TAP nerve blocks were shown to minimize immediate post-operative pain, the need for extra analgesics, and the risk of persistent discomfort after hernia surgery [12, 13].

Santos et al. [6] assessed postoperative pain, analgesic consumption amounts, and time of discharge in their adult inguinal hernia treatment patients who received spinal anesthesia (SA) and iliohypogastric nerve block (IHNB)+SA. Postoperative VAS scores and amounts of analgesics used were lower and the time of discharge was earlier. Similarly, another study compared the postoperative pain and the need for analgesics of adult patients with SA and SA+IHNB in inguinal hernia surgery and indicated that IHNB with SA decreased postoperative pain and the need for analgesics for nearly six hours [21]. Gurkan et al. [14] compared SA and II/IHNB in patients who underwent unilateral inguinal hernia repair and found that the patients were

first mobilized about 150 min earlier with II/IHNB, and sensory block lasted 145 minutes longer. Our study was compatible with similar studies, as IINB in addition to spinal anesthesia resulted in a decrease in the amount of tramadol use, early patient mobilization, and discharge. VAS values were significantly higher at the 12th hour in the spinal anesthesia group, which may be associated with the wear-off of the spinal block. The ilioinguinal block yields a more prolonged sensorial block. We also think that ilioinguinal block administration provides a significant decrease in VAS values at the postoperative 12th hour.

The effects of different anesthesia and analgesia techniques on postoperative chronic pain are still not clear. In a study comparing general anesthesia combined with IHNB and SA+IHNB, the combination of IINB with spinal anesthesia provided only a short and sudden analgesia [15]. Patients who received general anesthesia were discharged earlier from the hospital than those who received SA. Unlike our study, Yılmazlar et al. [16] compared SA and IHNB separately to determine the optimal technique of anesthesia on 126 adult patients who underwent inguinal hernia surgery. IHNB was performed with 40 ml of 0.25% bupivacaine, and SA was performed with 3 ml of 0.5% hyperbaric bupivacaine. They found that patients who underwent IHNB were fed orally and discharged earlier. Sakalli et al. [21] evaluated the effect of GA+IHNB on postoperative pain and analgesic consumption elective cesarean section and showed that VAS scores, as well as the analgesic consumption of the IINB group, were significantly lower than those who received GA only. They stated that IHNB was a successful and preferable technique in acute pain treatment. Chronic pain was not assessed in this study. Studies comparing iliohypogastric block with other blocks reported that Transversus Abdominis Plane Block (TAP) decreased acute postoperative pain, the need for analgesics, and chronic pain incidence [12]. There are many different opinions about the superiority of these blocks to one another. Avleine et al. [17] showed that VAS scores of the patients who underwent inguinal hernia repair with TAP were lower within the first postoperative 24 hours than those who received IHNB. The pain scores at the 3rd and 6th postoperative months were similar between the two groups. Seyed Hamid et al. [18] observed that IHNB yielded better outcomes than TAP block in the follow-ups of patients with chronic pain, who underwent inguinal hernia repair. In the study of Okur et al., IHNB and TAP were performed on 30 patients each who underwent inguinal hernia repair with SA, and the results were compared with a control group of another 30 patients [13]. A decrease was noted in acute and chronic pain scores. In a similar study evaluating chronic and acute pain on 200 patients who underwent inguinal hernia repair, less acute and chronic pain were observed in the ones who underwent TAP block compared to the ones who underwent IHNB [19]. In our study, we preferred to compare the effects of the ilioinguinal block with patients who underwent spinal anesthesia only and observed significantly decreased LANSS and VAS scores in the third and sixth postoperative months among patients who received IINB. Also, chronic neuropathic pain was less common in these patients postoperatively.

Demographic features are also emphasized in pain studies. The female gender, young age, and high body mass index were effective in chronic pain development after herniotomy [3]. Decrease of peripheric nociceptive function with age and analgesic agent excretion were the presumed factors [7, 20]. In our study, the mean ages of groups 1 and 2 were 62 years and 59 years, respectively. Although the gender distribution of the groups was similar, the number of females in both groups was very low. Therefore, it is not possible to comment on gender-related pain in our study. The mean BMI values of the groups were also similar.

Although IHNB is an easy and reliable technique, the side effects, such as transient femoral nerve paralysis, abscess, hematoma, colon perforation, local anesthetic toxicity, should be kept in mind [6,14]. We did not observe any complications in our study. We attribute this to the use of the ultrasound and the increased experience of our clinic.

Limitations

Our study has a limited number of patients. The Visual Analog Scale score was not measured on knee flexion. Also, the analgesic use of the patients was not questioned preoperatively or postoperatively.

Conclusion

The ultrasound-guided ilioinguinal nerve block is easy and safe. It may be commonly used in inguinal hernia surgeries due to its outcomes of lessened acute and chronic neuropathic pain.

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Dermoscopic and histopathological correlation in macular hyperpigmented facial lesions

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Ethics Committee Approval
The study was conducted with the approval of the Ethics Committee of Clinical Research at Cukurova University (approval number: 2006/10-1).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Solar lentigo, seborrheic keratosis, actinic keratosis, lentigo maligna are confusable hyperpigmented lesions. Dermoscopy is an important tool to distinguish the pigmented lesions on the face. This study aimed to determine the reliability of dermoscopy by comparatively analyzing dermoscopic findings with the histopathologic examination of facial hyperpigmented flat lesions.
Methods: Patients with hyperpigmented flat lesions on the face such as solar lentigo, seborrheic keratosis, and actinic keratosis were included in this retrospective cohort study. Those with other causes of facial hyperpigmentation were excluded from the study, based on history, clinical evaluation, Wood's lamp examination, and dermoscopic findings. The dermoscopic criteria form, prepared for solar lentigo, seborrheic keratosis, actinic keratosis, and lentigo maligna were filled out. Biopsy was taken for histopathologic evaluation.
Results: Fifty-one patients, 26 males, and 25 females, with 53 skin lesions were evaluated. We did not statistically evaluate 3 lesions that had a histopathologic diagnosis of actinic keratosis + solar lentigo. The other 50 lesions' histopathologic diagnoses were actinic keratosis in 32 lesions, seborrheic keratosis in 9, and solar lentigo in 9. Kappa test was used for statistical analysis, which revealed a value of 0.645 (P<0.001). This shows that the dermoscopic and histopathological diagnoses of the hyperpigmented flat lesions on the face were moderately compatible.
Conclusion: Since the dermoscopic diagnosis of facial pigmented lesions cannot be based on the presence of one criterion, we deduce that histopathology is still the gold standard for accurate diagnosis.

Keywords: Actinic keratosis, Dermoscopy, Seborrheic keratosis, Solar lentigo

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Introduction

Facial diseases can cause pigmentation either during the natural course of the disease or secondarily. Ephelis, melasma, nevus of Ota, nevus spilus, Cafe au lait spots, drug eruption, post-inflammatory hyperpigmentation, photosensitive dermatitis, verruca plana, tinea versicolor, erythromelanosis follicularis faciei et colli, erythema dyschromicum perstans, Riehl melanosis, actinic lichen planus, lentigo simplex, solar lentigo, seborrheic keratosis, actinic keratosis, and lentigo maligna melanoma are among the diseases that can cause facial pigmentation [1]. Some of these lesions can be easily identified because of their significant clinical features. However, difficulties may be encountered in distinguishing lesions such as solar lentigo, seborrheic keratosis, actinic keratosis, and lentigo maligna from each other due to their overlapping clinical appearances. Since actinic keratosis and lentigo maligna are pre-malignant, they must be diagnosed and treated in the early stage [2, 3].

Dermoscopy, an in vivo, non-invasive method, aids in the differential diagnosis of skin lesions and early diagnosis of melanoma [4]. The use of dermoscopy helps in the classification of skin lesions as melanocytic or non-melanocytic, and the differentiation of benign and malignant lesions [5-7]. Recent studies demonstrated that dermoscopy increases the diagnostic accuracy of pigmented lesions by up to 5-30% [8, 9]. Kreusch and Rassner demonstrated that well-organized honeycomb pigmentation was replaced by a rough pigment network in the hyperpigmented lesions on the face independent from the deposition of melanin in the rete ridges. This structure is called a "pseudo-pigment network". Hypopigmented follicles or the orifices of the sweat glands perforate the hyperpigmented skin surface, and thus bright-colored openings are formed. A thick network structure with large holes is seen with the help of a dermoscopy [10]. Pseudo-network structure is a common finding in solar lentigo, lentigo simplex, seborrheic keratosis, pigmented actinic keratosis, and lentigo maligna [8]. Features of the pigmented lesions on the face differ from the lesions on the other parts of the body. Novel dermoscopic criteria are identified for the facial lesions [9].

In this study, we aimed to determine the correlation between dermoscopic and histopathological findings in the diagnosis of hyperpigmented flat facial lesions.

Materials and methods

The patients who presented to the Dermatology Department of Cukurova University School of Medicine with flat hyperpigmented lesions, such as facial solar lentigo, seborrheic keratosis, and actinic keratosis were included in the study. Based on the history, clinical evaluation, Wood's lamp examination, and dermoscopic evaluation, the patients with diseases that form hyperpigmentation on the face such as melasma, nevus of Ota, nevus spilus, ephelis, Cafe au lait spots, drug eruption, post-inflammatory hyperpigmentation, photosensitive dermatitis, verruca plana, tinea versicolor, actinic lichen planus were excluded. Participants' names, ages, and skin phenotypes based on Fitzpatrick's classification were recorded. The study was conducted with the approval of the Ethics Committee of Clinical Research of Cukurova University (approval number: 2006/10-1).

A dermoscopy device (MoleMax II, DermaInstruments, Vienna Austria), which can magnify the lesions 30 times, was used during the dermoscopic evaluation. The pictures of the lesions were recorded in JPEG format in 640x480 pixels and 24-bit color. Evaluations were made by two researchers at the same time and the findings were recorded on a form of dermoscopic diagnostic criteria, prepared for solar lentigo, seborrheic keratosis, actinic keratosis, and lentigo maligna.

The dermoscopic diagnostic criteria of solar lentigo, seborrheic keratosis, actinic keratosis, and lentigo maligna were deduced from the Color Atlas of Dermatoscopy [10], An Atlas of Surface Microscopy of Pigmented Skin Lesions [5], Color Atlas of Melanocytic Lesions of the Skin [11], and the studies of Stolz et al. [12], Pock et al. [13], Peris et al. [14], Stante et al. [15], Zalaudek et al. [16], Braun et al. [17], Schiffner et al. [18], Robinson JK [19], Cognetta et al. [20] and Elgart et al. [21] were used as the references. Since the references classified the diagnostic criteria of actinic keratosis as non-pigmented and pigmented, our cases were also categorized accordingly.

The patients signed the consent forms before the skin biopsy, and photographs of the lesions were taken. The biopsy samples were sent to Cukurova University Pathology Department for histopathological evaluation.

Statistical analysis

Statistical analysis of the numerical variables was performed using SPSS (Statistical Package for the Social Sciences) 16 software (IBM Corporation, Armonk, New York, US). Frequencies and percentages were calculated for demographic parameters. *P*-values of less than 0.05 indicated significance. Statistical analysis was performed with the Kappa test. A score between 0-0.40 indicates weak consistency, 0.40-0.75 indicates moderate consistency and 0.75-1.0 indicates excellent consistency in the Kappa test [22].

Results

A total of 53 skin lesions of 51 patients (26 males (51%) and 25 females (49%)) were evaluated in the study. The mean age of the patients was 64.47 (11.24) years (range: 40-83 years). Type II skin phenotype was present in 30 patients, and type III phenotype was present in the rest (n=21). Histopathological evaluation revealed the following diagnoses: Seborrheic keratosis in 9, actinic keratosis in 32, solar lentigo in 9, actinic keratosis plus solar lentigo in 3 patients. These findings were summarized in Table 1. Most patients had multiple lesions. Dermatological examination revealed various symptoms of photoaging such as atrophy, wrinkles, and telangiectasia surrounding the lesions.

The most common dermoscopic finding was white-yellow squama (n=25, 47%) on the flat hyperpigmented lesions on the face. The rest of the findings included annular-granular pattern (n=22, 41%), pink-to-red pseudo-network (n=18, 34%), brown-to-gray segmented pseudo-network structure (n=18, 34%) and moth-eaten border (n=17, 32%).

Table 1: General Information of the patients included in the study

Patients	Age	Gender	Skin phenotype	Dermoscopic diagnosis	Histopathological diagnosis
Patient 1	54	M	3	SK	SK
Patient 2	60	M	2	AK	AK
Patient 3	42	M	3	AK	AK
Patient 4	73	M	2	AK	AK
Patient 5	65	M	2	AK	SK
Patient 6	77	M	3	SL	AK
Patient 7	64	F	2	SL	AK + SL
Patient 8	63	M	2	SK	SL
Patient 9	50	F	2	AK	AK
Patient 10	62	F	2	AK	AK
Patient 11	77	F	2	AK	AK
Patient 12	78	M	2	SL	AK + SL
Patient 13	49	F	2	SK	SK
Patient 14	77	M	2	SL	SL
Patient 15	83	M	2	AK	SK
Patient 16	58	M	2	AK	AK
Patient 17	65	M	2	SK	AK
Patient 18	76	F	2	AK	AK
Patient 19	57	M	3	SL	SL
Patient 20	67	F	2	AK	AK
Patient 21	72	M	2	SK	SK
Patient 22	50	F	3	AK	AK
Patient 23	44	F	3	AK	AK
Patient 24	40	F	3	AK	AK
Patient 25	73	F	3	SL	SL
Patient 26	60	F	3	AK	AK
Patient 27	64	M	2	AK	AK
Patient 28	77	M	2	AK	SK
Patient 29	71	F	2	AK	AK
Patient 30	80	M	2	SK	SK
Patient 31	80	M	2	SL	SL
Patient 32	80	M	2	AK	AK
Patient 33	69	M	3	AK	AK
Patient 34	79	M	2	AK	AK
Patient 35	70	M	3	SL	SL
Patient 36	57	F	2	AK	AK
Patient 37	60	F	2	SL	SL
Patient 38	80	F	2	AK	SL
Patient 39	61	F	2	AK	AK
Patient 40	45	F	2	SL	AK
Patient 41	65	M	2	AK	AK + SL
Patient 42	57	M	3	AK	SL
Patient 43	42	F	3	AK	AK
Patient 44	65	F	3	AK	AK
Patient 45	64	F	2	AK	AK
Patient 46	67	F	2	AK	AK
Patient 47	62	M	3	AK	AK
Patient 48	69	F	3	AK	AK
Patient 49	71	F	3	AK	AK
Patient 50	80	M	3	AK	AK
Patient 51	67	F	3	SK	SK
Patient 52	76	M	3	SK	SK
Patient 53	54	M	3	AK	AK

Diagnoses are compatible	One of the diagnoses is compatible	Diagnoses are incompatible

SK: Seborrheic Keratosis, AK: Actinic Keratosis, SL: Solar Lentigo

The most common dermoscopic findings of the solar lentigo patients were moth-eaten border and jelly sign (Figure 1), of the seborrheic keratosis patients, sharp border and sudden cessation of pigmentation, moth-eaten border, and jelly sign (Figure 2), and in patients with actinic keratosis, white-yellow squama, brown-to-gray segmented pseudo-network structure, annular-granular pattern and pink-to-red pseudo-network (Figure 3). These findings were summarized in Table 2.

Figure 1: Moth-eaten edge and jelly sign. Dermoscopically and histopathologically diagnosed with solar lentigo

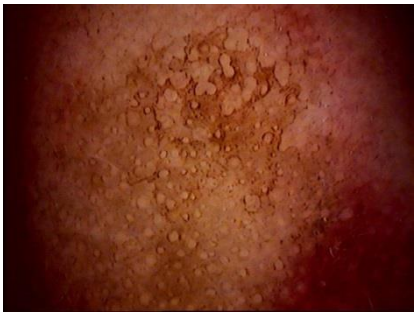

Figure 2: Brain-like appearance and white-yellow scale. Dermoscopically and histopathologically diagnosed with seborrheic keratosis

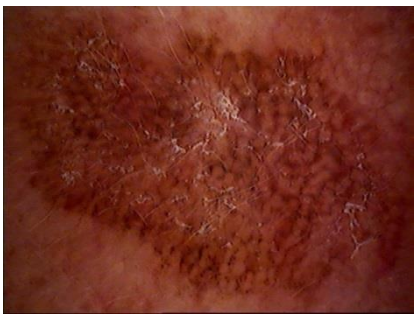

Figure 3: White-yellow scales, brown-gray patchy pseudo-meshwork, dark brown or black follicular openings showing asymmetric pigmentation. Dermoscopically and histopathologically diagnosed with actinic keratosis

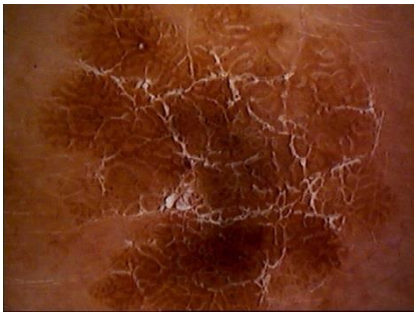

Table 2: Evaluation of the patients according to the dermoscopic diagnostic criteria

Diagnosis	Dermoscopic Diagnostic Criteria	Number of positive lesions	Percentage of positive lesions
Solar Lentigo	Homogeneous color	0	0
	Moth-eaten border	7	78
	Jelly sign	6	66
	Fingerprint pattern	0	0
	Thin, brown pseudo-network	0	0
Seborrheic Keratosis	Milia-like cysts	0	0
	Comedone-like openings	0	0
	Fissures and ridges (brain-like appearance)	2	22
	Moth-eaten border	4	44
	Jelly sign	4	44
	Fingerprint pattern	0	0
	Sharp border and sudden cessation of pigmentation	5	55
	Hairpin vessels	0	0
Non-pigmented Actinic Keratosis	a-Pink-to-red pseudo-network	15	47
	b-White-yellow squama	18	56
	c-Linear-wavy vessels surrounding the hair follicle	11	34
	d-White halo around the hair follicle with yellowish keratotic plug	11	34
	Strawberry view (a+b+c+d)	5	15
	Non-specific pattern-yellow color (if hyperkeratosis is evident)	2	6
Pigmented Actinic Keratosis	Lead blue or dark brown spots and globules surrounding the follicle orifices	11	34
	Annular-granular pattern	16	50
	Rhomboidal structure	0	0
	Brown-to-gray segmented pseudo-network	17	53

Three patients whose lesions were histopathologically diagnosed with actinic keratosis plus solar lentigo were excluded from statistical evaluation. The dermoscopic preliminary diagnosis and the histopathological final diagnosis were inconsistent in 9 (18%) lesions. The histopathological diagnosis of 6 out of 9 lesions was confirmed as seborrheic keratosis with dermoscopy, and 3 lesions were diagnosed with actinic keratosis. Likewise, among actinic keratosis lesions (n=32), the dermoscopic preliminary diagnoses matched the histopathological results in 29 lesions; two lesions were assessed as solar lentigo and 1 lesion was classified as seborrheic keratosis with dermoscopy. Six out of 9 lesions with histopathological solar lentigo diagnosis were assessed as solar

lentigo, 2 as actinic keratosis, and 1 as seborrheic keratosis by dermoscopy (Table 3).

Table 3: Dermoscopic-histopathological diagnosis of the patients

	Histopathological			
	Seborrheic Keratosis	Actinic Keratosis	Solar Lentigo	Total
Dermoscopic				
Seborrheic Keratosis	6	1	1	8
Actinic Keratosis	3	29	2	34
Solar Lentigo	0	2	6	8
Total	9	32	9	50

The Kappa test result was 0.645 (P<0.001). Dermoscopic and histopathological diagnoses were moderately compatible in flat hyperpigmented facial lesions.

Discussion

Facial diseases can cause pigmentation either during the natural course of the disease or secondarily. Although some of these diseases are easily diagnosed due to non-facial localization and their specific clinical features, differential diagnosis can be difficult in solar lentigo, seborrheic keratosis, actinic keratosis, and lentigo maligna [23]. To resolve this issue, dermoscopy can be used in combination with clinical examination.

Facial lesions demonstrate special features in dermoscopic evaluation. Since the rete ridges in this area are flat, a conventional pigment network and the arising features cannot be found. Pseudo-network appearance can be observed during dermoscopic examination. Pseudo-network is an irregular network resulting from the puncture of the dark-colored skin surface by the hair follicles or sweat glands, or the combination of adjacent follicles surrounded by a hyperpigmented area. This structure can be seen in facial lesions such as solar lentigo, seborrheic keratosis, actinic keratosis, lentigo maligna and lentigo maligna melanoma [10, 13, 24].

It is quite difficult and sometimes even impossible to clinically differ the facial lentigo maligna from solar lentigo, seborrheic keratosis, and actinic keratosis. Furthermore, a single lesion can demonstrate the dermoscopic elements of seborrheic keratosis, actinic keratosis, and lentigo maligna at the same time. Even though dermoscopy is an important method in the differential diagnosis of facial lesions, histopathological evaluation still should be made to establish the final diagnosis of suspicious lesions [14, 25].

Stante et al. [15] clinically diagnosed solar lentigo in 4 cases with pigmented facial lesions. However, during the dermoscopic examination, these lesions were suspected to be lentigo maligna and the histopathological evaluation confirmed this diagnosis. This study emphasized that the early stage lentigo maligna, which could not be detected with clinical examination, could be accurately diagnosed with the use of dermoscopy.

Dermoscopic features of facial pigmented actinic keratosis include a large number of lead blue or dark brown spots and globules surrounding the follicle orifices. Histopathologically corresponding to this appearance is melanin-loaded macrophages in the upper dermis. An annular-granular pattern is formed with the conjugation of these spots and globules in time. Brown-to-gray segmented pseudo-network was suggested as a dermoscopic criterion in recent years [14].

The most common dermoscopic findings in the cases that were histopathologically diagnosed with actinic keratosis were as follows: White-yellow squama (18 lesions, 56%), brown-to-gray segmented pseudo-network (17 lesions, 53%), annular-granular pattern (16 lesions, 50%), pink-to-red pseudo-network (15 lesions, 47%), linear-wavy vessels surrounding the hair follicle (11 lesions, 34%), a white halo around the hair follicle with yellowish keratotic plug (11 lesions, 34%), lead blue or dark brown spots and globules surrounding the follicular orifice (11 lesions, 34%).

Nascimento et al. [26] emphasized the importance of an inner gray halo in distinguishing pigmented actinic keratosis from lentigo maligna dermoscopically. This manifestation was defined as a white halo around the hair follicle with a yellowish keratotic plug in our study and detected in 11 lesions (34%).

Akay et al. [27] reported that pigmented actinic keratosis has clinical and dermoscopic features similar to lentigo maligna. Therefore, they emphasized that histopathological examination is still the gold standard for accurate diagnosis.

In two patients with facial actinic keratosis, Zalaudek et al. [25] reported two patterns, which are specific for lentigo maligna: Annular-granular pattern involving asymmetric pigmented follicles, numerous small gray-brown spots surrounding the hair follicles, and brown-to-gray rhomboidal structure. Additionally, moth-eaten border and jelly sign, frequently seen in seborrheic keratosis and solar lentigo, were observed in these two patients.

In patients who were histopathologically diagnosed with actinic keratosis, dermoscopic findings were consistent with lentigo maligna: Short dark brown or black streaks in 7 (22%) and dark brown or black asymmetric pigmented follicular orifices in 3 (9%). Likewise, shared findings of seborrheic keratosis and solar lentigo, such as a moth-eaten border and jelly sign were seen in five (16%) and three (9%) lesions, respectively.

Seborrheic keratosis is usually diagnosed with clinical examination. However, in some cases, especially in the diagnosis of pigmented seborrheic keratosis, the following dermoscopic diagnostic criteria have significance: Milia-like cysts, comedone-like openings, structures similar to the brain sulci and gyri (cerebriform pattern), moth-eaten border, jelly sign, fingerprint pattern, sharp demarcation and hairpin vessels [10, 17, 28]. Among them, comedone-like openings and milia-like cysts are the most common [17, 29].

Braun et al. [17] identified 15 dermoscopic criteria in the study, which evaluated the dermoscopic findings of 203 patients with pigmented seborrheic keratosis for the presence of the above-mentioned criteria. They observed hairpin vessels in 63%, a sharp demarcation in 90%, comedone-like openings in 71%, milia-like cysts in 66%, fissures in 61%, and moth-eaten border in 46% of the lesions. The researchers noted that the majority of the lesions were papulonodular and plaque-type.

Lesions histopathologically diagnosed as seborrheic keratosis had the following dermoscopic findings in our study: A sharp demarcation and sudden cessation of pigmentation (in 5 lesions, 55%), moth-eaten border (in 4 lesions, 44%), jelly sign (in 4 lesions, 44%) and cerebriform pattern (in 2 lesions, 22%). Other dermoscopic findings consistent with actinic keratosis, such as a white-yellow squama was seen in 4 (44%) lesions, and a white halo surrounding the hair follicle with yellowish

keratotic plug, a pink-to-red pseudo-network, and the annular-granular pattern was observed in 2 (22%) lesions. The most common dermoscopic findings of seborrheic keratosis, such as comedone-like openings and milia-like cysts, were not observed since the lesions in our study were flat-surfaced.

The fingerprint pattern is a dermoscopic finding of seborrheic keratosis and solar lentigo. This pattern, described by Schiffner et al. [30] comprises light brown, delicate, and parallel arranged fingerprint-like structures. Braun et al. [17] noted the fingerprint pattern in 10% of the seborrheic keratosis lesions.

In our study, none of the seborrheic keratosis and solar lentigo lesions had the fingerprint pattern. The most common dermoscopic findings were moth-eaten border (n=7, 78%) and jelly sign (n=6, 67%) in cases that were histopathologically diagnosed as solar lentigo. Also, dermoscopic findings consistent with actinic keratosis, including lead blue or dark brown spots and globules surrounding the follicular orifices, and annular-granular pattern were demonstrated in 2 (22%) lesions.

In our study, no patient was diagnosed with lentigo maligna dermoscopically or histopathologically. In a multicenter retrospective study, Tiodorovic-Zivkovic et al. [31] reported that gray color is the most important dermoscopic criterion in the diagnosis of lentigo maligna.

Lallas et al. [32] emphasized that white and prominent follicular openings, squamous and red color in dermoscopy are important diagnostic clues to distinguish pigmented actinic keratosis from lentigo maligna; however, intense pigmentation and gray rhomboidal lines suggest lentigo malignancy.

Sahin et al. [9] compared the dermoscopic findings of facial pigmented lesions including solar lentigo, seborrheic keratosis, lentigo maligna, and lentigo maligna melanoma. In this study, they emphasized that milia-like cysts, pseudo-follicular openings, the cerebriform pattern, light brown globules, and light brown and yellow-opaque homogenous areas were the most common dermoscopic criteria of the benign pigmented skin lesions.

In our study, the most common dermoscopic finding in the flat hyperpigmented facial lesions was white-yellow squama (n=25, 47%). The rest of the findings were an annular-granular pattern (n=22, 41%), a pink-to-red pseudo-network (n=18, 34%), a brown-to-gray segmented pseudo-network (n=18, 34%) and a moth-eaten border (n=17, 32%).

In a meta-analysis, Bafounta et al. [33] assessed 8 studies and compared the diagnostic ratio of clinical evaluations and dermoscopic findings. They found that the diagnostic specificity and sensitivity of dermoscopy were higher. On the other hand, the use of dermoscopy still does not provide a 100% accurate diagnosis and it never substitutes histopathological evaluation.

Costa-Silva et al. [34] reported that dermoscopy increases the diagnostic accuracy of flat pigmented facial lesions; however, histopathological evaluation is the gold standard for accurate diagnosis.

Dermoscopy had a sensitivity and specificity of 66.7% and 95.1%, respectively, in seborrheic keratosis, 90.6%, and 72.2%, respectively, in actinic keratosis and 66.7%, and 95.1%, respectively, in solar lentigo. These findings are consistent with the studies in the literature. In the light of the previous and the present study findings, we can state that dermoscopic examination contributes to a more accurate diagnosis of pigmented lesions.

In a study comparing the dermoscopic and histopathological diagnoses in nevi, Sahin et al. [35] found the two methods well compatible. In ours, the two were moderately consistent.

The coexistence of two different types of neoplasms is called a collision tumor. These types of lesions are relatively rare. Collision lesions located on the face usually show an atypical morphology. These lesions cause difficulties in differential diagnosis [36]. In this study, three lesions histopathologically diagnosed as actinic keratosis plus solar lentigo were excluded.

Limitations

The most important limitation of our study was the small number of patients. Secondly, the number of patients with solar lentigo, seborrheic keratosis, and actinic keratosis differed. Also, none of our patients had lentigo maligna**.**

Conclusion

We observed a moderate agreement between dermoscopic examination and histopathological evaluation. One should not be contented with the clinical examination of the pigmented lesions on the face; if possible, a dermoscopic examination should also be performed for a more accurate diagnosis. The use of new dermoscopic criteria to be determined over time will support a more accurate diagnosis. Since a dermoscopic diagnosis of facial pigmented lesions cannot be based on the presence of a single criterion, we can deduce that histopathological examination is still the gold standard for accurate diagnosis.

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Elevated blood MxA protein levels in children with newly diagnosed B-ALL: A prospective case-control study

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Ethics Committee Approval
The Ethics Committee of the Cemil Taşcıoğlu City Hospital approved the study (date: 19/04/2021 and numeral: 160).
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Abstract

Background/Aim: Although leukemia is thought to be triggered or initiated by viral infections, it is not clear which viruses are the causative agents for which stage of the disease. Previous studies have shown that the MxA protein is expressed from blood mononuclear cells in reply to inducement of type I interferons in viral infections. Viral infections may trigger childhood B-cell acute lymphoblastic leukemia (B-ALL), and the hypothesis of this study was the detection of the presence of viral infection by measuring MxA expression in blood mononuclear cells of recently diagnosed pediatric B-ALL patients as a surrogate viral marker.

Methods: This study consisted two groups; the study group consisted of 30 newly diagnosed B-ALL and the control group consisted of 29 healthy asymptomatic children of similar age. Proven bacterial infection and COVID-19 PCR positivity were exclusion criteria. Bacterial culture of peripheral blood, complete blood count, plasma CRP levels and whole blood MxA levels detected by ELISA (Enzyme-Linked ImmunoSorbent Assay) method were taken.

Results: The patients' mean age was 7.42 years in the leukemia group (previously mentioned as study group) and 7.25 years in the control group. Routine serologic studies for newly diagnosed leukemia patients (CMV, EBV VCA and Hepatitis B IgM, anti-HCV and anti-HIV) were negative in all patients without any bacterial infection detected. The MxA levels were found significantly higher in children with B-ALL than in control group (5.84 (2.18-199.38) and 2.45 (1.17-88.65) ngr/ml, respectively, with $P<0.001$). CRP levels were significantly elevated in children with B-ALL than the control group (27.40 (2.60-133.40) and 0.60 (0.12-4.90) mgr/L, respectively, with $P<0.001$).

Conclusion: Our study demonstrates that blood MxA levels are increased in children with newly diagnosed B-ALL when compared to healthy asymptomatic children. This study is the first in literature in testing MxA levels in children with B-ALL. This finding may underline the triggering effect of viral infections in the onset of leukemia.

Keywords: MxA, Blood, Acute Lymphoblastic Leukemia, Children

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Introduction

B cell acute lymphoblastic leukemia (B-ALL) is the most common type of pediatric malignancy [1]. Various studies have been designed to retrospectively evaluate the etiological risk factors leading to the development of leukemia [2]. A series of events, including breakage and inaccurate repair of DNA in response to infections, chemical agents, radiation, or other unidentified environmental factors, may be responsible for the occurrence of childhood leukemias [3-9]. These sequential interactions transform a preleukemic clone into leukemia. Infections have long been considered to be one of the possible reasons of pediatric leukemia [10]. There are three different hypotheses concerning infectious etiology of pediatric leukaemia: In utero or perinatal exposure, delayed exposure after the first age to common infectious agent (Greaves) and unusual population mixing (Kinlen) [11, 12]. According to "Greaves hypotheses", regular immune stimulation can lower the risk of leukemic development. In lack of these stimulations, children may overreact to the infectious agents subsequently exposed in school, and this is responsible for a cytokine "storm", which create secondary mutations that may lead to leukemia [11]. Kinlen pointed out that leukemia space-time clusters were occurred often after recent population mixing situations, and such mixing facilitated the transmission of a specific leukemia-initiating virus [12]. More recent studies have noted that ALL patients refer to their physicians for infections at the first year of life more frequently than children who do not develop leukemia [13, 14]. Infection may initiate a preleukemic clone but that may not trigger to leukemia in the absence of abnormal response to delayed infection. Population interaction rises the possibility of contagious exposure in susceptible persons [12]. Some recent studies revealed strong findings to support the hypothesis that exposure to infections may lead to the clonal evolution of preleukemic clones to overt leukemia [15-19]. Due to the detection of viral genomic inclusions in animals with leukemia, some researchers have suggested that childhood leukemia may be initiated by infection. [20-22]. However, it is not entirely clear which specific viral agents may be responsible, and at what stage exposure to these agents triggers leukemia. Human MxA protein (Myxovirus resistance protein 1), the product of the MX1 gene, is an interferon-inducible protein with antiviral activity, responsible for a wide range of viral infections [23, 24]. The expression of viral MxA protein is induced by IFN-alpha and IFN-beta, but not by IFN-gamma, IL-1, TNF-alpha or other cytokines. Several clinical research have suggested the use of MxA protein expression of peripheral blood mononuclear cells as a marker for differential diagnosis of viral and bacterial agents. In a study on children with acute pharyngitis, high blood MxA levels were determined in patients infected with both a respiratory virus and group A streptococcus, but not in only group A streptococcus infection [25]. It has been worked out as a marker of symptomatic viral infections because of its wide antiviral spectrum, long half-life, rapid increase in hours after start of symptoms and low basal levels in asymptomatic children [26, 27]. The purpose of this study was to investigate the presence of viral infection by measuring blood MxA protein levels in children with newly diagnosed B-ALL.

Materials and methods

This study was conducted as a prospective case-control study. 30 children with newly diagnosis of B-ALL and 29 asymptomatic children served as a control group were enrolled in the study. The Ethics Committee of the Cemil Taşcıoğlu City Hospital approved the study (date: 19/04/2021, number: 160). Parents of participating children gave their written informed consent. All patients with B-ALL were diagnosed by histopathological and immunophenotypic examination of bone marrow biopsy. Children with B-ALL were included in the study and samples were taken within the first 24 hours after diagnosis, before chemotherapy was started. Patients with culture-proven bacterial infection or without consent were excluded. The control group consisted of healthy children without any signs or symptoms of chronic or acute disease. COVID-19 PCR test was taken for all patients, for exclusion criteria and were found negative. COVID-19 RT- PCR tests (Direct Detect SARS-CoV-2 Detection Kit; Coyote Bioscience, Beijing, China) were performed with swab samples from nasopharyngeal and throat on children. Blood samples for bacterial culture (only for B-ALL group), complete blood count, plasma C-reactive protein (CRP), and blood MxA protein levels were collected by venous access, and assessed by routine methods in the main laboratory of the hospital. Whole blood samples for MxA protein measurement were collected in EDTA collection tubes and stored at − 80 °C until ELISA (Enzyme-Linked ImmunoSorbent Assay)was performed following the kit user manual (biovender).

Statistical analysis

IBM SPSS Statistics 22.0 (SPSS IBM, Turkey) program was used. The normality of distribution of the parameters was evaluated with the Shapiro Wilks test. Descriptive statistical methods (mean, standard deviation, frequency), were used to compare normally distributed parameters between groups for quantitative data. Independent-samples t-test and Mann Whitney U test were used for comparisons between two groups according to the results of the normality test. *P*-values of less than 0.05 indicated significance.

Results

The mean age of the cases was 7.42 years in the leukemia group and 7.25 years in the control group. The detailed characteristics of leukemia and control are shown in Table 1. One patient had clinically upper respiratory system infection symptoms and, 3 patients had fever. Routine serologic studies for newly diagnosed leukemia patients (CMV, EBV VCA and Hepatitis B IgM, anti HCV and anti-HIV) were negative in all, and bacterial infection was not detected. All children in the control group were asymptomatic. The basal level of blood MxA was significantly higher in children with B-ALL than in asymptomatic children 5.84 (2.18-199.38) vs 2.45 (1.17-88.65) ngr/ml ($P<0.001$). There was a statistically significant difference in MxA levels ($P<0.001$), CRP ($P<0.001$), %LY ($P<0.001$), #LY ($P<0.001$), %EOS ($P=0.045$), #EOS ($P=0.034$), %NEU ($P=0.007$), PLT ($P=0.008$) and HGB ($P=0.001$) values between the control and leukemia groups.

Table 1: Comparison of laboratory values of leukemia and control groups

	Control (n=29)	B-ALL (n=30)	*P*-value
Age	7.25 (1.91-17.75)	7.42 (1-17.66)	0.282
Gender (Male)	22 (75.9 %)	17 (56.7 %)	0.200
MxA-ElLSA (nonogram/ml)	2.45 (1.17-88.65)	5.84 (2.18-199.38)	<0.001
WBC(μL)	7.65 (4.38-18.05)	10.46 (2.10-153.87)	0.120
LY%	41 (8.20-79.10)	12 (0.10-70.90)	<0.001
#LY	3.25 (1.45-7.23)	1.07 (5-6.82)	<0.001
EOS%	1.20 (0.11-13.10)	0.80 (0-7.90)	0.045
#EOS	0.11 (0.01-6.56)	46 (0-6.56)	0.034
BASO%	0.02 (0-0.60)	0.20 (0-0.90)	0.810
#BASO	0.01 (0-0.04)	0.01 (0-0.11)	0.568
NEU%	51.40 (8.54-66)	28.40 (1-64.90)	0.007
#NEU	3.07 (1.05-15.62)	2.37 (0.16-14.55)	0.110
PLT (10^3μL)	294 (176-475)	147 (10-688)	0.008
MPV	9.46 (1.43)	9.01 (1.16)	0.197
MONO%	6.23(1.65)	5.41(3.29)	0.226
MONO	0.42 (0.18-5.25)	0.48 (0.05-1.54)	0.519
HGB (gr/dl)	12.36 (1.57)	10.26 (2.64)	0.001
BLAST%	-	83.50 (0-100)	-
BLAST	-	3,234.50 (0-153,60)	-

WBC: White Blood Cell, EOS: Eosinophil, NEU: Neutrophil, BASO: Basophil, PLT: Platelet, MPV: Mean Platelet Volume, MONO: Monocyte, HGB: Hemoglobin

Discussion

B cell acute lymphoblastic leukaemia (B-ALL) is the most prevalent type of pediatric malignancies [28]. Existence of a clinically silent preleukaemic condition is a biological feature of many types of pediatric B-ALLs [28]. However, most likely owing to the presence of an environmental trigger, a small percentage of those preleukaemic children will develop B-ALL. One of these environmental risk factors that may trigger childhood leukemia is the exposure to viral infections [28]. The relationship between infection and the development of B-ALL has been the subject of many studies over the years. [28, 29]. Findings such as the seasonal increase in leukemia after viral epidemics or the detection of viral genomes in leukemic animals in experimental studies drew attention to this relationship [30-33]. At what stage viral infections play a role in the development of leukemia or which viruses are responsible are controversial issues [28-30, 33]. In a newly diagnosed B-ALL patient, there may be several viruses that may have triggered the disease, and detection of these viruses is time-consuming and not cost-effective. In this study, we tried to detect the presence of viral infection in children with newly diagnosed B-ALL by measuring MxA expression in blood mononuclear cells as a surrogate viral marker. MxA protein has previously been found to be expressed in circulating mononuclear cells in response to stimulation by type I interferons in the presence of viral infections [34, 35]. Interferons are difficult to detect in patients due to their short half-life (1-2 hours), but MxA is quite long (2.3–2.5 days) [34, 35]. The detection of an elevated level of MxA should be diagnostic for viral infection. This is supported by studies showing increased MxA protein concentrations in patients with suspected or proven viral infections [34, 36-41]. Although MxA levels were investigated in many patient groups (infections, autoimmune diseases), we could not find a study that determined MxA levels in children with newly diagnosed B-ALL. In our study, we found that blood MxA levels were increased in newly diagnosed B-ALL patients compared to age-matched healthy asymptomatic children. There are only two publications that have studied MxA in children with pediatric malignancies. Koskenvue et al. observed MxA protein expression in blood leukocytes of 26 febrile and nonfebrile pediatric patients receiving chemotherapy and showed that determination of MxA protein expression provides a promising parameter to distinguish viral infections from bacterial infections in immunosuppressed children with malignancy [42]. The patient group consisted of various malignancies, not just a certain subtype of leukemia as in our study. They determined that some patients have elevated MxA expression after administration of chemotherapy agents and concluded that the reason of this could be cytotoxically mediated or direct effect on mononuclear cells or reactivation of unknown viruses [42]. In our study we collected samples before administration of cytotoxic therapy to avoid this effect of chemotherapy. Manabe et al. studied the cellular expression of MxA protein, as a reliable marker of viral infection, at diagnosis in children with juvenile myelomonocytic leukemia (JMML) to estimate the prevalence of viral infections [43]. They found 67% of 18 patients had increased levels of the MxA protein, with viral infections proven in three patients and concluded that the possibility of viral contribution to JMML pathogenesis by stimulating malignant clones necessitates more research [43]. Although a homogeneous disease group (pediatric patients with JMML) was selected in this study, the number of patients was low and there was no control group.

Many methods have been tried for the measurement of MxA [39, 40]. Manabe et al. studied MxA by flow cytometry in children with JMML [43]. Vallittu et al. evaluated MxA in whole blood by enzyme immunoassay (EIA) in multiple sclerosis (MS) patients treated with interferon [44]. The MxA-EIA was considered by the researchers as a faster and more reliable method compared with flow cytometric analysis of MxA in peripheral blood mononuclear cells [45]. We consider the MxA-EIA as a more reliable and practical method in pediatric patients.

C-reactive protein (CRP) is an acute phase biomarker which is used in routine clinical practice and increased in inflammatory processes such as severe infections [46]. In general, CRP levels were found to be elevated in all infections, quite higher in acute bacterial infections than viral infections [46]. It has been reported that CRP is more valuable than white blood cell counts and ESR in detecting bacterial infections [47]. We used CRP assay to rule out subclinical infections in the control group and detected low levels of CRP in these healthy children compared to the patient group. CRP is increased not only in infections but also in malignancies as an acute phase marker [48]. Therefore, it is expected to be higher in patient group than control group.

In this study, since we wanted to test the hypothesis that viral infections may trigger childhood B-ALL, we tried to detect the presence of viral infection by measuring MxA expression in blood mononuclear cells as a surrogate viral marker. As it was practically impossible to specifically test large number of viruses in pediatric patients that may trigger leukemia, we tried to determine the presence of a viral infection using a surrogate viral marker. To our knowledge, MxA protein was tested for the first time and found to be increased in such a group of newly diagnosed pediatric B-ALL patients.

The small number of cases was the limitation of this study.

Conclusion

In this prospective case-control study, MxA levels are increased in patients with newly diagnosed B-ALL compared to age-matched healthy children, which supports the relationship

between leukemia and viral infection. Further studies with larger patient groups are necessary to explain the significance of MxA protein expression in pediatric patients with newly diagnosed B-ALL. The understanding of the interaction between preleukaemic cells and exposure to infections may provide us new strategies to prevent childhood B-ALL development.

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Management of aneurysmal subarachnoid hemorrhage with surgical clipping: A single center perspective

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Ethics Committee Approval
The study was approved by the research ethics committee of Sivas Cumhuriyet University (2021-08/08). 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.

Conflict of Interest
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Abstract

Background/Aim: There is no consensus on the optimal treatment for intracranial aneurysm rupture due to subarachnoid hemorrhage (SAH). In this study, we analyzed a series of ruptured intracranial aneurysms treated with the clipping method at our center.

Methods: In this retrospective cohort study; we searched our patient database for patients who developed SAH due to ruptured intracranial aneurysm treated at the Neurosurgery Clinic of Sivas Cumhuriyet University. A total of 304 patients who underwent the clipping operation due to aneurysmal SAH between 2010 and 2020 were included in the study. Cases with aneurysmal SAH who underwent endovascular coiling which is consisted of 22 patients were excluded.

Results: A significant inverse correlation was found between age and Glasgow coma scores (GCS) ($r=-0.137$, $P=0.017$). Hunt–Hess and Fisher grades increased significantly with increasing age ($r=0.187$, $P<0.001$ and $r=0.185$, $P<0.001$). The mean age of men was significantly lower than that of women ($P=0.005$). Aneurysms located in the anterior communicating artery were significantly more frequent in men than in women ($P<0.001$). There was no significant difference in the distribution of other aneurysm locations by gender ($P>0.05$). No significant differences were observed in GCS scores and Hunt–Hess and Fisher grades between genders ($P>0.05$). There were no significant effects of aneurysm locations on mortality ($P>0.05$). Conversely, GCS scores were significantly lower and Hunt–Hess and Fisher grades were significantly higher in the surviving group than in the deceased group ($P<0.001$).

Conclusion: Our study presented the outcomes of patients treated in our clinic with surgical clipping. Based on our findings, we believe that surgical clipping is still a safe and valid treatment method.

Keywords: Subarachnoid hemorrhage, Surgical clipping, Aneurysm, Vasospasm

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Introduction

Subarachnoid hemorrhage (SAH) due to intracranial aneurysm rupture is a serious health issue with high mortality and morbidity. SAH accounts for approximately 5% of all strokes, mortality within the following month is 36%, and the incidence is 9/100,000 per year [1–3]. SAHs due to intracranial aneurysm rupture constitute 75%–85% of SAHs from nontraumatic causes [4].

In the post bleeding period, neurological complications such as further hemorrhage, vasospasm, cerebral edema, hydrocele, epileptic seizures and systemic complications such as pulmonary edema, cardiomyopathy and infections may occur. There is no consensus on the optimal treatment for intracranial aneurysm rupture due to SAH. Endovascular coiling and transcranial clipping are the preferred methods in various centers based on experience or individual cases [1-3].

In this study, we analyzed a series of ruptured intracranial aneurysms treated with the clipping method at our center.

Materials and methods

We retrospectively searched our patient database for patients who developed SAH due to ruptured intracranial aneurysm treated at the Neurosurgery Clinic of Sivas Cumhuriyet University. A total of 304 patients who underwent the clipping operation due to aneurysmal subarachnoid hemorrhage between the years 2010 and 2020 were included in the study. Cases with aneurysmal SAH who underwent endovascular coiling which is consisted of 22 patients were excluded.

All surgical procedures were performed by the same team with experience in neurovascular surgery. The data analyzed was demographic information, aneurysm location and size, preoperative Glasgow coma scores (GCS), Hunt–Hess grades, Fisher grades, morbidity and surgical mortality (mortality in the 30 days after surgery, during the same period of hospitalization) and neurological complications such as temporary or permanent hydrocephalus and vasospasm.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics software, v.25.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to examine the distribution of continuous and discrete numerical variables. Levene's test was used to determine the homogeneity of variances. For continuous and discrete numerical variables, descriptive statistics were expressed as mean (SD) or median (25th to 75th percentile), while categorical variables were shown as the number of cases and (%). As a result of the goodness-of-fit tests, the differences between the groups for continuous numerical variables in which the parametric test criteria were met were evaluated with the student's t-test. The differences between the groups for continuous numerical variables in which the parametric test criteria were not met were examined using the Mann–Whitney U test. We used 2 × 2 crosstabs and, if the expected frequency was below five in at least 25% of the cells, the categorical data were evaluated with Fisher's exact probability test. When the expected frequency was between five and 25, the $\chi 2$ test with continuity correction was used. Otherwise, Pearson's test was used. The examination was performed using the $\chi 2$ test. Correlations between GCS, Hunt–Hess and Fischer scores were investigated with Spearman's ordinal number correlation test. Results with $P<0.05$ were considered statistically significant.

Results

A total of 304 patients who underwent the clipping operation for aneurysmal SAH between January 1, 2010, and December 31, 2020, were included in this study. Data on the demographic and clinical characteristics of these 304 patients were collected and are shown in Table 1. A statistically significant inverse correlation was found between age and GCS scores (r=−0.137, $P=0.017$), Hunt–Hess and Fisher grades increased significantly with increasing age (r=0.187, $P<0.001$ and r=0.185, $P<0.001$) (Table 2).

Table 1: Demographic and clinical characteristics of patients

	n=304
Age (years) mean (SD)	53.2 (13.0)
Age range (years)	11–86
Gender	
Male n (%)	117 (38.5%)
Female n (%)	187 (61.5%)
Aneurysm location	
MCA n (%)	133 (43.8%)
ACOM n (%)	132 (43,4%)
PCOM n (%)	32 (10.5%)
ACA n (%)	23 (7.6%)
AChA n (%)	6 (2.0%)
ICA n (%)	6 (2.0%)
PICA n (%)	3 (1.0%)
Basilar n (%)	1 (0.3%)
Mean dimension of aneurysms (mm)	5.0 (4.0–7.0)
Multiple aneurysms n (%)	29 (9.5%)
Surgery day (range)	8.0 (4.0–12.0)
GCS score	14.0 (13.0–15.0)
Hunt–Hess grade (range)	2.0 (2.0–2.0)
Fisher grade (range)	3.0 (2.0–4.0)
Hydrocephalus n (%)	22 (7.2%)
Vasospasm n (%)	70 (23.0%)
Vasospasm day after surgery (range)	7.0 (5.75–10.0)
Morbidity n (%)	67 (22.0%)
Mortality n (%)	34 (11.2%)

ACA: Anterior cerebral artery, AChA: Anterior choroidal artery, ACOM: Anterior communicating Artery, GCS: Glasgow coma scale, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCOM: Posterior communicating artery, PICA: Posterior inferior cerebellar artery, SD: standard deviation

Table 2: Correlation coefficients and significance levels between the ages of patients who underwent surgical clipping for ruptured aneurysms due to subarachnoid hemorrhage and their Glasgow coma scale, Hunt–Hess and Fischer scores

	Correlation coefficient	*P*-value†
Glasgow coma scale	−0.137	0.017
Hunt–Hess	0.187	<0.001
Fisher	0.185	<0.001

† Spearman's ordinal correlation test

The mean age of men was statistically significantly lower than that of women ($P=0.005$). Aneurysms located in the ACOM were significantly more frequent in men than in women ($P<0.001$). There was no significant difference in the distribution of other aneurysm locations by gender ($P>0.05$). No significant differences were observed in GCS scores and Hunt–Hess and Fisher grades between genders ($P>0.05$) (Table 3).

Between the groups with and without morbidity, there were no significant differences in mean age or gender ($P=0.069$ and $P=0.282$). There was no significant effect of aneurysm location on morbidity ($P>0.05$). On the other hand, GCS scores were significantly lower and Hunt–Hess and Fisher grades significantly higher in the group with morbidity compared to the group without morbidity ($P<0.001$) (Table 4).

There were no significant differences between the surviving group and the deceased group in mean age or gender ($P=0.355$ and $P=0.334$). There were no significant effects of

aneurysm locations on mortality (P>0.05). On the other hand, GCS scores were statistically significantly lower and Hunt–Hess and Fisher grades were significantly higher in the surviving group than the deceased group (P<0.001) (Table 5).

Table 3: Demographic and clinical characteristics of patients who underwent surgical clipping for ruptured aneurysms due to subarachnoid hemorrhage by gender

	Male (n=117)	Female (n=187)	*P*-value
Age (years) mean (SD)	50.6 (12.5)	54.9 (13.1)	0.005†
Aneurysm location			
MCA n (%)	47 (40.2%)	86 (46.0%)	0.320‡
ACOM n (%)	65 (55.6%)	67 (35.8%)	<0.001‡
PCOM n (%)	7 (6.0%)	25 (13.4%)	0.064¶
ACA n (%)	7 (6.0%)	16 (8.6%)	0.547¶
AChA n (%)	0 (0.0%)	6 (3.2%)	0.086¥
ICA n (%)	1 (0.9%)	5 (2.7%)	0.412¥
GCS score (range)	14 (14–15)	14 (13–15)	0.260§
Hunt–Hess grade (range)	2 (1.5–2)	2 (2–2)	0.084§
Fisher grade (range)	2 (2–4)	3 (2–4)	0.265§

† Student's t-test, ‡ Pearson's χ2 test, ¶ Continuity corrected χ2 test, ¥ Fisher's exact probability test, § Mann–Whitney U test, ACA: Anterior cerebral artery, AChA: Anterior choroidal artery, ACOM: Anterior communicating Artery, GCS: Glasgow coma scale, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCOM: Posterior communicating artery, SD: standard deviation

Table 4: Demographic and clinical characteristics of patients with and without morbidity who underwent surgical clipping for ruptured aneurysms due to subarachnoid hemorrhage

	Morbidity (−) (n=237)	Morbidity (+) (n=67)	*P*-value
Age (years) mean (SD)	52.5 (12.8)	55.8 (13.5)	0.069†
Gender			0.282‡
Male n (%)	95 (40.1%)	22 (32.8%)	
Female n (%)	142 (59.9%)	45 (67.2%)	
Aneurysm location			
MCA n (%)	100 (42.2%)	33 (49.3%)	0.304‡
ACOM n (%)	105 (44.3%)	27 (40.3%)	0.559‡
PCOM n (%)	22 (9.3%)	10 (14.9%)	0.270¶
ACA n (%)	20 (8.4%)	3 (4.5%)	0.412¶
AChA n (%)	5 (2.1%)	1 (1.5%)	>0.999¥
ICA n (%)	3 (1.3%)	3 (4.5%)	0.123¥
GCS score (range)	14 (14–15)	13 (10–14)	<0.001§
Hunt–Hess grade (range)	2 (2–2)	3 (2–4)	<0.001§
Fisher grade (range)	2 (2–4)	4 (2–4)	<0.001§

† Student's t-test, ‡ Pearson's χ2 test, ¶ Continuity corrected χ2 test, ¥ Fisher's exact probability test, § Mann–Whitney U test, ACA: Anterior cerebral artery, AChA: Anterior choroidal artery, ACOM: Anterior communicating Artery, GCS: Glasgow coma scale, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCOM: Posterior communicating artery, SD: standard deviation

Table 5: Demographic and clinical characteristics of patients who underwent surgical clipping for ruptured aneurysms due to subarachnoid hemorrhage with and without subsequent mortality

	Alive (n=270)	Dead (n=34)	*P*-value
Age (years) mean (SD)	53.0 (13.0)	55.2 (13.2)	0.355†
Gender			0.334‡
Male n (%)	107 (39.6%)	10 (29.4%)	
Female n (%)	163 (60.4%)	24 (70.6%)	
Aneurysm location			
MCA n (%)	120 (44.4%)	13 (38.2%)	0.614‡
ACOM n (%)	115 (42.6%)	17 (50.0%)	0.524‡
PCOM n (%)	27 (10.0%)	5 (14.7%)	0.378¶
ACA n (%)	20 (7.4%)	3 (8.8%)	0.731¶
AChA n (%)	6 (2.2%)	0 (0.0%)	>0.999¶
ICA n (%)	5 (1.9%)	1 (2.9%)	0.512¶
GCS	14 (14–15)	13 (8.75–15)	<0.001¥
Hunt–Hess	2 (2–2)	2 (2–4)	<0.001¥
Fisher	2 (2–4)	4 (3–4)	<0.001¥

† Student's t-test, ‡ Pearson's χ2 test, ¶ Fisher's exact probability test, ¥ Mann–Whitney U test, ACA: Anterior cerebral artery, AChA: Anterior choroidal artery, ACOM: Anterior communicating Artery, GCS: Glasgow coma scale, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCOM: Posterior communicating artery, SD: standard deviation

There were no significant differences in the mean age according to the location of the aneurysm (P>0.05). There were no significant differences in GCS scores or Hunt–Hess and Fisher grades according to the location of the aneurysm (P>0.05), with the exception that Fisher grades were significantly lower in those with aneurysms located in the ACA than those with aneurysms in other locations (P=0.049). There were no significant differences in the incidence of vasospasm according to aneurysm location (P>0.05). In addition, there was no significant difference in the postoperative day on which vasospasm occurred according to aneurysm location (P>0.05) (Table 6).

There were no significant differences in the mean age or gender of those who had multiple aneurysms and those who did not (P=0.390 and P>0.999). In addition, no significant differences were observed in the Hunt–Hess and Fisher grades of those who had multiple aneurysms and those who did not (P=0.863 and P=0.661) (Table 7).

Table 6: Ages, GCS scores, Hunt–Hess grades, Fisher grades, vasospasm development and vasospasm development times according to aneurysm location in patients who underwent surgical clipping for ruptured aneurysms due to subarachnoid hemorrhage

	n	Age mean (SD)	GCS score (range)	Hunt–Hess Grade (range)	Fisher Grade (range)	Vasospasm development n (%)	Vasospasm development time Post-operative day (range)
MCA							
No	171	54.0 (13.2)	14 (13–15)	2 (2–2)	3 (2–4)	39 (22.8%)	7 (5–10)
Yes	133	52.3 (12.7)	14 (13–15)	2 (2–2)	2 (2–4)	31 (23.3%)	7 (6–12)
P-value		0.283†	0.862‡	0.430‡	0.767‡	0.918¶	0.541‡
ACOM							
No	172	53.0 (13.2)	14 (13–15)	2 (2–2)	2 (2–4)	33 (19.2%)	7 (4.5–12)
Yes	132	53.6 (12.8)	14 (14–15)	2 (2–2)	3 (2–4)	37 (28.0%)	6 (7–9.5)
P-value		0.676†	0.860‡	0.750‡	0.289‡	0.069¶	0.603‡
PCOM							
No	272	53.0 (12.9)	14 (13–15)	2 (2–2)	3 (2–4)	63 (23.2%)	7 (5–10)
Yes	32	55.2 (13.7)	14 (13–15)	2 (1–2.75)	2 (2–4)	7 (21.9%)	10 (7–12)
P-value		0.383†	0.714‡	0.974‡	0.865‡	>0.999¥	0.183‡
ACA							
No	281	53.6 (12.9)	14 (13–15)	2 (2–2)	3 (2–4)	67 (23.8%)	7 (6–10)
Yes	23	49.0 (13.6)	14 (14–15)	2 (1–2)	2 (2–3)	3 (13.0%)	4 (4–7)
P-value		0.106†	0.721‡	0.503‡	0.049‡	0.355¥	0.102‡
AchA							
No	298	53.3 (13.1)	14 (13–15)	2 (2–2)	3 (2–4)	70 (23.5%)	7 (5.75–10)
Yes	6	53.2 (5.0)	14,5 (13.75–15)	2 (1.75–2)	2 (2–3.25)	0 (0.0%)	N/A
P-value		0.986†	0.494‡	0.612‡	0.406‡	0.342§	N/A
ICA							
No	298	53.3 (12.9)	14 (13–15)	2 (2–2)	3 (2–4)	69 (23.2%)	7 (5.5–10)
Yes	6	52.2 (16.9)	14 (9–15)	2 (0.75–4)	2 (1.5–4)	1 (16.7%)	N/A
P-value		0.836†	0.491‡	0.905‡	0.409‡	>0.999§	0.886‡

† Student's t-test, ‡ Mann–Whitney U test, ¶ Pearson's χ2 test, ¥ Continuity corrected χ2 test, § Fisher's exact probability test, N/A: Not applicable, ACA: Anterior cerebral artery, AChA: Anterior choroidal artery, ACOM: Anterior communicating Artery, GCS: Glasgow coma scale, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCOM: Posterior communicating artery, SD: standard deviation

Table 7: Demographic and clinical characteristics of patients who underwent surgical clipping for ruptured aneurysms due to subarachnoid hemorrhage with and without multiple aneurysms

	Multiple aneurysms (−) (n=275)	Multiple aneurysms (+) (n=29)	*P*-value
Age (years) mean (SD)	53.5 (13.2)	51.3 (10.7)	0.390†
Gender			>0.999‡
Male n (%)	106 (38.5%)	11 (37.9%)	
Female n (%)	169 (61.5%)	18 (62.1%)	
Hunt–Hess grade (range)	2 (2–2)	2 (1,5–2,5)	0.863¶
Fisher grade (range)	3 (2–4)	2 (2–4)	0.661¶

† Student's t-test, ‡ Continuity corrected χ2 test, ¶ Mann–Whitney U test, SD standard deviation

Finally, the Fisher grades of those that developed vasospasms [median=4, (IQR: 2–4)] were significantly higher than those of the patients who did not [median=2, (IQR: 2–4)] (P<0.001). There was no significant correlation between the postoperative day of vasospasm and the Fisher scores of those who developed vasospasm (r=−0.140 and P=0.249).

Discussion

Aneurysmal SAH is a serious neurological issue with high mortality and morbidity rates. Depending on the patient, their clinical condition, aneurysm location and the clinical experience of the treating physicians, the treatment for this patient group varies. In this study, we analyzed 304 patients who underwent surgical clipping for aneurysmal SAH in our clinic. Approximately 5.6% of the patients were evaluated as having a poor grade of aneurysmal SAH. This rate is low compared to those reported in other studies [5, 6]. This may be explained by the fact that we only included patients that we surgically clipped in this study.

Aneurysmal SAH can occur at any age but is most frequently in the sixth decade of life. Women are more at risk than men [7]. In our study, the mean age and the gender distribution were in line with the literature. In addition, the frequency of anterior circulation aneurysms was high in our study, again in line with the literature [8, 9].

The mean aneurysm size in our study was 5 mm. In a study of 248 poor grade SAH patients evaluated by Patrick et al.

[8], the mean aneurysm size was 8.5 mm. A study of SAH patients under 35 years of age by Chalouhi et al. [10] found that more than half of the patients had an aneurysm size below 7 mm.

As is known, aneurysmal SAHs most commonly arise from anterior circulation aneurysms [7]. In our study, middle cerebral artery and anterior communicating artery aneurysms were the most common cause of SAH, with rates of 43.8% and 43.4%, respectively.

While other studies have reported mortality rates between 0% and 34% following treatment [8, 10], our surgical clipping patients showed total mortality and morbidity rates of 11.2% and 22%, respectively.

The timing of surgical intervention in aneurysmal SAH is a matter of debate. Although there is no consensus on this issue, different centers have different timing preferences. While early surgery has the advantage of preventing rebleeding, late surgery is better suited to combating vasospasms. A large multicenter study reported that the overall outcomes of early surgery were superior to late surgery, but better surgical outcomes were obtained in late surgery [11]. In another study of 32,048 patients (75.2% of whom received intervention within the first 48 hours), early treatment was found to shorten the length of hospital stay and the rate of disability at discharge was lower [4, 12]. The rate of rebleeding is nearly 40% in cases that do not receive early surgery [9, 13]. We performed surgical intervention within the first 48 hours in 50 (16.5%) of this patient group. Although we favor late intervention at our institute, patients with conditions such as acute hydrocephalus, intracerebral hematoma and diffuse cerebral edema are treated earlier. Our rebleeding rate was 1.6% in the group that underwent intervention after 48 hours. The reason this rate was low compared to the literature may be that only patients who underwent surgical clipping were examined in our study and patients who died without intervention but without rebleeding were not included. The mean time of intervention for all patients in our study was the eighth day of hospitalization. In those who suffered from vasospasm, the mean time of surgery was the seventh day of hospitalization. This is consistent with the literature.

In our study, 41.4% of the patients we examined had an admission GCS score of 15, 59.5% had a Hunt–Hess grade of 2, and 43.4% had a Fisher grade of 2. Morbidity and mortality were significantly higher in patients with low GCS scores and high Hunt–Hess grade and Fisher grades on admission. These rates may explain the lower mortality and morbidity rates seen in our study, compared to the literature, as the majority of aneurysmal SAH patients treated in our clinic were not poor grade.

The high number of patients we treat in our clinic, the fact that all patients are treated and followed up by the same surgical team and the fact that our data covers a period of ten years were strengths of our study.

Limitations

A limitation of our study was that, although endovascular aneurysm treatment has been possible in our center for the last few years, referrals for endovascular treatment cannot be made quickly due to the location of our clinic; therefore we could not compare surgical clipping and endovascular treatment due to the insufficient number of patients who have received endovascular treatment. Another limitation was that complications such as vasospasm and rebleeding, total mortality rates and the relationship between mortality and functional outcome were not included in our study. However, we hope to include these in future research.

Conclusion

Aneurysmal SAH is an important neurological condition. The need for sufficient expertise and experience in the medical personnel involved in treatment and follow-up is indisputable. The development and improvement of endovascular interventions in recent years has led to increased research into the outcomes of surgical clipping and endovascular treatment of aneurysmal SAH. Our study presented the outcomes of patients treated in our clinic with surgical clipping and, based on our findings, we argue that surgical clipping is still a safe and valid treatment method.

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The effect of telerehabilitation on early outcomes in patients undergoing primary total knee replacement: A prospective randomized study

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Ethics Committee Approval
It was approved by the ethics committee of the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital. File number: 2019/06/146
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 continuity of rehabilitation is a problem after arthroplasty operations. There is a need for accessible rehabilitation programs for patients. The purpose of this study is to determine the difference in knee functions and patients' quality of life between patients doing home telerehabilitation and home rehabilitation after total knee arthroplasty (TKA).
Methods: This prospective study was conducted on 90 patients, between June 2019 and January 2021. Patients are divided into three groups. Patients in group 1 are told to continue with the daily routine exercises which began in hospital. Group 2 patients got an information message to their mobile phones every day for the first month, reminding them of their postoperative exercises, whereas patients in group 3 are called by mobile phone for the same reminding. All patients participating in the study were evaluated by completing the Universities of Western Ontario and McMaster Osteoarthritis Index (WOMAC) scores, the Knee Society Clinical Evaluation System (KSS), the Barthel Index (BI) and the Quality of Life Scale Short Form 36 (SF-36) preoperatively and in the first and third months postoperatively, and the differences between the groups based on these scores were evaluated.
Results: There was a statistically significant difference in WOMAC between the groups regarding first-month and third-month postoperatively (P=0.004 and P<0.001, respectively), as well as in KSS values between the same groups (P=0.048 and P=0.036, respectively). There was no statistically significant difference between the groups regarding postoperative first-month BI (P=0.826) and SF-36 values (P=0.264). There was a statistically significant difference between the groups regarding postoperative third-month BI and SF-36 values (P=0.035 and P<0.001, respectively).
Conclusion: The telerehabilitation therapy appears to be more effective and successful than the control group, as shown by improvements in overall physical functions.

Keywords: Total knee arthroplasty, Telerehabilitation, Knee society score, WOMAC, Barthel index, SF-36

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Introduction

Osteoarthritis (OA) is the most prevalent form of joint disease in elderly worldwide, and knees are the most commonly affected joints. One of the leading causes of disability, OA has a severe social impact and adverse effects on public health [1]. About 10% of men and 13% of women over the age of 60 present with symptoms of knee OA. The proportion of the population with symptomatic knee OA is expected to increase due to general ageing and obesity. There has been a steady increase in the number of total knee arthroplasties performed over the past few years, along with shorter hospital stays and earlier return home [2].

Total knee arthroplasty (TKA) is an effective surgical procedure in patients with severe knee OA. It is typically performed in elderly patients to correct a deformity of the knee joint, increase function, maintain mobility and reduce pain. The procedure involves replacing injured bone as well as cartilage with a prosthesis [3]. As a very stable and predictable procedure, TKA is successful in more than 90% of patients after 10 years after surgery [4]. Physical rehabilitation is an important factor in the recovery of patients after TKA. Rehabilitation usually begins in the hospital and continues after discharge, both as outpatient and at home [5, 6]. Physical rehabilitation is essential to achieve successful results following TKA. Preferably, it should be initiated preoperatively and continued for several months postoperatively [7]. For effective management of post-TKA rehabilitation, outcome measures, including patient range of motion, scar conditions, joint inflammation, and detailed and complex knee functions are the basis for assessing the needs of patients undergoing rehabilitation, developing a personalized therapy plan, and re-evaluating the condition and post-therapy development [8]. Currently, rehabilitation optimizes postoperative physical activity and increases the clinical and social benefits resulting from surgery. Access to this rehabilitation can be difficult for many patients after TKA, especially for those living in rural or remote areas. The distance and associated travel costs, funding limitations and lack of health care providers in these communities limit health care availability [9]. One possible solution is to use telerehabilitation technology to enable remote delivery of rehabilitation care [10].

A growing body of literature supports the use of telerehabilitation to improve patient satisfaction and health outcomes for various clinical conditions such as neurological diseases [11, 12], stroke [13], cancer [14], and cardiac and pulmonary rehabilitation [15]. Compared to face-to-face rehabilitation, remote services by phone or internet are more affordable and accessible, especially for people living in rural areas [16].

Home telerehabilitation is defined as rehabilitation services provided at home from a remote location through a telecommunications system and information technology [17]. This innovative way of delivering rehabilitation services has been the source of increased interest in the healthcare community, mainly because of its potential to reduce costs, improve access to services, and increase the efficiency of providing rehabilitation services to the community. Some studies have indeed shown that telerehabilitation after TKA is effective [10, 18, 19].

The efficacy of subsequent rehabilitation for patients after knee replacement has been well established [20, 21]. However, its mid-and long-term sustainability remains a significant challenge for maintaining therapeutic success. Exercise therapy is required for this purpose after rehabilitation [20, 22], but recent data [23] suggest that only half of the patients continue with the recommended aftercare options. Reasons for this may be a lack of reconciliation with job demands and long trips to facilities that offer treatment. More flexible and individualized treatment options are needed to increase the sustainability of postoperative exercise therapy [23]. Telerehabilitation may have the potential to increase access to treatment in structurally weak areas where appropriate healthcare structures and supplies are deficient. In addition, telerehabilitation can be performed at any time, and can therefore increase patients' compliance, especially in working patients. There is growing evidence that orthopedic telerehabilitation has positive effects on a variety of clinical conditions. Previous research has shown that telerehabilitation interventions after knee replacement are not inferior to face-to-face interventions [9, 18, 19, 24].

The purpose of this study is to determine the difference of home telerehabilitation and home rehabilitation in knee functions and rehabilitation on patients' quality of life after TKA.

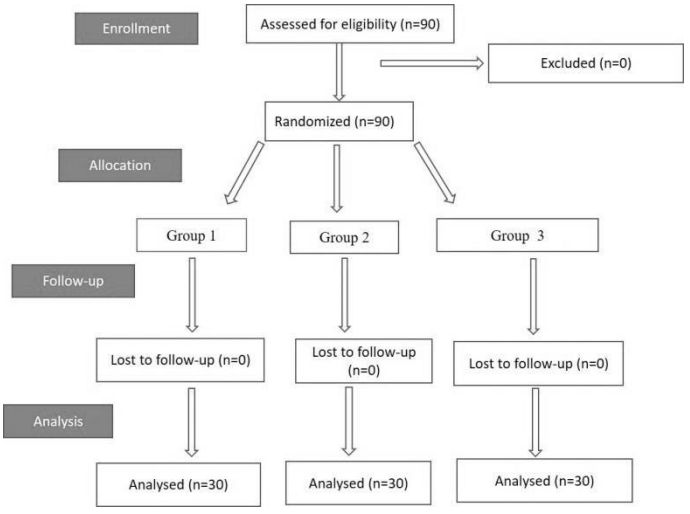
Materials and methods

The Institutional Review Board and Ethics Committee of the University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital approved this prospective study (2019.06.146). The study was conducted on patients who underwent surgery for primary knee OA. Excluded from the study were the following:

- Patients who develop OA secondary to rheumatologic disease.
- Patients with OA knee contracture before surgery.
- Patients with traumatic OA.
- Patients with hip OA that may affect functional results or who were operated for this reason.
- Patients with lumbar pathology that may affect functional results.
- Patients with vascular pathologies in the lower extremities.
- Patients who underwent arthroplasty that cut the posterior cruciate ligament.

The flowchart of the study is shown in figure 1.

Figure 1: Flow chart



Knee arthroplasty protecting the posterior cruciate ligament was applied to all patients. All operations were carried out under the supervision of the senior operator/author (C.E.). The isometric exercise programme was started in all patients on the first postoperative day, and patients were mobilized with the help of a walker next day. On the following days, quadriceps strengthening exercises were started. All movement and mobilization of patients were performed by a physiotherapist with 10 years of professional experience.

Uncomplicated patients who could exercise in postoperative follow-up were randomly divided into three groups. Randomization of the patients was carried out online with the help of a computer program. The number of patients required to achieve statistical significance was determined by power analysis. With an alpha of 0.05 and a power of 80%, 28 patients per group were needed. Taking into account the possibility of deficiencies in patient follow-up, each group was formed from thirty patients.

- Group 1: patients are told to continue with the daily routine exercises which began before discharge.
- Group 2: patients got an information message to their mobile phones every day for the first month, reminding them of their postoperative exercises.
- Group 3: patients are called by mobile phone at the same time every day for one month after surgery to remind and inform them about their exercises.

All patients participating in the study were evaluated by completing the Universities of Western Ontario and McMaster Osteoarthritis Index (WOMAC) scores, the Knee Society Clinical Evaluation System (KSS), the Barthel Index (BI) and the Quality of Life Scale Short Form 36 (SF-36) preoperatively and in the postoperative first and third months. The differences of these scores between the groups were evaluated.

The primary measurement tool for the study was WOMAC, which measures the participant-reported effect of OA on pain, stiffness, and disability [25]. WOMAC is a valid, reliable and responsive self-reporting assessment recommended for use in patients with lower extremity OA [25].

KSS consists of two parts: 1) the knee score, which evaluates the knee joint only, and 2) the functional score, which evaluates the patient's ability to walk and climb stairs [26]. As a result of the dual score, misleading low knee score is prevented due to reasons not related to knee such as ageing or weakness. In this evaluation system, pain, stability and range of motion are determined, and points are reduced for flexion contracture, hyperextension and malalignment, if present. With this system, even mild and painless anteroposterior and mediolateral instability scored 100 points, only if knees are in proper alignment, with 125 degrees of motion range. Walking distance and using stairs were evaluated for a functional score. Points were reduced if a walking aid (crutches, walker, etc.) was used. The highest functional score was 100, indicating that the patient could walk without distance restriction and use the stairs easily [26].

BI was developed to assess disability in patients with neuromuscular and musculoskeletal disorders undergoing rehabilitation and was recommended for routine use in the assessment of the elderly by the Royal College of Physicians [27]. The index is an ordinal scale that includes ten activities of daily living. The BI is scored in five-points increments, with a maximum total of 100 points.

SF-36 is a self-assessment scale consisting of 36 items providing the measurement of eight dimensions. The dimensions include physical function, social function, role limitations due to physical problems and emotional issues, mental health, energy/vitality, pain and general perception of health [28]. Subscales evaluate health between 0-100 points; a score of 0 indicates poor health, while a score of 100 indicates good health [28].

Statistical analysis

While evaluating the findings obtained in the study, the IBM Statistical Package for the Social Sciences (SPSS) 22 (IBM SPSS, Turkey) programme was used for statistical analysis. While reviewing the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro Wilks test. In addition to descriptive statistical methods (mean, standard deviation, frequency), the one-way analysis of variance (ANOVA) was used to compare the normally distributed parameters in the quantitative data. The Tukey HDS test and Tamhane's T2 test were used to identify the group that caused the difference. ANOVA with Repetitive Measurements was used for within-group comparisons of normally distributed parameters, and the Bonferroni test was used to determine the period causing the difference. Significance was evaluated by $P<0.05$.

Results

This study was conducted on 90 patients, in three groups of 30 patients each, between June 2019 and January 2021. The mean age of the participants was 66.8 (51-79). The operated knee was right and left knee in 39 (43.3%) and 51 (56.7%) patients, respectively. Patients in group 1 were followed up with routine physiotherapy, whereas patients in group 2 were reminded of their exercises with daily text messages, and group 3 patients were reminded of their physiotherapy with daily phone calls.

There was no statistically significant difference between the groups regarding preoperative WOMAC values ($P>0.05$). There was a statistically significant difference between the groups regarding first-month WOMAC values ($P=0.004$). As a result of pairwise comparisons, the first-month WOMAC values for Group 1 were statistically significantly lower than Group 3 ($P=0.002$). There was no statistically significant difference between the other groups regarding WOMAC values ($P>0.05$). There was a statistically significant difference between the groups regarding the third-month WOMAC values ($P<0.001$). As a result of the pairwise comparisons, the third-month WOMAC values for Group 1 were statistically significantly lower than Group 2 and Group 3 (P:0.047 and $P<0.001$, respectively). The third-month WOMAC values for Group 2 were statistically significantly lower than Group 3 ($P=0.035$) (table 1).

Table 1: Evaluation of WOMAC levels between and within groups

WOMAC	Group 1 (Min-Max) (Mean(SD))	Group 2 (Min-Max) (Mean(SD))	Group 3 (Min-Max) (Mean(SD))	Total (Min-Max) (Mean(SD))	[1]*P*-value
Preop	(73-86) (82.2(2.94))	(74-88) (82.43(2.91))	(74-89) (82.37(2.85))	(73-89) (80.31(4.33))	0.950
1st month	(64-78) (31.57(2.86))	(63-79) (29.87(4.33))	(65-80) (27.97(4.67))	(63-80) (70.2(4.25))	0.004*
3rd month	(9-20) (18.1(2.94))	(9-20) (15.9(3.85))	(10-19) (13.07(4.56))	(9-20) (13.67(2.87))	<0.001*
[2]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-1st month [3]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		
1st month-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		

[1] Analysis of Variance in Repeated Measurements, [2] Friedman Test, [3] Bonferroni Test, * $P<0.05$

There was no statistically significant difference between the groups regarding preoperative KSS values ($P>0.05$). There was a statistically significant difference between the groups regarding first and third month KSS values ($P=0.048$ and $P=0.036$, respectively). As a result of the pairwise comparisons, the first-month KSS values for Group 2 were statistically significantly lower than Group 3 ($P=0.037$). There was no statistically significant difference between the other groups regarding KSS values ($P>0.05$). As a result of the pairwise comparisons, the third-month KSS values for Group 2 were statistically significantly lower than Group 3 ($P=0.034$). There was no statistically significant difference between the other groups regarding KSS values ($P>0.05$) (table 2).

Table 2: Evaluation of KSS levels between and within groups

KSS	Group 1 (Min-Max) (Mean(SD))	Group 2 (Min-Max) (Mean(SD))	Group 3 (Min-Max) (Mean(SD))	Total (Min-Max) (Mean(SD))	[1]*P*-value
Preop	(15-38) (25.17(5.57))	(14-37) (26.4(5.33))	(12-35) (24.6(5.12))	(12-38) (24.72(5.52))	0.163
1st month	(77-98) (84.63(5.25))	(74-96) (83.13(5.17))	(74-96) (86.33(4.37))	(74-98) (84.7(5.06))	0.048*
3rd month	(79-99) (86.7(4.88))	(80-99) (85.9(4.82))	(83-99) (88.83(3.6))	(79-99) (87.14(4.59))	0.036*
[2]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-1st month [3]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		
1st month-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		

[1] Analysis of Variance in Repeated Measurements, [2] Friedman Test, [3] Bonferroni Test, * $P<0.05$

There was no statistically significant difference between the groups regarding preoperative and postoperative first-month BI values ($P>0.05$). There was a statistically significant difference between the groups regarding postoperative third-month BI values ($P=0.035$). As a result of the pairwise comparisons, the postoperative third-month BI values for Group 2 were statistically significantly lower than Group 3 ($P=0.029$). There was no statistically significant difference between the other groups regarding the postoperative third-month BI values ($P>0.05$) (table 3).

There was no statistically significant difference between the groups regarding preoperative and postoperative first-month SF-36 values (physical function, social function, role limitations due to physical problems, role limitations due to emotional issues, mental health, energy/vitality, pain and general perception of health) ($P>0.05$). There was a statistically significant difference between the groups regarding postoperative third-month SF-36 values ($P<0.001$). As a result of the pairwise comparisons, third-month SF-36 values of Group 1 were statistically significantly lower than Group 3 ($P<0.001$). There was no statistically significant difference between the other groups regarding postoperative third-month SF-36 values ($P>0.05$) (table 4).

Table 3: Evaluation of BI levels between and within groups

Barthel index	Group 1 (Min-Max) (Mean(SD))	Group 2 (Min-Max) (Mean(SD))	Group 3 (Min-Max) (Mean(SD))	Total (Min-Max) (Mean(SD))	[1]*P*-value
Preop	(81-96) (88.6(3.86))	(80-95) (87.17(4.04))	(81-95) (88.3(3.83))	(80-96) (88.02(3.91))	0.330
Postop 1st month	(50-62) (55.97(3.1))	(51-62) (56.2(3.11))	(51-63) (56.47(3.19))	(50-63) (56.21(3.11))	0.826
Postop 3rd month	(93-99) (95.9(1.67))	(90-99) (95.43(2.19))	(92-99) (96.77(2.06))	(90-99) (96.03(2.04))	0.035*
[2]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-1st month [3]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		
1st month-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		

[1] Analysis of Variance in Repeated Measurements, [2] Friedman Test, [3] Bonferroni Test, * $P<0.05$

Table 4: Evaluation of SF-36 levels between and within groups

SF-36	Group 1 (Min-Max) (Mean(SD))	Group 2 (Min-Max) (Mean(SD))	Group 3 (Min-Max) (Mean(SD))	Total (Min-Max) (Mean(SD))	[1]*P*-value
Preop	(25-46) (36.07(5.72))	(26-46) (35.43(4.46))	(26-44) (35.9(4.11))	(25-46) (35.8(4.77))	0.870
Postop 1st month	(50-77) (61.33(6.4))	(52-72) (62.47(5.04))	(52-80) (63.77(5.69))	(50-80) (62.52(5.76))	0.264
Postop 3rd month	(72-90) (80.67(4.49))	(75-92) (83.3(4.34))	(74-94) (85.87(4.98))	(72-94) (83.28(0.03))	<0.001*
[2]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-1st month [3]*P*-value	<0.001*	<0.001*	<0.001*		
Preop-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		
1st month-3rd month [3]*P*-value	<0.001*	<0.001*	<0.001*		

[1] Analysis of Variance in Repeated Measurements, [2] Friedman Test, [3] Bonferroni Test, * $P<0.05$

Discussion

The primary finding of this study was that the patients' scores of knee function and general survival rehabilitated by telephone every day were better than the patients who underwent self-rehabilitation at home. The sustainability of maintaining the therapeutic success of rehabilitation programmes remains a significant challenge. Treatment options after rehabilitation are often remote and difficult to access. Therefore, as telerehabilitation promises to increase patient access, to improve quality of healthcare and to reduce costs, it may have the potential to increase access to treatment in structurally weak areas where appropriate healthcare structures and supplies are deficient. The telerehabilitation appears to be a promising proposition for improving patients' motor function, especially after orthopedic surgery [28, 29]. It may be beneficial for moving longer distances and coping with the challenges of daily life.

It is well known that the compliance of patients exercising at home should be improved, and the flexible use of telerehabilitation can improve compliance [29]. The reason for patient's non-adherence to the programme includes the lack of positive feedback and a degree of experienced helplessness [30]. Solutions to this problem may be setting targets, monitoring and receiving feedback using telerehabilitation systems [31].

Kauppila et al. [32] compared telerehabilitation versus inpatient rehabilitation, even after early hospital discharge. They noted that when telerehabilitation and inpatient rehabilitation outcomes following primary total hip or knee replacement were compared using validated outcome measures, there was no

difference in clinical outcomes at 3 and 12 months postoperatively. Both treatment groups achieved improvement in pain and function similar to other studies [33, 34]. Because we obtained similar results in this study, we believe patients may need a combination of inpatient and outpatient rehabilitation to meet their needs and preferences at each stage of the continuing rehabilitation process.

In a non-randomized Australian study, Tribe et al. [35] compared the functional outcomes of patients who received home rehabilitation and inpatient rehabilitation after total hip and knee replacement for primary OA. There was not any difference in functional outcomes at one-year follow-up.

In light of the suggestion that telerehabilitation therapy can increase the therapeutic relationship, patient motivation, and patient and family involvement in rehabilitation, it can be assumed that telerehabilitation will also improve performance and outcomes [36, 37]. Coordinating the rehabilitation process across disciplines and increasing patient engagement can help improve the consistency and quality. The findings suggest that telerehabilitation programmes are at least as effective as inpatient postoperative rehabilitation programmes in achieving functional outcomes. In terms of future research directions, determining the optimal setting for community rehabilitation and the impact of that setting on results are key priority. It is also a key in optimizing treatment and diversifying resources for people who need it most.

This study has several limitations. The patient numbers in groups in the study were limited, and there is a need to study on a larger population. A limited follow-up period of three months has implications for interpreting results because the long-term effects of this rehabilitation programme are unknown. Therefore, future research should use long follow-up periods to define the long-term impacts of this alternative form of service delivery better.

The absence of a fourth group receiving inpatient rehabilitation is another limitation in this study. In addition, the inability to compare the costs of traditional rehabilitation programmes with the rehabilitation used in this study is another drawback. Future research should also include economic analyses to evaluate the financial impact of remote physical therapy. Such analyses are critical as healthcare providers are unlikely to implement telerehabilitation without clear evidence of its financial viability and sustainability.

Conclusion

Our study shows that telerehabilitation therapy appears to be more effective and successful than the control group, as evidenced by improvements in overall physical functions. As teletherapy is feasible and acceptable for clinicians and patients, the next step will be to conduct controlled trials to compare the cost-benefit of two treatment alternatives: telerehabilitation and inpatient rehabilitation.

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Is hypnosis an effective alternative to medical therapy for hyperemesis gravidarum?

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Ethics Committee Approval
The study was approved by Dr. Sami Ulus Education and Research Hospital Clinical Research Ethics Committee, 2021/01-074. 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: Not only because of the deterioration of the general condition of pregnant women, but also considering the extra burden of long hospitalizations, in patients with hyperemesis alternative treatments become even more important. The aim of this study was to determine whether medical hypnosis is an effective and tolerated treatment for nausea and vomiting of pregnancy thus can be a good alternative to medical therapy for pregnant women with severe hyperemesis that would require hospitalization.
Methods: A cross sectional study was conducted with 40 pregnant women who were hospitalized for hyperemesis gravidarum between 6-20 weeks of pregnancy. The PUQE test was performed in a face-to-face interview to determine nausea and vomiting severity. All patients were given the same medical treatment and hypnosis was performed with alternate patients after stabilization, by the same trained hypnotist**.** After the day of hypnosis all patients were again given the PUQE test. The groups were compared according to PUQE test results, the length of hospital stay and the time of first enteral feeding.
Results: The groups were similar in terms of socio-demographic characteristics. The median PUQE scores were lower and the median hospitalization time was significantly shorter in the hypnosis group ($P<0.001$; $P=0.010$). The hypnosis group switched to oral nutrition earlier than the control group and this was statistically significant ($P=0.034$).
Conclusion: Hypnotherapy should be regarded as the treatment of choice in hyperemesis gravidarum, not only by increasing women's emotional well-being during pregnancy but also reducing unnecessary and prolonged hospitalizations.

Keywords: Feeding, Hyperemesis, Hypnosis, Hospitalization, Pregnancy

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Introduction

Nausea and vomiting of pregnancy (NVP) is one of the most common complaints of pregnant women, affecting 70-80% of them in adolescent and reproductive age [1,2]. Although it is generally considered as a physiological condition resolving after 16-20 weeks, hyperemesis, the severe form of NVP, can cause weight loss (exceeding 5 percent of prepregnancy body weight), dehydration, electrolyte disturbances, and it may require hospitalization. It is one of the most common reasons for hospitalization during pregnancy and can affect 0.3-2% of pregnant women [3]. Although it is a condition that seriously decreases the quality of life as well as causing health-related problems, there is still no definite consensus on its etiology. It is thought to be a multi-factorial condition influenced by hormonal, biological and socioeconomic factors. The multifactorial etiology complicates treatment and requires individualization of the treatment. Medical treatments usually lighten the symptoms and improve the general condition of the patient, but unfortunately they are insufficient to relieve nausea and vomiting [4]. In recent years, the lack of medical therapies and possible effects of psychological factors on nausea and vomiting have necessitated an emphasis on alternative treatment methods such as hypnosis [5]. Hypnosis is a state of trance, a special state of consciousness created by suggestion. During this trance, while the person turns off or does not care about all the stimuli coming from the environment (sound, light, smell, etc.), they listen to the hypnotist's suggestions with increased attention, and understand and apply them with voluntary participation [6]. Hypnosis has been recognized by organizations, including the British Medical Association, the American Medical Association and the British Psychologica Society as an effective clinical tool. Although there are studies showing that hypnosis is effective in pregnant women with hyperemesis, generally the study groups include a small number of cases. The aim of this study was to determine whether medical hypnosis is an effective and tolerated treatment for NVP thus can be a good alternative to medical therapy in pregnant women with severe hyperemesis requiring hospitalization.

Materials and methods

A prospective cross-sectional study was conducted with pregnant women who were hospitalized for hyperemesis at the obstetric clinics of a major tertiary maternity hospital in Ankara, Turkey, from November 2020-January 2021. The study group consisted of 40 primigravida pregnant women aged between 20-35 years, who were in viable singleton pregnancies ≤20 weeks without congenital malformations. Patients with systemic disease that could lead to nausea and vomiting (diabetes, thyroid dysfunction, urinary-hepatobiliary or gastrointestinal disease, hematologic diseases, depressive disorders), threatened abortion, and patients who were not appropriate to hypnotize (obsessive-compulsive disorder or severe psychiatric disorder, patients diagnosed with psychiatric illness) were excluded. Weight loss exceeding 5 percent of prepregnancy body weight, ketonuria unrelated to other causes and vomiting more than three times per day were used as diagnostic criteria for hyperemesis. The study was approved by the Ethics Committee. After giving detailed information about the study and hypnosis, written informed consent was obtained from all patients.

Gestational age was determined by obstetric ultrasonography. Complete blood count, kidney, liver, thyroid function tests and urinalysis were conducted and recorded. After the patients were hospitalized and their general condition was improved by hydration, a questionnaire (age, educational level and employment status of both the women and their husbands, total monthly income, whether the baby was planned, etc.) prepared by the researcher was applied to collect the socio-demographic characteristics of the study group and PUQE test was applied for determining the frequency and severity of nausea and vomiting with a face-to-face interview.

After this stage, all patients were informed in detail about hypnosis. All patients were given the same medical treatment (hydration, electrolyte replacement in patients with electrolyte imbalance, 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) and hypnosis was done with alternate patients. Hypnosis was conducted by the same trained hypnotist for all women, who had the authority and certificate to use hypnosis through the Turkish Ministry of Health. Hypnosis sessions were performed in the patient's room, with the patient and the hypnotist alone. After the day of hypnosis (second day of hospitalization), all patients were again given the PUQE test.

Hypnosis session: After the patient laid in her own bed, she was hypnotized with eye fixation and body relaxation by the hypnotist. The hypnosis was then deepened with the ladder imagery technique. She was then asked to imagine that she was inside a safe place, a stream where the water had healing powers. She was asked to go to the source of the stream and to examine whether there were any obstacles to the flow of the stream and to remove the obstacles that she saw. After removing the obstacles in the stream bed, just like the strong flow of water, she envisioned that her stomach too had been liberated and that her stomach and intestines were performing all their functions in a healthy and natural way. She was ensured that drinking from the stream, with its healing abilities, would cleanse her stomach and intestines, ensure that she ate in a healthy manner, and that the food would easily pass through her stomach to her intestines without any discomfort, that her symptoms would disappear and that she could begin a healthy diet again. Every morning when she awoke, during the afternoon and before night time, she can lift the obstacles in the stream bed by enclosing her right thumb with her other 4 fingers and breathing for a total of 7 times, and in doing so, her gastrointestinal functions will work efficiently, and by drinking from the healing stream water, she can digest all the food without any distress, and finally, be encouraged to internalize that she was happy, peaceful and healthy. All of the patients came out of the hypnosis session with a smile on their face and stated that they felt good, did not have any nausea, and that it felt comforting to know how to deal with their nausea.

The PUQE test was developed by Koren et al. [7] in 2002. It is a simple, clinically relevant and easy to complete scoring system that is one of the most commonly used scales for evaluating the presence and severity of NVP. The test consists of three questions, validated for symptoms that occurred in the past 12 hours, which is based on length of nausea period, the number of times of vomiting and the number of retching episodes. The

total score of the test ranges from 3-15; a score <6 is considered no NVP, 7-12 moderate and ≥13 severe NVP.

The groups were compared according to PUQE test results, hospitalization times and first oral feeding times.

Statistical analysis

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 24; SPSS Inc., Chicago, IL). As a result of the power analysis using the G*Power 3.0.10 program, a total of at least 40 samples were found to be sufficient with 90% power, 5% margin of error and 0.265 effect size (n1: 20; n2: 20). Frequency tables and descriptive statistics were used in interpretation of the variables. Continuous variables are presented as median (min-max) and categorical variables are presented as percentages (%). Parametric tests were used for normally distributed variables, otherwise analyses were done with non-parametric tests. In the comparison of two independent groups, "Independent Sample-t" test (t-table value) was used as a parametric test and "Mann-Whitney U" test (Z-table value) was used as a non-parametric test. The "Paired Sample" test (t-table value) was used to compare measurement values of two dependent groups. "Pearson-χ2 cross tables" were used to examine the relationship between two qualitative variables. *P*-values <0.05 were considered statistically significant.

Results

The socio-demographic characteristics of the patients are shown in Table 1. The groups were found to be similar in terms of age, educational level, employment status, employment status of the spouse, planned pregnancy and total monthly income.

Table 1: Distribution of socio-demographic characteristics and family features of the groups

Characteristic	Study Group (n=20)		Control Group (n=20)		Statistical analysis[+]
	n	%	n	%	
Age (years)					
<25	4	20.0	4	20.0	χ^2=2.424
25-27	5	25.0	6	30.0	*P*=0.489
28-30	3	15.0	6	30.0	
>30	8	40.0	4	20.0	
Educational Level					
Elementary School/Lower	8	40.0	9	45,0	χ^2=0.110
High School	12	60.0	11	55,0	*P*=0.946
Employment Status					
Employed	7	35.0	8	40.0	χ^2=0.107
Unemployed	13	65.0	12	60.0	*P*=0.744
Employment Status of Spause					
Employed	18	90.0	19	95.0	χ^2=0.360
Unemployed	2	10.0	1	5.0	*P*=0.548
Planned pregnancy					
Yes	18	90.0	18	90.0	χ^2=0.000
No	2	10.0	2	10.0	*P*=1.000
Total monthly income (TL)					
<5000	6	30.0	6	30.0	χ^2=1.511
5.000-7.500	4	20.0	6	30.0	*P*=0.680
7.501-10.000	6	30.0	3	15.0	
>10.000	4	20.0	5	25.0	

[+] Pearson-χ2 cross tables

The median PUQE score of the study group was 11.30 (1.81) (min 8-max 15), the control group was 11.20 (1.64) (min 8-max 14),and there was no significant difference between the two groups in terms of median PUQE scores on the day of hospitalization (*P*>0.05). Although a significant decrease in the second day PUQE scores (after medical treatment in the control group, and after medical treatment plus hypnosis in the study group) was found for both groups (study group 5.50 (1.36); control group 8.35 (1.92)), the decrease within the experimental group (3.531) was more pronounced than that of the control group (2.517). The second day median PUQE scores of the study group were lower than the control group, which means that a statistically significant difference was found between the groups in terms of PUQE scores after hypnosis (t=-5.408; *P*<0.001) (Table 2).

Table 2: Comparison of PUQE scores of the groups

Characteristic	Study group (n=20)		Control group (n=20)		Statistical analysis[+]	Effect Size
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]		
PUQE Scores						
At the day of hospitalization	11.30(1.81)	11.0 [2.8]	11.20(1.64)	11.0 [2.8]	t=0.183 *P*=0.856	0.058
2nd day	5.50(1.36)	5.0 [1.8]	8.35(1.92)	8.5 [2.0]	t=-5.408 *P*<0.001	1.713
Statistical analysis	t=15.801 *P*<0.001		t=11.213 *P*<0.001			
Effect Size	3.531		2.517			

[+] "Independent Sample-t" test; "Paired Sample" test

The median hospitalization time was 3.50 (1.05) (2- 5 days) in the study group, whereas it was 4.90 (1.80) (2- 8 days) in the control group, which indicates that the hospitalization time was significantly shorter in the hypnosis group (Z=-2.592; *P*=0.010).

When the groups were compared in terms of their first oral / enteral feeding times, it was found that the hypnosis group switched to oral nutrition earlier than the control group and this was statistically significant (Z=-2.115; *P*=0.034) (1.80 (0.70) (1- 3rd day); 2.40 (0.94) (1- 5th day) (Table 3).

Table 3: Comparison of the groups according to hospitalization time and first oral feeding times

Characteristic	Study group (n=20)		Control group (n=20)		Statistical analysis[+]
	Mean (SD)	Median [IQR]	Mean (SD)	Median [IQR]	
Hospitalization time	3.50 (1.05)	3.5 [1.0]	4.90 (1.80)	5.0 [2.8]	Z=-2.592 *P*=0.010
First oral feeding time	1.80 (0.70)	2.0 [1.0]	2.40 (0.94)	2.5 [1.0]	Z=-2.115 *P*=0.034

[+] "Mann-Whitney U" test (Z-value)

Discussion

Hyperemesis is the most common and important reason for hospitalization during early pregnancy. Not only the deterioration of the general condition of pregnant women, but also the insufficiency of medical treatment shows the importance of alternative therapies such as hypnosis in recent years. However, there are still limited studies on alternative therapies in patients with hyperemesis. The aim of this study was to determine whether medical hypnosis is an effective and tolerated treatment for NVP thus can be a good alternative to medical therapy in pregnant women with severe hyperemesis requiring hospitalization. This study demonstrated two important findings. First, although a significant decrease in the 2nd day PUQE scores was found in both groups, the decrease within the hypnosis group was more pronounced than that of the control group. Second, the hypnosis group switched to oral nutrition earlier and was discharged from the hospital in a significantly shorter time, which can be a meaningful indicator of the faster improvement of their general condition.

In contrast to women with mild NVP, abnormal laboratory findings (electrolyte, thyroid and liver abnormalities), physical signs of hypovolemia and orthostatic hypotension usually occur in women with hyperemesis, which often requires hospitalization. This distressing situation does not only manifest itself physically in the pregnant woman, but may also cause psychological distress by causing anxiety for both herself and her

baby. Considering the extra burden of long hospitalizations, alternative treatments become even more important.

Although psychotherapeutic techniques are effective, they usually require a long treatment period. The urgency of ensuring the safety of the baby and the mother for a pregnant woman with hyperemesis, whose general condition is very poor, reduces the applicability of these treatments. For this reason, medical hypnosis appears to be a good alternative, especially in patients with severe nausea and vomiting, because of its lack of side effects due to drugs and its rapid response [8]. In their meta-analyses, Hauser et al. [9] examined the efficacy, safety and applications of medical hypnosis for many medical indications, such as pain and labor pain, emotional stress, duration of convalescence, and drug consumption in interventional procedures and operations, and stated that hypnosis was superior to standard treatment or attention control in reduction of stress, pain and drug consumption In fact, hypnosis has a very long history. In an article published in the British Medical Journal in 1949, it was suggested that hypnosis can be effective in the removal of symptoms of disease [10]**.** In their study in which they hypnotized 4 pregnant women with persistent nausea and vomiting, Madrid et al. [11] stated that hypnosis was very effective in all 4 patients, all awoke free of nausea after hypnosis and had a healthy pregnancy until they gave birth. According to our results, the significant decrease observed in the PUQE scores of both groups on the 2nd day, shows the effectiveness of medical treatment, which has been the first choice for hyperemesis for years. However, the fact that the decrease in scores was more defined and significant in the hypnosis group is an important finding of our study, it supports the results of other studies in the literature in terms of demonstrating the effectiveness of hypnosis. Similar to the study of Madrid et al., all patients in our study came out of the hypnosis with a smile on their faces and stated that they felt good, did not have any nausea, and that it felt good to know how to deal with the nausea from now on.

The most common problem in patients with hyperemesis is nutritional disorders caused by decreased oral intake [12]. Generally, the inability of patients to tolerate oral nutrition despite treatment is one of the most common problems observed in hospitalized patients. Therefore, we believe that the significantly shorter transition period of the hypnosis group to oral intake is important for pregnant women who require immediate care and resolution of symptoms to ensure their safety and that of their fetus. Another important point about nausea and vomiting in pregnancy is the long-term hospitalization caused by the deteriorated general condition of the mother. It is the second most common diagnosis of antenatal hospitalization with a rate of 11.4% of indications and the mean hospital stay is 2.7 days [13]. Piwko et al. [14] analyzed the economic burden of NVP in the USA and found that the estimated costs for drug treatment for mild and severe NVP were $40 and $267, respectively, and the estimated total hospital cost associated with HEG was an average of $12,453 per patient admission. Considering both the extra burden of medical treatment and long hospitalizations, the importance of the significantly shorter hospital stay in the hypnosis group as we revealed in our study becomes more evident.

Since the use of hypnosis in hyperemesis is still limited, there is still no consensus on the subject, such as which hypnotherapy method to use and how many sessions of hypnosis should be performed for hyperemesis. In their study, Madrid et al. [11] treated four cases with hypnosis who were nauseated throughout their pregnancy. They used a psychodynamic investigation of the cause of the problem and stated that all the patients came out of hypnosis saying that they were no longer nauseous and remained free from nausea till delivery. Torem [15] applied different hypnotic techniques in different patients such as ego strengthening, cognitive restructuring, symbolic guided imagery, future-oriented guided imagery techniques and the hypnotic relaxation suggestion technique, which we used in our study, and concluded that no matter which technique is used, hypnosis is effective in pregnant women with hyperemesis. Fucs et al. [16] stated that the motivation of the patients is more important in the ease and effectiveness of hypnosis rather than the number of sessions, and that hypnosis applied by a trained physician is an important treatment option that may be preferred in the treatment of hyperemesis.

Some points that were considered during the study in order to prevent bias were as follows. All patients were selected from among those who had their first pregnancy in order to prevent the positive and negative effects of their previous pregnancy history. All patients were hypnotized by the same hypnotist with the same technique and in their own rooms to avoid individual differences between the hypnosis sessions.

Limitations

The cross-sectional nature of this study, the small number of participants, its homogeneity, and the pregnant women not being followed up after discharge are limitations of this study in interpreting the results and for the future. Larger prospective studies in which the applied hypnosis methods are personalized and various techniques of hypnosis can be compared are needed to clarify the role of hypnosis in hyperemesis gravidarum. Despite these limitations, our work broadens the understanding of the importance of hypnosis in hyperemesis.

Conclusion

In conclusion, as hyperemesis is the most common and important reason for hospitalization during early pregnancy, and not only the deterioration of the general condition of the pregnant women, but also considering the extra burden of long hospitalizations, alternative treatments become even more important. Hypnotherapy should be regarded as the treatment of choice in hyperemesis gravidarum, not only by increasing women's emotional well-being during pregnancy but also by preventing many unnecessary and prolonged hospitalizations.

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Effect of systemic immune inflammation index on symptom development in patients with moderate to severe carotid stenosis

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Ethics Committee Approval
The study was approved with the protocol of Bursa YüksekİhtisasTraining and Research Hospital Clinical Research Ethics Committee dated 28.04.2021 and numbered 2011-KAEK-25 2021/04-01.
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: Recent studies have shown that various inflammatory parameters obtained from routine blood tests can be used in the diagnosis and follow-up of cardiovascular diseases. Stroke is the second most common cause of death in the world. In this study, we aimed to investigate the role of systemic immune inflammation index (SII) value in predicting symptom development in patients with moderate to severe carotid artery stenosis (CAS).
Methods: Patients between the ages of 41 and 94 with moderate to severe CAS who were followed up and treated electively in our clinic between October 01, 2016 and October 31, 2021 were included in this retrospective observational cohort study. A total of 314 consecutive patients were included in the study. The patients were divided into two groups as asymptomatic (Group 1) and symptomatic group (Group 2).
Results: There were 245 and 69 patients in Groups 1 and 2, respectively. The median ages of patients in Groups 1 and 2 were 62 (41-86) years and 69 (49-94) years, respectively (P<0.001). In multivariate analysis, advanced age (OR: 1.692 CI 95%: 1.150-2.398 P=0.012), hypertension (OR: 1.114, CI 95%: 1.080-1.866, P=0.036) and SII (OR: 1.954, CI 95%: 1.090-2.942, P<0.001) values were determined as independent predictors of symptom development in patients with moderate-serious carotis artery stenosis. There was no statistically significant difference between the groups in terms of body mass index, gender, smoking, diabetes mellitus and chronic obstructive pulmonary disease rates (P>0.05 for all).
Conclusion: In this current study we demonstrated that high SII value detected in asymptomatic patients with stenosis of 50% or more in the carotid arteries may be a useful marker to predict symptom development.

Keywords: Inflammation, Carotid artery, Stenosis, Cerebrovascular event, Blood cells

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Introduction

Stroke is the second most common cause of death in the world [1]. Considering the etiology of stroke, it is seen that carotid artery stenosis causes stroke at a rate of approximately 30% [2]. In the presence of carotid artery stenosis (CAS), the symptoms are not always evident. It is of vital importance to recognize these patients and to predict the development of symptoms before the occurrence of conditions with high morbidity and mortality such as stroke.

Both the investigation of the etiopathogenesis of cardiovascular diseases, the examination of the progression of these diseases and the search for prognostic markers that can be used as biomarkers on these issues have been the subject of many recent studies [3]. Recent studies have shown that various inflammatory parameters obtained from routine blood tests can be used in the diagnosis and follow-up of cardiovascular diseases [4]. Two of the most important parameters checked for this purpose are the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR). There are studies showing that these parameters have a prognostic value for cardiovascular diseases [5, 6]. The systemic immune inflammation index (SII) value obtained by formulating neutrophil, lymphocyte and platelet values was determined in a recent study as an independent predictor of poor outcomes after coronary bypass operations [7]. In this study, we aimed to investigate the role of SII value in predicting symptom development in patients with moderate to severe CAS.

Materials and methods

Ethical approval for this study was obtained from Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee with date 28.04.2021 and number 2011-KAEK-25 2021/04-01. Patients between the ages of 41 and 94 with moderate to severe CAS who were followed up and treated electively in our clinic between October 01, 2016 and October 31, 2021 were included in this retrospective observational cohort study. Patients with a previous history of endovascular or surgical intervention to the carotid artery, a known systemic inflammatory disease, stroke with permanent sequelae, a history of intracerebral hemorrhage and hematological disease were excluded from the study. A total of 314 consecutive patients were included in the study. The data of patients were obtained from the hospital registry system. Demographic data and additional diseases (age, sex, smoking, hypertension, diabetes mellitus, hyperlipidemia, presence of chronic obstructive pulmonary disease) and routine laboratory data (hemogram [White blood cell (WBC)], neutrophil, lymphocyte, NLR, PLR, SII), biochemistry (creatinine, urea, [C-reactive protein (CRP)], albumin) were recorded.

The patients were divided into two groups as asymptomatic Group 1 and symptomatic group 2, and the factors affecting symptom development were examined.

Evaluation of carotid artery stenosis

All patients included in the study were first evaluated with Doppler ultrasonography (DUSG). All patients had 50% or more stenosis in the DUSG evaluation. These patients were then evaluated with digital subtraction angiography (DSA). Angiographic evaluations were performed according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) classification [8]. All patients with 50% or more lesions were included in the study.

Calculation of SII value

Blood parameters were obtained from the blood samples taken from the peripheral venous structures of all patients at the time of admission. SII values were obtained from the data in these parameters using the formula below.

SII=Platelet count (10^3/μL) x Neutrophil (10^3/μL) / Lymphocyte (10^3/μL)

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk,NY, USA). Data were expressed in mean (standard deviation (SD)) or median (minimum- maximum) or number and frequency. The Student's t-test was used for numerical values with normal distribution, while the Mann-Whitney U test was used for numerical data without normal distribution. The chi-square test was carried out to compare categorical variables. A multivariate logistic regression analysis was utilized to evaluate significant parameters in the univariate analysis for predicting symptomatic patients. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value SII for symptoms and the area under the curve (AUC) was calculated. A *P*-value of <0.05 was considered statistically significant.

Results

There were 245 and 69 patients in Groups 1 and 2, respectively. The median ages of patients in Groups 1 and 2 were 62 (41-86) years and 69 (49-94) years, respectively ($P<0.001$). There was no statistically significant difference between the groups in terms of body mass index, gender, smoking, diabetes mellitus and chronic obstructive pulmonary disease (COPD) rates ($P>0.05$ for all). Hypertension and hypercholesterolemia rates were significantly higher in Group 2 ($P<0.001$ and $P=0.030$, respectively) (Table 1).

Table 1: Demographic and laboratory features of the patients

Variables	Group 1 (N= 245)	Group 2 (N= 69)	*P*-value
Age (years)	62 (41- 86)	69 (49- 94)	<0.001‡
Male gender, n(%)	139 (56.7%)	38 (55.1%)	0.806*
Smoking, n (%)	63 (25.7%)	21 (30.4%)	0.434*
BMI (kg/m^2)	26.8 (23.7- 36)	27.1 (23- 35)	0.197
Hypertension, n (%)	150 (61.2%)	59 (85.5%)	<0.001*
Diabetes mellitus, n (%)	52 (21.2%)	17 (24.6%)	0.545*
Hypercholesterolemia, n (%)	54 (22%)	24 (34.8%)	0.030*
COPD, n (%)	37 (15.1%)	13 (18.8%)	0.453*
White blood Cell (10^3/μL)	7.2 (4.6- 10.1)	7.7 (4.2- 9.9)	0.319‡
Hematocrit (%)	38.5 (34- 56)	41.2 (36- 54)	0.128‡
Platelet (10^3/μL)	272 (156.4- 450)	284 (144.8- 398)	0.071‡
Neutrophil (10^3/μL)	4.1(2- 9.6)	4.6 (1.9- 8.8)	0.094‡
Lymphocyte (10^3/μL)	1.9 (1- 4.1)	1.7 (0.9- 3.7)	0.119‡
NLR	2.1 (1.1- 6.1)	2.9 (1.2- 8.4)	<0.001‡
PLR	151.2 (121-238)	168.4 (119- 240)	<0.001‡
SII	690 (534-2328)	1190 (625- 2990)	<0.001‡

* Chi-square test, ‡Mann Whitney U test (Data is expressed as median (minimum-maximum)), BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune inflammation index

Laboratory values of the patients are presented in Table 1. There was no difference between the groups in terms of hematocrit, platelet, white blood cell, neutrophil and lymphocyte levels ($P>0.05$ for all). NLR, PLR and SII values were significantly higher in Group 2 ($P<0.001$, for all).

Univariate and multivariate logistic regression analysis was applied to predict parameters supporting symptom development in patients with moderate- seriosus CAS (Table 2).

Table 2: Logistic regression analysis to identify factors affecting symptom onset in patients with moderate-serious carotis artery stenosis

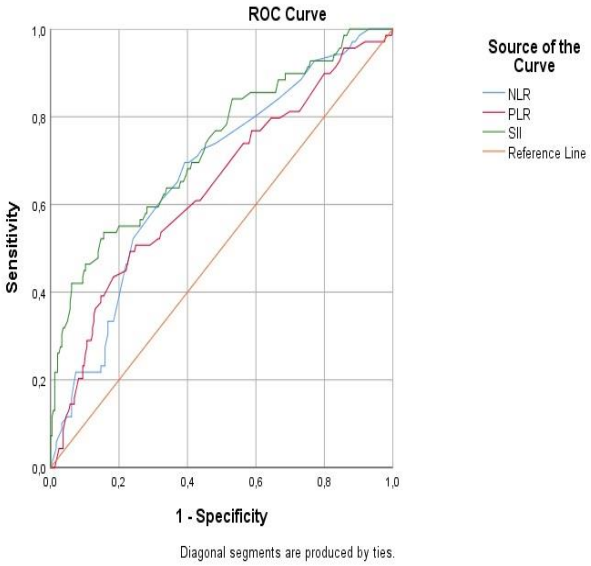
Variables	Univariate analysis			Multivariate analysis		
	P-value	Exp(B) Odds Ratio	95% C.I. Lower Upper	*P*-value	Exp(B) Odds Ratio	95% C.I. Lower Upper
Age	<0.001	1.992	1.364-2.869	0.012	1.692	1.150-2.398
Hypertension	<0.001	1.794	1.218-2.887	0.036	1.114	1.080-1.866
Hypercholesterolemia	0.034	0.790	0.660-0.894	0.347	1.112	0.796-1.236
Diabetes Mellitus	0.590	0.694	0.554-1.196	--	--	--
NLR	<0.001	1.125	1.096-1.956	--	--	--
PLR	<0.001	0.896	0.676-0.994	--	--	--
SII	<0.001	2.498	2.164-3.495	<0.001	1.954	1.090-2.942

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic immune inflammation index

In univariate analysis, advanced age (OR [odds ratio]: 1.992, 95% CI [confidence interval]: 1.364-2.869, *P*<0.001), hypertension (OR: 1.794, 95% CI: 1.218-2.887, *P*<0.001), NLR (OR: 1.125, 95% CI: 1.096-1.956, *P*<0.001), PLR (OR: 0.896, 95% CI: 0.676-0.994, *P*<0.001), and high SII (OR: 2.498, 95% CI: 2.164-3.495, *P*<0.001) values were found to be significantly correlated with the development of symptom in patients with moderate-serious carotis artery stenosis. In multivariate analysis, advanced age (OR: 1.692 CI 95%: 1.150-2.398 *P*=0.012), hypertension (OR: 1.114, CI 95%: 1.080-1.866, *P*=0.036) and SII (OR: 1.954, CI 95%: 1.090-2.942, *P*<0.001) values were determined as independent predictors of symptom development in patients with moderate-serious carotis artery stenosis.

ROC curve analysis was applied to predict parameters supporting symptom development in patients with moderate-serious CAS. In this analysis, the cut-off value for preoperative NLR was 2.5 (AUC: 0.673, 95% CI: 0.603-0.743, *P*<0.001, 61.4% sensitivity and 58.7% specificity), cut-off value for PLR was 158.2 (AUC: 0.642, 95% CI: 0.566-0.718, *P*<0.001, 59.8% sensitivity and 56.6% specificity) and cut-off value for SII was 896.9 (AUC: 0.733, 95% CI: 0.663-0.803, *P*<0.001, 71.2% sensitivity and 61.7% specificity) (Figure 1).

Figure 1: Receiver operation characteristic (ROC) curve and area under the curve (AUC) for NLR, PLR and SII to predictsymptom onset in patients with moderate-serious carotis artery stenosis



Discussion

Carotid artery stenosis (CAS) has a high morbidity and mortality and it has an important place among cardiovascular diseases in which atherosclerosis plays a role in its etiology. CAS symptoms usually occur due to embolizations caused by plaque structure. These symptoms can be seen as amaurosis fugax, syncope and transient ischemic attack (TIA) or they can appear as stroke and death [9]. The most important parameter in making the decision to intervene in patients is the presence of symptoms. If the patient is asymptomatic, even if there is 90% or less stenosis, it is followed up medically. However, for patients with symptoms and radiologically detected stenosis exceeding 50%, there is an indication for invasive intervention [10]. In this study, we investigated possible factors that may affect the development of symptoms in patients with moderate to severe CAS. Our study results showed that advanced age, hypertension, and SII were independent predictors of symptom development in these patients.

Inflammation has a very important role in the development of cardiovascular diseases [11]. In fact, recent studies show that the risk of developing cardiovascular disease decreases with suppression of inflammation and immune-modulation treatments [4]. In addition, there are some blood parameters that can be routinely checked in practice in terms of showing vascular inflammation. These are mainly platelets, neutrophils and lymphocytes [12]. Neutrophils have a role in the development of atherosclerosis, plaque rupture, plaque remodeling and reperfusion injury. The number and density of neutrophils in the plaque causing stenosis can reveal both the risk of plaque rupture and the high probability of microembolization [13-15].

Platelets play a very active role both in the early stage of chronic vascular pathology associated with atherosclerosis and in plaque rupture [16, 17]. Platelets invading the atherosclerotic plaque cause leukocytes to proliferate through direct receptor interactions, and cause an increase in leukocyte activity through the pathways they activate. The role of platelets in CAS was also examined, and the relationship between mean platelet volume (MPV) and platelet distribution width (PDW), which are platelet activation markers and the rate of stenosis in the carotid artery was revealed [18, 19]. Similarly, there are some studies such as monitoring the severity of carotid artery disease and the development of symptoms, and predicting the development of stroke with the PLR value [20, 21]. In addition to platelets, it has been shown that neutrophils and lymphocytes play a decisive role in the development of symptoms, especially in stroke, in patients under medical follow-up and in patients undergoing carotid endarterectomy [22]. In our study, we found that NLR and PLR values were correlated with symptom development.

The SII value has recently been used as a prognostic marker in the clinical follow-up of some diseases. The SII value obtained by a formula from platelet, lymphocyte and neutrophil values was formerly used to evaluate the prognosis of malignancies [23-25]. After its weak efficacy in predicting malignancy-related clinical outcomes, its relationship with cardiovascular diseases, another inflammation-related condition, was investigated. In cases of heart failure, infective endocarditis, acute myocardial infarction, major cardiovascular adverse

events, and death from cardiovascular disease, SII was found to be significantly successful in predicting prognosis [7, 26-28]. In our study, we showed that a high SII value is an independent predictor of symptom development in patients with moderate to severe CAS.

Large multicenter studies show that interventions for stenosis, especially carotid endarterectomy (CEA), have significant advantages over medical treatment in symptomatic patients with CAS of 50% or more [29, 30]. However, in symptomatic patients, it is known that the main factor causing the development of symptoms is embolizations originating from the unstable plaque structure and the main mechanism causing these embolisms, especially plaque rupture, is inflammation occurring on the plaque [31]. In this case, it is very important to examine the plaque structure and detect the presence of inflammation in the plaque in asymptomatic patients. Being able to detect inflammation in the plaque will enable to predict the presence of carotid stenosis before the patient develops symptoms. In studies conducted for this purpose, magnetic resonance (MRI) imaging was used to detect the structure of atherosclerotic plaque to predict the risk of developing cerebrovascular attack. Plaque morphology has been shown to be directly related to embolization risk [32, 33]. In addition, it has been reported that it is possible to detect the existing inflammation on the plaque with advanced examinations such as 18 F-fluorodeoxyglucose-Positron emission tomography (18FDG/PET), thus providing a risk prediction in asymptomatic patients [34, 35]. As can be seen, detection of inflammation in the presence of atherosclerotic plaque is of vital importance. Our study showed that there is a significant relationship between inflammation and symptom development due to carotid artery stenosis, similar to previous studies. Unlike previous studies, we showed that a risky patient group can be detected without the need for expensive and advanced examinations such as MRI, 18FDG/PET, which are used for imaging plaque morphology or for radiological detection of inflammation. Inflammatory data such as SII obtained by cheaper and easily accessible blood parameters provide a prediction of risk in asymptomatic patients with 50% or more carotid artery stenosis.

Limitations

The most important limitations of our study are being single-centered, retrospective, and having low number of patients. More comprehensive publications with larger numbers of patients are needed to support existing data.

Conclusions

In this study, the relationship between SII and CAS-related symptom development was investigated in the literature for the first time. In the light of the analyzes performed, it has been shown that high SII values detected in asymptomatic patients with stenosis of 50% or more in the carotid arteries are an independent predictor of symptom development. This predictive ability will provide a great advantage to the physicians in terms of taking the necessary precautions before the development of adverse outcomes such as morbidity and mortality for the sensitive patient group mentioned.

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Patient anxiety levels in orthopedic outpatient clinics at hospitals with different patient population densities

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Ethics Committee Approval
The study was reviewed and approved by the Ethics Committee of Istinye University (Date: 05.03.2021 No: 2/2021.K12).
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: Prolonged wait times for examination and delayed hospital appointment times can negatively affect patients. Increased anxiety in orthopedic outpatient clinic patients can disrupt diagnosis and treatment, and increase psychological tension in both patients and healthcare professionals. The aim of our study is to compare the anxiety levels of patients at institutions with different patient population densities.

Methods: This cross-sectional survey study included 189 patients who voluntarily completed the Beck Anxiety Scale while registering for treatment of non-traumatic conditions at the orthopedics and traumatology outpatient clinics of two tertiary health care hospitals. Patients were grouped by hospital attended. The study assessed patients' age, education level, estimated monthly income levels, and anxiety levels.

Results: 99 patients from the public hospitals and 90 from the private hospitals participated in the survey. A significant positive correlation existed between educational status and income level ($P<0.001$). No significant difference in income level existed between the two groups ($P=0.063$), but the education level of patients in the private hospital group was significantly higher than in the public hospital group ($P<0.001$). The anxiety levels of the patients in the private hospital group was significantly higher ($P=0.043$); this difference was correlated to education level rather than income level. Patients with higher education levels demonstrated significantly higher anxiety levels ($P<0.001$).

Conclusion: The study concluded that the anxiety levels of patients who applied to the orthopedic outpatient clinics were independent of facility patient density and related primarily to patient attributes. Prospective studies are needed examining the relationship between patient anxiety levels and waiting time.

Keywords: Anxiety, Outpatient clinics, Patient density, Orthopedics

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Introduction

Mental and physical health are interrelated. Mental disorders are associated with patient-reported diminished functionality, increased pain, and less satisfaction with orthopedic treatment [1–4], but they are mostly modifiable and addressing them may directly improve orthopedic treatment outcomes. In routine orthopedic practice, it is not always possible to identify mental disorders. Public orthopedic outpatient clinics are characterized by high patient population density such that patients experience more frequent delays in evaluation and treatment compared to private hospitals with lower density. Our study aimed to compare the patient anxiety levels at the two types of hospitals, looking specifically at patient-specific factors like income, educational status, and demographic properties.

Materials and methods

This cross-sectional survey study evaluated 189 patients over the age of 18 who first applied to public and private hospital orthopedic outpatient clinics in the 6-month period between January 2020 and June 2020. The study excluded patients with acute traumatic conditions or history of psychiatric illness. Before being physically examined, patients were asked to complete the Beck Anxiety Scale and supply information regarding income level and educational status (Table 1). A research assistant uploaded the answers to the online database (Microsoft Forms).

Table 1: Questionnaire form (Beck Anxiety Scale, Income and Educational Status Levels)

	Age: Male / Female	Not at all	Mildly, but it didn't bother me much		Moderately – it wasn't pleasant at times	Severely – it bothered me a lot
1	Numbness or tingling	0	1		2	3
2	Feeling hot	0	1		2	3
3	Wobbliness in legs	0	1		2	3
4	Unable to relax	0	1		2	3
5	Fear of worst happening	0	1		2	3
6	Dizzy or lightheaded	0	1		2	3
7	Heart pounding / racing	0	1		2	3
8	Unsteady	0	1		2	3
9	Terrified or afraid	0	1		2	3
10	Nervous	0	1		2	3
11	Feeling of choking	0	1		2	3
12	Hands trembling	0	1		2	3
13	Shaky / unsteady	0	1		2	3
14	Fear of losing control	0	1		2	3
15	Difficulty in breathing	0	1		2	3
16	Fear of dying	0	1		2	3
17	Scared	0	1		2	3
18	Indigestion	0	1		2	3
19	Faint / lightheaded	0	1		2	3
20	Face flushed	0	1		2	3
21	Hot / cold sweats	0	1		2	3
22	Estimated monthly income	Under 5.000 TL	5.000-10.000 TL	10.000-20.000 TL	20.000-30.000 TL	Above 30.000 TL
23	Educational status	Elementary	High	College	University	Postdoc

Above is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

Statistical analysis

The minimum number of patients in each group was determined as 83 before the study began. To prevent bias, an independent blind research assistant not working at either clinics performed the statistical analyses; these were performed by SPSS version 25 for MacOS. The effect size was calculated with the power analysis program (G*Power) according to the reference study at a test power of 0.80 and a significance level of 0.05. An independent sample t-test compared the anxiety levels from the two types of outpatient clinics. Pearson Correlation analysis determined the correlation between educational status, mean monthly income, and anxiety levels. *P*-values smaller than 0.05 were considered statistically significant. The study was reviewed and approved by the Istinye University's ethics committee (Date: 05.03.2021, No: 2/2021.K12).

Results

There were 99 patients in the public hospital group and 90 in the private hospital group. Table 2 presents patient demographics. A significant positive correlation exists between education level and mean monthly income ($P<0.001$) (Figure 1). There was no significant difference in income level between the groups ($P=0.063$). The education level of the private hospital group was significantly higher ($P<0.001$) than the public hospital group. When the private and public hospital groups were compared, a significant difference was observed in patient anxiety levels ($P=0.043$) (Figure 2) and the study concluded that this difference was related to education status rather than income level, as anxiety levels of people with high educational status were found to be significantly higher ($P<0.001$). Although positively correlated with education levels ($P<0.001$), anxiety levels were not correlated with monthly income ($P=0.624$) (Table 3). When comparing the clinic types, significantly lower anxiety levels were found in the private clinics ($P<0.001$).

Table 2: Demographics, educational, Beck anxiety scale, and income levels of patients

		Private (n=90)	Public (n=99)	Total (n=189)	*P*-value
Sex	Male	38	39	77	0.283
	Female	52	60	112	
Age	18-24	5	11	16	0.116
	25-35	35	30	65	
	36-45	36	16	52	
	46-55	13	21	34	
	56-65	1	9	10	
	Above 66	0	12	12	
Education	Elementary	8	22	30	<0.001
	High	20	46	66	
	College	23	17	40	
	University	37	9	46	
	Postdoc	2	5	7	
Estimated monthly income	Under 5.000 TL	51	75	126	0.063
	5.000-10.000 TL	28	17	45	
	10.000-20.000 TL	8	3	11	
	20.000-30.000 TL	3	2	5	
	Above 30.000 TL	0	2	2	
Anxiety Level	Mild	74	48	122	0.043
	Moderate	12	41	53	
	Severe	4	10	14	

Figure 1: The relationship between educational status & monthly income

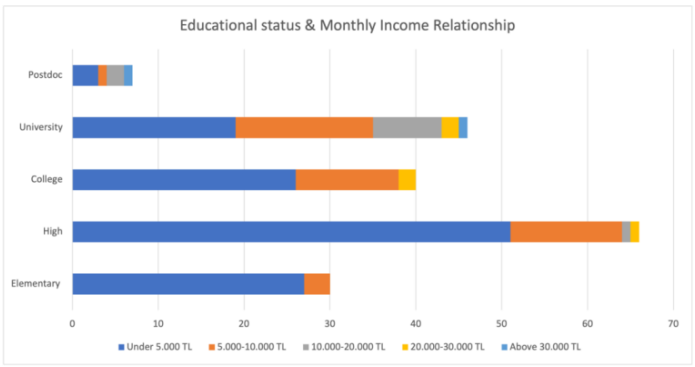

Figure 2: Anxiety level distribution of the groups

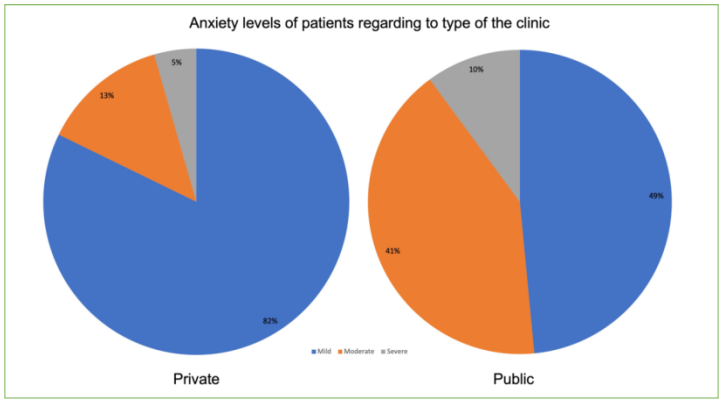

Table 3: Results of the correlation analysis

			Education Level	Monthly income	Anxiety
Spearman's rho	Education Level	Correlation Coefficient	1.000	0.388**	-0.323**
		P-value	-	<0.001	<0.001
		n	189	189	189
	Monthly Income	Correlation Coefficient	0.388**	1.000	0.036
		P-value	<0.001	-	0.624
		n	189	189	189
	Anxiety Scale Score	Correlation Coefficient	-0.323**	0.036	1.000
		P-value	<0.001	0.624	-
		N	189	189	189

Discussion

There are many studies of the increased rates of depression and anxiety resulting from orthopedic trauma [5, 6]. Anxiety symptoms emerge in the early stages following acute orthopedic trauma, but depressive symptoms appear in the later phases. Our primary aim was to determine the factors affecting the anxiety levels of patients who applied to the orthopedic outpatient clinic for non-traumatic conditions. The most important finding of our study is that anxiety levels are related to patient education level. Large-scale survey studies have associated higher education levels with lower long-term depression or anxiety [7, 8], but our study produced results to the contrary, and Demir et al. [9] also found a positive correlation between education level and stress in patients with chronic orthopedic disease. We believe the explanation for this phenomenon is that when highly educated people have a health problem, their anxiety level may be higher in relation to their awareness. We also suspect that lower income levels may be associated with higher anxiety levels, but we could not identify statistically significant differences between anxiety levels and mean monthly income levels. Ridley et al. [10] reviewed studies about anxiety and poverty and found that economic adversity may cause mental illness, which may be improved by anti-poverty programs.

Disorders like in-toeing or flexible *pes planus* in pediatric patients may cause increased anxiety levels in parents. Haberal et al. [11] found that mothers who take their children for orthopedic examination more than once a month have a history of psychiatric treatment and at age 20-40 years have significantly higher anxiety levels. Recurrent metacarpal fractures are also associated with higher anxiety. A recent study by Duramaz et al. [12] found that higher anxiety and impulsivity adversely affects the clinical outcome of metacarpal fracture treatment; the researchers suggest a psychiatric consultation for metacarpal fracture patients to improve treatment outcomes and prevent recurrent injuries. Our study observed that patients with higher anxiety levels have problems adapting to treatment, reducing success rates. A prospective study assessing finger stiffness after volar plating of distal radius fractures found the defining factor to be catastrophic thinking six weeks after surgical treatment [13]. Skeppholm et al. [14] concluded that preoperative mental distress in patients undergoing surgical treatment for cervical radiculopathy resulted in worse outcomes. And patients undergoing total knee replacement who evidenced higher anxiety levels at preoperative evaluation exhibited marked dissatisfaction following surgical treatment [15]. A study comparing the psychological situations of patients with chronic shoulder pain suggests that psychological factors are associated with clinician and patient shoulder outcome expectations and advises that these patients undergo appropriate screening for psychological problems [2]. Bagheri et al. [4] showed that patients with frozen shoulder are more likely to have high pain and disability secondary to depression and anxiety than demographic features. Anxiety and similar psychological problems can cause increased postoperative pain intensity in the long term as well as the short term. Pinto et al. revealed the influence of psychological factors on acute pain and anxiety 48 hours after total hip and knee arthroplasty [16]. Referring patients with high levels of anxiety for psychiatric evaluation is a discrete problem. Vrancenau et al. [17] examined how orthopedic surgeons should address and manage the psychological aspects of orthopedics disorders. They found standardized questionnaires to be the least preferred method among surgeons for determining psychological condition; yet they are more rapid, accurate, easy to administer to patients awaiting visits, and more efficient than methods like medical records reviews or interviews. The most significant barriers to psychiatric consultation were lack of time, stigma, and patient discomfort.

Our study's greatest strength is that we conducted the evaluations in a prospective manner. Our study's most important limitation is the low sample sizes of the groups. Multicentered prospective studies with a greater number of patients are needed to determine the factors affecting the anxiety levels of patients who present to orthopedic outpatient clinics.

Conclusion

The anxiety levels of patients at orthopedic clinics are related to patient education level and clinic population density. We think anxiety levels of patients and physicians can be reduced by properly arranging appointments and developing health policies that do not put pressure on physicians to evaluate too many patients.

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Evaluation of stress and cognitive skills in individuals with tinnitus complaints

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Ethics Committee Approval
The study protocol was approved by Gazi University Ethics Committee (with the approval number: E-77082166-604.01.02-262593). 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 sense of sound in the absence of external acoustic stimuli is known as subjective tinnitus, or phantom tinnitus. The purpose of this study was whether tinnitus complaints have an impact on perceived stress and cognitive skills like attention and memory.

Methods: This prospective case-control study comprised 60 healthy volunteers between the ages of 18 and 25, all of whom had normal hearing. Using the G*Power program, it was established that a minimum of 50 people should be worked with an 80 percent power and a 5% margin of error. The study group consisted of 30 people with tinnitus complaints in their daily lives, whereas the control group consisted of the remaining people. Tinnitus Handicap Inventory and Perceived Stress Scale were applied to the participants within the scope of the working hypotheses. In terms of cognitive skills, the Stroop Test Form was applied to evaluate selective attention, focused attention and disruptive effects, and the Visual Auditory Digit Sequence Test Form was applied to evaluate short-term memory and working memory skills. The findings were analyzed with the SPSS program. Type 1 error level is determined as 5%.

Results: According to Tinnitus Handicap Inventory, tinnitus complaint of all individuals in the study group is very mild. The statistically significant differences were found between the perceived stress level, Stroop and Visual Auditory Digit Sequence Test scores between people with and without tinnitus complaints. The poorer performance was observed in the group with tinnitus complaint. (P=0.037, P=0.017, P=0.010). No statistically significant relationship was found between perceived stress level, tinnitus and cognitive skills (P=0.067, P=0.160, P=0.208).

Conclusion: Tinnitus is becoming a more common cause of health problems, sometimes coupled by psychological stress, and it affects cognitive skills. The study adds to the knowledge regarding the use of cognitive tests as a supplemental measurement in the evaluation of tinnitus and the impact of tinnitus on daily cognitive abilities.

Keywords: Tinnitus, Cognition, Stress

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Introduction

Subjective tinnitus, or phantom tinnitus, is the perception of sound in the absence of external acoustic stimulation [1]. Individuals with tinnitus account for around 12% to 30% of the population, with 1% to 3% of the population suffering seriously from the illness [2]. Tinnitus is most commonly associated with damage to the peripheral auditory system, which results in abnormal plasticity of the auditory pathway [3].

Tinnitus' connections with other clinical manifestations, particularly emotional aspects including depression, anxiety, and stress, have been thoroughly researched. Tinnitus is strongly linked to neurological causes, according to established evidence [4,5]. Tinnitus Handicap Inventory (THI) categorizes tinnitus severity as very mild, mild, moderate, severe, and very severe [6]. For many years, the association between tinnitus and associated psychological problems has attracted people's interest and been studied. Tinnitus has been shown to have a significant impact on psychological health and lower the quality of life of those who suffer from it [7-9]. Subjective tinnitus is characterized as a common, debilitating hearing impairment that produces considerable emotional stress and psychological distress, according to another study. When people are stressed, their tinnitus gets worse. Hormones linked to biological stress markers were shown to play a crucial function in tinnitus patients in this study. The available data has been shown to definitely support the existence of extensive correlations between tinnitus and psychological stress [10].

The relationship between tinnitus and cognitive skills has also been another focus of researchers. Many studies addressing the association between tinnitus and various cognitive skills such as attention, working memory, executive functions, language ability, and intelligence quotient (IQ) have been found in literature reviews [11, 12]. Psychometric data from 107 people with chronic subjective tinnitus were evaluated in another research. In this study, a significant correlation was found between tinnitus and the performance of selective and sustained attention tasks, similar to earlier investigations. The most important predictor of cognitive performance has been identified as the tinnitus problem [13]. In a study focusing on the relationship between stress and tinnitus, it was stated that this relationship remained causal and directionally uncertain [14]. Tinnitus, according to another study, has a unique impact on cognitive performance, particularly general or crystallized intelligence and executive skills. It has been suggested that more research on the relationship between tinnitus complaint and cognitive skills required for daily functioning is needed [15].

Although there are many studies in the literature on cognitive skills and stress in individuals with tinnitus, there are limited studies close to the current working hypotheses. While the findings of the reviewed correlational research demonstrate that tinnitus reduces cognitive performance in terms of attention and executive functions, there have also been reports of invalid or opposite findings. The main aim of the current study is to investigate whether tinnitus complaints have effects on perceived stress and cognitive skills such as attention and memory in individuals aged 18-25 years with normal hearing.

The current study focuses on the various effects and correlational analyses on cognition in people with tinnitus complaints, as well as the differences between them and healthy controls.

While some earlier studies have reported initial report on tinnitus stress and cognitive skills, our investigation, with its unique study design and assessment methods, would make a significant contribution to the literature. In addition, it is aimed to reveal the importance of cognitive tests in the evaluation of tinnitus and to raise awareness about stress and cognitive problems associated with tinnitus.

Materials and methods

This study was approved by Gazi University Ethics Committee with an approval number of E-77082166-604.01.02-262593. The informed consent forms were obtained from each of the volunteer participants in the study. The study was conducted per the principles of the Helsinki declaration.

The study comprised 60 people between the ages of 18 and 25 who had normal hearing. The study group consisted of 30 people with tinnitus complaints in their daily lives, whereas the control group consisted of the remaining people. Individuals with additional disabilities, such as a history of ear infection or surgery, noise exposure, use of ototoxic medications, active middle ear pathology, neurological problems, and so on, were excluded from the study.

The Perceived Stress Scale was applied to all volunteers in the study to assess their stress levels in daily life [16]. In terms of cognitive skills, the Stroop Test Form was applied to evaluate selective attention, focused attention and disruptive effects, and the Visual Auditory Digit Sequence Test Form (VADS) was applied to assess the short-term memory and working memory skills. Tinnitus Handicap Inventory was applied to individuals who reported that they had tinnitus complaints.

The Perceived Stress Scale is a 14-question test that ranges from 1 (never) to 5 (always) scores. A maximum score of 70 is given, and high scores indicate a high level of stress, according to the questions.

The Stroop Test Form indicates the ability to modify perceptual setup in response to changing demands, as well as the ability to suppress a regular behavior pattern and conduct an unexpected activity under a "disruptive effect" [17]. In this test, participants are asked to say the color of the color names printed in different colors, not what they write. In the meantime, the time to complete the test, the number of corrections and errors are determined.

The VADS is a test developed by Koppitz [18] that measures short-term memory (SSD) capacity. The person is expected to repeat the digits he or she hears or sees in this test. The number of the longest recalled sequence of the test is stated in the "Score" section of the form.

The THI was applied to the volunteer participants with tinnitus complaints. This test consists of 25 questions about the characteristics of tinnitus and its effects on life. The answers such as Yes, No, Sometimes are recorded. The scale score is calculated by multiplying the number of Yes answers with 4 points, Sometimes the number of answers with 2 points, and the number of No answers with 0 points [19].

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 25 was used for statistical analyses. The variables were investigated using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/ Shapiro Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using mean and standard deviation for normally distributed variables and the p values result from the Independent Samples t-test in the groups which demonstrated normal distribution. The relationship between stress score, tinnitus level, Stroop test time and VADS score were evaluated by Pearson regression analysis. Type 1 error level is determined as 5%.

Results

The participants' mean age was 19.27 (1.57) years in the study group and 20.07 (2.05) years in the control group who did not have tinnitus complaints. While 18 of the 30 individuals in the study group were females and 12 were males, there were 14 females and 16 males in the control group (Table 1). There was no statistically significant difference between the two groups in terms of age and gender (P=0.095).

Table 1: Descriptive data of participants

	Gender		Age (years)
	Male	Female	Mean (SD)
The study group	12 (40%)	18 (60%)	19.27 (1.57)
The control group	16 (53.3%)	14 (46.7%)	20.07 (2.05)

SD: Standard deviation

The participants with tinnitus complaints in the study group received an average THI score of 11.90 (2.86). As a matter of fact, these values reveal that all participants in the study group have a very mild tinnitus problem. According to the Perceived Stress Scale, the mean scale scores of the participants in the study and control groups were 44.80 (3.32) and 43.10 (3.11), respectively.

The Stroop Test and the VADS test scores evaluating neuropsychological performance are presented in detail in Table 2. The mean completion time of the Stroop test in the study group was 20.73 (2.05) seconds, the mean VADS auditory-verbal response score was 8.77 (0.86), and the VADS visual-verbal response score was 8.03 (0.72) on average. These scores were 19.51 (2.36) seconds, 9.37 (1.03), and 8.63 (1.00) in the control group without tinnitus complaints, respectively.

Table 2: The findings of the stroop test and the VADS test

	Study group Mean (SD)	Control group Mean (SD)	*P*-value
Stroop time (sec)	20.73 (2.05)	19.51 (2.36)	0.037*
VADS auditory	8.77 (0.86)	9.37 (1.03)	0.017*
VADS visual	8.03 (0.72)	8.63 (1.00)	0.010*

SD: Standard deviation VADS: Visual Auditory Digit Sequence

In the Stroop Test, 9 people in the study group and 3 people in the control group made correction only once.

A statistically significant difference was found between the study and control groups in terms of the Perceived Stress Scale score (P=0.045). In terms of Stroop Test completion time, a statistically significant difference was detected between the study and control groups (P=0.037). The statistically significant differences were found between the two groups in terms of VADS visual-verbal response and auditory-verbal response scores (respectively P=0.010 and P=0.017).

No statistically significant correlation was found between the Tinnitus Handicap Inventory score and the Perceived Stress Scale score (P=0.274).

Similarly, no statistically significant correlation was found between the Perceived Stress Scale score and the findings of the Stroop test and the VADS test (Table 3).

Table 3: The correlation findings of perceived stress scale score, the stroop test and the VADS test

The Perceived Stress Scale	Pearson Correlation	*P*-value
Stroop time (sec)	0.029	0.829
VADS auditory	-0.009	0.944
VADS visual	-0.163	0.214

VADS: Visual Auditory Digit Sequence

The Tinnitus Handicap Inventory score, the Stroop test, and the VADS scores had no statistically significant correlation (Table 4).

Table 4: The correlation findings of tinnitus handicap inventory score, the stroop test and the VADS test

Tinnitus Handicap Inventory score	Pearson Correlation	*P*-value
Stroop time (sec)	0.338	0.067
VADS auditory	-0.263	0.160
VADS visual	-0.237	0.208

VADS: Visual Auditory Digit Sequence

Discussion

Tinnitus is an auditory symptom resulting from psychological distress, high levels of anxiety, and depression symptoms. The people with stress-related tinnitus complaints have a variety of problems, including insomnia, bad quality of life, lack of attention, susceptibility to stress, and irritability. According to the findings of the current study, the significant difference between the Perceived Stress Scale scores between the tinnitus complaining group and the control group is consistent with this relationship. Previous studies in both animals and humans have looked into the impact of stress on the auditory system. As a result, the stress has an effect on mineral and glucocorticoid receptors in the inner ear [21]. Similarly, when stress was eliminated, corticosterone levels increased, offering a protective mechanism against noise-induced hearing loss [22]. Similarly, Mazurek et al. reported that regularly occurring psychological stress causes significant impairments in evoked auditory potentials and an increase in the expression of inflammation genes in the inferior colliculus [23, 24].

Although this causal relationship between tinnitus and stress has been the focus of research, it has been limited to anecdotal and clinical observations. Nonetheless, evidence from these researches suggests that there is an indirect relationship between stress and the clinical course of tinnitus. The people with sudden hearing loss and tinnitus have been reported to experience more stressful events in their lives, as well as poorer coping abilities, compared to other clinical groups [5, 13, 25]. Subjective anxiety, perceived stress, and tinnitus discomfort were shown to reduce in tinnitus patients after a stress-reduction therapy program [26]. The functional and electroencephalographic neuroimaging studies in tinnitus patients have shown abnormal connections between the limbic system and auditory system structures [27]. From this point of view, although the participants in our study had normal audiograms, the presence of tinnitus complaint may be due to the disorder in these connections with the limbic system. On the other hand, the absence of a significant relationship between the Perceived Stress Scale score and THI score in the current

correlation analyzes may be due to the small sample size. Since it has been noticed that the participants in the study commonly experience conditions such as exam stress and employment anxiety between the ages of 18 and 25, the stress scale scores are expected to be high.

Another topic that experts in this discipline are interested in is the relationship between tinnitus and cognitive abilities. Tinnitus has been shown to negatively affect attention, cognitive processing, and memory in studies combining neurophysiological tests, neuroimaging techniques, and behavioral tests of cognitive performance [11, 12, 17, 28]. Similarly, in the current study, the group with tinnitus had a significantly lower performance in selective attention, interference, focusing ability, working memory and short-term memory skills evaluated with the Stroop test and the VADS. It has been suggested that the possible reason for this finding is that tinnitus affects executive control of attention and impairs cognitive functions [12]. At the same time, cognitive performance may be negatively affected by adding anxiety and depression to tinnitus. On the other hand, although tinnitus patients had delayed P300 responses, behavioral responses were found to be within normal limits in cognitive tests [29]. There was no significant correlation between the Stroop test and the VADS test scores in our current study, and THI score Gabr et al. [29] can be explained as in his work. Similar to the literature, in the current study, it was reported that anxiety, depression and somatic sensitivity levels, which are responsible for many variables, have an effect on executive control of attention. People with tinnitus complaints need more attention resources [15].

Limitations

The inclusion of participants with very mild tinnitus levels may be among the limitations of the study.

Conclusion

Tinnitus is becoming a more common cause of health problems, sometimes coupled by psychological stress, and it affects people from all walks of life. Although many causes of tinnitus are unavoidable, psychological stress can be managed with professional help and a therapeutic approach. The negative effects of tinnitus on cognitive skills can also be diagnosed and prevented by multidisciplinary approach. Therefore, close cooperation of audiologists, psychiatrists, psychologists, psychotherapists and neurologists is important for the effective treatment of these people.

The current study, on the other hand, creates awareness about the use of cognitive tests as a supplemental measurement in the evaluation of tinnitus and the disruptive effect of tinnitus on daily cognitive skills. As in this study, investigating the relationship between tinnitus and cognitive skills can guide the therapy treatment methods to be more comprehensive and competent. The future studies with large sample groups and detailed assessment tools on tinnitus, cognitive skills and stress are needed.

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The impact of the COVID-19 pandemic on the mental health of medical students

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The ethical approval was obtained from the Ethics Committee of Gazi University on date 14.01.2019 with the number 28.
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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Medical students are at high risk for mental problems with already increased levels of stress and depression. The literature shows that the COVID-19 pandemic has affected the mental health of the population including medical students. However, yet, there is insufficient data to compare the mental health of medical students before and after the pandemic. In this study, it was aimed to investigate the impact of COVID-19 pandemic on medical students' mental health.

Methods: First part of these two cross- sectional studies was conducted in 2019, before the pandemic, and the second one was performed in 2021. A sociodemographic data form, The Center for Epidemiologic Studies Depression Scale (CES-D), Perceived Stress Scale (PSS), and Maslach Burnout Inventory-Student Survey (MBI-SS) were applied to 1306 students in 2019 and 898 students in 2021, from all 6 grades studying at a Turkish medical school. Prevalence of depression, PSS and MBI-SS scale scores were compared in terms of year of the study, grades and some demographic variables.

Results: The prevalence of depression was 64.2% in 2019 and increased to 90.9% after the pandemic. Participants with a personal or family history of being COVID-19 (+) had higher scores in CES-D (P=0.002 and P=0.001, respectively) and PSS (P=0.015 and P=0.004, respectively). Regression analysis showed that female gender, studying in preclinical phases, and living alone were significant predictors of CES-D and PSS scores.

Conclusion: The COVID-19 pandemic negatively affected the mental health of medical students as well as the entire society. Preventive mental health practices are required for this vulnerable population, especially for groups determined to be at risk.

Keywords: COVID-19 pandemic, Burnout, Stress, Mental health, Depression, Medical student

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Introduction

Medical students are a vulnerable population for mental health problems. This is because most psychiatric disorders coincide with the age of onset and medical education adds its own unique stressors. All these also happen, usually at a time when they are leaving home for the first time and starting a new life. The literature is quite rich in terms of publications showing a high prevalence of mental problems in medical students. The prevalence of depression in this population has been reported as 22% – 49% [1], anxiety as 33.8% [2], suicidal ideation as 11.1% [3], and burnout as 45% – 71% [4]. According to a recent study with 3766 medical students from 12 different countries; 75% of all students had any minor psychiatric disorder assessed with General Health Questionnaire-12 (GHQ-12). Burnout rates were 78% for disengagement and 87% for exhaustion [5].

While the mental health of medical students is alarming enough, medical education, nowadays also has to deal with the effects of the pandemic. In Turkey, all faculties were transitioned to distance education with the regulation of the Council of Higher Education in March 2020. Most of the students left the dormitories or the houses where they lived with their friends and returned to their families, which caused them to leave the city or even the country they live in. While all bedside and practical lessons, laboratory sessions, and small group interactions have been postponed, theoretical lessons have started to be given online. The internship training which includes the last year of medical education and is entirely based on clinical practice has been suspended. Online education required a serious technological adaptation process for both students, educators, and faculty management. Despite the difficulties it can be said that medical faculties rapidly adopted online education, however, lack of face-to-face interaction with patients, educators, and peers led to a decrease in learning motivation.

The pandemic has affected both the medical education and mental wellbeing of medical students. Giliyaru et al. [6] stated that half of the students participated in the survey reported deterioration in their physical and mental wellbeing and 60% of them thought that the pandemic affected their decisions of their specialty goals. Another study reported that 84% of 156 medical students experienced nervousness and stress due to pandemic conditions, and new learning environment was reported as the most challenging aspect [7]. Subjective mental health status of Japanese medical students was reported to be worsened [8]. It has been shown that healthcare workers are at risk for negative mental health outcomes during the pandemic [9], on the other hand, the result of a study comparing medical students, medical staff, and the general population is so remarkable that depression, stress, and anxiety scores of medical students were higher than the general population and other medical staff [10].

Even under ordinary circumstances, medical students are known to be a high-risk group for mental health problems and this is more evident in those living in the Middle East and Asia (2). Another point to be underlined is that medical students are not successful enough to find the right ways of getting psychiatric support [11]. Considering the impact of poor mental health on the academic performance of medical students, who are the future physicians, and its indirect effect on public health, it is crucial to investigate the effect of the pandemic on this already at-risk population especially in the aforementioned regions. The main limitations of the literature in this field are the small sample sizes, lack of structured scales, and most importantly, lack of prolonged follow-ups. This study aimed to prospectively investigate depression, stress, and burn-out levels of medical students and the effect of the COVID-19 pandemic on the mental health of students.

Materials and methods

Participants

This study was primarily planned to examine and prospectively observe the mental health of the medical students studying at Gazi University Medical Faculty in Ankara, the capital city of Turkey. It was aimed to determine the annual data and the associated factors to make appropriate interventions for the mental well-being of the students. The first part of the study was performed in 2019 with 1306 participants from all grades (1st to 6th). In Turkey, 1/30 of all Turkish medical students are in Gazi University, which has the highest medical student quota in the country [12]. The authors decided to reapply the same scales in 2021 to investigate if there is a difference between the two years. Snowball sampling was used. The first page of the survey included the information about the study and consent was obtained by the participants marking their acceptance of the study on the form. Anonymity was assured as no identifying data were collected. All informed consent taken students were included in the study. It was aimed to reach the whole universe, therefore, all students were invited to the study. A total of 898 students constituted the sample of the second part of the study. 37.6% of the total number of students in the faculty was reached. Ethics Committee of Gazi University has approved the study on date 14.01.2019, number 28.

Instruments

The survey consisted of socio-demographic data form, Maslach Burnout Inventory-Student Survey (MBI-SS), Perceived Stress Scale (PSS), and The Center for Epidemiologic Studies Depression Scale (CES-D). Demographic data included questions about, gender, year of medical school, income, residency, smoking, alcohol or substance use, and psychiatric applications. Questions such as personal or family history of COVID(+), or losing a family member of being COVID(+) were added to the second part of the survey.

CES-D, a self-report scale with a four-point scale (0 to 3) was used for assessing depression [13]. Higher scores represent more depressive responses and cut-off score for indicating depressive disorder is considered as ≥16. Tatar and Saltukoğlu performed the Turkish validity and reliability [14].

PSS, a 5-Likert type, 14-item self-report scale (0 to 4) was used for assessing stress levels. [15]. Higher scores indicate increased stress levels. Turkish validity and reliability study was performed by Eskin at al. [16].

MBI-SS, a 5 – Likert type scale was used to determine burn-out levels. It consisted of three subscales and 16 items (exhaustion, cynicism, and efficacy) [17]. In the exhaustion and cynicism subscales, higher scores indicate burnout, whereas in the efficacy subscale, lower scores indicate burnout. The scale has been adapted to Turkish by Çapri et al. [18].

Statistical analysis

Statistical analysis was performed using SPSS 22.0 for Windows (SPSS, Inc.; Chicago, USA) package program. Descriptive values were stated as number (n), percentage (%), mean, standard deviation (SD). Normality of data was tested visually using the Q-Q plots and statistically using the Kolmogorov–Smirnov test. To compare categorical variables (gender, smoking, and alcohol use), the independent t-test was used, and to compare parametric variables (year of medical school, residence status, and monthly family income) the one-way ANOVA test was used. When an overall significance was observed, pairwise post hoc tests were performed using Tukey's test. Statistically significant factors in the bivariate analysis were included in the multiple linear regression analysis to determine independent predictors of PSS and CES-D scores. An overall *P*-value of less than 0.05 was considered to show a statistically significant result.

Results

The sociodemographic characteristics of the students who participated in the first (n=1306) and the second part (n=898) of the study were shown in table 1. The rate of participation was relatively high in females and in preclinical years. Monthly family income levels were grouped according to the limits of hunger and poverty stated by the Confederation of Turkish Trade Unions at the time of the study [19]. The rate of students having a family income below the limit of hunger increased from 6.4% to 8.7%. The rate of living in dormitories was decreased from 37.4% to 14.8% whereas, the rate of living with family increased from 38.9% to 68.5%. The prevalence of smoking, alcohol, and substance use were 23.7%, 31.4%, and 4.1% in 2019 and they were 18.5%, 30.5%, and 4.3% in 2021, respectively. 21.7% of the students reported psychiatric application in 2019 which was increased to 25.7% in 2021. Psychiatric drug use was reported to be increased from 8.3% to 9.6%. The mean scale scores and their changes over time can be seen in Table 1. The prevalence of depression assessed with the CES-D scores higher than the cut-off point of 16 was 64.2% in 2019 and 90.9% in 2021.

Table 1: Sociodemographic characteristics and scale scores of the participants

		2019		2021	
		n	%	n	%
Gender					
	Female	774	59.3	599	66.7
	Male	532	40.7	299	33.3
Year of Medical school (grades)					
	1	381	29.2	195	21.7
	2	263	20.1	157	17.5
	3	284	21.7	226	25.2
	4	132	10.1	122	13.6
	5	168	12.9	143	15.9
	6	78	6.0	55	6.1

Monthly Family Income (TL)	2019		2021	
	n	%	n	%
Between the limits of hunger and poverty	616	47.2	495	55.1
Above the limit of poverty	607	46.5	325	36.2
Residence				
Home - with family	508	38.9	615	68.5
On-campus housing	488	37.4	133	14.8
Home-with friend(s)	234	17.9	94	10.5
Home-alone	76	5.8	56	6.2
Smoking	309	23.7	166	18.5
Alcohol use	410	31.4	274	30.5
Substance use	54	4.1	39	4.3
Psychiatric application	283	21.7	231	25.7
Psychiatric medication use	108	8.3	86	9.6

	2019 Mean(SD)	2021 Mean (SD)
MBI-SS		
Exhaustion	15.6(4.8)	17.9(4.6)
Cynicism	10.4(3.7)	12.9(3.6)
Efficacy	11.7(3.3)	10.1(2.8)
CES-D	21.2(11.5)	33.2(12.5)
PSS	28.3(8.3)	35.0(8.2)

TL: Turkish Liras, MBI-SS: Maslach Burnout Inventory-Student Survey CES-D: The Center for Epidemiologic Studies Depression Scale, PSS: Perceived Stress Scale

To compare the scale scores according to the demographic variables of the 2021 data, independent t-test was used in categorical variables, and one-way ANOVA with post-hoc Tukey test was used in parametric variables. Female students scored significantly higher scores in MBI-SS exhaustion (P=0.013), CES-D (P<0.001), and PSS (P=0.013), (P=0.001). Efficacy scores were lower in female students which inversely shows more burnout (P=0.013), and there was no significant difference in cynicism scores between genders (P=0.074).

A statistically significant difference was found in all scales between students in preclinical and clinical phases that preclinical students had poorer results in all scales (P<0.001for all scales). We also compared all grades with each other, and the highest mean in all scales was observed in 2nd grades and lowest in 6th grades. Post hoc tests showed that 6th grades scored significantly lower than all the other grades in the CES-D (P=0.004, 0.001, <0.001, 0.027, 0.015 respectively), and lower than 1st (P<0.027), 2nd (P<0.001), and 3rd grades (P<0.001) in the PSS.

There was a significant difference in all scales according to the residence status. Post hoc tests showed that in CES-D, participants living with family (P=0.037), and living alone (P=0.005) scored higher than the ones living with friends. PSS scores of participants living with friends were significantly lower than the other groups (P=0.002, 0.047 and 0.020 respectively). Burnout levels in exhaustion and efficacy subscales were higher in students living with family (P=0.035) than the ones living with friends (P=0.028), however, in cynicism subscale, students living alone had higher scores than the others (P=0.037, 0.001, 0.017, respectively).

No significant difference was found between scale scores and family income. Students with a personal or family history of being COVID-19 (+) had significantly higher scores in CES-D (P=0.002, 0.001), and PSS (P=0.015, 0.004), and those who have lost a family member due to COVID-19 had higher scores in CES-D (P=0.015) (Table 2).

Statistically significant factors in the bivariate analysis were included in the multiple linear regression analysis to identify independent predictors of CES-D and PSS scores.

A multiple linear regression model was conducted to examine the independent effects of predictors on CES-D scores (Table 3). As a result of the analysis, it was found that a significant regression model (P<0.001), and 0.051% of the variance in CES-D scores were explained by independent variables. Female gender, studying in preclinical phases and living alone significantly predicted CES-D scores.

Table 2: Comparison of the scale scores according to demographic variables

	MBI-SS Mean (SD)			CES-D Mean(SD)	PSS Mean(SD)
	Exhaustion	Cynicism	Efficacy		
Gender					
Female	18.2(4.5)	12.7(3.6)	9.9(2.7)	34.5(12.5)	35.7(8.1)
Male	17.4(4.6)	13.2(3.7)	10.5(3.1)	30.6(12.1)	33.8(8.3)
P-value	0.013	0.074	0.007	<0.001	0.001
Study grades (years)					
Preclinical(1,2,3)	18.4(4.5)	13.3(3.6)	9.8(2.9)	34.2(12.3)	35.9(7.8)
Clinical (4,5,6)	17.0(4.5)	12.2(3.6)	10.7(2.7)	31.4(12.8)	33.4(8.6)
P-value	<0.001	<0.001	<0.001	<0.001	<0.001
Residence Status					
Home - with family	18.1(4.5)	13.0(3.6)	10.0(2.9)	33.3(12.5)	35.4(8.0)
On-campus housing	17.6(4.5)	12.2(3.8)	10.0(2.8)	33.9(12.6)	35.0(8.9)
Home- with friend(s)	16.7(4.3)	12.5(3.2)	10.9(2.7)	29.6(12.7)	32.1(8.7)
Home-alone	18.6(4.8)	14.4(3.6)	10.0(2.6)	36.6(11.5)	36.1(6.8)
P-value	0.027	0.002	0.041	0.006	0.003
Monthly Family Income (TL)					
Below the limit of hunger	17.6(4.8)	12.5(4.1)	10.1(2.2)	34.1(12.7)	36.5(7.7)
Between the limits of hunger and poverty	17.9(4.6)	13.0(3.6)	10.1(2.9)	33.7(12.5)	35.2(8.0)
Above the limit of poverty	17.9(4.4)	12.9(3.6)	10.2(2.9)	32.4(12.6)	34.5(8.6)
P-value	0.823	0.543	0.771	0.283	0.122
History of being COVID-19 (+)					
No	17.9(4.6)	12.9(3.7)	10.2(2.9)	32.7(12.6)	34.7(8.2)
Yes	18.1(4.3)	12.8(3.4)	9.9(2.6)	36.2(11.7)	36.5(7.8)
P-value	0.586	0.780	0.362	0.002	0.015
Family history of being COVID-19 (+)					
No	17.7(4.6)	12.8(3.7)	10.2(2.9)	32.1(12.6)	34.4(8.4)
Yes	18.1(4.4)	13.0(3.5)	10.0(2.7)	34.9(12.3)	36.0(7.8)
P-value	0.186	0.475	0.469	0.001	0.004
Losing a family member due to COVID-19 (+)					
No	18.0(4.5)	12.9(3.6)	10.1(2.8)	32.7(12.5)	34.9(8.2)
Yes	17.5(4.8)	12.8(3.8)	10.2(2.8)	35.2(12.4)	35.6(8.2)
P-value	0.240	0.755	0.718	0.015	0.314

TL: Turkish Liras, MBI-SS: Maslach Burnout Inventory-Student Survey CES-D: The Center for Epidemiologic Studies Depression Scale, PSS: Perceived Stress Scale

Table 3: Multiple linear regression results for predicting CES-D scores

				95% CI		
	β	SE	t	LL	UL	*P*-value
Gender[a]	4.028	0.874	1.735	2.313	5.743	<0.001
Grade[b]	2.773	0.870	3.189	1.066	4.479	0.001
Residence status[c]	5.125	1.722	4.609	1.746	8.504	0.003
Being COVID-19 (+)	2.002	1.293	2.997	-0.536	4.540	0.122
Family history of being COVID-19 (+)	1.708	0.991	1.548	-0.238	3.653	0.085
Losing a family member due to COVID-19 (+)	1.324	1.016	1.304	-0.669	3.317	0.193

Adjusted R^2= 0.051 *P*<0.001; LL, lower limit; UL, upper limit; [a] female; [b] preclinical phases; [c] living alone

A multiple linear regression model was conducted to examine the independent effects of predictors on PSS scores (Table 4). As a result of the analysis, it was found that a significant regression model (*P*<0.001), and 0.040% of the variance in PSS scores were explained by independent variables. Female gender, studying in preclinical grades, and living alone significantly predicted PSS scores.

Table 4: Multiple linear regression results for predicting PSS scores

				95% CI		
	β	SE	t	LL	UL	*P*-value
Gender[a]	1.907	0.575	3.315	0.778	3.036	0.001
Grade [b]	2.637	0.573	4.605	1.513	3.760	0.000
Residence status[c]	2.294	1.134	2.024	0.069	4.518	0.043
Being COVID-19 (+)	0.726	0.851	0.852	-0.945	2.396	0.394
Family history of being COVID-19 (+)	1.272	0.653	1.948	-0.009	2.553	0.052
Losing a family member due to COVID-19 (+)	-0.133	0.669	-0.198	-1.445	1.180	0.843

Adjusted R^2=0.040 *P*<0.001; LL, lower limit; UL, upper limit; [a] female; [b] preclinical phases; [c] living alone

Discussion

According to the results of this study, the prevalence of depression among medical students increased from 64.2% to 90.9% from 2019 to 2021 through the pandemic. There was also a significant increase in stress and burnout levels.

Despite scientific advances in the treatment and prevention of COVID-19, people all over the world are still struggling to cope with the risks posed by the disease itself and the related measures. As a result, a high prevalence of psychiatric symptoms is reported in the general population such as 81.9% stress, 50.9 anxiety, 48.3% depression, or 53.8% post-traumatic stress disorder [20]. It is thought to be crucial from a public health perspective to identify risk groups in order to address mental health interventions correctly in such conditions which almost lead to mental health crises. Children, adolescents, elder people, patients with prior physical and psychiatric diseases, and healthcare workers are stated at risk in COVID-19 pandemic [21]. We believe that medical students, particularly, are a vulnerable population with already high baseline levels of stress and prone to have psychiatric symptoms and it can be hypothesized that they would report higher levels of stress and burnout in these unprecedented times. On one hand, they are exposing to the common aspects of the pandemic that affected all human-kind, and on the other hand, they had to deal with the difficulties related to medical education.

With the progress of the pandemic, as one of the lockdown measures, online education was started in medical faculties in Turkey like the rest of the world. This brought some challenges for both students and faculty staff despite some advantages such as freedom of time and place. The nature of medical education requires some on-site clinical practices that online lessons will not be adequate enough to form a qualified doctor identity. One of the compounds of this identity is gaining good communication skills with colleagues and patients which was interrupted by digital learning. Cancellation of the practical exams, changes in preset timetables and curricula, with the uncertainty and constant changes of these, may have increased the stress levels of the students day by day [22]. Adapting to a new system that requires advanced technological skills, devices, and connectivity may also have been difficult for those of different socioeconomic levels. According to a study investigating medical students' attitudes towards online learning, 64.7% of the students reported facing a challenge and 54.8% thought that online learning was not useful for clinical aspects [23].

In addition to the qualification problems of online education, there have also been social implications. With the lockdown measures and closure of the dormitories, most of the students have had to return to their families and the city or even the country they lived in has changed. In our study, while the rate of those staying in a dormitory or living with friends decreased, the rate of living with family has almost doubled with the pandemic. This situation resulted in a loss of peer interaction, social isolation, and a lack of attachment to the faculty. It is also a remarkable result that the proportion of those having a family income below the hunger limit has increased from 6.4% to 8.7% and those above the poverty limit have decreased from 46.5% to 36.2%. Pandemics have economic impacts and put an extra burden on the students with the social consequences.

The reflection of these conditions can be seen in the literature that is reporting alarming rates of mental problems in medical students. A study from Germany reported high distress levels measured by STAI and mild anxious and depressive

symptoms [24]. Moderate levels of psychological distress and deterioration in mental well-being were reported from two-thirds of Australian medical students [25]. In the United Arab Emirates, half of the medical students reported mild to moderate/severe anxiety according to GAD-7 [26]. Another study using DASS-21 reported a prevalence of 70.5% depression, 53.6% anxiety, and 47.8% stress in Egyptian medical students [27]. Aker et al. stated that 52.4% of medical students reported feeling mentally unwell in a different region of our country [28].

Two studies using the same scale, PHQ-4, have prospectively examined the mental state of all college students before and after the pandemic and reported an increase in symptoms of anxiety and depression [29,30]. Isralowitz et al. followed up Russian medical students from May to November 2020 without any data from the pre-pandemic period, and found a significant decrease in the Fear of COVID-19 Scale [31]. Another study from the UK reported a significant decrease in medical students' mood, however, this was based on participants' verbal statement of a decline in their mood after the onset of pandemic instead of a prospective examination by the researchers [32]. The cross-sectional studies provide important knowledge revealing the mental health of medical students but the literature lacks prospective research that will give more decisive data about the effect of the pandemic on the students' mental health. To our knowledge, the only prospective study is from India. Saraswathi et al., prospectively investigated 217 medical students with DASS-21 before and during the pandemic. They found the 6-month incidence of anxiety as 11.98% stress as 4.15%, and depression as 2.3%. In this study, the prevalence of baseline depression was 33.2% which was increased to 35.5% during the pandemic. It was also stated that during COVID-19, 44.7%, 41.01%, and 65.44% of the study population scored higher in depression, anxiety, and stress sub scores, respectively [22]. Compared to these results, 90% prevalence of depression found in our study seems quite high. Using different scales and the time of their application may be effective for this outcome. Saraswathi used DASS-21 in June 2020, however, we measured depression with CES-D between January- April 2021. The intervening time between two studies may have led to the cumulative effect of the pandemic, causing the students to be more affected and an increase in depressive symptoms in our study. Besides, the unique systems of the faculties and sociocultural differences may also have affected the results. In a recent study investigating cultural variations in wellbeing and burnout of medical students in 12 countries including India, the rate of minor psychiatric disorders in Indian medical students was found to be lower compared to many other countries before the pandemic [5]. Since it is known that sources of stress and related mental problems in medical students vary across the countries, their levels of being affected by the pandemic may also vary accordingly. Further knowledge can be obtained in cross-cultural studies focusing on this issue.

When looking at the overall correlates of scale scores; female gender, preclinical phases, living alone and living with family, having a history of being COVID-19 (+), having a family member of being COVID-19 (+), or losing a family member due to COVID-19 were associated with higher levels of depression, stress, and burnout. Regression analyses showed that female gender, preclinical phases, and living alone were significant predictors of stress and depression. Being infected with COVID-19 (+) has a major impact on mental health not only for direct neuropsychiatric consequences but also experiences such as quarantine, concerns about the prognosis of the disease, or stigmatization. As a result, it is reported to be strongly associated with depression [33]. Besides the catastrophic effects of having a family member or losing him/her due to COVID-19 (+), pandemic conditions have also disrupted grieving processes and coping mechanisms. Because of the contagiousness, family members could not be with each other during illness and death, funeral procedures did not work in the usual process. All these together have a synergistic effect on increasing the risk of depression and stress in such individuals, as can be seen from the results of our study which are compatible with the literature [27, 34].

We found the female gender as a significant predictor of stress and depression. A recent meta-analysis with 96 thousand participants showed that the female gender was positively associated with higher levels of stress and depression [35]. Except for a few contradictory results [22], studies with medical students are also compatible in this respect, that being a female medical student may increase the risk of anxiety [26]; depression, anxiety, and stress [27]; depression and anxiety [36]; and distress [25].

While being a 4th-grade student was found as a predictor for depression and stress in our first study before the pandemic [37], highest scale scores were found to be in preclinical phases, particularly in 2nd grades, after the pandemic. Saddik et al. [26] reported that students in their clinical years, as in contact with COVID-19 patients, reported higher anxiety levels. Lyons et al. [25] stated that 1st grades had the highest score of psychological distress but found no significant difference between year groups. At the time of our study, all lessons including practical ones were conducted online and the students had no direct contact with the COVID-19 patients. This can be one reason for relatively lower levels of depression and stress in clinical phase students. The other reason may be the psychosocial interventions performed by the student mental health unit of our faculty such as psychoeducation conferences, or online support meetings. These interventions were planned and have been conducting since the first results of the study in 2019, so the upper grades had more chance to benefit from them. As the year of medical education passes, the increase in the level of knowledge about the diseases may also be a protective factor for clinical phase students.

Limitations

The results of this study should be interpreted with some limitations. First, this study is in longitudinal nature, however, the samples of the two parts of this study did not consist of the same participants. The large sample size and issues of anonymity and confidentiality appeared as barriers to follow up the same students hence it was not possible to calculate incidence or odd ratios. Second, it was aimed to reach the whole universe but this could not have been achieved in all two parts of the study because students were not forced and participation was based on giving consent. Therefore, the large sample size may reduce this effect, despite the ability of generalization of the

results to all faculty is limited. The response bias should also be mentioned in these studies that participants with mental health problems or interested in these issues may be more open and willing to participate and this will result in higher scale scores than expected. Besides, in both two parts of our study, low rates of participation in male students and clinical phases may have restricted their representation. The instruments used in this study are screening scales and may not reflect the real prevalence. Longitudinal studies in which the same students are routinely screened with scales and the ones above the cut-off point are evaluated clinically will yield better results.

Conclusion

This two-year prospective study shows a 17% increase in the prevalence of depression with a significant increase in stress and burnout levels in medical students after the COVID-19 pandemic. Students with female gender, studying at preclinical phases and living alone have higher levels of stress and depression. Medical students can be considered as a high-risk population with high baseline levels of mental health problems and prone to be affected by the pandemic. Because of these risk factors and the importance of the mental health of these future doctors for public health, it is crucial to prioritize protective mental health practices at the university and government level. It is thought to be beneficial for medical faculties from different countries and cultures to share their experiences for promoting the wellbeing of medical students. From our perspective, constituting separate mental health units in medical faculties in collaboration with public health, psychiatry, medical education departments, and the dean's office, and conducting educations, meetings, routine screening programs to protect the mental health of the students may be helpful. It is also necessary to ensure psychiatric support that students can easily apply without stigmatization.

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Is there a relationship between patient age, tumor multifocality, and capsular invasion in papillary thyroid carcinoma? Retrospective evaluation of pathology specimens

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Ethics Committee Approval
The study was approved by the ethical board of Istanbul University, Cerrahpasa Medical Faculty IRB review board (approval Number: 04.09.2014-02-173816).
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: Papillary thyroid carcinoma (PTC) is the most prevalent of thyroid gland cancers. Although PTC generally is successfully treated, risk factors such as age, tumor size, thyroid capsule invasion, multifocality, and presence of metastases can negatively affect the prognosis. We aimed to assess the relationship between multifocality, capsular invasion, and patient age (≤45 vs >45 years of age) in PTC, along with other relevant tumor characteristics.

Methods: In this retrospective cohort study, evaluation of pathology findings in patients with a PTC diagnosis or thyroid nodules suspicious for PTC, the frequency of multiple specimen related prognostic factors by age was compared. Only patients initially operated with papillary thyroid cancer suspicion or definite diagnosis without distant organ metastasis were included. All the other patients with recurrent disease were excluded.

Results: Between 2008 and 2014, 466 patients with PTC tumors were operated. Tumors were multifocal in 62 (13.3%) patients and unifocal in 404 (86.7%). When multifocality was compared in two patient groups (≤45 years vs. >45), it was slightly higher in patients >45 years old (14.4%) vs ≤45 (11.5%; P=0.374). The multifocality rate in patients with a tumor size of >1 to ≤2 cm was significantly higher (17.5%) than in all other tumor size groupings (0.0-13.7%; P=0.002). Thyroid capsule invasion occurred in 39.1% of patients in the younger group vs 33.6% in the older group (P=0.05).

Conclusion: In light of our study's findings, including confirmation by multivariate analysis, age, as represented by the >45 year cutoff value, should not be considered an independent prognostic risk factor in planning treatment of PTC. The individual patient, tumor characteristics, and local and distant metastases status should remain the most important criteria for treatment selection and follow-up care in all patient age groups.

Keywords: Papillary thyroid carcinoma, PTC, Multifocality, Age, Capsule invasion, Metastasis

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Introduction

Thyroid cancers are the most frequently detected malignancies of the endocrine system. Papillary thyroid carcinoma (PTC) is the most common of well-differentiated thyroid cancers and is associated with a favorable outcome compared to other cancers. The long-term survival rates for adults with PTC is 92% to 98% at 10 years. Unfortunately, between 5% and 20% of these patients develop local or regional recurrences that necessitate further treatment, and 10% to 15% may develop distant metastases [1-3].

There are several factors that determine the prognosis for PTC. Age has been thought to be the main prognostic factor to consider; however, in recent years, gender, tumor multifocality, and the presence of thyroiditis have been found to influence the course of PTC. While PTC frequently presents with multifocal tumors, unilateral or bilateral multifocal PTC is not uncommon. The prevalence of multifocal PTC ranges widely between 18% and 87%, depending on methodological factors [4]. In addition, tumor multifocality increases the risk of recurrence, and of distant metastases. Although accuracy in diagnosing PTC has greatly improved due to widespread use of ultrasound-guided fine-needle biopsy and point-of-care sonography with fine-needle aspiration biopsy (FNAB), multifocality, as yet, can only be detected definitively in pathology specimens after surgery [4-7].

Tumor size and capsular invasion are also crucial parameters for determining the prognosis of PTC. Some studies have found that when tumors are >1 cm in size, they tend to spread aggressively beyond the thyroid, causing distant metastases [8]. For this reason, we included these variables in our study of prognostic indicators to analyze their level of correlation with multifocality and patient age.

Although a correlation between older age and a poor PTC prognosis has been demonstrated [9-11], there is a dearth of evidence regarding the interactive nature of known PTC prognostic factors. In this study, we aimed to assess the relationships between patient age and tumor characteristics (size, multifocality, capsular invasion, presence of thyroiditis) through retrospective analysis of pathology reports of patients who underwent thyroidectomy due to a diagnosis of PTC.

Materials and methods

Study design and approval

This study was designed as a retrospective cohort evaluation of pathology data obtained from specimens of patients operated due to suspicious thyroid nodules, or patients who were diagnosed with PTC. Only patients initially operated with papillary thyroid cancer suspicion or definite diagnosis without distant organ metastasis were included. All the other patients with recurrent disease were excluded. This study was approved by the ethical board of Istanbul University Cerrahpasa Medical Faculty. (approval date: 04.09.2014 and number: 02-173816).

Surgical technique

Each patient underwent total or near subtotal thyroidectomy performed by one of five surgeons. This is the standard approach in our clinic for patients diagnosed with multinodular bilateral disease, or PTC diagnosed with FNAB. Total, or near total thyroidectomies were preferred for patients with suspicious thyroid nodules on sonography findings who had an insufficient sample or benign findings in their FNAB results. Central lymph node dissection was performed if there was evidence of lymph node metastases, or if palpable lymph nodes were detected on examination.

Data collection and PTC groups

Demographic data and pathology findings were obtained. Patients were classified for study into two age groups (≤45 and >45 years old), and into five distinct subgroups in accord with PTC pathology: papillary microcarcinoma (PMC), follicular variant papillary carcinoma (FVPC), classical papillary thyroid cancer (CPAP), oncolytic variant papillary thyroid cancer (OVPC), and Warthin-type papillary thyroid cancer (WTPTC).

Tumor characteristics

PTC tumor data were classified further into: dominant tumor size; anatomic location (isthmus, left thyroid lobe, right thyroid lobe, tumor behavior (thyroid capsular invasion, extra-thyroidal invasion, lymph node metastasis (LNM) [n<1 and n≥1]); and tumor morphology (capsular, non-capsular, presence or absence of necrosis, Hashimoto or lymphocytic thyroiditis). Tumor staging was determined by the 'tumor, node, metastasis' (TNM) classification system characterized by the AJCC-TNM 2018 Cancer Staging Manual [12].

Statistical analysis

The SPSS statistical package version 22.0 (IBM, Armonk, NY, USA) was used for all analyses. Continuous variables were presented using means and standard deviations, and group comparisons were made using the independent samples t-test. Qualitative variables were presented as frequency and percentage, and analyzed using the chi-square test, or Fisher's exact test, as appropriate. Multivariate analysis was carried out using logistic regression. All statistical tests were two-sided, and a *P*-value of <0.05 was considered statistically significant

Results

The descriptive characteristics of 466 patients operated between 2008-2014 due to suspicious thyroid nodules or who had been diagnosed with PTC, histological subgroups of tumor types, multifocality, presence or absence of LNM, and results of FNAB are summarized in Table 1. The sample was comprised of 374 (80.3%) females and 92 (19.7%) males; mean age was 49.6 (13.4) years. The two most common PTC subtypes were PMC (39.5%) and CPAP (28.8%). Tumors were multifocal in 62 patients (13.3%) and unifocal in 404 patients (86.7%). Mean tumor size was 1.54 (1.24) cm, with 283 (60.7%) patients diagnosed with a maximum tumor size >1 cm. Thirty-two patients (6.8%) were positive for LNM, and 34 (7.3%) PTC patients were also diagnosed with Hashimoto thyroiditis (Table 1).

Patients were classified into two age groups (i.e., ≤45 years [n=174, 37.3%] vs. >45 years [n=292, 62.7%]) and evaluated for proportional differences in PTC prognostic factors. Both age groups were fairly well matched with respect to frequency distributions of tumor subtypes (Table 2) and tumor size categories (Table 3). However, there was a significant difference between age groups in mean tumor size, with the

younger patient group diagnosed with slightly larger tumors, on average (1.7 (1.0) cm vs 1.4 (1.3) cm; $P<0.05$). Also, there was a significant between-group difference in gender composition, with males comprising 12.6% of patients ≤45 years of age and 24.0% of patients >45 ($P<0.05$). Multivariate analysis revealed that none of the aforementioned between-group difference variables were independent predictors of multifocality (Table 4).

Table 1: Descriptive characteristics (n=466 patients)

	n	%
Gender		
Female	374	80.3
Male	92	19.7
Multifocality		
Multifocal	62	13.3
Unifocal	404	86.7
LNM		
Positive	32	6.8
Negative	434	93.2
Pathological subtypes		
PMC	184	39.5
FVPC	110	23.6
CPAP	134	28.8
OVPC	28	6.0
WTPTC	10	2.2
FNAB		
Not done	224	48
Positive	144	30.9
Negative	98	21.0
Papillary >1 cm	283	60.7
Micropapillary ≤1 cm	183	39.3
Thyroiditis		
Hashimoto	34	7.3
Lymphocytic	84	18.1

LNM: lymph node metastases, PMC: papillary microcarcinoma, FVPC: follicular variant papillary carcinoma, CPAP: classical papillary thyroid cancer, OVPC: oncolytic variant papillary thyroid cancer, WTPTC: Warthin-type papillary thyroid cancer, FNAB: fine-needle aspiration biopsy

Table 2: Tumor subtypes by age

	≤45 years old n (%)	>45 years old n (%)	*P*-value	Total n	%
PMC	56 (32.2)	128 (43.8)	<0.05	184	39.5
FVPC	42 (24.1)	68 (13.3)	0.677	110	23.6
CPAP	56 (32.2)	78 (26.7)	0.209	134	28.8
OVPC	16 (9.2)	12 (4.1)	<0.05	28	6.0
WTPTC	4 (2.2)	6 (2.1)	0.990	10	2.2
Total	174	292	—	466	100

PMC: papillary microcarcinoma, FVPC: follicular variant papillary carcinoma, CPAP: classical papillary thyroid cancer, OVPC: oncolytic variant papillary thyroid cancer, WTPTC: Warthin-type papillary thyroid cancer, FNAB: fine-needle aspiration biopsy

Table 3: Tumor size by age

	≤45 years old n (%)	>45 years old n (%)	*P*-value	Total n	%
≤1 cm	60	144	<0.05	204	43.8
>1≤2 cm	66	94	0.207	160	34.3
>2≤3 cm	34	24	<0.05	58	12.5
>3 cm	14	30	0.631	44	9.4
Total	174	292	–	466	100

Table 4: Multivariate analysis of multifocal and unifocal papillary thyroid cancer

	P-value	OR	%95 CI
Tumor size*	0.125	2.778	0.752-10.266
Age†	0.147	0.459	0.160-1.316
Tumor type§	0.304	0.335	0.041-2.699
Gender	0.919	1.071	0.282-4.077

*Tumor size >1 cm, †Age ≤45 years or >45 years, §Tumors with mixed types

Multifocal involvement in PTC tumors was found in 11.5% of patients ≤45 years and in 14.4% of the >45 group ($P=0.374$); capsular invasion was seen in 39.1% vs 33.6% ($P<0.05$), respectively. In addition, significantly higher rates of multifocality (17.5% vs 13.7%, 10.3%, 0.0%; $P<0.05$) (Figure 1) and capsular invasion (57.5% vs 18.6%, 41.4%, 27.3%; $P<0.001$) were found in tumors from >1cm to <2cm in diameter relative to other tumor size ranges (Figure 2). In turn, capsular invasion was found to be significantly correlated with LNM ($P<0.001$). When LNM and age were examined jointly, the LNM rate was found to be 11.5% in the ≤45 age group and 4.1% in the >45 age group ($P<0.05$).

Figure 1: Tumor size and capsular invasion

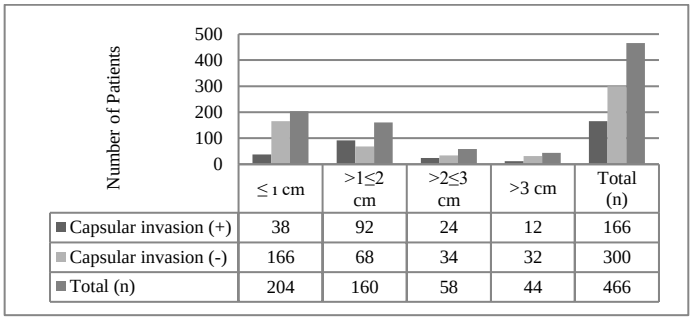
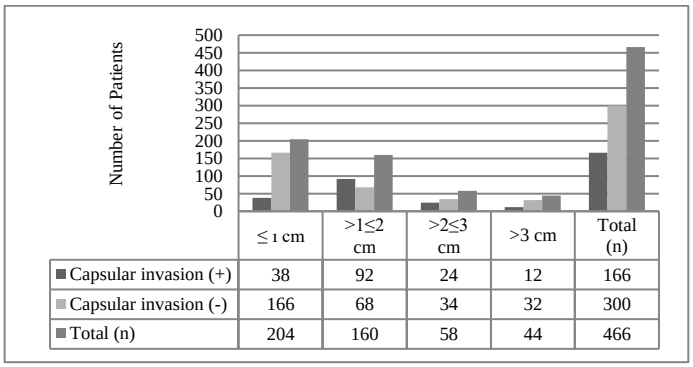


Figure 2: Tumor size and multifocality



When age groups were examined independently, capsular invasion was more prevalent when multifocal involvement was observed. Within the ≤45 age group, the capsular invasion rate in multifocal cases was 50.0% vs 37.7% in unifocal cases ($P<0.01$); within the >45 age group, the capsular invasion rate in multifocal cases was 38.1% vs 32.8% in unifocal cases ($P<0.05$). Capsular invasion in PTC was also found to be correlated with lymphocytic thyroiditis ($P<0.05$), but was unrelated to Hashimoto thyroiditis. The incidence rates of lymphocytic and Hashimoto thyroiditis within the ≤45 and >45 age groups were, respectively: 18.4%, 6.9%, and 17.8%, 7.5%, with no significant differences between groups.

Discussion

Age is often viewed as a central, independent, prognostic risk factor for well-differentiated thyroid cancers [13, 14]. Yet, the presence of other pathological risk factors (e.g., multifocality, thyroid capsule invasion, vascular invasion, extrathyroidal spread, and LNM) have been found in some studies to increase with patient age [15, 16]. Thus, the interrelationships between these factors in PTC require further elucidation.

In a retrospective study by Coburn et al. [17] of 318 patients with well-differentiated thyroid cancers, operated patients were examined in 3 different age groups (group 1, 21-50 years; group 2, 51-70 years; group 3, >70 years). Patients received postoperative adjuvant radioactive iodine (I-131) therapy if deemed necessary. In contrast to our findings, Coburn et al found that in the older age group, multifocality did not increase linearly with age (23%, 28%, and 15% in groups 1, 2, and 3, respectively) while capsular invasion was significantly increased (38%, 49%, and 74%) [17]. These data suggest that factors other than age (e.g., histological or morphological tumor characteristics) play meaningful roles in predicting cancer progression.

Tumor size has a marked impact on PTC prognosis. Numerous studies have shown that the prognosis for patients

with microcarcinomas, especially those with tumor sizes of ≤1 cm, is better than that for larger tumors [18, 19]. However, size alone is not a sufficient parameter to determine prognosis or optimum treatment. In the current study, when tumor size and capsule invasion were examined jointly, a significantly higher rate of capsule invasion (57.5%) was found for tumors between 1 and 2 cm in diameter relative to other tumor size groups. In addition, multifocality rate was also found to be significantly greater (17.5%) within this tumor size range.

In a related manner, a study by Pellegriti et al [20] of 299 patients with tumor sizes ≤1.5 cm, patients with tumor sizes of ≥1 cm had a 30.3% higher extrathyroidal spread than the other group (13%). Bilateral extrathyroidal spread and lymph node involvement have been found to be prevalent in thyroid capsule invasion, especially in patients with tumors of >1≤2 cm, providing evidence that these T1b tumors (as classified in the TNM staging system) may be more aggressive than micropapillary tumors [20].

In a retrospective study of 174 patients by Cheema et al [21], patients with tumor sizes of ≥2 cm had 20% more LNM than patients with tumor sizes of <2 cm, and one-third of these patients had LNM at the time of diagnosis. In addition, the rate of disease recurrence in all tumor sizes was determined to be equivalent. As a result, LNM status at diagnosis, rather than tumor size, determined the rate of recurrence [21]. In our study, patient age and LNM rate were examined jointly. The LNM rate was 11.5% in patients ≤45 years of age vs 4.1% in patients >45 years old. In addition, LNM was found to be significantly correlated with capsular invasion.

Although Pelizzo et al. [22] did not identify capsular invasion as a prognostic factor, a number of studies have done so [23, 24], and there appear to be strong relationships between capsular invasion, multifocality, extrathyroidal spread, and LNM. Mercante et al. [25] found that extrathyroidal spread and LNM were important risk factors in disease progression in a study of 445 patients with PTC. Still other studies define detection of thyroid capsule invasion as having a similar prognostic value as that of extrathyroidal extension, even in the absence of invasion of the surrounding soft tissue. In our study, we examined the inter-relationship between multifocality and capsular invasion with respect to age group. Interestingly, capsular invasion was significantly greater in multifocal cases relative to unifocal cases within each age group studied. That is, in the ≤45-year-old group, capsular invasion rate in multifocal cases was 50.0% vs 37.7% in unifocal cases. Similarly, but less significantly, the capsular invasion rate in multifocal cases in patients >45 years old was 38.1% vs 32.8% in unifocal cases.

In a corroborative study by Lin et al. [26] covering 1682 PTC patients, multifocality was seen in 337 patients, and extrathyroidal spread was seen in 28% of multifocal cases and 21% of unifocal cases. In consideration of these data, in conjunction with our own, the greater presence of capsule invasion and extrathyroidal extension in multifocal cases suggest that a more aggressive treatment strategy is needed in multifocal cases in patients of all ages.

In recent years, a number of studies were conducted that evaluated cancer development and prognosis in patients with chronic lymphocytic thyroiditis and Hashimoto thyroiditis [27, 28]. Although predominantly, Hashimoto thyroiditis has been associated with an increased risk of PTC, there is some evidence suggesting that patients with Hashimoto thyroiditis and PTC appear to have a more favorable prognosis [29]. In our study, the incidence of lymphocytic thyroiditis in patients ≤45 years old was 18.4%, and the incidence of Hashimoto thyroiditis was 6.9%. In >45-year-olds, the rate of lymphocytic thyroiditis was 17.8%, while the rate of Hashimoto thyroiditis was 7.5%: these rates did not significantly differ between age groups. Interestingly, in our study, capsular invasion was found to correlate with lymphocytic thyroiditis, and PTC patients without Hashimoto thyroiditis, had slightly higher rates of LNM (6.9% vs 5.9%).

Limitations

A limitation of the study was that it was retrospective. Also, while the large sample size was study strength, the lack of follow-up data precluded estimation of survival findings. In addition, study outcomes would have been strengthened by inclusion of a patient sample more evenly distributed between unifocal and multifocal carcinomas.

Conclusions

The current study aimed to assess the relationship between multifocality, capsular invasion, and patient age (≤45 vs >45 years of age) in PTC, along with other relevant tumor characteristics. PTC patients >45 years of age were found to have only slightly higher rates of multifocal involvement, and significantly lower rates of capsular invasion. However, capsular invasion rates were significantly higher in multifocal cases within each age group, and, capsular invasion was independently related to LNM. This study also indicated that capsular invasion and multifocal involvement in PTC were significantly related to tumor size, which was independent of age. In light of our study's findings, including confirmation by multivariate analysis, age, as represented by the >45 year cutoff value, should not be considered an independent prognostic risk factor in planning treatment of PTC. The individual patient, tumor characteristics, and local and distant metastases status should remain the most important criteria for treatment selection and follow-up care in all patient age groups.

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The relationship of antibodies detected in the Western Blot test with clinical and immunological stages in HIV-infected patients

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Ethics Committee Approval
The approval for this study was granted by the Ethics Committee of Bakirkoy Sadi Konuk Training and Research Hospital, and the National Ethics Committee (Number: 04.10.2021-2021/459).
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: The laboratory diagnosis of human immunodeficiency virus (HIV) infection is based on detection of anti-HIV antibodies in an initial ELISA (enzyme-linked immunosorbent assay) test and its confirmation with the Western Blot (WB) procedure. Even though the specificity of WB is high for the detection of antibodies against various viral proteins, there are important differences in the timing of the appearance of antibody bands and intensities in different stages of HIV infection. The aim of this study was to evaluate antibodies detected in WB testing and the relationship to clinical and immunological stages in HIV-infected patients.
Methods: Newly diagnosed 78 patients with HIV/AIDS (Acquired Immunodeficiency Syndrome) in our outpatient department between April 2009 and September 2012 were included in the study as a retrospective cohort. Age, gender, complaints, clinical signs, CD4+ T lymphocyte counts and HIV RNA level at diagnosis were collected retrospectively from medical records. WB band patterns obtained from the reference laboratory of the Istanbul Public Health Center were examined retrospectively.
Results: Of the 78 HIV/AIDS cases, 68 (87.2%) were male. Mean age was 38.87(13.09) years (range, 17-83 years). Median CD4+ T lymphocyte count at diagnosis was 410.2 /mm³ (range, 3-1114). Mean HIV RNA level at diagnosis was 592.894 copies/ml. Rare band profiles were seen in 29.4% (23/78). According to World Health Organization (WHO) clinical staging, 59 (75.6%) patients were at stage I, 4 at stage II, 10 at stage III and 5 at stage IV. Gp120, gp160 and gp41, known as envelope glycoproteins in WB band antibodies, were seen in all patients. There was determined to be a decrease in the p17, p51, p55 and p39 bands in WB tests of the advanced grade (Grade IV) of HIV infection.
Conclusions: Reduction of p17, p51, p55, p39 antibodies in advanced stages were related with the progression of HIV infection. This shows that WB test is an important parameter not only in the diagnosis of HIV infection, but also in the follow-up of clinical progression in the absence of these antibodies.

Keywords: Western Blot, ELISA, HIV/AIDS

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Introduction

In the laboratory identification of human immunodeficiency virus (HIV), 4th generation ELISA (enzyme-linked immunosorbent assay) method is used based on the determination of anti-HIV antibodies, and positive samples are confirmed with Western Blot (WB), Line Immunoassay (LIA), or the HIV-1/2 antibody differentiation rapid confirmation test [1, 2]. HIV-RNA examined for viral load in patients diagnosed with HIV/AIDS can be determined 12 days after HIV infection is encountered. The first serological marker detected during acute infection is p24 antigen of the virus [3].

When seroconversion occurs, antibodies emerge against both gp120 and p24 antigens. At this stage, p24 antigen disappears. While p24 antibodies are lost, gp 120 antibodies are determined in the AIDS-related complex (ARC) cycle, which is seen as fever together with generalized lymphadenopathy, diarrhea, weight loss and opportunistic infections. In this period, the lost p24 antigen re-emerges. When it comes to the stage of AIDS, anti-p24 is not determined in serum, while p24 antigen is detected at a high level [3]. Opportunistic infections (bacteria, viruses, fungi and protozoa) are defined as more severe and more frequent infections due to immunosuppression [4]. As HIV-related immunosuppression improves with early antiretroviral therapy, opportunistic infections are prevented [5].

Despite the high specificity of WB for the determination of antibodies which develop against various viral proteins, there are significant differences in the timing at which antibody bands are seen and their severity at different stages of HIV infection. The aim of the current study was to evaluate the relationship of antibody profiles which develop in the WB test of HIV infected individuals, according to clinical and immunological stages.

Materials and methods

Study design and participants

The study included 78 cases who presented at the Infectious Diseases and Clinical Microbiology Department with HIV/AIDS diagnosis between April 2009 and September 2012.

Approval for this retrospective study was granted by the Ethics Committee of Bakirkoy Sadi Konuk Training and Research Hospital, and the National Ethics Committee (Number: 04.10.2021-2021/459). Retrospective data were collected from outpatient records and the age, gender, reason for presentation, clinical findings, CD4+ T cell count and HIV RNA levels at diagnosis, were evaluated. The WB test results were obtained from the Ministry of Health, which is the reference laboratory of the Istanbul Public Health Directorate, and the WB band patterns were retrospectively examined. The laboratory methods listed below were used in the study:

1- ELISA: Genscreen ULTRA HIV Ag-Ab method
2- Quantitative methods used in the determination of HIV RNA in serum: RT-PCR method Cobas Taqman 48 (Roche), <47 copies/ml - >10,000,000 copies/ml
3- Methods used in the determination of serum CD4+ T cell count: CD4 FITC monoclonal antibodies, (Becton Dickinson Immunocytometry Systems, San Jose, CA).
4- Western Blot method: HIV BLOT 2.2 kit was used (MP Biomedicals Asia Pasific Pte Ltd.). The gp160, gp120, p66, p55, p51, p39, gp41, p31, p24, p17 band proteins found in this test were evaluated.

Within the scope of this study, patients with CD4+ T lymphocyte count <350 cell/mm^3 were defined as infected with late-diagnosed HIV [6].

Clinical grading of patients was applied according to the World Health Organization (WHO) classification [7].

Statistical analysis

SPSS version 22 (Version 22.0. Armonk, NY: IBM Corp.) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, ratio, minimum, maximum) were used when evaluating the study data. The relationships between the CD4+ T lymphocyte count, WHO clinical grading at diagnosis and WB band patterns were evaluated using the Pearson Chi-square test. A value of $P<0.05$ was accepted as statistically significant.

Results

78 cases, who were admitted at the Infectious Diseases and Clinical Microbiology Department and were newly diagnosed with HIV/AIDS between April 2009 and September 2012, comprised 68 (87.2%) males and 10 (12.8%) females with a mean age of 38.87 (13.09) years (range, 17-83 years). At diagnosis, the mean CD4+ T lymphocyte count was 410.2 cells/mm^3 (range, 3-1114) and the mean HIV RNA level was measured as 592,894 copies/ml.

All patients who presented at the outpatient clinic were determined to be infected with HIV-1 and all WB band proteins were found to be positive in 70.51% (55/78). Rare band profiles were observed in the remaining 29.48% (23/78). The envelope glycoproteins, gp120, gp160, and gp41, were observed to be present in the band profiles of all the cases.

WB band patterns of the 78 patients were examined according to the WHO grading.

Grade I: This grade was determined in 59 patients. The envelope proteins of gp160, gp120 and gp41 were positive in all patients, and p24 in 57 (96.6%). The presence of p17, p31, p39, p51, p55 and p66 proteins were determined in 53 (89.8%), 52 (88.1%), 47 (79.7%), 48 (81.4%), 52 (88.1%), and 51 (86.4%) patients, respectively.

Grade II: In all 4 (5.1%) patients at this grade, gp160, gp120, gp41 and p24 and p17 bands were detected. From the other proteins, p66, p55, p51, p39, and p31 proteins were present in 3 (75%) patients.

Grade III: In all 10 (12.8%) patients at this grade, gp160, gp120, gp41, and p55, p51 proteins were present. From the other proteins, p66, p31, p24, and p17 were present in 9 (90%) patients, and p39 protein was present in 8 (80%).

Grade IV: In all 5 (6.4%) patients at this grade, gp160, gp120, gp41 and p31 and p24 bands were present. From the other proteins, p66 was present in 4 (80%) patients, and p55, p51, p39 and p17 in 2 (40%) patients. There was determined to be a decrease in the p17, p51, p55 and p39 bands of the WB test in the advanced grade (Grade IV) of HIV infection. This decrease was evaluated statistically significant in p17, p51, p55, p39 bands ($P=0.001$, $P=0.002$, $P=0.016$, and $P=0.042$; respectively) (Table 1).

Table 1: Distribution of WB band patterns according to the WHO grading system

Band proteins	Grade I-II-III(73)	Grade IV(5)	*P*-value
p17	66	2	0.001
p55	65	2	0.002
p51	61	2	0.016
p39	58	2	0.042

Pearson Chi-square test

While CD4+ T lymphocyte counts were <350 cells/mm^3 in 33 patients, CD4+ T lymphocyte counts were ≥350 cells/mm^3 in 45 patients, which does not represent any statistical difference (P>0.05) (Table 2).

Table 2: Distribution of WB antibody bands according to immunological grading

WB antibody bands	<350 cells/mm^3 n(%)	≥350 cells/mm^3 n(%)	*P*-value
p66	30(90.9)	37(82.2)	0.276
p55	29(87.9)	38(84.4)	0.667
p51	29(87.9)	34(75.6)	0.172
p39	27(81.8)	33(73.3)	0.380
p31	31(93.9)	38(84.4)	0.195
p24	31(93.9)	44(97.8)	0.384
p17	27(81.8)	41(91.1)	0.225

Pearson Chi-square test

Discussion

Despite the high sensitivity and specificity of the WB test in the identification of viral proteins, there are variations in the time of formation of antibody bands and their severity at different stages of HIV infection [8]. After infected with HIV, the earliest antibodies determined in the WB test are p24 and its precursor, p55, and at advanced stages of the disease, their detection frequencies are decreased [9]. In the current study, p24 antibody was detected at the same rates in both the early and advanced stages of HIV infection. This was contrary to studies from Europe and North America which have explained that the loss of p24 is a marker of advanced HIV/AIDS infection [10, 11]. However, studies conducted in Africa and India have similarly found positive rates of p24 antibody at both early and advanced stages of HIV infection [8, 12]. Moreover, it has been reported that envelope precursor protein gp160 and envelope proteins gp120 and gp41 can be seen in all HIV infected cases, independent from clinical stage [9]. Similarly, in the current study, gp160, gp120, and gp41 antibodies were detected in the WB test, independent from clinical stage in all patients.

In 67 (85.9%) cases, p55 band was detected. The p55 reactive group was found in 89% of grade I-II-II patients and in 40% of the grade IV patients. In other studies, p55 antibody usually cannot be determined at advanced stages [13-15]. By fragmenting the precursor protein p55, which is a gag gene product, protease enzyme forms p17 and p24 which are in mature capsid. The p55 antibody band emerges in WB when there are very high levels of p24 or p17 antibody proteins in the samples.

In a study by Sivakumar et al. [12], antibodies developing against p17 were determined in 64% of WHO grade I patients and in only 33% of grade IV patients. In this study, the p17 antibody band was determined in only 40% at advanced grade. With grade progression of HIV infection, the positivity of p17 and p55 antibody bands was found statistically significantly decreased. The decrease in antibody level and increase in p17 antigen are in the matrix between the virion nucleocapsid and membrane, and play a role in the fusion of the infection virion and the target cell [16]. Consistent with the current study findings, previous studies have found a relationship between antibodies against p17 and slower progression of HIV disease [17].

In the current study, the p51 band, which affects reverse transcription, was found to be reactive at a rate of 83.6% in grade I-II-III, and 40% in grade IV. The decrease in positivity of p51 antibody band together with disease progression was found to be statistically significant. This finding was similar to the study by Srikanth et al. [18] in India. In studies by Fiebig et al. [19] and Hecht et al. [20], p31 band was determined to be the last antibody of the WB band proteins formed (2-4 months) after infection with HIV. Srikanth et al. [18] reported a correlation between AIDS grade and the non-determination of p31 band. Sudha et al. [8] reported that p31 was the antibody most frequently not determined at both initial and advanced stages. In the current study, p31 protein was detected in 88.1% at grade I and in 100% at grade IV.

The presence of p39 band, which is a fragment of p55, is in %79.5 of early stages HIV/AIDS infection and in 40% at an advanced stage, which shows statistical significance. Sivakumar et al. [12] observed p39 band in 35% at the early stage and in 44% at advanced stages, both similar to the current study. In a study of antiretroviral-naive pregnant HIV-infected patients, Duri et al. [21] emphasized the absence of p39 band in the WB test and reported that advanced stage HIV infection was correlated with a high viral load.

p66, which plays a role in reverse transcription, was determined by Sivakumar et al. [12] and Sudha et al. [8] at the rates of 81% and 97.8%, respectively, in the early stage, and at 100% and 88.9% at advanced stages, respectively. Similar findings were obtained in the current study with the determination of p66 at 86% in the early stage and at 80% at the advanced stage.

Positivity was observed in all the WB band proteins in 70.51% (55/78) of the current study, and rare band profiles were seen in 29.48% (23/78). Sudha et al. [8] determined rare band profiles at a rate of 7.09%. This rate seems to be extremely low compared to the current study results.

Limitations of the current study were low number of patients and the design in a single hospital.

Although studies in different countries have shown different band parameters in WB tests, when the relationship with the clinical status of the patient is examined, similar results to those of the current study have been obtained. This is the first national study in Turkey investigated the relationship between WB antibody bands and the clinical grade of HIV infection.

Conclusion

Although a statistically significant relationship was determined between clinically advanced stages of HIV infection and the absence of p17, p51, p55 and p39 antibodies in WB test, significance was not found immunologically. HIV patients are offered treatment as soon as they are diagnosed. It should be kept in mind that opportunistic infections may be seen more frequently in advanced clinical stage due to antibody deficiency. In treatment, diagnosis and treatment of opportunistic infections should be considered with or before antiretroviral therapy. This can be shown that the WB test is an important parameter not only in the diagnosis of HIV infection but also in the follow-up of clinical progression, even in the absence of these antibodies.

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The effect of preoperative prognostic nutritional index on outcome in glioblastoma multiforme patients

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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: Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor subtype with a poor prognosis despite various treatments. Some prognostic markers on survival (such as age, Eastern Cooperative Oncology Group Performance Score (ECOG-PS), isocitrated hydrogenase (IDH) status, alpha thalassemia/mental retardation syndrome X-linked (ATRX) mutation status, possibility of extensive surgery) have been defined. Prognostic Nutritional Index (PNI) has been evaluated in various cancers (such as lung, esophagus, and pancreas), and patients with a low PNI score have been associated with a poor prognosis for overall survival (OS). Our study aimed to examine the effectiveness of molecular and demographic characteristics and preoperative PNI score that may affect OS in GBM patients.
Methods: In this retrospective cohort study, GBM diagnosed patients who were 18 years old or older, were included in the study. We measured their pretreatment PNI score and performed multivariate Cox regression analyses of OS in GBM patients.
Results: A total of 107 patients were included in the study. Median age was 58 (range, 32-83) years. 72 patients (67.3%) were male and 35 patients (32.7%) were female. The mean preoperative PNI level was calculated as 50.5. The median overall-survival (mOS) was 19.7 months and the median time to progression (mTTP) was 8.1 months. There was no statistically significant result on overall survival in the univariate analysis of patients with PNI>50.5 (P=0.121). In multivariate analysis, being 70 years or older (P=0.012), IDH-1 wild and ATRX mutant patients (P=0.016), IDH-1 mutant and ATRX wild patients (P=0.037), and TTP 12 months and older (P<0.001) were considered as independent risk factors on overall survival.
Conclusions: In our study, the effect of preoperative PNI score on survival could not be demonstrated. Further studies are needed to elucidate the potential impact of PNI on outcomes in patients with GBM.

Keywords: Glioblastoma multiforme, Prognostic nutritional index, IDH, ATRX, Overall survival

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Introduction

Glioblastoma multiforme (GBM), is the most common primary malignant brain tumor subtype with a poor prognosis despite various treatments. With standard treatments of extensive tumor resection followed by radiotherapy concurrent with temazolamide, the median overall survival (mOS) is around 15 months [1, 2]. Some prognostic markers of survival such as age, ECOG-PS, isocitrated hydrogenase (IDH) mutation, alpha thalassemia/ mental retardation syndrome X-linked (ATRX) mutation status have been defined for the possibility of extensive surgery [3]. While IDH mutation is detected in 90% of secondary GBM, its incidence is rare in primary GBM and the presence of IDH mutation is associated with a good prognosis. Similarly, while ATRX mutation is observed more frequently in secondary GBM, and rare in primary GBM, the prognostic existence of the ATRX mutation is not yet proven [4, 5]. More prognostic markers are needed for the poor survival of the disease. PNI is an indicator that evaluates the patient's nutritional and immune status, calculated with the following formula: 10 x serum albumin (g/dl) + 0.005 x total lymphocyte count (per mm^3). There are studies emphasizing the prognostic importance of preoperative malnutrition and inflammation status on OS in various cancers [6-8]. Although some studies showed preoperative PNI score as an independent risk factor in OS of GBM patients, significant difference was not obtained in other cancers [9-12]. Our study aimed to examine the effectiveness of molecular and demographic characteristics, and preoperative PNI score that may affect OS in GBM patients.

Materials and methods

107 GBM patients diagnosed at University of Health Sciences Umraniye Training and Research Hospital and Marmara University School of Medicine between 2012-2020 were included in the study. The Ethics Committee approved the study protocol at the University of Health Sciences, Ümraniye Education and Research Hospital, (Date: 17.06.2021, Number: B.10.1.TKH.4.34.H.GP.0.01/207). Eligible patients for the study were aged 18 years and older, being diagnosed with histologically/cytologically proven high-grade glioma. Exclusion criteria were presence of secondary primary malignancy, having signs of active infection or chronic liver disease.

Age, gender, ECOG-PS, laboratory values, treatment regimens and survival data of the patients were obtained retrospectively.

Statistical analysis

Categorical variables are presented as number of patients and percentages. The Kaplan-Meier method was used to estimate OS. Log-rank test was used for comparison of the survival functions for each variable. For the assessment of prognostic variables, Cox regression model is used for proportional hazards, calculating the hazard ratio (HR) and confidence intervals of 95%. The selection of variables for Cox model was carried out using the significance obtained from the univariate analysis, considering the significance level of $P \leq 0.10$. All reported *P*-values were two-sided and a *P*-value <0.05 was considered of statistical significance. These analyses were performed using SPSS version 18 (SPSS Inc., Chicago, USA).

Results

A total of 107 patients were included in the study. Median age was 58 (range, 32-83) years. 72 patients (67.3%) were male and 35 (32.7%) were female. There were 74 patients (69.2%) with ECOG-PS of 0-1, and 33 patients (31.8%) with ECOG-PS 2 or above. While diagnosis was made by stereotactic biopsy in 18 patients (16.8%), incomplete surgery was performed in 37 patients (34.6%), and extensive resection was performed in 52 patients (48.6%). 99 patients (92.5%) received adjuvant chemoradiotherapy (radiotherapy + temozolamide), continued with temozolamide, 1 patient (0.9%) received only adjuvant radiotherapy, whereas 7 patients (6.5%) did not receive any treatment postoperatively. From 90 patients (84.1%) examined for IDH-1 mutation, 7 patients (6.5%) were found to be mutant and 83 patients (77.6%) were of wild type. From 84 patients (78.5%) investigated for ATRX mutation, 18 patients (16.8%) were found to be mutant and 66 patients (61.7%) were of wild type (Table 1). The mean serum albumin and lymphocyte level measured preoperatively was 3.9 g/dl and 2100/mm^3, respectively. The mean preoperative PNI level was calculated as 50.5 (Table 2). The median overall-survival (mOS) was 19.7 months and the median time to progression (mTTP) was 8.1 months (Figure 1, 2).

Table 1: Patients characteristic

	n (%)
Gender	
Male	72 (67.3)
Female	35 (32.7)
Age	58 (range, 32-83)
ECOG PS 0	28 (26.2)
1	46 (43)
2	23 (21.5)
3	8 (7.5)
4	2 (1.9)
Surgery; stereotactic biopsy	18 (16.8)
Incomplete resection	37 (34.6)
Maximal resection	52 (48.6)
Adjuvant Treatment	
Crt+temozolamid	99 (92.5)
Radiotherapy	1 (0.9)
No treatment	7 (6.5)
IDH-1 Mutation	90 (84.1)
Mutant	7 (6.5)
Negative	83 (77.6)
ATRX Mutation	84 (78.5)
Mutant	18 (16.8)
Negative	66 (61.7)

Crt: Chemoradiotherapy

Table 2: Patients' serum laboratory parameters

Parameters	Median values
WBC	7800 mm^3
Neutrophil	5250 mm^3
Lymphocyte	2100 mm^3
Thrombocyte	240000 mm^3
Albumin	3.9 g/dl
PNI	50.5

WBC: White Blood Cell

Figure 1: Kaplan-Meier curves in GBM patients. The median overall-survival (mOS) was 19.7 months

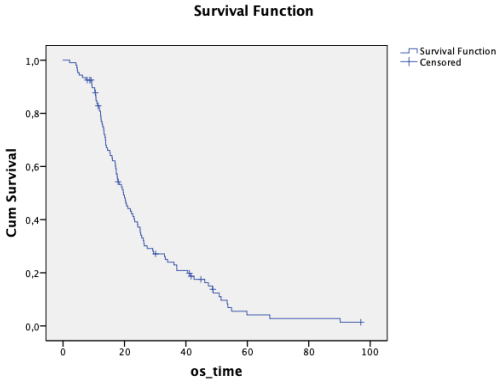
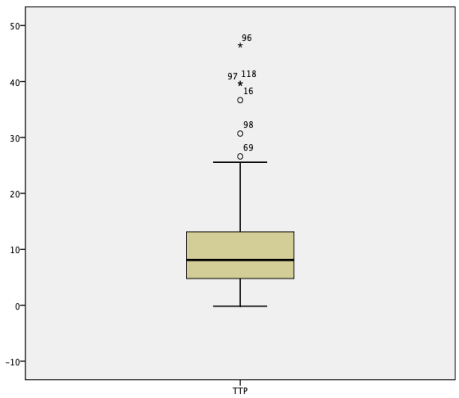


Figure 2: The median time to progression (mTTP) was 8.1 months



In univariate analysis, being 70 years or older, ECOG-PS-2 or above, IDH-1 wild and ATRX mutant patients, IDH-1 mutant and ATRX wild patients, and TTP 12 months and above were found to have significant effect on overall survival (P=0.027, P=0.004, P=0.006, P=0.064 and P<0.001, respectively). In multivariate analysis, being 70 years or older, IDH-1 wild and ATRX mutant patients, IDH-1 mutant and ATRX wild patients and TTP 12 months and older were considered as independent risk factors on overall survival (P=0.012, P=0.016, P=0.037 and P<0.001, respectively) (Table 3). There was no statistically significant result in overall survival in the univariate analysis of patients with PNI >50.5 (P=0.121).

Table 3: Univariate and Multivariate analysis of potential factors associated with OS

		Univariate		Multivariate
	n	OS(months)	*P*-value	*P*-value
Age				
>70	20	20.6 (17.3-23.9)	0.027	0.012
<70	87	12.8 (10.8-14.9)		
Gender				
Female	35	25.1 (18.2-31.9)	0.198	
Male	72	17.7 (14.7-20.6)		
ECOG PS				
0-1	74	21.9 (17.7-26)	0.004	0.330
2-3-4	33	14.4 (9.7-19.1)		
IDH-1 wild, ATRX mutant	15	12.8 (10.2-15.4)	0.006	0.016
IDH-1 mutant, ATRX wild	4	26.1 (0-57)	0.064	0.037
IDH-1 wild, ATRX wild	58	20.4 (18.2-22.5)	0.867	
Time to progression				
More than 12 months	34	34 (21-46.9)	<0.001	<0.001
Less than 12 months	76	15.3 (12.4-18.2)		
PNI				
>50.5	50	23.1 (14.3-31.8)	0.121	
<50.5	49	19.6 (16.8-22.5)		

Discussion

Primary GBMs usually have a poor prognosis. Despite local and systemic treatments (re-resection, re-irradiation, targeted therapy and systemic chemotherapy), the median survival is less than 15 months [1, 13]. It has been stated in various studies that some genetic and molecular markers such as O-6-methylguanine-DNA methyltransferase (MGMT) status, IDH-1, phosphatase and tensin homolog (PTEN), p53, ATRX and telomerase reverse transcriptase gene promoter (TERT) are prognostic factors [13, 14].

However, it is not always possible to assess these molecular and genetic markers. For these reasons, there is a need for prognostic tools of simple, applicable and inexpensive methods that predict which patients will get a better response from the treatment.

The Prognostic Nutritional Index (PNI) is mainly a marker that evaluates the nutritional and immunological status of patients who undergone gastrointestinal surgery, and is calculated by serum lymphocyte and albumin levels [15]. PNI has been evaluated in various cancers (such as lung, esophagus, and pancreas), and patients with a low PNI score have been associated with a poor prognosis for OS [16-18]. There are several studies evaluating the prognostic effect of the PNI score in GBM patients. In a GBM related study by Xu et al. [10], preoperative PNI score (PNI >48) was found to be an independent predictive factor for OS.

In another study, Zhou et al. evaluated the preoperative PNI score in GBM patients and found a prognostic effect on OS in the group with PNI >44.4 [11]. In our study, patients with PNI >50.5 had numerically better OS, however statistical significance could not be proven. In the literature review by Ding et al., statistically significant results were not obtained on OS in the group with PNI >44.4 [19]. Rigamonti et al. [14] emphasized the same results, although the OS results were numerically better in patients with PNI >45.9. Similarly, in the study of He et al. [20], statistical significance was not found, although OS results of PNI >52.55 group were numerically better. This situation may be masked by the fact that the patient population is older than other studies, and other genetic and molecular factors have more negative effects on OS.

Presence of IDH mutation is less frequently detected in primary GBM and is associated with good prognosis [4]. In a meta-analysis of nine studies evaluating IDH mutation status, it was concluded that the presence of IDH mutation was prognostic and correlated with improved survival outcomes [21]. Another molecular marker, ATRX mutation, is seen more frequently in low-grade gliomas and secondary GBM, but is less common in primary GBM patients [22]. The effect of ATRX mutation on survival in GBM patients was investigated in various studies. In the study of Cai et al. [23], better survival results were obtained in ATRX wild and IDH mutant GBM patients. Similarly, in the study of Leeper et al. [24], worse survival results were obtained in ATRX wild, glioma patients. In accordance with the literature, the best survival results were obtained in the IDH mutant and ATRX wild groups, while the worst survival results were obtained in the ATRX mutant and IDH wild groups in our study.

Limitations

Having retrospective design might cause selection bias in the study. Relatively low number of recruited patients and having immunohistochemical ATRX and IDH mutations in 74.8% of the patients, but not in the entire patient population are other limitations. The prognostic effect of other molecular markers could not be evaluated.

The existing data support further investigation on how the patients can be followed closely according to the PNI score, and their nutritional status and survival can be forced for improvements in future.

Conclusion

Despite being an easily calculated, cost-effective indicator and its promising effect on outcomes in earlier studies, PNI could not be shown to have positive impact on overall survival in our study. More studies are needed to assess whether PNI score is prognostic.

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Do steroid injections to the peripheral nerve increase perineural fibrosis? An animal experimental study

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Ethics Committee Approval
This study was approved by the local Animal Research Ethics Committee of Çukurova University (meeting date 2017.04.14, meeting 4, decision 5.)

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Abstract

Background/Aim: Perineural fibrosis may be seen in some surgeries after unsuccessful transforaminal injections. This animal experiment aims to investigate the effect of steroids and/or local anesthetic substances used in epidural/transforaminal injections on fibrosis.

Methods: A total of 14 male Wistar-Albino rats were separated into two groups of 7. After intraperitoneal anesthesia, right and left sciatic nerves were explored in all groups. In group 1, appropriate dose of methylprednisolone acetate and bupivacaine hydrochloride, and in group 2 only methylprednisolone acetate was administered to the explored left sciatic nerves. The right sciatic nerves were identified and explored without the application of any procedure to secure the control side of the groups. All explored areas were marked for later sampling. After 3 weeks, rats were sacrificed and samples were taken around the sciatic nerve for histopathological examination.

Results: In group 1, perineural fibrosis around the left sciatic nerve (intervention side) was seen at grade 3 in five rats and at grade 0 in two. In right sciatic nerve as the control side, grade 2 fibrosis was observed in 5 rats, and fibrosis was not observed in two rats. No statistically significant difference was defined with respect to perineural fibrosis (P=0.128). In group 2, perineural fibrosis was seen around the left sciatic nerve (intervention side) at grade 3 in 5 rats, at grade 4 in one rat, and not observed in one rat. In the control side of the second group, perineural fibrosis was seen at grade 3 and 1 in one each, and was not seen in five rats. The difference between intervention side and control side in the rate of perineural fibrosis seen was statistically significant (P=0.026).

Conclusions: The application of steroids alone to the nerve was determined to increase the risk of perineural fibrosis development. The addition of local anesthetics to the steroid in the injection may reduce the possibility of perineural fibrosis.

Keywords: Perineural fibrosis, Sciatic nerve, Methylprednisolone, Bupivacaine, Transforaminal injections

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Introduction

Lumbar spinal stenosis is characterized by various degrees of lower back and leg pain due to pressure in neural and vascular tissues in the lumbar spine [1]. Spinal stenosis may be central or lateral [2], and regardless of its anatomic position, the resulting pain is explained by two mechanisms. The first of these is mechanical pressure on the nerve root with the narrowing of the bone foramen. The second is inflammatory immunological processes occurring in this region with or without mechanical pressure, which may result in radicular and neurological signs that include neural hyperemia, venous congestion and edema [3, 4] .

Treatment method of patients with radicular leg pain is determined by the severity of symptoms, comorbidities, presence of risk factors for anesthesia and surgery, and patient expectations [5, 6]. Physical treatment exercises, non-steroid anti-inflammatory drugs (NSAIDs) and activity modifications combined with epidural/foraminal steroid injections are possible options [7], from which, transforaminal injection of steroids at the closest point of the nerve root is accepted as the most definitive and effective management algorithm [8]. Transforaminal or epidural steroid injection are shown to reduce symptoms in 60-75% of patients with stenosis [9-11].

In cases where pain persists or relapses despite transforaminal injection, surgical treatments are considered, but perineural fibrosis on the affected nerve makes surgery more difficult and reduces the chance of success. Perineural fibrosis is often encountered in revision surgeries in particular.

Our hypothesis is that substances frequently used in injections may cause or increase perineural fibrosis.

Materials and methods

Experimental animals

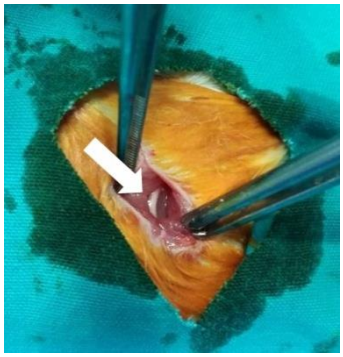
This study was approved by the local Animal Research Ethics Committee of Çukurova University (meeting date 2017.04.14, meeting 4, decision 5). Principles of laboratory animal care (NIH publication No. 86-23, revised 1985) were followed and all animal rights have been complied with throughout the entire study.

A total of 14 young adult male Wistar-Albino rats, each weighing 200±20 g, were obtained from the breeding colony. The number of rats was determined to be the minimum suitable for statistical analysis. The rats were randomly separated into two groups for the application of Methylprednisolone acetate or the combination of Methylprednisolone acetate and Bupivacaine hydrochloride. A single appropriate dose of methylprednisolone acetate+ Bupivacaine hydrochloride was applied to the left sciatic nerve of seven rats (Group 1) and a single appropriate dose of Methylprednisolone acetate was applied to the left sciatic nerve of seven rats (Group 2). All animals were followed up in a temperature-controlled room (23±1°C), with a day/night light cycle and free access to laboratory food and tap water.

Sciatic nerve dissection

All rats were anesthetized with the intraperitoneal administration of a mixture of 10 mg/kg ketamine and 10 mg/kg xylazine. Following anesthesia both hind limbs were shaved and then prepared with 10% povidone iodine solution. A 2-cm incision was made and using soft dissection, the right and left sciatic nerves were exposed through the gluteal muscle (Figure 1).

Figure 1: White arrow indicates the sciatic nerve exposed through the gluteal muscle



Application of drugs

The animals in group 1 received a mixture of 0.57 mg/kg Methylprednisolone acetate and 0.07 mg/kg Bupivacaine hydrochloride in same syringe, and animals in group 2 received 0.57 mg/kg Methylprednisolone acetate solution. The injections were made to the left sciatic nerve after dissection. In calculating the dose of the drug to be administered, mg/kg equivalent to one drug dose administered to adult humans was calculated. After the drug injections, a prolene marker suture (4/0) (ETHICON, San Lorenzo, USA) was placed adjacent to the nerve to create a landmark for pathological sampling. In both groups, the right sciatic nerves were identified and only marker sutures were placed adjacent to the nerve without any drug administration. In all groups, the layers on both sides were closed with vicryl (4/0) suture.

Histopathological examination

The animals were sacrificed at third week, the marked sutured areas were reopened, and tissue samples were obtained from an area of approximately 1 cm^2 surrounding the nerve. After the biopsy samples were fixed in 10% formaldehyde solution and prepared for pathological examination, 4-micron sections were stained with hematoxylin eosin. Trichrome staining was performed using the histochemical method. Pathologists performed single-blind evaluations for the samples. Perineural fibrosis around the sciatic nerve was evaluated according to the staging and histological parameters of Nahm et al. [12] by two different pathologists, on a 5-grade scale, where grade 0 defines absence of fibrosis, grade 1 defines loose or focal fibrosis, grade 2 defines loose or diffuse fibrosis (>50%), grade 3 is given in dense or focal fibrosis, and grade 4 is given in dense or diffuse fibrosis (>50%). Inflammation was evaluated based on the number of mononuclear cells and aggregation as defined by Salafia et al. [13]

Statistical analysis

Data obtained in the study was analyzed statistically using SPSS 24.0 software (IBM Corporation, Armonk, NY, USA). Comparisons between groups based on perineural fibrosis and chronic inflammation were made using the Kruskal-Wallis H Test. A value of $P<0.05$ was accepted as statistically significant.

Results

Complications or infection were not observed in the study group before the intervention or during the follow-up period of animals. In both left and right sides of all animals in

both groups, chronic inflammation was not observed according to the Salafia et al. [13] classification.

In group 1, perineural fibrosis around the left sciatic nerve (intervention side) was seen at grade 3 in 5 rats and at grade 0 in 2. In the right sciatic nerve (control side), grade 2 fibrosis was seen in 5, and perineural fibrosis was not observed in two rats. No statistically significant difference in perineural fibrosis was determined (P=0.128).

In group 2, perineural fibrosis around the left sciatic nerve (intervention side) was seen at grade 3 in 5 rats (figure 2) and grade 4 in 1, and was not seen in 1. In the right sciatic nerve (control side), perineural fibrosis was seen at grade 3 and 1 in one rat each, and was not seen in 5 (figure 3). The difference in the rate of perineural fibrosis seen was statistically significant in group 2 (P=0.026).

Figure 2: Group 2 left side (intervention side of the steroid-only group), histochemical staining with Masson's trichrome under x200 magnification. The arrow indicates fibrotic areas that have migrated into fat tissue consisting of fibroblasts and capillary vessels around nerve plexuses, consistent with grade 3 fibrosis.

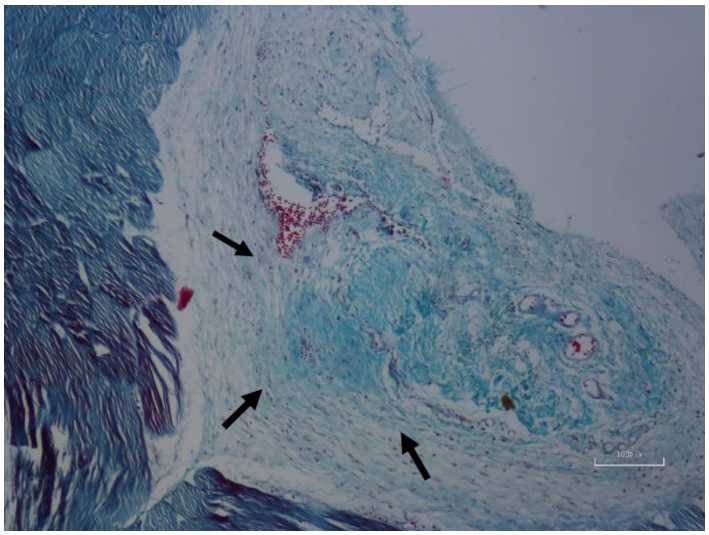
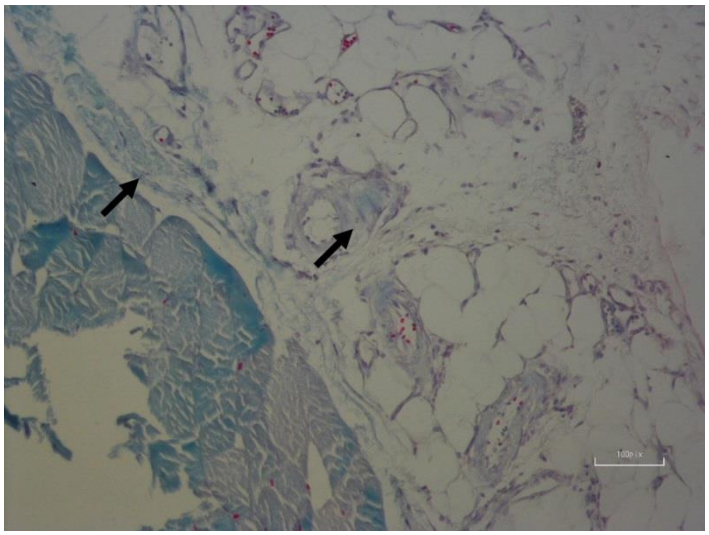


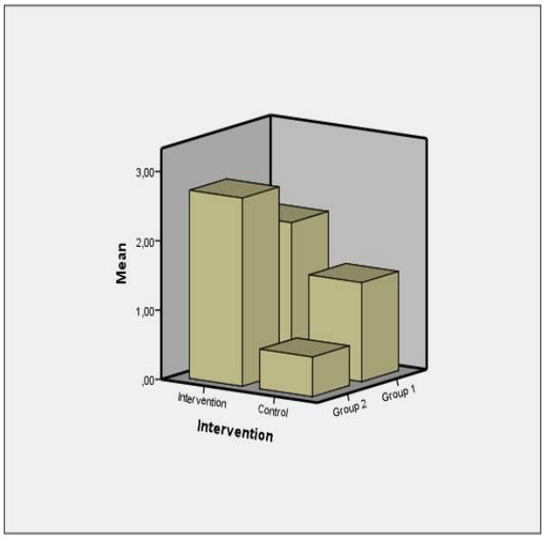
Figure 3: In Group 2 right side (control side of the steroid only group), histochemical staining of Masson's trichrome; the arrows indicate fine fibrotic band formation and small vessel proliferation detected at x200 magnification under microscope view, consistent with grade 0 fibrosis.



Mean perineural fibrosis was 2.14 (Min 0 - Max 3) on the intervention side and 1.43 (Min 0 - Max 3) on the control side in group 1 (Methylprednisolone acetate +bupivacaine hydrochloride group). Mean perineural fibrosis was 2.71 (Min 0 - Max 4) on the intervention side and 0.57 (Min 0 - Max 3) on the control side in group 2 (Methylprednisolone acetate group).

A 3-D graphic of the mean values on the intervention and control sides of both groups is shown in figure 4.

Figure 4: 3-D graphic of intervention and control mean values for both groups



Discussion

When all conservative treatment methods of spinal stenosis are unsuccessful, transforaminal-epidural steroid injection (TFESI) and surgery are possible options [6, 14]. TFESI results in less morbidity and is a much cheaper method than surgery. When the costs are compared, the costs of nerve root injection are approximately 600 GBP, while decompression of one or two levels is 3300-4000 GBP and decompression and posterior fixation or interbody fusion is about 5800-6400 GBP [6, 15]. Therefore, injections are the first choice of procedures in spinal stenosis cases that do not respond to more conservative methods.

It has been hypothesized that continuous compression of nerve roots in spinal stenosis damages micro vessels and leads to ischemia, edema, demyelination, and C-fiber activation [16]. When there is only neurological compression, there is known to be neurological deficit rather than pain. However, progression of the inflammatory process increases nerve root sensitivity, resulting in a continuous feeling of pain, even with mild stimuli, and this demonstrates the importance of inflammatory cytokines, especially in radiculopathy cases [6]. Thus, inflammation's important role in the formation of lower back and leg pain in spinal stenosis patients is a known fact. Steroids inhibit the expression and synthesis of pro-inflammatory substances and are used in treatment to suppress the production of arachidonic acid and metabolites [2, 17], reducing the inflammatory process.

There are various assumptions regarding the repetition times of steroid injections. The general practice is to repeat an injection when a patient partially benefits. If there is no benefit, the decision to repeat the injection or to intervene surgically should be shared and decided with the patient. It is possible that surgery may not resolve all symptoms. Furthermore, by creating a scar, each operation may cause the formation of re-stenosis in the spinal canal [9, 10]. In the presence of epidural fibrosis, whether it develops with the primary disease or not, tension in the dura and nerve roots after surgery or after injection creates chronic pain. In addition to making surgery more difficult, the presence of fibrosis reduces injection efficacy in all steroid applications by preventing a sufficient dose of the drug from

reaching the site [18, 19]. The procedure applied should not have a tendency to increase fibrosis.

Percutaneous adhesiolysis is a minimally invasive method used to reduce fibrosis [20]. Park et al. [7] compared percutaneous adhesiolysis with transforaminal epidural steroid injection for the treatment of chronic radicular pain caused by lumbar foraminal spinal stenosis and reported that both methods provided significant pain relief. With the removal of epidural space barriers themselves thought to contribute to the pain, percutaneous adhesiolysis allows the delivery of pain-relieving drugs [19].

In transforaminal steroid applications, the drug administered during injection may be only steroid or may be supplemented with local anesthetic substances added to the syringe. The full inflammation suppression of steroid may require a relatively long period, but the addition of a local anesthetic substance permits the patient to be mobilized after one hour and questioned whether the pain has diminished. Thus it can be re-confirmed that the injection location was correct. Patient satisfaction (a priority) increases.

Of the local anesthetics first used, 2% lidocaine hydrochloride was one of the most common. However, side-effects associated with sympathetic nerve or motor nerve blockage (nausea, hypotension, headache, and ataxia) were seen at 1-3%, and it is known that an excessive dose may cause systemic reactions like vasovagal reaction, convulsions and respiratory depression [21, 22]. For these reasons, there has been research into the use of other substances. Some studies recommended saline injection rather than lidocaine, in addition to steroid [2]. To provide superior pain relief for chronic radiculopathy back pain secondary to foraminal stenosis, Behnam et al. [23] added hypertonic saline to epidural steroid injections (ESI) but observed no significant difference between ESI with and without hypertonic saline. In addition, some studies have stated that hypertonic solutions may be more effective in high-grade or long-lasting nerve compression, and it has been reported that hypertonics may reduce pain due to the adhesiolysis mechanism in post lumbar surgery syndrome, seen in spinal stenosis [24, 25].

Hyaluronidase addition to injections has been attempted to reduce fibrosis. Yousef et al. [26] compared the treatment outcomes of 38 patients who received either caudal injections of bupivacaine+ hypertonic saline + methylprednisolone or same combination with 1,500 units of hyaluronidase added. In this small prospective study, only the patients who received hyaluronidase continued to experience benefits at sixth and twelfth months post-treatment. In another study, it was shown that the group receiving hyaluronidase with steroid had more relief than the group who received only steroid and/or bupivacaine [27]. There is moderate evidence supporting the use of hypertonic saline and limited evidence for the use of hyaluronidase to prevent adhesion and increase the benefit seen by the patient [7]. Ng et al. [28] reported no significant difference in outcome on three month follow-up examination between the use of steroid and local anesthetic combination and the use of only local anesthetic injection. In contrast, Sahu et al. [29] used a uniform pharmacological combination of long-acting local anesthetic (0.5% Bupivacaine) and steroid (Methylprednisolone) in patients and found a significant difference for up to six months.

It is thought that the long-term effect of local anesthetics may depend on the volume given during injection. In a study of fluid volume delivered to the epidural space during injection, injections of a greater volume were seen to provide greater pain relief. It was stated that the mechanism of this was not only that adhesiolysis was not made by the greater volume, but that by washing the epidural space, inflammatory cytokines were removed from the damaged nerves and blood flow was increased, even to ischemic nerve roots. This effect was reported to be related to the volume of the injection independent of the steroid dose, starting in short term with maintenance until the mid-term [30].

In this animal experimental study, the left leg was used as the intervention site, and the right leg as the control. This was intended to minimize individual differences in fibrosis development. In group 1, in which methylprednisolone acetate and bupivacaine hydrochloride were applied, perineural fibrosis was seen more on the intervention side than the control side, but the difference was not statistically significant. In group 2, where only methylprednisolone acetate was used, statistically significantly more perineural fibrosis was seen on the intervention side than the control side. The significant increase in fibrosis within only a three week period indicates that more fibrosis could be seen in the long term. The use of a lower volume in the group administered methylprednisolone only could have been responsible for the increase in fibrosis.

Limitations

The primary limitation of this study was the low number of animals included in the experiment population. Another limitation is that on subjects with dissection, the possibility of fibrosis caused by a drug given in injection was investigated. We think that we have overcome this handicap by exploring two of each subject's sciatica and applying medication to the left sciatica and not applying it to the right sciatica, thereby providing standardization. Thus, we evaluate only the fibrosis due to the medications given, not the open dissection and thus, overcome potential bias. Future research would be better with a third group as a combination of saline and steroid administered, to clearly understand whether the increased injection volume or the use of bupivacaine reduced the appearance of perineural fibrosis.

Conclusion

Steroid administration via injection is an effective treatment method for lumbar spine foraminal stenosis. Increasing the injection volume along with the addition of local anesthetic to the steroid may be helpful in adhesiolysis and may reduce the future development of fibrosis. Nevertheless, there is a need for further experimental studies of factors that decrease or increase fibrosis.

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Novel lateral support system increases stability and reduces angular error in total hip arthroplasty: A case control study

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Ethics Committee Approval
Informed consent was obtained from all individual participants included in the study. The study was approved by the Clinical Research Ethics Committee of Maltepe University (No: 2021 /900/42, Date: 5.01.2021).
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: Intraoperative changes in patient position or other changes that would disrupt the decisive position during preoperative preparation would directly have a negative impact on acetabular cup orientation in patients undergoing total hip arthroplasty. This study aimed to compare the standard support system and a novel lateral support system (Maltepe), which ensures stable lateral decubitus positioning during the perioperative period, in patients undergoing total hip arthroplasty with the posterolateral approach.

Methods: Patients operated in our department for osteoarthritis of the hip between 2012 - 2019 were included in this case-control study retrospectively. 46 and 41 patients were prepared for surgery in lateral decubitus position using the classical (Group 1) and novel (Group 2) lateral support systems, respectively. The groups were compared in terms of demographic characteristics, duration of preparation, anteversion and inclination, and Harris Hip scores.

Results: Mean patient age was 66.89 (7.53). There was no significant difference between the two groups in terms of age (P=0.546), gender (P=1.00), body mass index (P=0.302) and the operative side (P=0.724). Duration of preparation and absolute deviation values from 15 degrees and 45 degrees were significantly better in group 2 compared to group 1 (P<0.01). There was no significant difference between the Harris Hip Scores of two groups.

Conclusion: We demonstrated that the novel support system we developed provided more successful outcomes than the classical system in terms of acetabular cup orientation.

Keywords: Arthroplasty, Hip, Lateral decubitus, Surgical preparation time, Surgical positioning

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Introduction

Osteoarthritis (OA) has become a global health problem due to the increase in elderly population and increased prevalence of obesity, thereby leading to a gradually increasing number of arthroplasties relative to other orthopedic surgeries [1, 2]. Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are the two most common types of arthroplasty, although the prevalence of different arthroplasty procedures exhibit variations throughout the world [3]. Due to its unquestionable ability to restore function and relieve pain, THA has been included among the most successful procedures for end-stage hip arthritis [4]. Although THA is a highly successful surgical procedure, the frequency of joint instability remains as a challenge. Various surgical approaches to the hip joint have been described in attempts to solve this problem [5, 6]. In particular, the direct anterior approach (DAA) is reported to yield low rates of dislocation in the literature [7]. However, recent studies have shown that there is no significant difference in terms of dislocation between DAA and the posterolateral approach (PA), which was claimed to have the highest rate of dislocation, when performed by experienced teams [8]. This indicates that component positioning may in fact be a better determinant of dislocation as compared to surgical approach in THA [9]. In THA performed in lateral decubitus position, determining the femoral component position is relatively easier than determining the position of the acetabular component. Femoral component can be properly aligned according to femoral version and epicondylar axis [10]. However, bone and soft tissue landmarks used for acetabular cup orientation are based on the assumption that the pelvis is maintained in a firm and fixed lateral position during surgery. Therefore, intraoperative changes in patient position or other changes that would disrupt the position during preoperative preparation would directly have a negative impact on acetabular cup orientation [11].

Our hypotheses were as follows: (1) Novel lateral support system can shorten the time to start surgery, (2) since this system provides full stability over the perioperative time, the probability of angular error is reduced. In this study, it was aimed to compare the standard support system with the novel lateral support system (Maltepe), which ensures stable lateral decubitus positioning during the preoperative-intraoperative period in patients undergoing THA with the standard PA.

Materials and methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Clinical Research Ethics Committee of Maltepe University (date: 19/01/2021, no: 2021/900/14). Informed consent was obtained from all individual participants included in the study. According to descriptive statistics (effect size Cohen's d=0.788) in the study by Buğlak et al. [12] sample size of 36 for each group (72 in total) achieves 90% power at the two-sided 0.05 significance level. Sample size was calculated by using two-sample t-test power analysis via PASS 11. (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.).

The patients who underwent THA with the PA in the lateral decubitus position for primary OA of the hip between 2012 and 2019 were retrospectively evaluated. Patients between 55 and 75 years of age, who received surgical treatment with a Kellgren and Lawrence classification grade of 3–4, and attended follow-up examinations for at least 12 months were included in the study. Patients who were lost to follow-up, those who had a history of hip surgery or traumatic dislocation and those who needed revision surgery were excluded.

Eighty-seven patients who fulfilled the aforementioned criteria were included in the analyses. All patients were operated by two surgeons (M and K). While the operations were carried out with classical support from 2012 to the beginning of 2016, this novel system was started to be implemented after 2016 in order to reduce the time and the possibility of angular errors. All patients were prepared for surgery in the lateral decubitus position and PA was used in THA. The surgery was performed by these two surgeons in 46 patients (30 males, 16 females) (i.e., Group 1) using the classical lateral support system (Figure 1A), and by Surgeon K on 41 patients (27 males, 14 females) (i.e. Group 2) using the novel Maltepe support system.

Figure 1: Images of the support units used. A. Classical lateral support system. B. One side was supported with classical support system, while other side was supported by the Maltepe novel support system. C. Maltepe novel support system

In the hip joint surgery, the shape of the surgical lateral support unit (Maltepe support system) that allows the patient to be given a fixed lateral decubitus position by applying to the lower abdomen and the waist, and the appearance of patient application are given in Figure 1B and 1C. In fact, it is a simply designed pillow. Due to its design and stretching feature, it compresses the patient completely into the middle. This pillow consists of 2 pieces and is applied from the front and the back. Its main feature is that it has a stretching capacity like a sponge. Due to its flexibility, this pillow can be used regardless of the patient's height and body weight. The application of this unit is done directly after the patient is anesthetized and is suitable for positioning. First, the patient is turned to the lateral decubitus position deemed appropriate by the surgeon, and then the front pillow is applied to the patient's lower abdomen with the surface facing the patient. Then, the back pillow is applied to the patient's waist region with its surface facing the patient. The pillows applied to the patient from the front and the back are fixed to the side support apparatus of the operating table with their own supports after the final corrections are made in the patient position. Thus, the patient is positioned quickly and fixation is made easily in this position. Since the pillows are made of viscoelastic material, they can be shaped according to the shape of the body, on the other hand, they firmly fix the patient. Thus, owing to its large surface area, it does not cause any problems in the patient's body, but has the potential to reduce angular errors and complications due to full lateral lying and continuity.

Data of the patients in both groups were examined and age, gender, BMI, operative side and duration of preparation for surgery were recorded. Harris Hip Score was used to evaluate the clinical outcomes during postoperative follow-up examinations compared to the preoperative period. In addition, postoperative acetabular cup placement was checked by measuring anteversion and inclination from direct anterior-posterior and lateral radiographs of the pelvis, as described in the study by Seagrave et al [13].

Statistical analysis

All analyses were performed with SPSS v21 (SPSS Inc., Chicago, IL, USA). The Shapiro Wilk test was used for the normality check. Data were expressed with mean (standard deviation; SD) or median (minimum - maximum) values for continuous variables according to the normality of distribution, and with frequency (percentage) values for categorical variables. Normally distributed variables were analyzed with the independent samples t-test. Non-normally distributed variables were analyzed with the Mann–Whitney *U* test. Categorical variables were compared for distribution with Chi-square tests. $P<0.05$ was considered as the threshold for statistical significance.

Results

The study included 87 patients in total. Males comprised 65.22% and 65.85% of the patients in group 1 and 2, respectively. The mean patient age was 67.37 (6.27) years in Group 1, and 66.37 (8.79) years in Group 2. The mean BMI was 25.26 (4.60) and 26.27 (4.41) in Group 1 and Group 2, respectively. Operative side was the right side in 50% of the patients in Group 1 and 44% of the patients in Group 2 (Table 1).

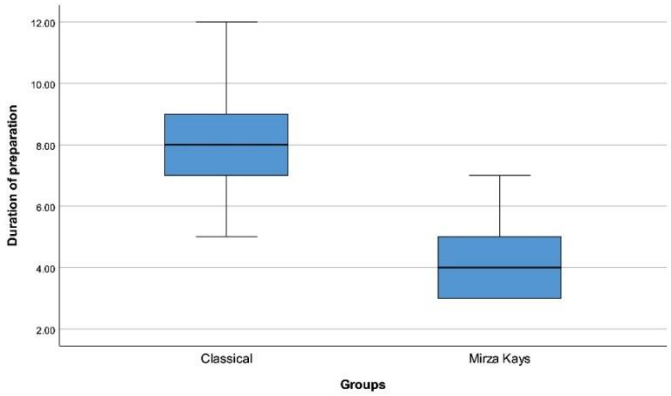
Table 1: Summary of the variables with regard to groups

	Groups		
	Classical (n=46)	Maltepe (n=41)	*P*-value
Age	67.37 (6.27)	66.37 (8.79)	0.546
Gender			
Female	16 (34.78%)	14 (34.15%)	1.000
Male	30 (65.22%)	27 (65.85%)	
Body mass index	25.26 (4.60)	26.27 (4.41)	0.302
Underweight	4 (8.70%)	2 (4.88%)	0.528
Normal	20 (43.48%)	13 (31.71%)	
Overweight	14 (30.43%)	17 (41.46%)	
Obese	8 (17.39%)	9 (21.95%)	
Side			
Right	23 (50.00%)	18 (43.90%)	0.724
Left	23 (50.00%)	23 (56.10%)	
Duration of preparation	8 (5 - 12)	4 (3 - 7)	<0.001
Underweight	9.5 (9 - 12)	3.5 (3 - 4)	0.060
Normal	8 (5 - 9)	4 (3 - 5)	<0.001
Overweight	7.5 (6 - 9)	4 (3 - 5)	<0.001
Obese	10.5 (9 - 12)	6 (5 - 7)	<0.001
Anteversion angle	20 (7 - 32)	16 (12 - 20)	0.029
< 15 degrees	13 (28.26%)	8 (19.51%)	0.247
15 degrees	3 (6.52%)	7 (17.07%)	
> 15 degrees	30 (65.22%)	26 (63.41%)	
Absolute deviation from 15 degrees	6 (0 - 17)	1 (0 - 5)	<0.001
Inclination angle	45.5 (19 - 70)	45 (30 - 54)	0.762
< 45 degrees	17 (36.96%)	12 (29.27%)	0.375
45 degrees	6 (13.04%)	10 (24.39%)	
> 45 degrees	23 (50.00%)	19 (46.34%)	
Absolute deviation from 45 degrees	11 (0 - 26)	2 (0 - 15)	<0.001
Harris hip score	67.5 (60 - 88)	70 (56 - 90)	0.534

Data are given as mean (standard deviation) or median (minimum - maximum) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables

The mean duration of preparation for surgery in the operating room was 8 minutes in Group 1 and 4 minutes in Group 2, the difference was found to be statistically significant ($P<0.001$, Table 1, Figure 2). Considering the duration of preparation for surgery in the operating room according to BMI, there was a statistically significant difference between the two groups in normal-weight, overweight and obese patients ($P<0.001$) but no significant difference in underweight patients ($P>0.05$, Table 1). Dislocation was detected in 4 cases in group 1 and in 1 case in group 2 ($P=0.201$).

Figure 2: Duration of preparation with regard to groups



Comparison of the two groups in terms of acetabular cup orientation showed no statistically significant difference between the groups in terms of anteversion and inclination ($p>0.05$, Table 1, Figure 3 and 4). On the other hand, there was a statistically significant difference in terms of absolute deviation from 15 degrees of anteversion and absolute deviation from 45 degrees of inclination of the acetabular cup ($P<0.001$, Table 1).

Comparison of the two groups in terms of Harris Hip Scores did not show statistically significant difference at postoperative month 12 (Group 1: 67.5 points vs. Group 2: 70 points; $P=0.534$, Table 1).

Figure 3: Absolute deviation from ideal anteversion angle with regard to groups

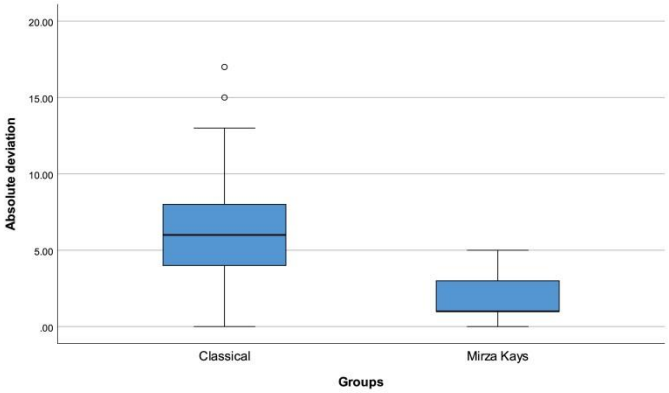
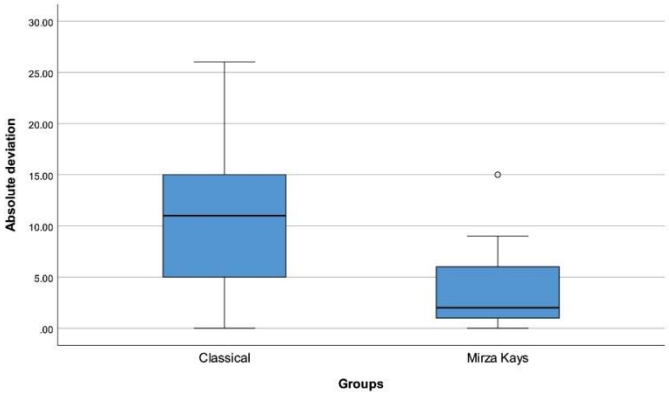


Figure 4: Absolute deviation from ideal inclination angle with regard to groups



Discussion

The most important finding of this study is that the novel (Maltepe) lateral support system significantly shortens the duration of preparation for surgery. In addition, it was determined that the better support provided by this system reduced the rate of angular error caused by the surgeon in acetabular cup orientation in patients undergoing THA in the lateral decubitus position via PA.

In THA, a malpositioned acetabular component constitutes a modifiable risk factor for component impingement, wear of the bearing surface and postoperative instability [9, 14-16]. Implant stability and wear can be optimized by placing the cup within "safe zone" parameters [9, 14-17]. According to a retrospective case series by Lewinnek et al. [9], the safe zone is defined as 15 +/- 10° anteversion and 40 +/- 10° inclination. However, the incidence of malpositioning remains high. The known risk factors for malpositioning consist of obesity, low experience of the surgeon and the use of minimally invasive approaches [18]. In addition, it was reported that intraoperative changes in pelvic position could lead to malpositioning of the acetabular cup [11]. In this study, we showed that more successful outcomes could be obtained by using our novel lateral support system that rapidly provides a more stable lateral decubitus position and appears to enable better acetabular cup positioning.

It was reported that high anteversion could lead to a decreased risk of dislocation [19]. In this study, we could achieve optimal anteversion and inclination angles in most of our patients with the novel lateral support system we developed.

In our study, this difference was not statistically significant, although the frequency of dislocation was lower in the cases in which the novel system was applied. This may be due to the small number of patients. We thought that with the implementation of this system, better support was provided and this reduced the anteversion error. Consistent with this idea, Fujishiro et al. reported that combined anteversion greater than normal limits after THA increased the frequency of anterior dislocation, while a combined anteversion less than normal limits increased the frequency of posterior dislocation [20]. In addition, it has been reported in various studies that dislocation develops between 1% and 4% after THA, and that the developing dislocation is due to the inability to provide anteversion within optimal limits [20-22].

To the best of our knowledge, there are no studies in the literature elaborating proper patient positioning for surgery during THA performed with the PA. Existing studies generally focus on anesthesia and operational time, and report highly varying results [23]. In this study, duration of patient positioning was compared using two different lateral support systems, which have not been previously discussed in the literature, and it was found that the system we developed provided a significantly shorter duration of patient preparation. In this respect, our study is the first in the literature.

This study had some limitations. First of all, the study was retrospective. Second, follow-up duration was short, although treatment groups had comparable characteristics. Third, factors (age, gender, BMI etc.) that could affect treatment results could not be evaluated in depth due to the small sample size.

Conclusion

Acetabular cup orientation is directly associated with dislocation in THA performed with the PA, wherein proper patient preparation in lateral decubitus position is important for achieving successful outcomes. Here, we showed that more successful THA outcomes could be obtained with the use of the novel lateral support system compared to the classical support system, especially with regard to its positive effects on acetabular cup orientation.

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The effects of the functional levels of children with cerebral palsy on the quality of life of caregivers

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Ethics Committee Approval
The ethics committee of the Istanbul Medeniyet University Goztepe Training and Research Hospital approved the study (Approval date and number: 09.08.2021/0396).
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: Psychological status and quality of life of caregivers with children with cerebral palsy are lower than the population. The functional status of the child is one of the factors affecting the caregiver's quality of life. However, the relationship between gross motor and hand functions, communication, oromotor skills, oropharyngeal functions and the caregiver's quality of life remains unclear. The aim of the study is to examine the effects of the functional levels of children with cerebral palsy on the quality of life of their caregivers.

Methods: Two hundred and seventeen children with cerebral palsy and their caregivers were included in this cross-sectional study. Inclusion criteria were; (i) Children aged 0-18, diagnosed with cerebral palsy (CP), followed in the pediatric rehabilitation outpatient clinic of the university, (ii) individuals who care for children with CP and volunteer to participate in the study, (iii) individuals who have a literacy level of understanding the purpose of the study and the forms to be filled in. Children's demographic information (age, gender), cerebral palsy types were recorded and detailed functional evaluation was made. The identity of the caregiver was recorded and quality of life was evaluated with the Short Form-12 (SF-12). Functional classification of the children were evaluated with Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Communication Function Classification System (CFCS) and Eating and Drinking Ability Classification System (EDACS). The relationship between the child's functional level in each scale and the caregiver's SF-12 score was investigated.

Results: Of the 117 children with a mean age of 7.62 (4.08), 52.5% were male (n=114) and 47.5% (n=103) female. According to CP types, 89.3% were spastic (n=191) (78.1% of them bilateral, 21.9% unilateral), 5.6% ataxic (n=12) and 5.1% dyskinetic (n=11). Median SF-12 PCS and MCS were 51.69 (25.76-62.92) and 55.36 (26.64-60.69), respectively. When the SF-12 scores were evaluated according to the functional levels of the children, both SF-12 PCS and SF-12 MCS scores differed significantly according to the GMFCS, MACS, CFCS and EDACS levels ($P<0.01$).

Conclusion: The caregiver's quality of life is related to the gross motor and hand functions, oropharyngeal functions, communication and oromotor skills of the children with cerebral palsy. Therefore, comprehensive functional evaluation of children with cerebral palsy is important.

Keywords: Cerebral palsy, Caregiver, Functional status, Quality of life

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Introduction

Cerebral Palsy (CP) refers to a group of permanent disorders of movement and posture that occurs in the developing fetus or infant brain, and causes activity limitation. Neurological and musculoskeletal disorders may be accompanied by sensorial, perceptual and cognitive problems, communication and behavioral problems, and epilepsy [1].

Because of all these primary and secondary problems, children with CP need help at various levels in their daily life activities and social interactions. Different needs of care arise, especially depending on the severity of the limitations caused by CP. Personal care includes services such as washing, feeding, going to the toilet, dressing, while social care includes services such as shopping and household chores, money management, financial assistance and living together [2]. The mentioned care services are usually provided by family members, and they do not only increase the functional, psychosocial and personal development of the child, but also bring many negativities and difficulties for the caregiver [3].

In the literature, it has been reported that the psychological status and quality of life of caregivers with children with cerebral palsy are lower than the population [3-5]. However, the results are contradictory in studies investigating the relationship between the child's functional status and the caregiver's quality of life [4,6-9]. Also most of the studies have investigated the functional status of the child only with GMFCS [3,5,6].

International Classification of Functioning, Disability and Health (ICF) of the World Health Organization (WHO) created a new system for health and disease classification which describes a universal way to define health conditions and suggests a relationship between these conditions and contextual factors. It represents a biopsychosocial approach to health, functioning and disability. ICF model has been used to guide clinical thinking in patients with CP [10]. Thus, functional scales are being used currently for evaluation of various functions in CP such as communication, gross motor, hand function, and oral motor/oropharyngeal functions.

To the best of our knowledge there is no study investigating the relationship between gross motor, hand function, communication, oromotor/oropharyngeal functions specified in the ICF core set and the caregiver quality of life.

Therefore in this study, it is aimed to examine the quality of life levels of caregivers whose children have cerebral palsy, depending on the impairments in the child's functional status (gross motor, hand function, communication, oromotor/oropharyngeal functions).

Materials and methods

Study design

The design of this study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) guidelines as an observational cross-sectional study. The medical ethics committee of the Istanbul Medeniyet University Goztepe Training and Research Hospital approved the study (Approval date and number: 09.08.2021/0396) in accordance with the Declaration of Helsinki and written informed consent was obtained from all patients.

Sample selection

Inclusion criteria were; (i) Children aged 0-18, diagnosed with CP, followed in the pediatric rehabilitation outpatient clinic of the university, (ii) individuals who care for children with CP and volunteer to participate in the study, (iii) individuals who have a literacy level to understand the purpose of the study and to fill in the forms. Patients were excluded if they did not have a definitive diagnosis of cerebral palsy.

217 children with cerebral palsy and their caregivers who met the inclusion criteria were included in the study.

Data collection

Demographic data and functional status of the children were evaluated by an experienced physical medicine and rehabilitation specialist.

The protocol recommended by the SCPE group was used for SP classification. SCPE grouped children with CP into four categories: spastic (bilateral, unilateral), dyskinetic (dystonic, chorea-athetoid), ataxic, and unclassifiable [11].

Functional classification of the children were evaluated with Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Communication Function Classification System (CFCS) and Eating and Drinking Ability Classification System (EDACS) according to the ICF model. [10]. Short Form-12 was used to evaluate the quality of life of the caregivers participating in the study.

1. **Gross Motor Function Classification System (GMFCS)**

Gross motor function levels of people with CP were determined using GMFCS. GMFCS based on self-initiated movements with an emphasis on sitting, relocation and mobility. The main criterion in five-level classification system is having significant differences between the levels in daily life [12]. The Turkish validity and reliability of the scale was established [13].

2. **Manual Ability Classification System (MACS)**

Manual Ability Classification System was developed to classify the ability to handle objects in children. It was developed as a 5-point likert scale, similar to GMFCS. It is a scale that evaluates the ability of the children to take necessary objects and use their hands in activities of daily living, such as eating and dressing. It does not distinguish different capacities between hands [14]. The Turkish validity and reliability of the scale was established [15].

3. **Communication Function Classification System (CFCS)**

Communication Function Classification System was developed in a 5-point Likert type to determine daily communication performance in individuals with CP. CFCS classifies individuals according to the effectiveness of their daily communication performance. All elements of communication performance are considered when defining the CFCS level. The child's communication performance items include ability to speak, using facial expressions, having verbal behaviors, making eye contact, using facial expressions as well as using alternative communications. In this scale, the changes in the levels are determined according to the communication flow between the source and the receiver [16].

4. Eating and Drinking Ability Classification System (EDACS)

Eating and Drinking Ability Classification System (EDACS) is developed to classify how individuals with CP eat and drink in daily life. The focus is on functional activities such as sucking, biting, chewing, swallowing, and holding food or liquid in the mouth. The distinction between different levels of EDACS is based on functional skills, the need for adaptation in the texture of the food or drink, the used technique, and some other environmental characteristics. It classifies overall performance, including both the motor and sensory components of eating and drinking [17]. The Turkish validity and reliability of the scale was established [18].

Quality of life assessment

Short Form-12 (SF-12) was used to determine quality of life. SF-12 is a scale that was developed in 1994 to evaluate the quality of life for the last four weeks without focusing on a specific age and disease group. It consists of 12 questions, all selected from SF-36 Health Questionnaire. SF-12 consists of physical functioning, role physical, pain, general health, role emotional, mental health, social functioning and vitality sub-components. The Physical Component Summary Score (PCS), which is a single score showing the physical domain of quality of life, was calculated from the sub-components of physical functionality, role physical, general health, and pain. The Mental Component Summary Score (MCS) was calculated from the role emotional, mental health, vitality, and social functioning sub-components. The score that can be obtained from each sub-component and summary score ranges from 0-100, and a high score indicates a high quality of life. A score of 50 or less in PCS-12 is recommended as the cut-off point to identify a physical problem, whereas a score of 42 or less on the MCS-12 may indicate 'clinical depression' [19]. The Turkish validity and reliability of the scale was established [20].

Statistical analysis

The descriptive statistics of the categorical variables in the study are given as numbers and percentages, and the descriptive statistics of the numerical variables are given as median, minimum and maximum. The conformity of the variables to the normal distribution was examined using the Shapiro Wilk test. Kruskal Wallis Analysis of Variance test was used for the median comparisons of the groups consisting of more than two categories. Bonferroni Corrected Mann Whitney U test was used for the analysis of the groups that caused the difference. The incidence of cerebral palsy in Turkey has been determined as 4.4 per 1000 live births. According to this rate, the sample size was determined as 60 with 5% margin of error at 95% confidence level. Statistical significance level was taken as 0.05 and SPSS 22.0 package program was used in the analysis.

Results

In table 1, descriptive statistics for categorical and numerical variables are given as numbers and percentages. The functional status of children is shown in table 2 as median (min-max) and number of children in each level (n-%).

Table 1: Characteristics of the children and caregiver

	n (%), median (min-max)
Gender, n(%)	
Male	114 (52.5%)
Female	103 (47.5%)
Age, median (min-max)	6 (2-16)
Cerebral palsy subtype, n(%)	
Spastic	191 (89.3%)
Spastic bilateral	150 (78.1%)
Spastic unilateral	42 (21.9%)
Right	26 (61.9%)
Left	16 (38.1%)
Dyskinetic	11 (5.1%)
Ataxic	12 (5.6%)
Caregiver, n(%)	
Mother	201 (92.6%)
Father	15 (6.9%)
Grandmother	1 (0.4%)
SF-12 PCS, median (min-max)	51.69 (25.76-62.92)
SF-12 MCS, median (min-max)	55.36 (26.64-60.69)

Table 2: Functional status of the children

	n (%), median (min-max)
GMFCS, median (min-max)	2 (1-5)
Level 1	55 (25.3%)
Level 2	28 (12.9%)
Level 3	50 (23.0%)
Level 4	42 (19.4%)
Level 5	42 (19.4%)
MACS, median (min-max)	2 (1-5)
Level 1	57 (26.3%)
Level 2	52 (24.0%)
Level 3	45 (20.7%)
Level 4	31 (14.3%)
Level 5	32 (14.7%)
CFCS, median (min-max)	1 (1-5)
Level 1	67 (30.9%)
Level 2	46 (21.2%)
Level 3	32 (14.7%)
Level 4	40 (18.4%)
Level 5	32 (14.7%)
EDACS, median (min-max)	1 (1-5)
Level 1	59 (27.2%)
Level 2	50 (23.0%)
Level 3	31 (14.3%)
Level 4	38 (17.5%)
Level 5	39 (18.0%)

GMFCS: Gross Motor Functional Classification System, MACS: Manual Ability Classification System, CFCS: Communication Function Classification System, EDACS: Eating and Drinking Ability Classification System

When the quality of life of the caregivers was examined according to GMFCS levels of their children, it was found that the quality of life of caregivers differed according to GMFCS level of the children, and SF-12 score decreased with the increase in GMFCS level of the children with CP (P<0.01) (Table 3). According to GMFCS between 1st and 2nd, 1st and 3rd, 1st and 4th, and 1st and 5th levels of caregivers of children with CP, both SF-12 PCS and SF-12 MCS of the caregivers were differed (P<0.01), while other levels were similar (P>0.05) in the pairwise comparison.

Table 3: Evaluation of caregiver's quality of life according to GMFCS levels

GMFCS	SF-12 PCS Mean (SD)	SF-12 PCS Min-Max	Chi Square †	*P*-value	SF-12 MCS Mean (SD)	SF-12 MCS Min-Max	Chi Square †	*P*-value
Level I	52.98 (5.90)	25.68-62.92	32.87	<0.001	53.32 (8.64)	26.41-60.69	47.14	<0.001
Level II	48.30 (6.51)	24.55-55.91			52.12 (6.93)	32.72-64.44		
Level III	49.11 (5.91)	37.40-59.49			48.89 (7.64)	17.31-59.74		
Level IV	45.86 (8.04)	24.93-61.93			46.01 (9.74)	16.54-57.96		
Level V	46.43 (9.06)	25.76-59.53			45.06 (7.02)	26.64-57.82		

† Kruskal Wallis Analysis of Variance, GMFCS: Gross Motor Functional Classification System, SF-12 PCS: Short Form-12 physical component score, SF-12 MCS: Short Form-12 mental component score

When the quality of life of the caregivers was examined according to MACS levels of their children, it was found that the quality of life of the caregivers differed according to MACS level of the children, and SF-12 score decreased with the increase in MACS level of the children with CP (P<0.01) (Table 4). According to MACS levels between 1st and 3rd, 1st and 4th, and 1st and 5th levels of caregivers of children with CP, SF-12

PCS of the caregivers were differed (P<0.01), and MACS levels between 1st and 2nd, 1st and 4th, 1st and 5th, and 3rd and 5th levels of caregivers of children with CP, SF-12 MCS of the caregivers were differed (P<0.01), while other levels were similar (P>0.05) in the pairwise comparison.

Table 4: Evaluation of caregiver's quality of life according to MACS levels

MACS	SF-12 PCS Mean (SD)	Min-Max	Chi Square †	*P*-value	SF-12 MCS Mean (SD)	Min-Max	Chi Square †	*P*-value
Level I	52.62 (5.07)	33.03-62.92	24.99	<0.001	52.68 (9.33)	17.31-60.69	34.97	<0.001
Level II	49.31 (7.37)	24.93-59.53			48.66 (8.58)	23.83-64.44		
Level III	46.43 (7.50)	24.55-56.81			50.13 (6.61)	32.43-58.09		
Level IV	47.27 (7.40)	28.50-61.93			46.32 (8.38)	28.10-56.93		
Level V	46.24 (9.18)	25.76-59.37			44.89 (8.37)	16.54-57.82		

† Kruskal Wallis Analysis of Variance, MACS: Manual Ability Classification System, SF-12 PCS: Short Form-12 physical component score, SF-12 MCS: Short Form-12 mental component score

When the quality of life of the caregivers was examined according to CFCS levels of their children, it was found that the quality of life of the caregivers differed according to CFCS level of the children, and SF-12 score decreased with the increase in CFCS level of the children with CP (P<0.01) (Table 5). According to CFCS levels between 1st and 4th, and 1st and 5th levels of caregivers of children with CP, SF-12 PCS of the caregivers were differed (P<0.01), and CFCS levels between 1st and 2nd, 1st and 3rd, 1st and 4th, and 1st and 5th levels of caregivers of children with CP, SF-12 MCS of the caregivers were differed (P<0.01), while other levels were similar (P>0.05) in the pairwise comparison.

Table 5: Evaluation of caregiver's quality of life according to CFCS levels

CFCS	SF-12 PCS Mean (SD)	Min-Max	Chi Square †	*P*-value	SF-12 MCS Mean (SD)	Min-Max	Chi Square †	*P*-value
Level I	52.08 (5.34)	33.03-62.92	18.78	<0.001	53.15 (8.78)	17.31-64.44	45.02	<0.001
Level II	48.38 (7.13)	24.93-59.10			49.02 (8.58)	23.83-57.96		
Level III	48.29 (6.61)	27.82-56.81			49.31 (5.04)	37.16-57.88		
Level IV	46.49 (8.70)	25.68-59.49			45.93 (9.28)	16.54-56.93		
Level V	46.19 (9.30)	24.55-61.93			44.69 (7.50)	26.64-57.82		

† Kruskal Wallis Analysis of Variance, CFCS: Communication, Function Classification System, SF-12 PCS: Short Form-12 physical component score, SF-12 MCS: Short Form-12 mental component score

When the quality of life of the caregivers was examined according to EDACS levels of their children, it was found that the quality of life of the caregivers differed according to EDACS level of the children, and the SF-12 score decreased with the increase in EDACS level of the children with CP (P<0.01) (Table 6). According to EDACS levels between 1st and 4th, and 1st and 5th levels of caregivers of children with CP, SF-12 PCS of the caregivers were differed (P<0.01), and EDACS levels between 1st and 2nd, 1st and 3rd, 1st and 4th, and 1st and 5th levels of caregivers of children with CP, SF-12 MCS of the caregivers were differed (P<0.01), while other levels were similar (P>0.05) in the pairwise comparison.

Table 6: Evaluation of caregiver's quality of life according to EDACS levels

EDACS	SF-12 PCS Mean (SD)	Min-Max	Chi Square †	*P*-value	SF-12 MCS Mean (SD)	Min-Max	Chi Square †	*P*-value
Level I	52.21 (5.27)	33.03-62.92	17.94	<0.001	53.61 (8.66)	17.31-64.44	44.96	<0.001
Level II	49.04 (5.86)	37.40-59.49			49.00 (8.10)	16.54-57.88		
Level III	47.34 (9.43)	24.93-59.53			47.82 (9.07)	23.83-58.79		
Level IV	47.33 (8.26)	24.55-57.50			48.01(7.65)	27.72-56.93		
Level V	46.11 (8.46)	25.76-61.93			44.66 (7.52)	26.64-57.82		

† Kruskal Wallis Analysis of Variance, EDACS: Eating and Drinking Ability Classification System, SF-12 PCS: Short Form-12 physical component score, SF-12 MCS: Short Form-12 mental component score

Discussion

Cerebral palsy is the most common cause of motor disability in childhood. Disability has a significant impact not only on the child with disability, but also on the family responsible for the child. The quality of life of individuals with disabilities and their families has become an important area of research [21].

In this study, it was investigated whether the quality of life of the caregivers of children with CP changes according to the functional status of the children.

Having a child with disability, regardless of the type of disability, brings in some special difficulties. These difficulties are psychological and educational status, financial situation, lifestyle, family environment and relations with the social environment, besides the child's disability. Caring for a child with cerebral palsy and meeting his needs throughout his development affect all members in the family [22]. The mother takes a more active role in solving all these difficulties and puts more effort. The relationship of a mother with her disabled child is a lifelong relationship starting at birth. The majority of the participants in this study were mothers, in accordance. Mothers who spend most of their time and energy for their child with cerebral palsy cannot spare enough time for their spouses, other children and social life.

It has been reported that caregivers of children with cerebral palsy face more mental and physical difficulties than those who care for healthy children [23, 24]. Decreased participation in work and social life, decreased physical and mental health together with economic difficulties negatively affect the quality of life [6-8, 25].

Xia et al. evaluated the quality of life in the parents of children with different disabilities in their study and reported the mean SF-12 PCS score of 51.73 (6.72) and SF-12 MCS score of 29.32 (3.44) for mothers of children with cerebral palsy [26]. Yilmaz et al. [25] also evaluated the quality of life in the parents of children with cerebral palsy in their study and reported the mean SF-36 PCS score of 51.83 (23.10) and MCS score of 51.20 (24.49) for mothers of children with cerebral palsy. The results of Yilmaz et al. are consistent with this study. However, MCS scores of Xia et al. [26] were well below these values. They explained this result with China's one-child policy, which had been implemented for 30 years and parents had relatively poor capability of adapting themselves to the adversity.

Although it is a common result of studies that the quality of life of caregivers of children with cerebral palsy is decreased, there are conflicting results regarding the determinants of quality of life. Dilek et al. [6], Ones et al. [8] and

Tuna et al. [9] reported no relationship between the child's functional status and the mother's quality of life. Tuna et al. interpreted this result as once a catastrophic event occurs, its severity seems to have minor importance [9]. However, the number of participants in all three studies was limited and only GMFCS was used in functional assessment. Denghan et al. [5] investigated the relationship between quality of life and GMFCS in mothers of 494 children with cerebral palsy and reported a significant relationship between physical component summary score of SF-36 and motor function level. Eker et al. [27] also reported the relationship between quality of life of mother and GMFCS of children with CP in their study. Yun investigated the relationship between GMFM-88 and SF-36 in caregivers of 106 children with cerebral palsy and showed a significant relationship between physical functioning, physical role functioning, mental health, and bodily pain domains of SF-36 and GMFM-88 total score [7]. In this study, a significant relation was found between GMFCS and SF-12 PCS and MCS scores, concordant with studies of Denghan, Eker, and Yun.

Jamali et al. [28] reported that age, gender, GMFCS, MACS, EDACS, CFCS could not predict difficulty in caregiving, but could be correlated with them. Supporting our study, Yığman et al. [29] reported a relationship between GMFCS, MACS, and CFCS and caregiver burden. Otherwise there is no study in the literature investigating the relationship between MACS, EDACS and CFCS and the caregiver's quality of life. In this study, gross motor, hand function, communication and oromotor/oropharyngeal functions were all associated with caregiver's quality of life. The strong correlation between GMFCS, MACS, EDACS and CFCS in the literature supports our findings [30, 31].

Limitations

One of the main limitations of this study is being a single-center study. Moreover, the majority of the caregiver population consisted of mothers, and the limited participation of fathers may have affected the results of the study. Different results can be obtained in a study with a more homogeneous parent group. However, this is the first study in which the functional evaluations in the ICF core set are comprehensively discussed in a large sample. In this study, only functional evaluation was considered and sociodemographic (employment status, economic status, household data, etc.) evaluation was not made. In further studies, investigating the relationship between eating-drinking and communication functions and sociodemographic characteristics will contribute to the literature.

Conclusion

Evaluation of the child with GMFCS, MACS, EDACS and CFCS included in the ICF core set is important for the determination of child's comprehensive functional status. Trying to improve motor functions solitary is not a sufficient goal for functionality. Hand functions, eating-drinking and communication functions should not be forgotten in rehabilitation goals.

This study showed that comprehensive functional assessment of the child with cerebral palsy is important not only for the child but also for the caregiver's quality of life.

Evaluating and providing support for the caregivers of children with impaired motor functions, communication, eating and drinking functions can provide important gains such as enabling parents, who have a crucial role in the rehabilitation of the child, to take care of their children more effectively.

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The evolution of parenteral nutrition over the past 40 years: A bibliometric overview

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Abstract

Background/Aim: Malnutrition remains a significant problem in cancer patients, intensive care patients, and patients undergoing major surgery. Although the importance of nutritional support has been proven, the preferred route for nutrient delivery is still controversial. In recent years, the use of parenteral nutrition (PN) has been increasing, and the early use of PN has become widespread once again. However, there is still no bibliometric study in the literature about PN, which has increased the number of global studies in recent years. This study aimed to analyze the scientific articles on PN published between 1980 and 2020 with statistical methods and to evaluate the subject holistically.

Methods: Articles on PN published between 1980 and 2020 were analyzed using statistical and bibliometric methods. Spearman correlation coefficient was used for correlation studies. Nonlinear (cubic model) regression analysis was used to estimate the number of publications in the coming years. Keyword network visualization maps were used to identify trending topics and collaborations.

Results: A total of 9424 publications were found. Of these publications, 5461 (57.9%) were articles. The top 3 contributing countries to the literature were the USA (1901, 34.8%), UK (542, 10%), and France (437, 8%). The top 3 most active institutions were Harvard University (99, 1.8%), University of Toronto (98, 1.8%), and University of California, Los Angeles (84, 1.5%). The top 3 journals with the highest number of publications were Journal of Parenteral and Enteral Nutrition (894, 16.4%), Clinical Nutrition (337, 6.2%), and Nutrition (187, 3.4%). According to the average number of citations per article, the most influential journals were Annals of Surgery (88.2, 1.5%), Gastroenterology (85.8), and Gut (81.2), respectively.

Conclusion: In this comprehensive study on PN, a summary of 5461 articles were presented. The trend topics in PN research are determined and it can be said that most of them related with intensive care units and cancer patients. This article may be a valuable resource for clinicians and scientists on PN global outcomes.

Keywords: Parenteral nutrition, Nutrition support, Bibliometric analysis, Trends

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This article does not contain any studies with human participants or animals performed by any of the authors.

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Introduction

Malnutrition continues to be an important problem, especially in cancer patients, intensive care patients, and patients undergoing major surgery. Malnourished patients are more likely to suffer from increased morbidity and mortality, hospital stay-related infections, and wound-related complications [1]. Lack of malnutrition therapy is associated with a five-fold increase in mortality in malnourished patients compared to well-nourished patients (11.7% vs. 2.4%) [1, 2]. Identifying malnutritional surgical patients and providing appropriate nutritional support has long been an important issue in surgical studies [1]. Malnutrition can adversely affect the functioning of many organ systems, such as the gastrointestinal tract, kidneys, heart, and lungs. Parallel to the weakness of muscle strength and immune function in malnourished patients, the possibility of infection may increase, wound healing may deteriorate, and postoperative recovery time may be prolonged. All these factors can lead to longer hospital stays and increased healthcare costs [1-4].

Nutritional support can be given safely with oral, enteral, or parenteral nutrition (PN), which provides fluid, calories, carbohydrates, and essential nutrients [5]. PN is a medical nutrition therapy provided by intravenous administration of nutrients such as amino acids, glucose, lipids, electrolytes, vitamins, and trace elements [3, 4]. PN has been in use for over 50 years and is an essential and often life-saving therapy to provide nutritional support to patients who cannot tolerate adequate enteral nutrition. [3-5]. PN is the intravenous administration of necessary nutrients if the nutrients can be partially or not wholly taken enterally. It significantly reduces morbidity and mortality when given to patients in need, especially in major surgical procedures, severe burns, severe head trauma, severe malnutrition, and sepsis. However, PN is not without risk. Although the importance of nutritional support has been proven, the preferred route for nutrient delivery is still controversial. Both diets have advantages and disadvantages. PN has been associated with more infectious complications from meta-analysis studies [6, 7], but calorie targets are more easily achieved using this method. Alternatively, enteral feeding (EN) preserves gastrointestinal function as it is a more physiological route but also is associated with higher stomach and intestinal intolerance rates such as vomiting, reflux, aspiration, and even ischemic bowel syndrome [6].

Due to the lack of well-designed, sufficiently powerful randomized control studies on the efficacy of PN in hospital settings, the current use of PN is based mainly on international guidelines from professional communities [3, 4, 8].

Studies based on statistical and bibliometric analyses have been carried out on many key medical subjects in synchronization with the increasing number of publications in the literature, especially in recent years [9-13]. Bibliometrics is the analysis of scientific outputs in the literature using various statistical methods [9]. Bibliometric studies revealed using comprehensive statistical methods also offer researchers ideas about new studies that they can design by showing past and current trends [12, 13]. Researchers who read bibliometric studies created by analyzing the findings obtained as a result of many scientific studies carried out by different researchers on a subject can dominate the literature in a short time [10, 11]. In addition, international cooperation analyzes in bibliometric studies can also show the general research trend of a subject in the world [9-13]. PN use has shown a steady increase in recent years, and the early use of PN has become widespread once again [6, 14]. Despite the fact that the number of global studies on PN has expanded in recent years, no bibliometric study has been published. The goal of this study was to use bibliometric and statistical tools to assess scientific articles on PN published between 1980 and 2020. As a result of the analyses, it was aimed to identify the most influential studies, journals, authors, institutions, and countries on PN, reveal cooperation between countries, reveal past and current trend issues, and summarize the PN issue holistically.

Materials and methods

Web of Science (WoS) database (by Clarivate Analytics) was used for literature review. “Parenteral nutrition”, “parenteral feeding”, “parenteral nutrition” were used as search keywords in WoS. The publication search was done only in the "title" section of the studies. All articles with *parenteral nutrition*, *parenteral feeding*, and *parenteral nutritional* in the title were obtained by this search method and downloaded from the WoS database. The dates of the search process were determined as 1980-2020 (access date: 01.09.2021). Reproducibility codes for researchers to access similar documents (search findings may vary depending on different access dates): (title: ("parenteral nutrition") or title: ("parenteral feeding") or title: ("parenteral nutritional") Timespan: 1980-2020. Indexes: SCI-Expanded, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI). VOSviewer (Version 1.6.17, Leiden University's Center for Science and Technology Studies) package program was used for bibliometric network visualizations [15]. The website (https://app.datawrapper.de) was used for world map drawing.

Statistical analysis

Statistical analyzes were performed with the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normal distribution of data was tested with the Kolmogorov-Smirnov test. Spearman's correlation coefficient was used in accordance with the data distribution for the analysis of the correlations between the number of articles produced by the world countries and some economic development indicators of the world countries ((Gross Domestic Product (GDP), Gross Domestic Product per capita (GDP per capita), data obtained from the world bank, [16]) to determine whether there is an effect of economic power on the productivity of publications on PN. Non-linear regression analysis (cubic model) was used to estimate the number of publications in the coming years. R square (R^2) value was used to evaluate the model's success in the regression analysis. The limit of statistically significant difference was accepted as $P<0.05$.

Results

As a result of the literature review, 9424 publications about PN published between 1980 and 2020 were found in the Web of Science database. The distribution of these publications is Article (5461, 57.9%), Meeting Abstract (2299, 24.3%), Letter

(518, 5.4%), Review (468, 4.9%), Proceedings Paper (366, 3.8%) and 312 (3.7%) of the rest were in other publication types (Editorial Material, Note, Book Chapter, Correction, News Item, Book Review, Correction Addition, Early Access, Discussion, Reprint, Book, Retracted Publication, Biographical Item and Software Review). Bibliometric analyzes were carried out with 5461 articles from a total of 9424 publications. 89.8% (4908) of these articles were English, 3.9% (214) German, 2.4% (134) Spanish, 2.3% (130) French, 0.7% (41) Russian, and the rest were published in other languages (Portuguese (9), Turkish (8), Italian (5), Polish (5), Japanese (3), Chinese (1), Dutch (1), Hungarian (1), Serbian (1). The h-index of 5461 articles was 131, average citations per article 22.03, the sum of citations 120312 (without self-citations: 94671).

Active research areas

The top 10 research areas with the most studies about PN are Nutrition Dietetics (2396, 43.8%), Surgery (735, 13.4%), Pediatrics (640, 11.7%), Gastroenterology Hepatology (518, 9.4%), Medicine General Internal (426, 7.8%), Pharmacology Pharmacy (246, 4.5%), Endocrinology Metabolism (180, 3.2%), Oncology (139, 2.5%), Critical Care Medicine (132, 2.4%), Immunology (112, 2.1%).

Development and future trend of publications

The distribution of the number of published articles by year is shown in Figure 1. The non-linear cubic model regression analysis results used to predict the number of papers that can be produced in 2021 and beyond are also shown in Figure 1. The agreement of the Cubic model with the data (R^2=0.717) was 71.7%. Therefore, due to this model results, it was predicted that 236 (Confidence Interval %: 207-265) articles would be printed in 2021, and 332 (CI%: 290-379) articles will be produced in 2025 (Figure 1).

Active countries

The world map showing the distribution of the number of articles according to the countries and the column chart of the top 20 countries that produce the most publications are shown in Figure 2. Top 20 countries that have published the most articles about PN; USA (1901, 34.8%), UK (542, 10%), France (437, 8%), Germany (387, 7%), Canada (313, 5.7%), Spain (306, 5.6%), Japan (281, 5.1%), Italy (270, 4.9%), China (210, 3.8%), Sweden (148, 2.7%), Belgium (138, 2.5%), Netherlands (135) , 2.4%), Switzerland (105, 1.9), Australia (101, 1.8%), Denmark (95, 1.7%), Poland (91, 1.6%), Israel (72, 1.3%), Brazil (71, 1.3%)), Taiwan (60, 1.1%), and Turkey (54, 0.9%).

Total link strength scores of 41 countries that wrote at least 10 articles from 88 countries producing publications on PN and had international collaboration among their authors were calculated. The collaboration clustering network map created according to these scores is shown in Figure 3.a. According to the results, 5 different clusters related to international collaboration were formed (Cluster 1: Austria, Canada, Chile, England, Germany, Greece, Ireland, Netherlands, Switzerland, Cluster 2: Argentina, Australia, Brazil, India, Malaysia, Mexico, New Zealand, Singapore, Wales, 3: Croatia, Czech Republic, Hungary, Israel, Norway, China Slovenia, Sweden, Cluster 4: Finland, Iran, Japan, South Africa, South Korea, Taiwan, Turkey, USA, Cluster 5: Belgium, Denmark, France, Italy, Poland, Scotland, Spain). International collaboration density map is shown in Figure 3.b.

Correlation analysis

The amount of articles generated by countries on PN and their Gross Domestic Product (GDP) and GDP per capita had a statistically significant association (r=0.743, P<0.001; r=0.717, P<0.001).

Active authors

The top 10 most active and productive authors who have written the most articles on PN are Goulet O (64), Messing B (55), Ament ME (53), Kudsk KA (53), Ricour C (51), Bistrian BR (47), Jeejeebhoy KN. (43), Pironi L (42), Steiger E (41), Teitelbaum DH (39).

Active institutions

Top 15 institutions that produce the most articles about PN; Harvard University (99), University of Toronto (98), University of California Los Angeles (84), University of Michigan (70), University of Tennessee (69), University of Pennsylvania (67), University of Alberta (59), Rigshospitalet (affiliated with University of Copenhagen) (56), Necker-Enfants Malades Hospital (affiliated with University of Paris Descartes) (55), Osaka University (53), University of Wisconsin (53), Veterans Admin Medical Ctr (52), University of Texas (51), The Hospital for Sick Children (SickKids, affiliated with University of Toronto) (49), Baylor College of Medicine (48).

Active journals

In 967 different journals, 5461 articles about PN were published. Table 1 lists the first 56 most active journals that publish 15 or more papers, as well as the total number of citations obtained by the journals and the average number of citations per article. The citation network visualization map between these journals is illustrated in Figure 4.

Figure 1: Distribution of publications on parenteral nutrition by years and prediction of articles in the coming years with the non-linear cubic model

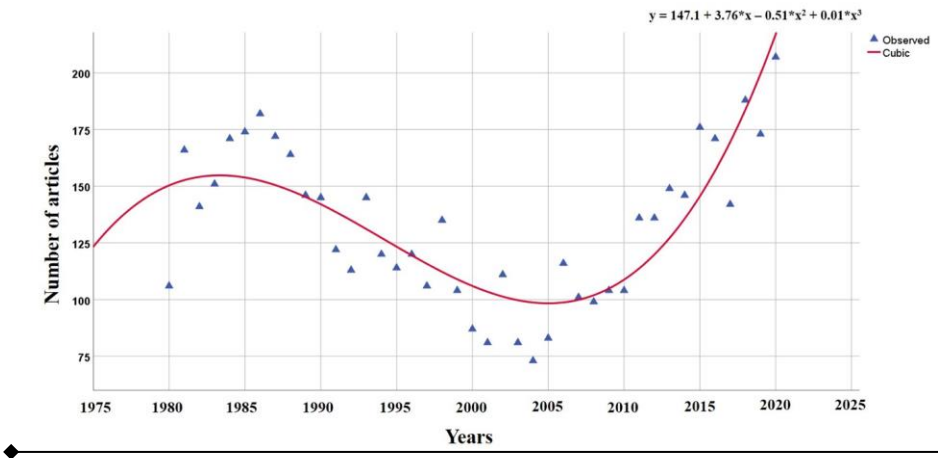


Figure 2: Distribution of publications on parenteral nutrition by world countries and column chart of the top 20 most productive countries (*productivity increases from light colors to dark colors)

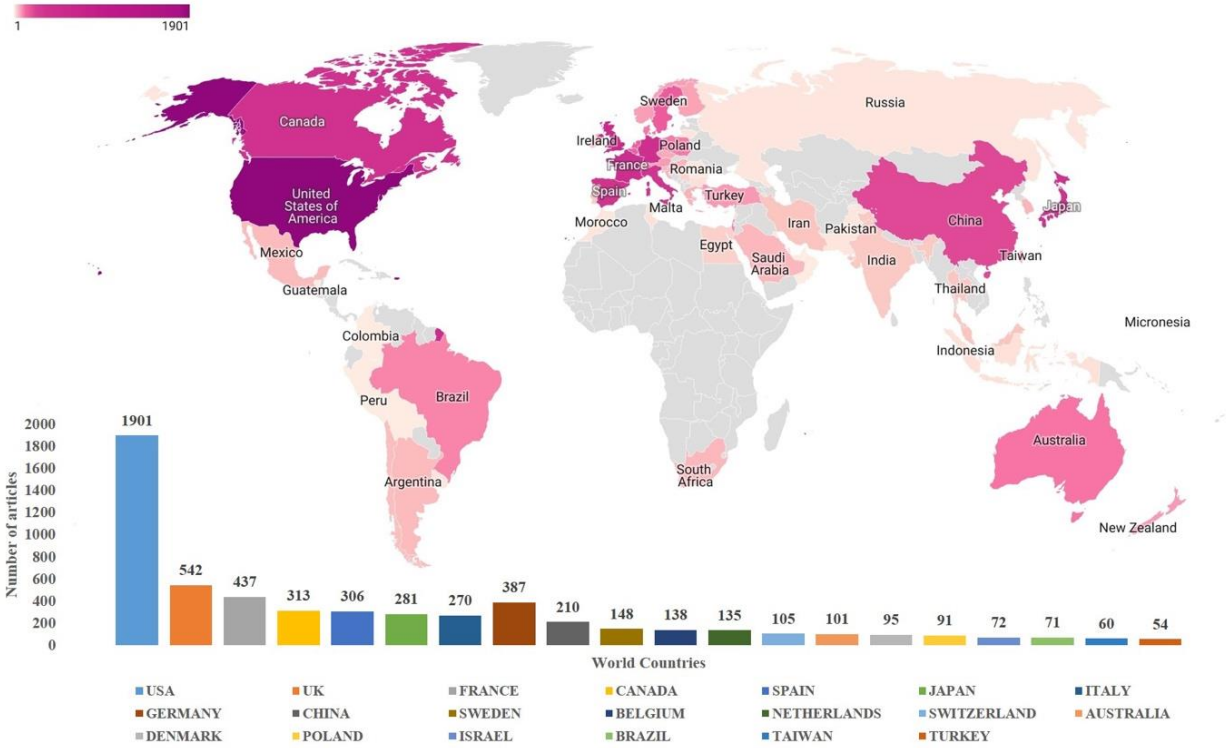


Figure 3: a. Network visualization map of cluster analysis on international collaboration on parenteral nutrition (*Colors show clustering. The size of the circles shows the number of articles.), b. Density map for international collaboration of worldwide countries on parenteral nutrition. (*The strength of ICS increases from blue to red (blue-green-yellow-red) (ICS: international collaboration score))

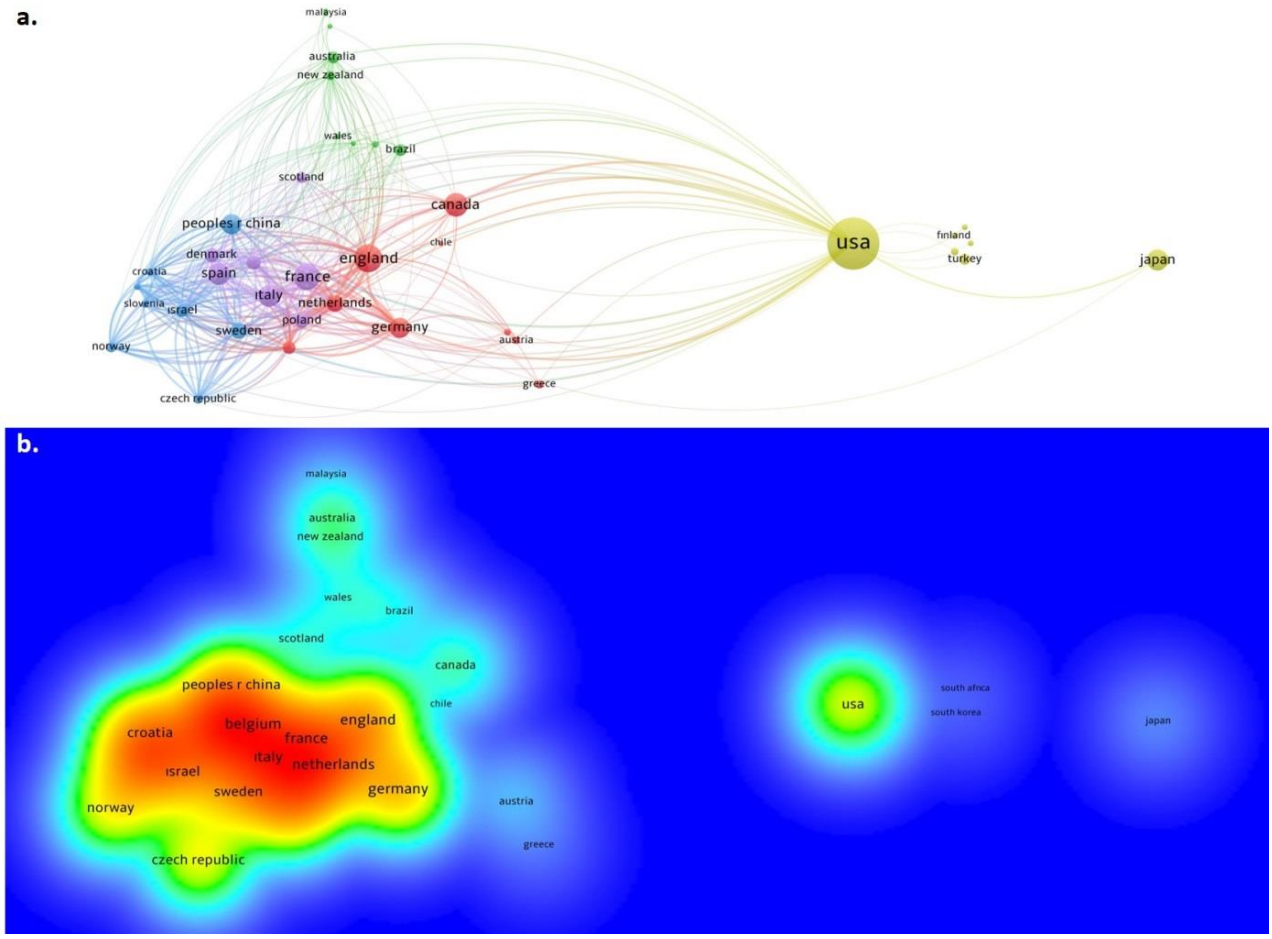


Table 1: 56 most active journals with more than 15 articles on PN

Journals	RC	C	AC	Journals	RC	C	AC
Journal of Parenteral and Enteral Nutrition	894	20068	22.4	Home Parenteral Nutrition, 2nd Edition	25	15	0.6
Clinical Nutrition	337	6678	19.8	Journal of The American College of Nutrition	25	444	17.8
Nutrition	187	4052	21.7	American Journal of Surgery	24	1037	43.2
American Journal of Clinical Nutrition	133	5664	42.6	Archives of Surgery	24	1220	50.8
Nutricion Hospitalaria	116	596	5.1	Metabolism-Clinical and Experimental	24	661	27.5
Nutrition in Clinical Practice	105	841	8.0	Surgery Gynecology & Obstetrics	24	940	39.2
Journal of Pediatric Gastroenterology and Nutrition	104	2217	21.3	American Journal of Physiology-Gastrointestinal and Liver Physiology	21	949	45.2
Journal of Pediatric Surgery	90	2692	29.9	Current Opinion in Clinical Nutrition and Metabolic Care	21	472	22.5
Annals of Surgery	70	6173	88.2	Journal of The American Dietetic Association	20	281	14.1
Gastroenterology	61	5235	85.8	Intensive Care Medicine	20	524	26.2
Journal of Pediatrics	60	3042	50.7	Archives of Disease in Childhood-Fetal and Neonatal Edition	18	385	21.4
Infusionstherapie UND Klinische Ernahrung	55	230	4.2	Asia Pacific Journal of Clinical Nutrition	18	106	5.9
Surgery	45	2373	52.7	Aktuelle Ernahrungsmedizin	17	44	2.6
Transplantation Proceedings	43	484	11.3	American Surgeon	17	187	11.0
Critical Care Medicine	39	1712	43.9	Gastroenterologie Clinique et Biologique	17	190	11.2
Journal of Surgical Research	38	1223	32.2	Gut	17	1380	81.2
Nutrients	35	137	3.9	Proceedings of hhe Nutrition Society	17	338	19.9
Nutrition Clinique et Metabolisme	35	37	1.1	World Journal of Surgery	17	365	21.5
Acta Chirurgica Scandinavica	34	279	8.2	American Journal of Gastroenterology	16	771	48.2
Journal of Nutrition	34	794	23.4	American Journal of Health-System Pharmacy	16	190	11.9
Pediatric Research	34	874	25.7	Current Opinion in Gastroenterology	16	18	1.1
European Journal of Clinical Nutrition	32	504	15.8	Nutrition Research	16	83	5.2
Clinical Nutrition Espen	29	139	4.8	Scandinavian Journal of Gastroenterology	16	521	32.6
Infusionstherapie UND Transfusionsmedizin	29	86	3.0	British Journal of Nutrition	15	534	35.6
British Journal of Surgery	28	1544	55.1	Home Parenteral Nutrition	15	19	1.3
Pediatrics	28	1565	55.9	Pediatric Surgery International	15	177	11.8
Digestive Diseases and Sciences	27	838	31.0	Plos One	15	206	13.7
Cancer	26	1075	41.3	World Journal of Gastroenterology	15	421	28.1

RC: Record Count, C: Number of Citation, AC: Average Citation Per Document

Citation analysis

Among the 5461 articles published between 1980 and 2020, the first 25 articles with the highest number of citations according to the total number of citations are presented in Table 2. Then, the average number of citations per year is shown in the last column of Table 2.

Table 2: Top 25 most cited articles according to total citations on PN

No	Article	Author Journal	PY	TC	AC
1	Early versus late parenteral nutrition in critically ill adults	Casaer, MP.et al. New England Journal of Medicine	2011	884	80.36
2	Enteral versus parenteral-feeding - effects on septic morbidity after blunt and penetrating abdominal-trauma	Kudsk, KA. et al. Annals of Surgery	1992	844	28.13
3	Perioperative total parenteral-nutrition in surgical patients	Williford, WO. New England Journal of Medicine	1991	705	22.74
4	Total parenteral-nutrition promotes bacterial translocation from the gut	Alverdy, JC. et al. Surgery	1988	604	17.76
5	Clinical and metabolic efficacy of glutamine-supplemented parenteral-nutrition after bone-marrow transplantation - a randomized, double-blind, controlled-study	Ziegler, TR. et al. Annals of Internal Medicine	1992	554	18.47
6	Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial	Heidegger, CP. et al. Lancet	2013	436	48.44
7	Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis	Windsor, ACJ. et al. Gut	1998	425	17.71
8	Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure	Cavicchi, M. et al. Annals of Internal Medicine	2000	422	19.18
9	Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial	Kalfarentzos, F. et al. British Journal of Surgery	1997	398	15.92
10	Influence of total parenteral-nutrition on fuel utilization in injury and sepsis	Askanazi, J. et al. Annals of Surgery	1980	396	9.43
11	Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition	Griffiths, RD. et al. Nutrition	1997	391	15.64
12	Enteral compared with parenteral nutrition: a meta-analysis	Braunschweig, CL. et al. American Journal of Clinical Nutrition	2001	379	18.05
13	Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome	Messing, B. et al. Gastroenterology	1999	375	16.3
14	Preoperative parenteral-feeding in patients with gastrointestinal carcinoma	Muller, JM. et al. Lancet	1982	363	9.08
15	Espen guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications)	Pittiruti, M. et al. Clinical Nutrition	2009	360	27.69
16	Total parenteral nutrition in the critically ill patient	Heyland, DK. et al. Jama-Journal of the American Medical Association	1998	360	15
17	Does total parenteral-nutrition induce gallbladder sludge formation and lithiasis	Messing, B. et al. Gastroenterology	1983	358	9.18
18	Respiratory changes induced by the large glucose loads of total parenteral-nutrition	Askanazi, J. et al. Jama-Journal of the American Medical Association	1980	343	8.17
19	Addition of glutamine to total parenteral-nutrition after elective abdominal-surgery spares free glutamine in muscle, counteracts the fall in muscle protein-synthesis, and improves nitrogen-balance	Hammarqvist, F. et al. Annals of Surgery	1989	332	10.06
20	Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial	Bozzetti, F. et al. Lancet	2001	320	15.24
21	Early parenteral nutrition in critically ıll patients with short-term relative contraindications to early enteral nutrition a randomized controlled trial	Doig, GS. et al. Jama-Journal of the American Medical Association	2013	312	34.67
22	Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease	Gura, KM. et al. Pediatrics	2008	305	21.79
23	The effect of parenteral-nutrition on gastrointestinal immunity - the importance of enteral stimulation	Alverdy, J. et al. Annals of Surgery	1985	281	7.59
24	Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis	McClave, SA. et al. Journal of Parenteral And Enteral Nutrition	1997	279	11.16
25	Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis	Marik, PE. et al. BMJ-British Medical Journal	2004	277	15.39

PY: Publication year, TC: Total citation, AC: Average citations per year

Co-citation analysis

The references sections of all 5461 papers studied contained a total of 67911 studies. The first 11 papers with the greatest co-citations (over 100 citations) were respectively; Alverdy (1988) (Number of co-citations (NC): 132), Cavicchi (2000) (NC: 146), Dudrick (1968) (NC: 175), Jeejeebhoy (1976) (NC: 101), Koletzko (2005) (NC:178), Kudsk (1992) (NC:132), Mirtallo (2004) (NC:116), Moore (1992) (NC:118), Sheldon (1978) (NC:119), Singer (2009) (NC:100), Staun (2009) (NC:110) [17-27].

Trending topics

In all of the 5461 articles published about PN, 4535 different keywords were used. Among these keywords, 102 different keywords used in at least 13 separate articles are shown in Table 3. The cluster network visualization map between these keywords is shown in Figure 5. Trend visualization network map is presented in Figure 6, and citation network visualization map is illustrated in Figure 7.

Table 3: The most frequently used keywords on PN

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
parenteral nutrition	1166	compounding	34	olive oil	17
total parenteral nutrition	402	newborn	30	outcomes research	17
home parenteral nutrition	267	surgery	28	cytokines	16
intestinal failure	151	home nutrition support	25	meta-analysis	16
nutrition	127	critical care	24	nutritional status	16
enteral nutrition	115	glucose	24	artificial nutrition	15
cholestasis	113	nutrition support	24	growth hormone	15
short bowel syndrome	106	child	23	hypophosphatemia	15
neonate (s)	94	liver	23	prematurity	15
nutritional support	73	manganese	23	preterm infants	15
glutamine	70	parenteral formulas	23	refeeding syndrome	15
pediatric (s)	69	growth	22	short-bowel syndrome	15
lipid emulsion (s)	68	omega-3 fatty acids	22	administration	14
sepsis	63	parenteral	22	gastric cancer	14
malnutrition	61	preterm	22	glutathione	14
children	56	safety	22	medication errors	14
complications	52	insulin	21	minerals	14
lipid (s)	51	quality	21	palliative care	14
TPN	51	survival	21	parenteral nutrition solutions	14
central venous catheter	49	aluminum	20	parenteral nutrition-associated cholestasis	14
quality of life	47	life cycle	20	patient safety	14
critical illness	45	nutrition support practice	20	randomized controlled trial	14
fish oil	44	bacterial translocation	19	apoptosis	13
trace elements	42	body composition	19	copper	13
infection	40	adult	18	crohn's disease	13
amino acids	37	oxidative stress	18	lipid peroxidation	13
liver disease	37	risk factors	18	mortality	13
cancer	36	stability	18	research and diseases	13
hyperglycemia	36	total parenteral nutrition (tpn)	18	selenium	13
parenteral nutrition-associated liver disease	36	catheter	17	steatosis	13
rat (s)	36	catheter-related bloodstream infection	17		

Figure 4: Network visualization map for citation analysis of active journals on Parenteral nutrition. (*The average number of citations per article by journals increases from blue to red. The size of the circles shows the number of articles.)

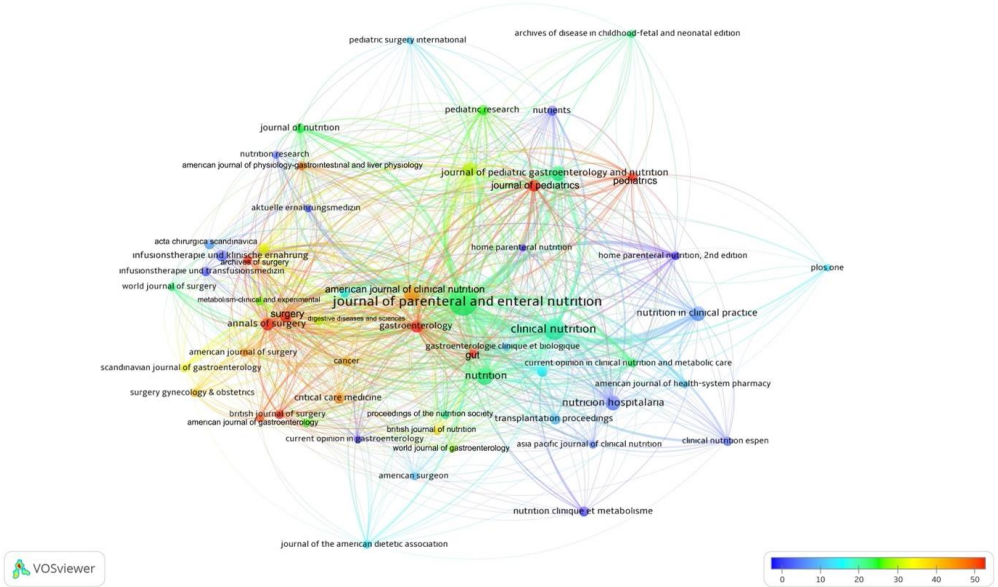


Figure 5: Network visualization map for cluster analysis based on keyword analysis on Parenteral nutrition. (* Clustering is shown by colors. The color of keywords in the same cluster is the same. The size of the circle represents the number of times the keyword has been used.)

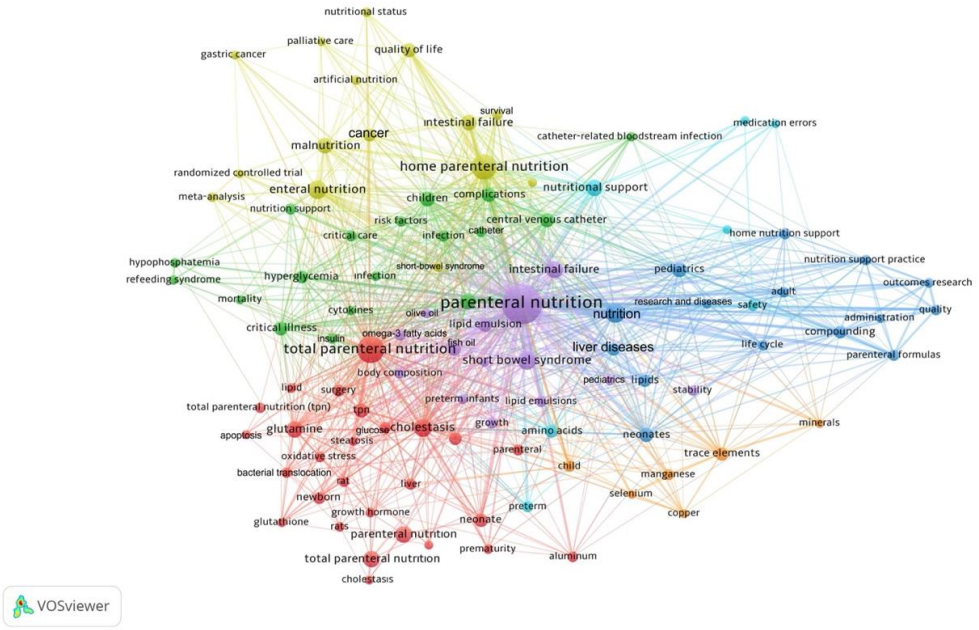


Figure 6: Network visualization map for trends on Parenteral nutrition. (* The article's topicality grows from blue to red as indicated by the indication in the upper left corner of the figure (blue-green-yellow-red). The size of the circle represents the number of times the keyword has been used.)

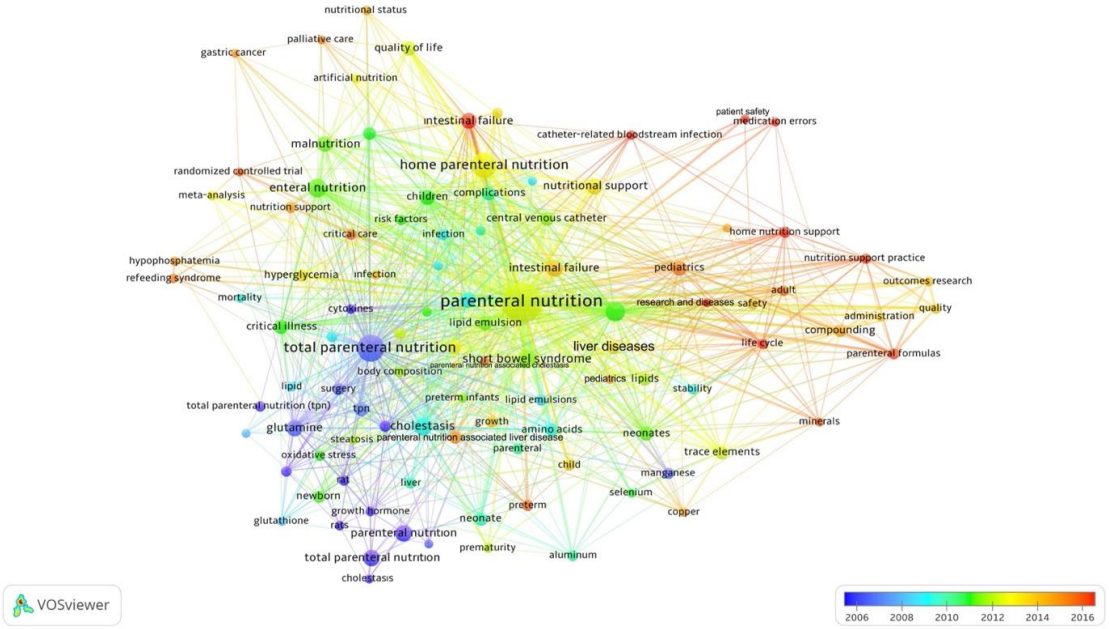
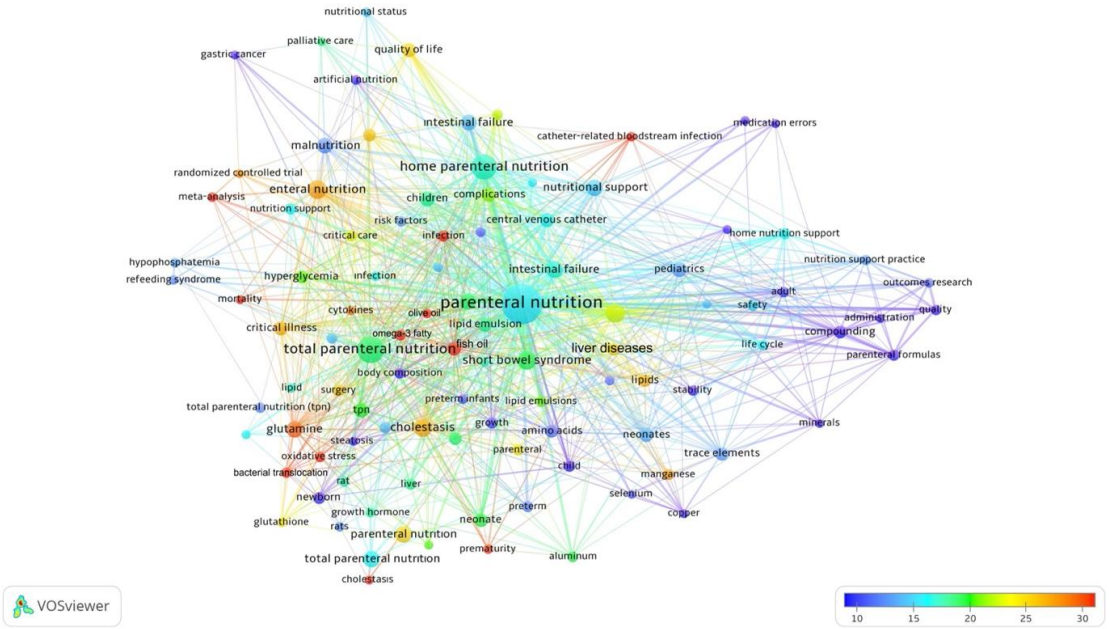


Figure 7: The most commonly mentioned subjects on parenteral nutrition are visualized in a network map. (* The amount of citations increases as the color changes from blue to red. The size of the circle represents the number of times the keyword has been used.)



Discussion

According to our findings, although there was an increasing trend in the number of articles on PN between 1980 and 1986, it showed a decreasing trend from 1987 to 2004. As of 2005, the number of articles on PN showed an increasing trend again until 2020, and the number of articles reached 207 in 2020. When the non-linear regression analysis results are evaluated, it is seen that the number of papers will continue with an increasing exponential trend.

When looking at the distribution of publications by world countries, 17 of the first 20 countries with the highest article productivity on PN were developed, while the other three (Brazil, China, and Turkey) were developing. However, although these three were developing countries, they were nations with relatively bigger economies. According to the findings of our study's correlation analysis, the high level of significant correlation between article productivity and metrics of economic development shows that the economic development level of countries is effective in the productivity of publications on PN. Furthermore, in the literature, bibliometric studies on many different medical subjects have been shown to be effective in publication productivity [10-12]. When the density map was developed based on the total score of cooperation between the countries, the countries with the most intensive cooperation were France, England, Italy, Belgium, Germany, Netherlands, Poland, Spain, Denmark, Sweden, and Switzerland, respectively. When the co-authorship cooperation of countries on PN is examined, it seems that collaboration based on geographical location is effective in the production of articles (Denmark, Spain, France, Italy, Poland), (England, Netherlands, Germany, Austria, Greece), (Croatia, Slovenia, Czech Republic), (Norway, Sweden), countries that are in the same cluster but not geographically close (USA, Turkey, Finland, Japan), (Canada, Chile), (Brazil, Australia, Wales) were working together. In some studies in the literature, it has been stated that geographical proximity is effective in the production of publications [10-12].

The journals that published the most articles on PN were determined as Journal of Parenteral and Enteral Nutrition, Clinical Nutrition, Nutrition, American Journal of Clinical Nutrition, Nutricion Hospitalaria, Nutrition in Clinical Practice, Journal of Pediatric Gastroenterology and Nutrition, Journal of Pediatric Surgery, Annals of Surgery, Gastroenterology, and Journal of Pediatrics, respectively. We recommend that authors who want to publish on PN look into these journals first. When journal citation analyses are compared, the most effective journals are determined based on the average number of citations per article they publish are Annals of Surgery, Gastroenterology, Gut, Pediatrics, British Journal of Surgery, Surgery, Archives of Surgery, Journal of Pediatrics, American Journal of Gastroenterology, American Journal of Physiology-Gastrointestinal and Liver Physiology, Critical Care Medicine, American Journal of Surgery, American Journal of Clinical Nutrition, and Cancer, respectively. Therefore, we recommend that researchers who want their articles to be cited more consider these journals first.

The most cited study was, determined by evaluating the assessed papers based on the total amount of citations they obtained, "Early versus late parenteral nutrition in critically ill adults" published in the New England Journal of Medicine by Casaer et al. [28]. The second most influential study is Kudsk et al., titled “Enteral versus parenteral-feeding - effects on septic morbidity after blunt and penetrating abdominal trauma” published in Annals of Surgery [22]. The third most influential study was Williford's (1991) article titled "Perioperative Total Parenteral-Nutrition in Surgical Patients" published in the New England Journal of Medicine [29]. The 4th and 5th most influential studies are written by Alverdy et al. and Ziegler et al. [17, 30]. When the papers are evaluated according to the number of citations per year, the most cited article belongs to Casaer et al. [28]. The second most influential article is from Heidegger et al., published in the Lancet. titled “Optimization of energy provision with supplemental parenteral nutrition in critically ill patients: a randomized controlled clinical trial” [31]. The third most influential study wrote by Fivez et al.'s article titled "Early versus late parenteral nutrition in critically ill children" was published in the New England Journal of Medicine [32]. The fourth most influential study belongs to Doig et al. article titled “Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition a randomized controlled trial” published in the Jama-Journal of The American Medical Association [33]. The fifth most influential study did by Kudsk et al. [22]. According to the co-citation numbers of all analyzed articles, studies from Alverdy (1988), Cavicchi (2000), Dudrick (1968), Jeejeebhoy (1976), Koletzko (2005), Kudsk (1992), Mirtallo (2004), Moore (1992), Sheldon (1978), Singer (2009), Staun (2009) were identified as the most influential [17-27]. We can recommend that clinicians and researchers interested in this subject read these publications first.

When the results of the keyword analysis were assessed, it was discovered that PN topics were divided into clusters into seven different colors as a result of the clustering analysis. The most cited keywords were fish oil, infection, omega-3 fatty, olive oil, mortality, oxidative stress, catheter-related bloodstream infection, bacterial translocation, meta-analysis, prematurity, glutamine, cytokines, and cholestasis. The keywords researched in recent years, according to the findings of the analysis done to determine the trend subjects, are; intestinal failure, life cycle, catheter-related bloodstream infection, medication errors, patient safety, home nutrition support, nutritional support practice, research and diseases, parenteral formulas, preterm, minerals, adult, randomized controlled trial, pediatrics, critical care, refeeding syndrome, palliative care, parental nutrition-associated cholestasis, hypophosphatemia, nutrition support, gastric cancer.

As a result of the literature review on PN, no bibliometric study was found. Therefore, it can be said that the comprehensive research we have done on this subject is the first bibliometric research. Pubmed and Scopus indexes were not used in the literature review of our study, and only the WoS database was used. This is due to the inability to perform citation and co-citation analyses in the Pubmed database and the fact that studies with low impact levels are also included in the Scopus database [9-13]. The WoS database is preferred because it indexes the articles published in more influential journals than other databases and provides comprehensive citation analysis. In

recent years, WoS has also been chosen more in bibliometric analyzes [9-13].

Conclusion

In this comprehensive bibliometric study, we shared a summary of 5461 articles published between 1980 and 2020 on PN, which has seen an increase in the amount of articles about it published. Therefore, it can be said that trend topics in PN research in recent years: Intestinal failure, life cycle, catheter-related bloodstream infection, medication errors, patient safety, home nutrition support, nutritional support practice, study and diseases, parenteral formulas, preterm, minerals, adult, randomized controlled trial, pediatrics, critical care, refeeding syndrome, palliative care, parental nutrition-associated cholestasis, hypophosphatemia, nutrition support, and gastric cancer. We think that this article on parenteral nutrition worldwide outcomes could be useful for physicians and scientists.

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Prevalence of high-risk human papilloma virus infection and cervical cytological abnormalities in female Turkish patients with rheumatologic disease

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Ethics Committee Approval
The Local Ethics Committee of Umraniye Training and Research Hospital, Istanbul, Turkey have approved this study (Ethics Committee Approval No: B.10.1.TKH.4.34.H.GP.0.01/254). 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: It is believed that patients with rheumatological diseases (RDs) are more prone to infectious diseases, possibly due to both disease-related immune dysfunction and chronic inflammation, and immunosuppressive agents used in the treatment of rheumatological diseases. In this context, we aimed to evaluate the prevalence of high-risk human papillomavirus (Hr-HPV) infection and cervical cytological abnormalities in Turkish female patients with RDs and compare them with healthy controls (HCs).

Methods: 362 sexually active patients with RDs followed up between January 2014 and June 2021 were included in this cross-sectional study. Patients with RDs were classified as autoimmune and non-autoimmune groups according to seropositivity. Data of 883 age-matched HCs were used for comparison. Demographic features, cervical cytology reports of the patients and HPV test results were retrieved from hospital database. Cervical cytological abnormalities was categorized according to Bethesda 2014. Cobas assay was used for detecting and typing for Hr-HPV.

Results: The RDs group and the HCs group were similar in terms of mean age, BMI, and rate of smokers (P>0.05). Cytological evaluation was carried out in all of 362 patients with RDs (161 autoimmune and 201 non-autoimmune) and in all of 883 HCs. HPV test was applied in 286 patients with RDs and 776 of HCs. 16 (4.4%) patients with RDs and 58 (6.6%) HCs had cervical cytological abnormality. Of the patients who underwent HPV testing; 22 (7.7%) patients with RDs and 75 (9.7%) HCs had Hr-HPV. The prevalence of cervical cytologic abnormalities and Hr-HPV infection rate were similar between patient groups and HCs (P=0.186 and P=0.400, respectively).

Conclusion: It was determined that chronic systemic inflammation, which plays a role in the pathogenesis of rheumatological diseases, and immunosuppressive agents used in the treatment did not increase the prevalence of Hr-HPV infection and cervical cytological abnormalities.

Keywords: Cervix uteri, Papanicolaou test, Papillomaviridae, Rheumatologic disease

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Introduction

Human papillomavirus (HPV) infection is known as the main cause of cervical premalignant lesions and cervical cancer [1]. Persistent infection with high-risk HPV (Hr-HPV) types, especially type 16 and 18, are significantly associated with cervical cancer [2]. While most HPV infections are cleared by the individual's immune system within a few years, persistent infections can lead to precancerous and invasive lesions [3].

Cervical cancer screening can be done only with Pap smear test or HPV test or with co-test in which both cervical cytological evaluation and HPV are examined together. The Bethesda system is commonly used for reporting cervical cytological abnormalities [4]. Cytological abnormality and/or HPV positivity may require colposcopic examination and biopsy [5].

Rheumatologic diseases (RDs) include a wide spectrum of disorders causing chronic inflammation affecting the joints and/or organ systems [6]. Corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) or immunosuppressives are frequently used for treatment of RDs [7]. Because HPV infection is controlled by both local and systemic immunity, immunocompromised individuals are thought to be more likely to have HPV infection and persistence [8].

Some studies demonstrated that patients with autoimmune disease such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), were found to be more likely to have abnormal cervical cytology and high prevalence of HPV infection [9, 10]. However, prevalence of cervical cytological abnormalities and HPV infection among other RDs, especially in patients with non-autoimmune rheumatologic diseases, are scarce.

The aim of our study was to assess the prevalence of Hr-HPV infection and cervical cytological abnormalities in Turkish female patients with different RDs including autoimmune and non-autoimmune spectrum, and compare them with a healthy control group.

Materials and methods

This retrospective, cross-sectional study was conducted in Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey. The study group consisted of 362 sexually active female patients with RDs who applied to the outpatient clinic for routine gynecological care between January 2014 and June 2021 and had Pap smears. Study patients were divided into two groups as autoimmune RDs and non-autoimmune RDs. Patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), dermatomyositis (DM), antiphospholipid syndrome (APS), Sjogren's syndrome and granulomatosis with poliangiitis (Wegener's) were classified as autoimmune inflammatory RDs (seropositive) group (n=161). Patients with ankylosing spondylitis and other seronegative spondyloarthropathies, psoriatic arthritis, Behçet's Disease, familial mediterranean fever (FMF), gout, seronegative arthritis and osteoarthrosis were classified as non-autoimmune (seronegative) group (n=201).

The control group consisted of 883 randomly selected, age-matched women who underwent cervical screening during the study period, who had not any of the following; known previous cervical cytological anomaly, HPV positivity, history of any cancer, rheumatological disease and history of immunosuppressive therapy or steroid use.

HPV Testing and Cervico-vaginal Cytology

Pap smear test and cytological evaluation was performed on all participants. Cervical cytology samples of patients with RDs and age-matched HCs were taken by gynecologist and collected in ThinPrep® PreservCyt® Solution (Hologic Inc., Marlborough, MA) and then sent to the pathology unit specialized in processing cervical cytology samples. Samples were examined by these experienced pathologists for cytological abnormalities and tested for HPV.

The cytology diagnoses were graded according to the 2014 Bethesda classification [11]. In this study, we classified those with cervical cytology results reported as atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) as low-grade disease (LSIL). We classified as high-grade disease (HSIL) those reported as a high-grade squamous intraepithelial lesion (HSIL) or atypical squamous cells cannot exclude HSIL (ASC-H) or atypical glandular cells (AGC) as a result of cervical cytology. Smears without any signs of significant abnormalities categorized as negative for intraepithelial lesion and malignancy (NILM).

HPV testing was performed by using the Cobas® Human Papilloma Virus Test System (Roche Molecular Systems, Branchburg, NJ, USA) to detect the 14 high-risk HPV types. The Cobas HPV testing system is a fully automated PCR-based HPV test that analyzes HPV DNA from cervical specimens collected in liquid-based cytology medium [12]. This system is one of five approved HPV test by the US Food and Drug Administration for HPV DNA typing [13]. The Cobas HPV test can separately report HPV 16 and 18, while a pooled test result of 12 other HR-HPV types together (31,33,35,39,45,51,52,56,58,59,66,68) [14].

Statistical analysis

Statistical analysis of the study was performed using SPSS 16.0 software (SPSS INC., Chicago, Il, USA). Quantitative data were expressed as mean (SD). Categorical data were described as percentages and numbers, and tested by using Pearson Chi square test or Fisher's exact test. $P<0.05$ was considered statistically significant.

Results

A total of 362 patients with RDs (mean age 37.6 (7.7) years) and 883 age-matched HCs (mean age 38.5 (5.5) years) were included in this study. In the RDs group, mean BMI was 26.87 kg/m^2 and smoking rate was 19.9%. In the HCs group, the mean BMI was 27.13 kg/m^2 and the smoking rate was 19.2%. The RDs group and the HCs group were similar in terms of mean age, BMI, and rate of smokers ($P=0.256$, $P=0.457$, $P=0.725$, respectively) (Table 1).

The distribution of cytologic abnormalities and HPV testing among patients with RDs were summarized in Table 2.

Table 1: Comparison of demographic characteristics of patients with RDs and HCs

	Patients with RDs n=362	Healthy Controls n=883	*P*-value
Age (years)	37.6 (7.7)	38.5 (5.5)	0.256
BMI (kg/m2)	26.87 (5.67)	27.13 (4.64)	0.457
Smoking			
Yes	72 (19.9%)	168 (19.2%)	0.725
No	290 (80.1%)	715 (80.9%)	

Table 2: The distribution of cytologic abnormalities and HPV testing among patients with RDs

	Autoimmune Group						Non- Autoimmune Group						
	RA (n=78)	SLE (n=22)	SSc/DM (n=13/1)	APL (n=5)	Sjögren (n=40)	GPA (n=2)	AS (n=21)	SpA (n=33)	PSA (n=14)	Behcet (n=30)	FMF (n=57)	Seronegative Arthritis (n=43)	Gout/OA (n=2/1)
LSIL	2	0	0	0	1	1	1	1	1	1	3	2	0
HSIL	0	0	1	0	0	0	1	0	1	0	0	0	0
NILM	76	22	13	5	39	1	19	32	12	29	54	41	3
HPV positive	4	2	1	0	1	1	4	0	1	2	4	2	0
HPV 16	0	0	0	0	0	0	3	0	0	0	1	0	0
HPV18	0	1	0	0	0	0	0	0	0	0	0	0	0
HPV others	4	1	1	0	1	1	1	0	1	2	3	2	0
HPV negative	58	16	11	3	26	1	15	29	12	22	39	29	3

RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, SSc: Systemic Sclerosis, DM: Dermatomyositis, APL: Antiphospholipid Syndrome, GPA: Granulomatosis with Polyangitis, AS: Ankylosing Spondylitis, SpA: Spondyloarthritis, PSA: Psoriatic Arthritis, FMF: Familial Mediterranean Fever, OA: Osteoarthritis, LSIL: Low Grade Squamous Intraepithelial Lesion, HSIL: High Grade Squamous Intraepithelial Lesion, NILM: Negative for Intraepithelial Lesion and Malignancy

Prevalence of cervical cytological abnormality

Among patients with RDs, 346 (95.6%) patients did not have malignancy or intraepithelial lesions, while 16 (4.4%) had cytological abnormalities (13 LSIL and 3 HSIL). Among HCs, 58 (6.6%) individuals were found to have cytological abnormalities (47 LSIL and 11 HSIL). The prevalence of cervical cytological abnormalities were similar between patients with RDs and HCs (P=0.186) (Table 3).

Table 3: The prevalence of cytological abnormalities between patients with RDs and HCs

Cytology	Patients with RDs n=362	Healthy Controls n=883	*P*-value
LSIL+HSIL n (%)	16 (4.4)	58 (6.6)	0.186
NILM n (%)	346 (95.6)	825 (93.4)	

LSIL: Low Grade Squamous Intraepithelial Lesion, HSIL: High Grade Squamous Intraepithelial Lesion, NILM: Negative for Intraepithelial Lesion and Malignancy

When autoimmune RDs, non-autoimmune RDs and control group were compared in terms of the cervical cytological abnormalities, five patients (3.1%) were found in the autoimmune and 11 (5.5%) in the non-autoimmune group. The prevalence of cervical cytological abnormalities were similar between autoimmune group, non-autoimmune group and HCs (P=0.221) (Table 4).

Prevalence of Hr-HPV

Of 362 patients with RDs, 286 had HPV testing and 22 (7.7%) had Hr-HPV. HPV 16 was detected in four patients, HPV 18 was detected in one patient, and other Hr-HPVs were detected in 17 patients. HPV testing was performed in 776 of 883 women in the control group, and Hr-HPV was detected in 75 (9.7%) of them. Of these, 14 had HPV 16, 5 had HPV 18 and 56 had other Hr-HPV. The prevalence of Hr-HPV was not statistically different between patients with RDs and HCs (P=0.400) (Table 5).

Table 4: The prevalence of cytological abnormalities between patient groups and HCs

Cytology	Autoimmune Group n=161	Non-Autoimmune Group n=201	Healthy Controls n=883	*P*-value*	*P*-value **
LSIL+HSIL n (%)	5 (3.1)	11 (5.5)	58 (6.6)	0.314	0.221
NILM n (%)	156 (96.9)	190 (94.5)	825 (93.4)		

* comparison between autoimmune vs non-autoimmune groups, ** comparison between all groups, LSIL: Low Grade Squamous Intraepithelial Lesion, HSIL: High Grade Squamous Intraepithelial Lesion, NILM: Negative for Intraepithelial Lesion and Malignancy

Table 5: The Prevalence of Hr-HPV between patients with RDs and HCs

Hr-HPV	Patients with RDs n=286	Healthy Controls n=776	*P*-value
Positive n (%)	22 (7.7)	75 (9.7)	0.400
Negative n (%)	264 (92.3)	701 (90.3)	

Of 22 RDs with Hr-HPV positivity, 9 (7.3%) (one patient HPV 18, and 8 other Hr-HPV) were in the autoimmune group and 13 (8.0%) (four patients HPV 16, and 9 other Hr-HPV) were in the non-autoimmune group. Autoimmune RDs, non-autoimmune RDs and control group were also compared in terms of HPV positivity. The prevalence of Hr-HPV was similar between three groups (P=0.598) (Table 6).

Table 6: The Prevalence of Hr-HPV between patient groups and HCs

Hr-HPV	Autoimmune Group n=124	Non-Autoimmune Group n=162	Healthy Controls n=776	*P*-value*	*P*-value **
Positive n (%)	9 (7.3)	13 (8.0)	75 (9.7)	1.000	0.598
Negative n (%)	115 (92.7)	149 (92.0)	701 (90.3)		

* comparison between autoimmune vs. non-autoimmune groups, ** comparison between all groups

Discussion

In this study, we could not find a statistical difference in the prevalence of cervical cytological abnormalities and Hr-HPV positivity between the patient group with rheumatological diseases and the age-matched healthy control group.

The third most common genital cancer in Turkish women is cervical cancer with an average incidence of 4.42 per 100,000 women [15]. There are different study results in the literature about Hr-HPV prevalence in Turkish population. In a study by Demir et al. [16] in which patients with normal cervical cytology were evaluated, the prevalence of HPV was found to be 17.9%. In a hospital based study conducted by Yuce et al. [17] the prevalence of high-risk HPV was 25.7%. In another study of Polat et al. [18] the prevalence of both Hr-HPV and abnormal cervical cytology were found to be 23%. Unlike the studies mentioned above, the prevalence of Hr-HPV in the healthy control group was found to be lower than the general average of the Turkish population in our study (9.7%).

Most of the studies investigating the prevalence of HPV and cervical cytological abnormalities in rheumatologic patients in the literature were conducted with SLE patients. In a study of 32 SLE female patients and controls, Al-Sherbeni et al. [19] found that there is a predisposition to cervical atypia in SLE women. In another study by Nath et al. [10] in which Pap smears of 30 female SLE patients and healthy controls were evaluated. The prevalence of abnormal Pap smear findings and the prevalence of Hr-HPV in female SLE patients was significantly higher than in healthy controls. Tam et al. [20] reported that cervical cytological abnormalities were more common among SLE patients than controls, even after adjusting for HPV status.

Klumb et al. [21] looked into HPV prevalence among SLE patients and reported that these patients have a high prevalence of HPV infection. Similarly, in a large multicenter croos-sectional study conducted in Korea, SLE patients were shown to have a greater prevalence of Hr-HPV infection and of abnormal cervical cytology compared with healthy controls (24.6% vs 7.9%, and 16.4% vs 2.8%, respectively) [22]. In a systematic literature review evaluating autoimmune patients, it was emphasized that the Hr-HPV prevalence was higher in SLE patients compared to the control groups, while it was comparable in studies on RA and SSc patients [9]. In an another study conducted with Mexican SLE and RA patients, the prevalence of cervical HPV infection was found to be higher compared to the control group [23]. In a population based study conducted in Sweden, the relationship between RA and cervical cancer was investigated and it was suggested that cervical dysplasia increased in RA patients compared to the general population, and invasive cervical cancer increased in RA patients treated with TNF [24]. On the other hand, some studies have shown that cervical dysplasia is not increased in RA patients [25].

In our study, we found that the overall prevalence of Hr-HPV infection was 7.7% among Turkish rheumatologic patients subjected to routine gynecologic examination. In autoimmune and non-autoimmune subgroups, it was 7.3% and 8.0%, respectively. Contrary to the studies in the literature, HPV prevalence was found to be slightly lower in Turkish rheumatology patients compared to the healthy control group without a statistical difference.

As with HPV, statistical difference was not found in terms of cervical cytological abnormalities between rheumatology patients and healthy controls. The overall prevalence of cytological abnormality was 4.4% in RDs and 6.6% in HCs.

Limitations

As in others, this study had some limitations. Patients were questioned by phone about clinical features that may affect the prevalence of HPV, birth control methods or the number of lifetime sexual partners. However, due to Turkey's socio-cultural characteristics, either no answers were received or reliable answers could not be obtained by phone. This was one of the important limitations of this study. The immune status of rheumatology patients is directly related to the immunosuppressive drugs used as well as the disease itself. In this study, drug use was not evaluated, and this was another important limitation.

Evaluation of both autoimmune and non-autoimmune groups by dividing rheumatology patients in a pool is the main strength of the study. Most of the studies in the literature were performed only with autoimmune disease patients.

Conclusion

It was determined that chronic systemic inflammation, resulting from the pathogenesis of rheumatological diseases, and immunosuppressive agents used in the treatment of rheumatological diseases, did not increase the prevalence of Hr-HPV infection and cervical cytological abnormalities. Therefore, sexually active female patients diagnosed with RDs should be screened similar to the normal healthy population in terms of Hr-HPV infection and cervical cytological abnormalities, even if they are receiving immunosuppressive therapy.

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Research article

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In vitro neuroprotective effects of allicin on Alzheimer's disease model of neuroblastoma cell line

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Ethics Committee Approval
Current study does not include any experiments with human participants or animals performed by any of the authors. Since SH-SY5Y cells are considered a cell-line, the ethical concerns associated with primary human neuronal culture are not involved with these cells.

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

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Abstract

Background/Aim: Alzheimer's disease is a progressive disorder that causes atrophy and neuronal death in the brain. Currently, there is not any effective therapy for Alzheimer's disease. The current research was designed to investigate the beneficial effects of allicin on Alzheimer's disease in SHSY-5Y cells in vitro and elucidating the neuroprotective mechanism of allicin.

Methods: Human neuroblastoma cell line (SH-SY5Y) was differentiated with retinoic acid to conduct the in vitro Alzheimer's Disease model. Amyloid β1-42 protein was applied to the cells for 24 hours (2.5 µM) to induce cytotoxicity. Allicin was applied to the cell cultures in a wide spectrum dose (10 µM, 50 µM, 100 µM) to investigate neuroprotective effect against amyloid β for 24 hours. MTT and LDH analyses were performed to assess the cell viability. MDA and ROS concentrations and SOD activity were analyzed to determine the oxidative stress. Moreover, the effects of allicin on the caspase-3 expression in amyloid β induced neurotoxicity were determined by the RT-PCR analysis.

Results: Amyloid β markedly decreased cell viability of SH-SY5Y in MTT analysis and elevated LDH levels. In contrast, in MTT analysis, the allicin markedly increased cell viability, indicating that allicin induces cell proliferation. Moreover, in LDH analysis, allicin treatment markedly decreased LDH release. Exposure to amyloid β markedly increased MDA and ROS levels, in comparison with the control. Moreover, amyloid β decreased activity of SOD in SH-SY5Y cells. Allicin markedly balanced out the amyloid β-induced MDA and ROS generation. In the same pathway, allicin increased activity of SOD in amyloid β -exposed SH-SY5Y cells. The caspase 3 expression was increased in amyloid β group in comparison to the control group and allicin markedly lowered the expression of caspase-3 levels.

Conclusion: The beneficial effects of allicin on amyloid β -induced neurotoxicity on SH-SY5Y cells were reported for the first time in terms of cell viability, oxidative stress and apoptosis.

Keywords: Allicin, Alzheimer's disease, Antioxidant, Apoptosis, SH-SY5Y cell line

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Introduction

Alzheimer's disease (AD), a progressive neuro-degenerative disease with a globally increasing prevalence, results from the aggregation of amyloid β (Aβ) protein and hyperphosphorylated Tau proteins, causing interruption of synaptic connections and neuronal-death [1, 2]. Patients with AD develop not only dementia, but also memory loss, difficulties in daily routine activities, and also psychological abnormalities such as depression. Pathophysiological characteristics of AD involve amnesia and cognitive deterioration [3].

Lesions of the cerebral cortex and hippocampus are found in neurons with abnormally hyperphosphorylated neurofibrillary tangles and extracellular Aβ plaques [4, 5]. Among these AD symptoms, the development of senile plaques and the accumulation of neurofibrillary tangles are considered as triggers in neuro-degenerative disorders. In fact, senile plaques often occur because of Aβ deposition in neuronal and glial cells. Aβ aggregation can cause oxidative damage, cell membrane/cell cycle disturbances, protein folding defects and DNA damage [6].

One of the contributing factors in most neuro-degenerative diseases is age and age might be connected with oxidative damage which enhances with age and participates in the pathology of neurodegeneration. When redox balance disrupts, oxidatively modified molecules accumulate in neuronal cells and cause dysfunction [7]. In extremely sensible cells like neurons, cell death may occur as a result of limited defense systems and failure [8]. The increase in chronic neuroinflammation also takes an important place in the pathophysiology of AD. Overexpression of proinflammatory cytokines was also associated with neuronal loss by increased Aβ aggregation and hyperphosphorylation of Tau [9]. In addition, abnormal accumulation of Aβ accelerates the inflammatory process by increasing proliferation and activation of microglial cells and increases the release of proinflammatory cytokines [9,10].

As an antioxidant, anti-inflammatory, neuroprotective and anti-cholinesterase molecule, allicin is being tested as a physiologically active compound due to its therapeutic potential in some neurological diseases [11]. It improves mitochondrial functioning, thus preserving neuronal cells by settling the cellular oxidative stress and reducing apoptosis [12]. It is also reported that allicin has an antioxidative effect and protects the brain from ischemia damage [13].

Current research is the first to examine the impacts of allicin against Aβ1- 42 induced AD model in vitro. The novelty of this study lies in investigating the effects of allicin on AD in SH-SY5Y cells in vitro and elucidating the neuroprotective mechanism of allicin. This study provides a new molecular treatment strategy for the clinical therapy of AD.

Materials and methods

Cell culture procedure

Human neuroblastoma SH-SY5Y cells were acquired from ATCC (USA) and cultured as manual provided by manufacture. The cells were placed in sterile 25 cm^2 flasks in DMEM (Dulbecco's Modified Eagle Medium) culture medium containing 10% FBS, 1% L-glutamine and 1% penicillin-streptomycin in a 5% carbon dioxide (CO_2) incubator. Cells were passaged with Trypsin/Ethylene Diamine Tetraacetic Acid (EDTA) when they covered 80% of the flask. Cells were differentiated with 10 µM alltrans retinoic acid for 6 days before the allicin treatment. Commercially purchased (Sigma Aldrich) lyophilized Aβ1-42 was prepared according to the recommended preincubation protocol to obtain the required peptide aggregates in neurotoxicity studies. Formation of peptide aggregates was achieved by dissolving the lyophilized peptide in 167 µl of molecular biological water. The final concentration in the vial was 1mg/ml to 1ml with 833 µl of sterile PBS. Allicin treatments (10 µM, 50 µM, 100 µM) [14] were applied to neuroblastoma cells in culture medium.

Cell viability

MTT assay

MTT test was utilized to examine the cell viability. MTT solution (Sigma-Aldrich) was supplemented to each well in accordance with the kit protocol. After incubation interval, formazan precipitate was dissolved in DMSO (150 µl) and the absorbance were read with spectrophotometer at 480 nm (BioTek Instruments, USA).

LDH assay

The cytotoxicity was evaluated via the LDH assay. Lactate dehydrogenase (LDH) levels were examined in accordance with the manufacturer's guideline (Elabscience, United States). The absorbance was read at 450 nm.

Evaluation of oxidative stress

The malondialdehyde (MDA) and reactive oxygen species (ROS) concentration and the activity of superoxide dismutase (SOD) were determined by using ELISA kits (Elabscience, United States) in conformity with kit protocol. ROS concentration was measured by using ELISA kit (LSBio, United states) according to manufacturer's guide.

RT-PCR analysis

mRNA extraction and cDNA synthesis were conducted with RNeasy easy kit (Qiagen, Hilden, Germany) as defined before [15]. cDNA was synthesized with a High-Capacity cDNA Reverse Transcription Kit in compliance with manufacturer's guidelines. Real-time RT-PCR analysis were conducted as previously defined [15]. The mRNA caspase-3 expressions were calculated by Rotor-Gene Q (QIAGEN). The mRNA expression level of each gene relative to β-actin. was determined by the $2^{-\Delta\Delta Ct}$ method. The sequences of sense and antisense primers for the human Caspase-3 was 5'- TTTTCAGTCCGGGGACAAAC-3' and 5'- GGGCAGCCGAGAATAACAAT-3'.

Statistical analysis

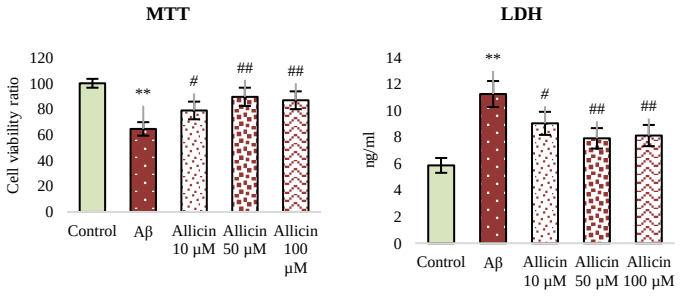
Data obtained in the study were analyzed statistically with IBM SPSS Statistics (Version 22.0, IBM Co., Chicago, IL, USA) software. All tests were conducted by one-way analysis of variance (ANOVA) with post hoc Tukey's test. The ANOVA is utilized to define whether there are any statistically significant differences between the means of independent groups. The Tukey Test is a post-hoc test designed to conduct a pairwise comparison of the means to see where a significant difference stands. Data were expressed as mean (SD). *P*-value <0.05 were assumed meaningful. The results are stated according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Results

MTT and LDH test results

MTT and LDH results are presented in Figure 1. Aβ markedly decreased the cell viability of SH-SY5Y by 35.46% in MTT analysis and elevated LDH levels by 91.65%. In contrast, in MTT analysis, the allicin treatment markedly increased cell viability indicating that allicin induces cell proliferation by 22.20%, 38.59% and 34.50% in cells treated with 10 µM, 50 µM and 100 µM of allicin, respectively, relative to the Aβ group. Moreover, in LDH analysis, allicin treatment markedly decreased LDH release by 19.64%, 29.68% and 27.82% in cells treated with 10 µM, 50 µM and 100 µM of allicin, respectively, relative to the Aβ group (P<0.05).

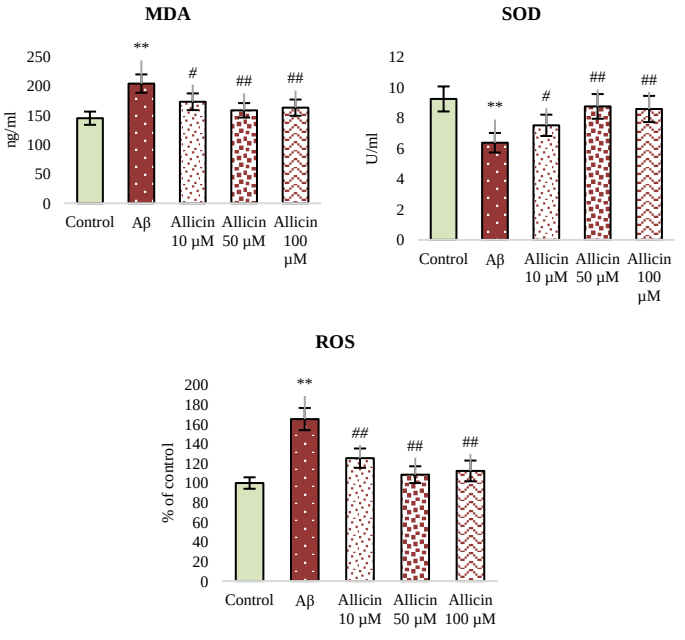
Figure 1: Effects of Allicin on cell viability test results. Data are expressed as the means (SD). ** P<0.001 vs control group, # P<0.05 vs Aβ group, ## P<0.001 vs Aβ group.



Oxidative stress results

Since the generation of free oxygen radicals and lipid peroxidation products are implicated in pathologic processes of neurotoxicity, we examined the oxidative and anti-oxidant biomarkers. Exposure to Aβ markedly increased MDA and ROS level by 40.7% and 65.21%, respectively, in comparison with the control (P<0.001) (Figure 2). Moreover, Aβ decreased the activity of SOD in SH-SY5Y cells by 31.06%. Allicin at concentrations of 50 µM markedly balanced out the Aβ-induced MDA and ROS production by 22.35% and 34.3% (P<0.001), respectively (Figure 2). Similarly, allicin at the dose of 50 µM increased the activity of SOD in Aβ-exposed SH-SY5Y cells by 37.36% (P<0.001).

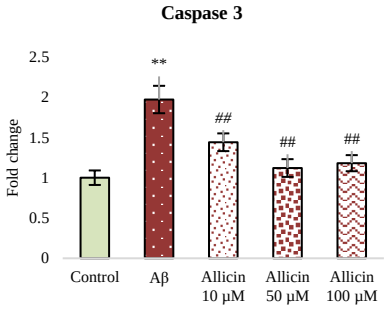
Figure 2: Effects of Allicin on oxidative stress markers. Data are expressed as the means (SD). ** P<0.001 vs control group, # P<0.05 vs Aβ group, ## P<0.001 vs Aβ group.



mRNA expression of Caspase 3

The effects of allicin on the caspase 3 expression in Aβ-induced neurotoxicity were determined by the RT-PCR analysis. Caspase 3 expression were upregulated in Aβ group by 1.97-fold in comparison to control group (Figure 3). Allicin at dose of 50 µM markedly lowered the expression of caspase 3 levels by 43.14%.

Figure 3: Effects of Allicin on apoptosis. Data are expressed as the means (SD). ** P<0.001 vs control group, ## P<0.001 vs Aβ group.



Discussion

In this study, we established neurotoxicity with Aβ on human SH-SY5Y cells to assess the protective effect of allicin in AD. Studies on AD patients have reported that Aβ plaque deposition causes cytotoxicity by increasing ROS production and oxidative stress [16]. Prevention or elimination of Aβ-mediated cytotoxicity associated with oxidative stress may be a novel and important approach for prophylactic/therapeutic purposes in AD. In recent years, natural antioxidants obtained from plants have come to the forefront to prevent oxidative damage, especially in the prevention of neuropsychiatric disorders associated with oxidative stress.

Allicin, one of the most important components of garlic, has many medicinal properties such as antioxidant and anti-apoptotic functions [13, 17]. Allicin's capability to easily cross the blood-brain barrier and its known neuroprotective properties make it worthy of investigation in neurodegenerative diseases [18-20]. Studies have shown that allicin increases SOD activity and decreases MDA levels by inhibiting signaling pathways related to oxidative damage. With these antioxidant mechanisms, allicin has shown beneficial effects in memory and learning disorders and ischemic brain damage [12, 13]. In line with previous studies, allicin significantly decreased MDA and ROS levels, and increased the SOD activity in our study. These antioxidant effects can be seen as an important reason for the positive effects of allicin on cell viability.

One of the important pathological processes associated with AD is apoptosis [21]. Activation of caspases is an important step in cellular apoptosis [22]. The caspase superfamily of cysteine proteases, including caspase 3, participates in the beginning and completion of the apoptotic process [23]. The increase in ROS production activates stress pathways associated with the mitochondria and endoplasmic reticulum. Mitochondria damage ultimately triggers the caspase 3, eventually induces mitochondria-dependent apoptosis [24]. Current research showed that allicin significantly reduced apoptosis by reducing caspase 3 expression, in accordance with previous reports.

Limitations

Although our study has strong evidences for the neuroprotective effects of allicin, it has some limitations. First of all, more studies should be done to determine whether these promising results obtained in cell culture can also be effective in sick individuals. In addition, allicin may exhibit different pharmacological properties such as antibiotic function apart from neuroprotection, and the existence of secondary effects of allicin on humans is unclear. These limitations will be eliminated with future studies on animal and human subjects to investigate the effects of allicin on AD.

Conclusion

In this study, the beneficial effects of allicin on Aβ-induced neurotoxicity on SH-SY5Y cells were reported for the first time in terms of cell viability, oxidative stress and apoptosis.

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Pharmacological treatment of asthma and allergic diseases in pregnancy

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Abstract

Allergy incidence in pregnancy is about 20% and frequently observed as rhinitis and asthma. Asthma often coexists with allergic rhinitis in adults, and severe nasal findings are present in one out of every three pregnant women. Asthma and allergic rhinitis may worsen or remain unchanged in pregnancy. Allergic reactions can also worsen the course of pregnancy. Appropriate drug selection should be made for asthma and other allergic diseases, and possible risks should be explained to the pregnant woman. Increased risk perception of drug use may cause the pregnant woman to stop taking the drug suddenly and the disease to worsen. The purpose of the treatment in pregnancy is controlling the mother's disease while ensuring a normal course of fetal development. Treatment should be started with the least number of drugs and the lowest dose possible. Inhaled beta-2 adrenergic agonists and theophylline can be used as bronchodilators during pregnancy. Chlorpheniramine, loratadine and cetirizine may be preferred in allergic conditions requiring antihistamine use. Prednisone and also pseudoephedrine can be used during pregnancy, if necessary. The use of alpha-adrenergic drugs other than pseudoephedrine and epinephrine should be avoided except for anaphylaxis.

Keywords: Asthma, Allergic Rhinitis, Anaphylaxis, Drug, Pregnancy

Introduction

Allergy is an immune-system-mediated hypersensitivity reaction of the body to foreign substances. Allergy incidence in pregnancy is about 20% and frequently observed as rhinitis and asthma [1,2]. Drug and food allergies, acute urticaria, allergic conjunctivitis and anaphylaxis are also allergic reactions that may occur in pregnancy. Allergic reactions can worsen the course of pregnancy. Similarly, pregnancy can worsen or trigger pre-existing allergic disease. Therefore, follow-up care is important for allergic conditions during pregnancy.

Hormonal changes due to pregnancy cause some physiological changes in the respiratory system. Respiratory volume (tidal volume), minute volume, alveolar-arterial oxygen gradient, oxygen partial pressure and partial blood pH (to respiratory alkalosis) increase during pregnancy, while functional residual capacity, residual volume, diffusing capacity and partial carbon dioxide pressure decrease. Respiratory rate generally does not change [3]. Therefore, respiratory symptoms in pregnant women with previous asthma may worsen gradually or remain unchanged [4].

Similar to asthma, allergic rhinitis may worsen or remain unchanged as a result of hormonal changes during pregnancy [5]. Severe nasal findings are present in one out of every three pregnant women [6]. Allergic rhinitis in adults often coexists with asthma. 80% of adults with asthma have allergic rhinitis, and 20-50% of adults with allergic rhinitis have asthma [7].

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Appropriate drug selection should be made for asthma and other allergic diseases, and possible risks should be explained to the pregnant woman. There may be an increased risk perception in pregnant women in terms of adverse drug-related consequences. Increased risk perception of drug use may cause the pregnant woman to stop taking the drug suddenly and the disease to worsen. For this reason, the most accurate treatment choice should be made for both pregnant women and the baby, and detailed up-to-date data on the possible effects of drugs on pregnancy should be known [8].

Asthma treatment in pregnancy

The purpose of the treatment of asthma during pregnancy is controlling the mother's disease while ensuring a normal course of fetal development. It is aimed that asthma symptoms and acute attacks do not occur, the daily activities of the pregnant are not limited and the quality of life does not decrease, and the lungs reach a respiratory capacity close to normal. Uncontrolled asthma during pregnancy will impair maternal lung functions and reduce the amount of oxygen in the blood, so it will have a greater effect on fetal development than asthma drugs. Therefore, treated asthma during pregnancy is considered a safer condition than untreated asthma with avoided drug use.

It is important to follow up the asthmatic pregnant during her pregnancy. It is recommended to evaluate the lung functions of pregnant women by performing a spirometry test with monthly follow-up. It should be ensured that the pregnant woman avoids allergens and especially smoking that may worsen asthma symptoms or cause attacks. The patient must be informed and educated about the control and treatment of asthma, its effects on pregnancy and fetal development, and the correct use of drugs. Treatment should be started with the least number of drugs and the lowest dose possible, and the dose and amount of the drug should be adjusted according to the clinical picture.

1. Bronchodilators (beta agonists)

Short acting bronchodilators are used in acute attacks and situations where a quick effect is desired. Albuterol (salbutamol), terbutaline, metaproterenol are among the drugs in this group and their use by inhalation is recommended during pregnancy. Studies conducted to date on its use in pregnancy suggest that short-acting bronchodilators are safe. An increased risk in terms of congenital defects or other pregnancy problems has not been detected in pregnant women using short-acting bronchodilators compared to those who do not use these drugs [9- 11].

Long-acting beta agonists such as salmeterol and formoterol are used in the long-term control of asthma and are generally preferred in combination with inhaled glucocorticoids. Having less information about their use in pregnancy than other asthma medications, these drugs are recommended to be used only when necessary. It can have tocolytic effects when used near birth. Additionally, it may have betamimetic effects such as tachycardia, tremor, tremor, and hypoglycemia in the newborn. Since their chemical structures are similar to short-acting beta mimetics but they have a long effect, it is thought that their benefits in asthma control during pregnancy are higher than the possible risk.

The United States National Institute of Health (NIH) reported that the use of beta agonists during pregnancy was safe in its 2004 report, in which the treatment of asthma during pregnancy was evaluated in detail [12]. Although some studies conducted in recent years have reported that it may be associated with fetal cardiac defects [13] and cleft palate development [14], researchers have stated that this may be due to medication, asthma or other reasons, and that there are some limitations in the studies.

2. Glucocorticoids

Glucocorticoids are used in asthma and in many conditions other than asthma. Studies on their use during pregnancy indicate that they do not create an increased risk for fetal development. Glucocorticoids used by inhalation such as beclomethasone, budesonide and fluticasone are among the drugs that can be preferred in pregnant women in the treatment of asthma [15]. Budesonide and fluticasone are the safest ones and beclomethasone is widely used during pregnancy.

Regarding the systemic (e.g. oral) use of glucocorticoids in pregnancy, some studies have concluded that first trimester exposures may be associated with slight increases in the risk of cleft palate and cleft lip [16]. There are also few studies reporting an increased risk of preterm birth and low birth weight. However, in these studies, it could not be concluded as to whether the severity of asthma in pregnant women or drugs caused this correlation. On the other hand, it is thought that a severe asthma picture during pregnancy will bring more risk than drug use.

Since gestational diabetes and hypertension are more common in pregnant women using oral glucocorticoids, it is important to follow-up them. Uncontrolled diabetes and high blood pressure during pregnancy are risky conditions for both mother and fetal development.

3. Theophylline

Theophylline is a drug that can be used orally in the treatment of asthma and chronic obstructive pulmonary disease during pregnancy; however, it has now been replaced by more effective inhaled glucocorticoids. There are case reports reporting cardiovascular defects, otocephaly (not developing lower jaw and joining ears below) and extremity anomalies following theophylline use during pregnancy [17-19]. However, case reports are not sufficient to assess drug-related risks and determine a correlation. Studies on the use of theophylline in pregnancy have not found a relationship with stillbirth or congenital defects [20-22]. On the other hand, it is stated that an increase in fetal respiratory movements may be observed due to the use of theophylline during pregnancy [23].

Due to the changes that may occur in theophylline pharmacokinetics during pregnancy, the drug level in the blood should be monitored in patients using theophylline. Especially drug-drug interactions (for example when used with beta agonists) and theophylline toxicity are among the factors that limit the use of theophylline in pregnancy. It is recommended to keep serum theophylline concentrations at 5-12 mcg / ml. It has been reported that theophylline toxicity findings such as tremor, tachycardia and vomiting can be observed in babies born to mothers using theophylline [24, 25], and these findings are

detected in pregnancies with theophylline concentrations above 10 mcg / ml [26,27].

4. Leukotriene receptor antagonists

Leukotriene receptor antagonists, such as montelukast and zafirlukast, are recommended as alternative drugs in the treatment and control of chronic asthma. In a study examining pregnant women who used montelukast during their pregnancy, the pregnancy outcomes of 180 pregnant women, 166 of which were in the first trimester, were compared with those with asthma and non-asthmatic pregnant women who did not use montelukast [28]. Although no difference was observed between the babies of the pregnant women using other asthma medications, it was reported that the babies of the pregnant women using montelukast had a lower weight than the babies of the pregnant women who did not receive asthma treatment. This result indicates that asthma rather than drugs may cause low birth weight during pregnancy. In this study, an increase in the risk of birth defects in pregnant women using montelukast was not identified. In another study, 96 pregnant women with asthma using montelukast or zafirlukast were followed up, congenital defects (clubfoot / pes equinovarus, neurofibromatosis, imperforate anus) were found in three babies, and no increase in the risk of congenital defects was identified [29]. In the national studies conducted in Switzerland and Denmark, an increase in the risk of congenital defects was not identified in pregnant women using montelukast, while the increases in preterm birth and preeclampsia rates were linked to the asthma diseases of pregnant women [13, 30].

A small number of cases have been reported with limb anomalies following the use of montelukast during pregnancy. In the post-marketing research conducted by the manufacturer company, 271 pregnancies using montelukast were examined, 221 of the pregnant women were reported to have first trimester exposure and 9 of the babies born had congenital defects. While no increase in the risk of congenital defects due to montelukast use during pregnancy was identified, amniotic band deformity, polydactyly, foot deviation, hypospadias and penile curvature, thoracoabdominal syndrome, cystic kidney, hydrocele, and bifid tongue have been reported among congenital defects [31-33]. No causal relationship was found between the use of montelukast during pregnancy and fetal limb anomalies [34].

5. Zileuton/5-Lipoxygenase inhibitors

Since there is insufficient data on the use of Zileuton in pregnancy, it is recommended for use in the treatment of severe asthma that does not respond to other drugs. In patients receiving zileuton therapy, regular monitoring of liver function is required, and if an alternative drug can be used, the use of zileuton can be discontinued during pregnancy.

6. Omalizumab

Omalizumab is an immunomodulator used in the control of severe asthma. This monoclonal antibody treatment (anti-Ig E), which is applied once or twice a month, should be performed in a place with emergency medical intervention and by health personnel due to the risk of anaphylaxis. In case reports about its use during pregnancy, it was reported that asthma treatment was successful, and no pregnancy complication or fetal anomaly was observed [35-37]. According to the results of the reports on the use of omalizumab in pregnancy, 20 out of 169 births, most of whom had first trimester exposure, had congenital defects, of which 7 had major defects (hypospadias, arteriovenous malformation, bilateral renal pelvis dilatation, cutaneous mastocytosis, patent foramen ovale, vesicoureteral reflux) have been described [38]. Since the major defects observed did not show a pattern, it was not thought to be associated with omalizumab use during pregnancy. In the same study, preterm birth rates are around 15%, and researchers think this may be related to asthma. When the structural defects seen in babies were examined in detail, the researchers who reported that 6 out of 20 infants with congenital defects had ankyloglossia, did not include any comments regarding this anomaly in their studies, and underlined the need to investigate the effect of omalizumab in pregnancy in detail with controlled studies. Consequently, data on omalizumab use in pregnancy are not sufficient to make a risk assessment.

Treatment of allergic diseases in pregnancy

Apart from asthma, allergic rhinitis is one of the other allergic conditions that may worsen or need treatment in pregnancy. Treatment of allergic rhinitis during pregnancy is no different from treatment for non-pregnant patients. Due to their low systemic effects, intranasal drugs (such as intranasal steroid and montelukast) are preferred in pregnancy. Second-generation antihistamines (such as loratadine, cetirizine) can also be used during pregnancy, if necessary [39].

1. Antihistamines (H-1 receptor blockers)

First generation antihistamines (such as dexchlorpheniramine, chlorpheniramine, diphenhydramine, hydroxyzine, clemastine) used in allergy treatment are drugs with sedative side effects. Sedative effect does not occur in second generation antihistamines such as loratadine, cetirizine, levocetirizine, fexofenadine, ebastine, rupatadine. Although data on ebastine, desloratadine, fexofenadine and levocetirizine are very limited, there is sufficient data on the use of loratadine and cetirizine in pregnancy. In studies conducted on the use of cetirizine during pregnancy, the results of more than 1000 pregnant women were evaluated and an increase risk of congenital defects was not identified [40, 41].

Some studies conducted on pregnant women using loratadine suggest that the use of loratadine during pregnancy increases the risk of hypospadias [42-45]. However, other prospective studies and many systematic analyzes revealed that the use of loratadine in pregnancy is not associated with the development of hypospadias [46]. Loratadine, as a non-sedating antihistamine, is one of the most preferred drugs in the treatment of allergies in pregnancy today.

There is no literature information on the possible effects of azelastine and olopatadine, which are used intranasally, during pregnancy. However, considering that the systemic effects of these drugs are negligible in terms of administration routes, it is not thought that they may affect fetal development.

2. Decongestants

Although decongestants are not used in the treatment of asthma, they are preferred for symptomatic treatment of upper respiratory tract allergies. Among the decongestants used orally or intranasally, pseudoephedrine is the most well-known, and oxymetazoline, phenylephrine and phenylpropanolamine are among these drugs. Because of vasoconstrictive effects, they

should not be used in pregnant women with high blood pressure and placental problems. Although some studies on decongestants' effects on pregnancy have shown associations with congenital defects such as extremity anomalies, gastroschisis, intestinal atresia and hemifacial microsomia, these findings have not been confirmed by other studies [47-49]. On the other hand, the absolute risk is considered quite low, since the defects mentioned in the studies are observed very rare. There is no conclusive evidence that decongestants are teratogenic.

Studies on the use of decongestants in pregnancy are rather limited and contain conflicting results. Therefore, until more detailed data are available, it is recommended to use pseudoephedrine as a nasal spray and not exceeding three days, if it is necessary to use it in the first trimester, which is important for organ development, It is not expected to cause problems in pregnant women who do not have high blood pressure and placental anomaly in the later stages of pregnancy. However, it should be kept in mind that nasal decongestants may lead to addiction in long-term use.

3. Corticosteroids

Corticosteroids such as triamnisolone, mometasone, budenoside, fluticasone can be used in pregnancy either intranasally or by inhalation. It may be preferred to use intranasal corticosteroids before the use of decongestants, especially in the treatment of allergic rhinitis. Similarly, since the systemic effects are unlikely when used at recommended doses, topical use of corticosteroids may also be required in the treatment of allergic dermatitis in pregnancy. However, applications on large surfaces should be avoided since it increases the possibility of systemic effects of glucocorticoids used topically.

Anaphylaxis treatment in pregnancy

Anaphylaxis is a life-threatening condition and therefore pregnant women should be treated like non-pregnant women; otherwise, fetal and maternal problems may occur. Oxygenation and volume replacement should be done primarily. In hypotensive conditions, the pregnant woman should be placed on her left side to eliminate possible vena cava inferior pressure [50]. Epinephrine can reduce uteroplacental blood flow; it can be used only if needed in the treatment of anaphylaxis. Systemic glucocorticoid therapy can be selected primarily in cases of life-threatening anaphylaxis. Intubation and tracheotomy may be required in cases with laryngeal spasm.

In a study on epinephrine use in the first trimester of pregnancy, several major and minor anomalies were observed. However, it has been reported that only the formation of inguinal hernia may be specifically related to the drug [51]. On the other hand, in a study examining 259 pregnant women with asthma using various sympathomimetics including epinephrine, no increase in congenital defects or adverse pregnancy outcomes was observed [52].

Although the prevalence of anaphylaxis during pregnancy is not known exactly, it can be said to be a rare condition [53]. Specific Ig-E antibodies are not expected to reach the fetus, since they do not pass through the placenta [54]. It is mainly maternal hypoxia or hypotension secondary to anaphylaxis that affects the fetus. In anaphylaxis, uteroplacental flow is disrupted and it may cause a series of complications that can lead to fetal distress, brain damage and death [55-57].

Conclusion

Inhaled beta-2 adrenergic agonists and theophylline can be used as bronchodilators during pregnancy. Chlorpheniramine, loratadine and cetirizine may be preferred in allergic conditions requiring antihistamine use. Prednisone and also pseudoephedrine can be used during pregnancy, if necessary. It is recommended that the use of alpha-adrenergic drugs other than pseudoephedrine and epinephrine should be avoided except for anaphylaxis.

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