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A new maneuver for classical laryngeal mask airway insertion: Prospective randomized study

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Laryngeal mask airway (LMA) has been frequently used for airway management. But the satisfaction of the insertion and trauma at insertion remain problems. We present a new insertion maneuver for classical LMA (cLMA) with a partially inflated cuff and examine its success and complication rate.

Methods: In 4 months, 158 patients who were classified as ASA I–III and older than 18 years old and were planned for LMA were included in this study consecutively (according to the study design, one patient was excluded during the study). Emergency cases, patients with any contraindications with LMA, patients who were expected to undergo surgery for more than 2 h, patients with preoperative respiratory tract infection or sore throat, patients undergoing oral or nasal surgery, and patients with aspirated oropharyngeal secretions after removal of LMA was excluded from the study. Age, gender, height, weight, ASA scores, comorbidities, and the duration of anesthesia and surgery of the patients were recorded. One-hundred-fifty-seven consecutive patients were randomized into two groups by a coin toss [control group (group C) and study group (group S)]. The groups were compared in terms of LMA insertion success, the number of insertion attempts, the presence of blood on the LMA or in secretions, and postoperative sore throat. Classical Laryngeal Mask Airway was inserted with Brain's standard technique in group C and with the new technique in group S. In the new technique, the head and neck of the patient were supported in a straight position, the mouth was opened, cLMA was held with a dominant hand from the tube part and inserted until the tip touches to the oropharynx. The index finger of the non-dominant hand was inserted into the mouth to pass by the cLMA and reach the tip of the cLMA. The tip of cLMA was directed to the caudal by the index finger. Then, cLMA was inserted by the guidance of the index finger until it reached the triangular base of the oropharynx.

Results: There was no statistically significant difference in terms of demographic data and placement success; placement success was better in the study group (100% versus 98.6% and $P = 0.45$). Similarly, the count of attempts was better in the study group. The mean attempt number was 1.11 in group S and 1.28 in group C ($P = 0.02$). Also, blood on LMA was seen to be more common in group C ($P = 0.04$). There were no statistical differences in sore throat, but it was less seen in group S.

Conclusion: The new maneuver was better than the standard technique and easy to use in daily practice.

Keywords: Airway management, Laryngeal mask airway, Complications

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Introduction

Laryngeal mask airway (LMA) was designed by Archie Brain [1] in 1981 and has been in clinical use since 1988. Brain [2] also described an insertion technique later called the "standard technique". LMA has been used as an important option in difficult airway conditions and cardiopulmonary resuscitation besides its use in many surgical procedures that do not require muscle relaxation and that are expected to continue for less than 2 h [2-12].

A few new LMA models have emerged to optimize the clinical use of the LMA, and Brain's LMA is now called the classic LMA (cLMA). Although some new recommendations have been made regarding the placement technique to increase the placement success of cLMA, which has an important role in LMAs that are currently used in clinical practice and to reduce complications, the placement success is still not 100%, and complications such as trauma, mucosal bleeding in the pharyngeal mucosa, and postoperative sore throat may be encountered during placement [1-12]. The main problems with placement appear to be that the tip of the cLMA may be buckled towards the cranial during placement, and/or the cLMA folds the epiglottis downward [2, 13-18]. Based on these, we planned this study to test the new insertion maneuver that we thought would improve placement success and reduce complications by eliminating the problem of the cLMA tip from buckling towards the cranial.

The primary outcome of this study was the success of placement and whether the new method tested can be used and recommended, and the secondary outcome was to show the complication and side effect profile according to current methods.

Materials and methods

Approval of the ethical committee of Bezmialem Vakif University (19.12.2012, 28/4) and informed consent of the patients were obtained. The study was planned to be completed in 4 months. During this time, 158 patients classified in the American Society of Anesthesiologists (ASA) I–III and older than 18 years old and planned for LMA were included in this study consecutively (one patient was excluded during the study). Emergency cases, patients with any contraindications with LMA, patients who were expected to undergo surgery for more than 2 h, patients with preoperative respiratory tract infection or sore throat, patients undergoing oral or nasal surgery, and patients with aspirated oropharyngeal secretions after removal of LMA were excluded from the study. Age, gender, height, weight, ASA scores, comorbidities, and the duration of anesthesia and surgery of the patients were recorded. None of the patients received premedication. Patients were randomly divided into two groups by coin toss.

Preoperative analgesia treatment, anesthesia induction, and maintenance were kept under standard conditions. Electrocardiogram (ECG), non-invasive blood pressure (NIBP), and peripheral blood oxygen saturation (SpO_2) follow-up were performed before anesthesia induction. During the induction, patients were administered 2 mg of midazolam and 1–1.5 μg/kg of fentanyl; and after 2 min, 2.5–3 mg/kg of propofol. Anesthesia was maintained with sevoflurane (MAC = 1.3–1.4) and 50:50% air-O_2. Patients received 500 mg of metamizole sodium in 100 ml of fluid and 1 g of paracetamol via intravenous infusion half an hour before the completion of the operation.

cLMA placements

It is stated in the standard technique of Brain [1, 3, 14] that the air of the cuff must be completely emptied so that a sharp line is obtained at the tip of the LMA, ensuring proper placement. However, some studies claim that partial or fully inflating of the cuff will provide a soft tip, resulting in less trauma and better placement success. In studies testing the cases where the cLMA cuff is fully deflated, half inflated, and fully inflated; conflicting results have been obtained for placement success, while complication rates seem to favor partially or fully inflated cLMAs [2, 9, 16-20]. In our study, we preferred to use half-inflated cLMA for both groups considering these studies. In addition, in this study, all cLMA placements were conducted by researchers with more than 8 years of experience working as staff anesthesiologists.

The cLMA (LMA North America, Inc.) size was determined for both groups according to the manufacturer's recommendations. In all patients, cLMA cuffs were half or fully inflated based on manufacturer recommendations

Control group (Group C): Brain's standard technique [3] was used as the placement method. However, contrary to Brain's description, the cuff was half-inflated. The patient's head was brought to the sniffing position (neck flexion, head extension), and the head was held in this position with the non-dominant hand. The cLMA was held at the junction point of the cuff and the tube, using the dominant hand just as holding a pen, and after the cuff was placed in the mouth, the cuff was pushed from the junction point towards the hypopharynx by pressing on the hard palate with the index finger. When the laryngeal mask was felt on the triangular base, the hand was removed from the mouth, the cLMA was released, and the cuff was inflated with air.

Study group (Group S): In this group, cLMAs with half-inflated cuffs were used. The patient's head was slightly extended, and the head and neck supported this position. The mouth was opened by the non-dominant hand, the cLMA was held by the dominant hand from the tube part, the cuff was inserted into the mouth, and the cLMA was advanced in the mouth until the tip reached the oropharynx (Figure 1). The index finger of the non-dominant hand was inserted into the mouth, passing by the ipsilateral side and slightly behind the cuff, and the tip of the cLMA in the mouth was detected and directed caudally (Figures 2 and 3). While the index finger of the non-dominant hand was in the mouth and the pulp of the finger was in contact with the posterior wall of the oropharynx at the lowest possible portion, the cLMA was advanced to the hypopharynx with the dominant hand while the tip of the cLMA was oriented caudally (Figure 4). When the laryngeal mask was felt on the triangular base, the hand was removed from the mouth, cLMA was released, and the cuff was inflated with the air.

Figure 1: Insertion of the cLMA into the oropharynx with the dominant hand

Figure 2: Putting the index finger of the non-dominant hand in the mouth passing by the cLMA

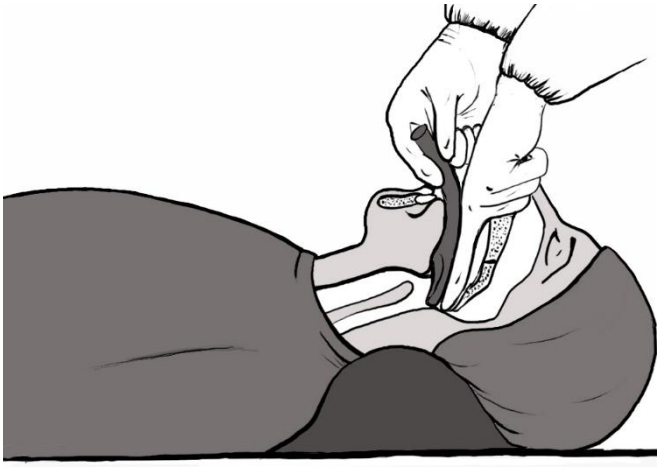


Figure 3: Directing the tip of the cLMA to caudally by the index finger of the non-dominant hand

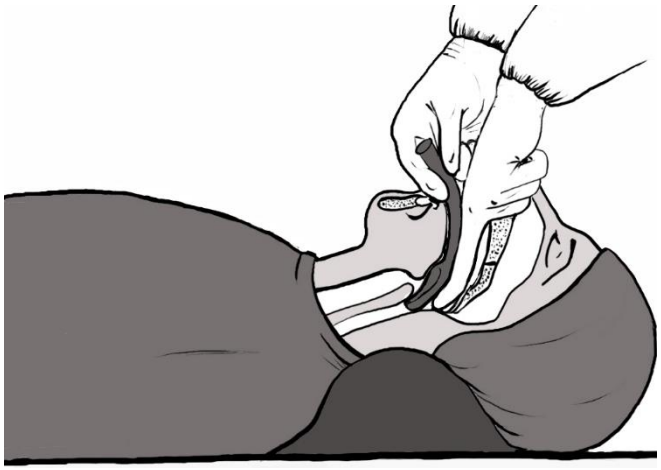
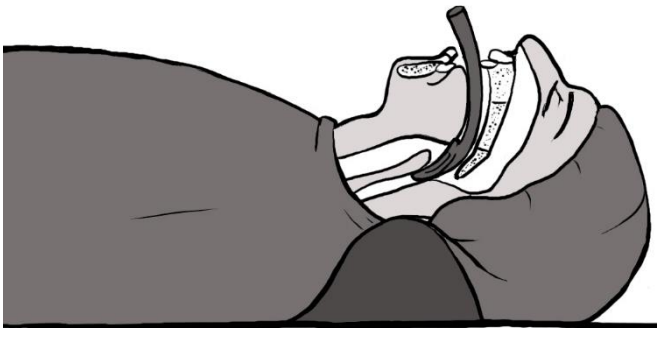


Figure 4: Advancing the cLMA over the index finger to its final position



The success of laryngeal mask placement was clinically confirmed in both groups. After placement, the cLMA-ventilator connection was achieved, and the patients were manually ventilated. Chest movement, capnography, SpO_2, airway resistance, and refilling of the reservoir bag were used to assess the success of cLMA placement. When these evaluations showed adequate ventilation, the patient was mechanically ventilated, and air leakage was evaluated. If the leakage during mechanical ventilation was less than 10% of the adjusted tidal volume, successful placement was considered, and if more than 10% leakage was observed, the placement was considered unsuccessful.

The number of placement attempts was recorded. One attempt was defined as the one-time advancing of the cLMA in the mouth. The maximum number of attempts is limited to three. The other placement method was tried if the cLMA failed in three attempts. If the other method was also unsuccessful in three attempts, orotracheal intubation was performed.

The data obtained up to this stage were recorded, and further evaluations were made by another anesthesiologist who was blind to the group distribution and the details of the cLMA placement. At the end of the surgery, the cLMA was removed, and cLMA and secretion were checked for the presence of blood. Patients were questioned for sore throat 30 min after being taken to the recovery unit and/or when the Aldrete score was ≥ 8. If the patient had a sore throat, the severity of the pain was assessed by a numerical analog scale (NAS). In this evaluation, patients were asked to score their pain between 0 and 10 (0 = no pain, 10 = the most severe pain they could imagine).

Statistical analysis

Frequency and descriptive analyses of cases were recorded. Qualitative data were analyzed using Fisher's exact test, and quantitative data were analyzed using Mann Whitney-U test. A logistic regression test was used for the subgroup analysis. The data analysis was performed using SPSS version 17 software (SPSS, Inc., Chicago, IL, USA). *P*-values < 0.05 were judged statistically significant.

Results

In a total of 158 patients, there were 22 female and 51 male patients (n = 73) in group C, and 27 female and 58 male patients (n = 85) in group S ($P = 0.72$). The median age, height, and body weights of the groups were similar ($P = 0.14$, $P = 0.68$ and $P = 0.27$, respectively) (Table 1). ASA scores, duration of operation, and anesthesia were also similar (Table 2).

One patient in group C was intubated due to insufficient ventilation emerging in the 55th min of surgery and was excluded from the study. This patient's surgery was completed without any complications.

Table 1: Comparisons of patient characteristics between the groups

Parameter	Number of patients	Mean (SD)	*P*-value
Sex			
Group C (n = 72)	21 female/51 male		0.72
Group S (n = 85)	27 female/58 male		
Age (y)			
Group C		51.78 (17.81)	0.14
Group S		47.48 (18.27)	
Height (cm)			
Group C		170.07 (8.71)	0.68
Group S		169.26 (15.03)	
Weight (kg)			
Group C		76.47 (14.39)	0.27
Group S		74.05 (13.27)	

SD: standard deviation

Table 2: Comparisons between the groups for ASA* statuses, comorbidities, operation durations, and anesthesia durations

	Number of patients group C/Group S	Minutes mean (SD)	*P*-value
ASA status			
ASA I	35/51		0.205
ASA II	31/25		
ASA III	6/9		
Operation duration			
Group C		59.83 (36.48)	0.95
Group S		60.21 (44.75)	
Anesthesia duration			
Group C		79.01 (38.49)	0.83
Group S		77.55 (46.35)	

ASA: American Society of Anesthesiologists, SD: standard deviation

The success rate of cLMA placement was 100% (85/85) in the study group and 98.6% (71/72) in the control group (P = 0.45). In 89.4% (76/85) of the patients in the study group, LMA was placed in the first attempt, it was placed in the second attempt in 10.6% (9/85) of the patients, and the third attempt was not needed in any patient. On the other hand, in the control group, LMA was placed at the first attempt in 79.2% (57/72) of the patients and in 13.9% (10/72) and 5.5% (4/72) at the second and third attempts, respectively. In one patient in the control group, cLMA could not be placed in all three attempts. Following the study plan, the other method (a new method tested in the study group) was tried, and cLMA was placed on the first attempt with this method.

The mean of the number of placement attempts in group S (1.11 [0.31]) was significantly lower than the group C (1.28 [0.58]) (P = 0.02). The incidence of blood on LMA was 1.2% (one patient) in the study group and 8.3% (6 patients) in the control group (P = 0.04). In the study group, the incidence of sore throat was 11.9% (ten patients), and in the control group, this incidence was 19.4% (14 patients) (P = 0.19).

Also, NAS values of patients with sore throats were obtained according to the study plan. The median NAS score in the Group S was (4.20 [2.34]) (min = 1, max = 8), while it was (3.93 [1.53]) (min = 1, max = 7) in group C (P = 0.73). Table 3 indicates the success rates, number of attempts, complication rates, and NAS scores between the two methods.

Table 3: Success of the techniques, numbers of attempts, complication rates, and VAS* scores between the groups

	n (%)			*P*-value
Number of attempts	1st Attempt	2nd attempt	3rd attempt	
Group C	57 (79.2%)	10 (13.9%)	5 (6.9%)	0.02
Group S	76 (89.4%)	9 (10.6%)	0 (0%)	
Successful insertion rates				
Group C	71 (98.6%)			0.45
Group S	85 (100%)			
Blood on the LMA/in secretions				
Group C	6 (8.3%)			0.04
Group S	1 (1.2%)			
Sore Throat				
Group C	14 (19.4%)			0.19
Group S	10 (11.9%)			
VAS scores for sore throat				
Group C (14/72)	3.93 (1.53)			0.73
Group S (10/72)	4.20 (2.34)			

Discussion

In this study, we compared the standard technique of Brain with the new insertion method described above for the placement of the half-inflated cLMA. The new insertion method tested was better than the standard technique in terms of placement success and complications. Therefore, it seems to be a viable and recommendable placement method.

Although many LMA models and placement techniques have been proposed after the initial LMA model (cLMA) and placement technique (standard technique) introduced by Dr. Archie Brain, several problems for patients and anesthesiologists are still present.

Different than Brian's [1] claim in his study published in 1983, more emphasis has been put on "the placement success on the first attempt" in later studies. According to the literature, the placement success rate in the first attempt ranged between 75% and 98% [2, 8-11, 19-24]. In our study, the success rates of placement at the first attempt was 79.2% and at the end of the third attempt 98.6% in Group C, while the first attempt success was 89.4% and at the second attempt was 100% in Group S. This results seems to be compatible with the literature. In their study, Matta et al. [20] placed fully deflated and half-inflated cLMA by applying the standard technique, and the first attempt success rate was 75% in the fully deflated group, and the success rate increased to 92% at the end of three attempts, while with the half-inflated cLMA these values were 88% and 97.7% respectively. The study conducted to investigate the use of cLMA in Pakistan by Khan et al. [12] revealed that the success rate using the standard technique of Brain at the first attempt was 84%, and the third attempt was performed successfully in all patients. With Brain's standard technique, McCrirrick et al. [21] reported first attempt success and total placement success rates of 76% and 94%, respectively. Brimacombe et al. [24] reported 96% success in the first attempt and 100% in the second attempt.

In our study, the mean number of attempts of Group S (1.11 [0.31]) was significantly lower than Group C (1.28 [0.58]). Goyal et al. [25], in their study including 40 patients in total on which half inflated cLMA was applied, compared the standard Brain technique with the thumb technique. In this study, the mean number of attempts was 1.20 (0.51) with the standard technique and 1.25 (0.5) with the thumb technique. In the study conducted by Jiwon et al. [26], it was observed that in the fully deflated and half-inflated cLMA applied to a total of 172 patients, the mean number of attempts was 1.1 (0.2) and 1.1 (0.3), respectively.

In our study, we evaluated the trauma related to cLMA by investigating the presence of blood on LMA and/or in the secretion and the sore throat complaints. In addition, we questioned the severity of pain in patients with sore throats. According to our study, the new method is safer regarding these side effects. One patient (1.2%) had blood on the LMA in group S, and six patients (8.3%) had blood in Group C. On the other hand, the rate of sore throat was 11.9% (ten patients) in Group S and 19.4% (14 patients) in Group C.

Following the study plan, the NAS values of patients with sore throats were also evaluated. The median NAS score in the group S was 4.20 (2.34) (min = 1, max = 8), while in group C this value was 3.93 (1.53) (min = 1, max = 7). Although there was no difference in the statistical significance between the two groups, the pain scores were higher in the study group.

Trauma due to placement has been mostly evaluated with blood and sore throat previously. Besides these parameters, odynophagia and hoarseness were also investigated in some studies. The incidence of the presence of blood varies between 1.7% and 32% in the studies in which the standard technique was applied, while the incidence of postoperative sore throat varied between 2.9% and 28% [2, 11, 15, 18, 19, 21-23, 25-28]. Similar to our study, the prevalence of the presence of blood found in

these publications is lower than sore throat rates. Therefore, it can be concluded that there is no direct connection between physical trauma and sore throat. However, in the user manual, cLMA sizes and the inflating quantities are fixed, but the pharynx anatomy may show natural variations among individuals. This may cause the pressure applied by the LMA on the pharynx wall to be relatively different and may cause differences in the perfusion of the mucosa. This reminds us that we have to consider ischemic pain, and LMAs should be inflated to a level that does not exceed the mucosal perfusion pressure or to a minimum amount to prevent air leakage.

Another point that we think is important is that sometimes it may be difficult to bring the patient's head to the sniffing position due to the patient's anatomical characteristics, and sometimes it may not be appropriate due to cervical disc problems. In the tested method, keeping the head in a normal position, except for a slight extension, could save us from problems such as head-on bringing sniffing position and holding in the air.

There were some limitations to our study. One of them is that the group in which the patient was involved and the number of attempts were known by the researcher who placed the cLMA. However, this awareness is inevitable. This bias was minimized by preventing the researchers, who collected and evaluated the data after the placement, from knowing which group the patient was from.

Another limitation was that fibreoptic observations did not evaluate the cLMA placement status. In many studies, cLMA was clinically checked for proper placement [2, 8-10, 13-15, 19-23, 25, 26, 28, 29]. The first paper that compares clinical findings and fibreoptic evaluations were published by J Payne [13]. It was concluded that the only reason for airway obstruction was failed down folding of the epiglottis. In the paper where Brain [14] comments on Payne's publication, he stated that the clinically good patients ventilated were evaluated with fiberoptic, and some observed that the epiglottis was folded down. He speculated that, despite this folding, the gap on the sides of folded-down epiglottis allows good ventilation. Rowbottom et al.'s study [10] placed cLMA with standard technique in a group of 100 pediatric patients and evaluated the cLMA position fiberoptically. In this study, it was seen that cLMAs were located in the appropriate position on only 49 patients, although there was no clinical problem in the ventilation of 98 patients. Similarly, Jiwon and colleagues [26] compared the placement of fully deflated and half-inflated cLMAs in their study, and they found that despite the difference in the number of attempts, the duration of the placement and the leakage around the cuff did not differ significantly, yet the fibreoptic scoring was statistically different between the groups. Considering these studies, we thought that it would be sufficient to evaluate the clinical findings of cLMA.

Conclusion

Based on our findings, the placement of the half-inflated cLMA with the new insertion maneuver is superior with regards to both the placement success and the complication rates when compared to the standard method of half-inflated cLMA and seems to be and viable and recommendable method.

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Experience with intraoperative extracorporeal membrane oxygenation in lung transplantation: intraoperative indicators

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Ethics Committee Approval
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Conflict of Interest
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Abstract

Background/Aim: Intraoperative extracorporeal membrane oxygenation (ECMO) is being used with increasing frequency in lung transplantation. However, the factors associated with the use of intraoperative ECMO in lung transplant patients are not yet conclusive. In this study, we aimed to determine the effective factors for providing intraoperative ECMO support in patients undergoing lung transplantation. In addition, we aimed to evaluate the effect of ECMO support on morbidity and mortality.
Methods: In this retrospective cohort study evaluating lung transplant patients, patients were divided into two groups: those who received intraoperative ECMO support and those who did not. Demographic data, the lung allocation score (LAS) and pulmonary arterial pressure (PAP), intraoperative data, postoperative complications, duration of mechanical ventilation (MV), length of stay (LOS) in intensive care and hospital, and mortality rates were recorded for both groups. Factors affecting entry to ECMO were analyzed by Multivariate Logistic Regression.
Results: In this period, 51.9% of 87 patients who underwent lung transplantation required intraoperative ECMO. The mean age, LAS, and PAP of the ECMO group were significantly higher than the non-ECMO group (P = 0.043, P = 0.007, and P = 0.007, respectively). In multivariate analysis, it was found that lower MAP averages were a predictive parameter in intraoperative ECMO requirements (OR: 1.091; CI: 1.009-1.179; P = 0.028). The ECMO group's mechanical ventilation time and hospital mortality were significantly higher than the other group (P = 0.004 and P = 0.025, respectively).
Conclusion: Preoperative indicators of intraoperative ECMO support were determined as age, LAS, and PAP elevation. In addition, low MAP levels and high lactate levels were always determined as intraoperative indicators in lung transplantation until the transition to ECMO support.

Keywords: Lung transplantation, Intraoperative extracorporeal membrane oxygenation, Mean arterial pressure, Age, Pulmonary arterial pressure, Lung allocation score

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Introduction

Lung transplantation (LT) is an effective treatment method for end-stage lung diseases. Thanks to the developing technology, experience and scoring systems in lung transplantation, the rate of critically ill patients who underwent lung transplantation have increased significantly. This made the management of these patients more complex. Due to excessive comorbidities in lung transplant recipients, it may be necessary to increase the frequency of cardiopulmonary support in the intraoperative period [1].

Extracorporeal membrane oxygenation has been used for years to provide cardiopulmonary support in patients with severe respiratory and heart failure [2]. In recent years, ECMO has been preferred to provide intraoperative cardiopulmonary support instead of cardiopulmonary bypass (CPB) in lung transplantation. Intraoperative ECMO is often used due to pulmonary hypertension, hemodynamic instability, and intolerance of single-lung ventilation [3-5].

Advances in ECMO technology, gained experience, and the fact that survival has increased from 25% to 75% over the years have played a convincing role in increasing the use of this treatment in lung transplantation [6]. Although some centers recommend the routine use of ECMO in lung transplantation, the decision to use intraoperative ECMO largely depends on the individual and institutional practice, and there is insufficient data in this area [7]. Considering the cost, morbidity-mortality, it is important to define the determinants of the use of intraoperative ECMO in lung transplantation.

In this study, we aimed to determine the effective factors for providing intraoperative ECMO support in patients undergoing lung transplantation and to evaluate the effect of ECMO support on morbidity and mortality.

Materials and methods

Study group and selection criteria

This study with retrospectively collected data was conducted by the principles of the Declaration of Helsinki. We evaluated data from all patients who had a lung transplant between March 2013 and April 2022 after approval by the Clinical Research Ethics Committee of a local hospital (E1-22-2541, 06.04.2022). Of 87 patients who underwent lung transplantation, three were excluded. Two patients were bridged to preoperative transplantation, and one was supported by intraoperative cardiopulmonary bypass (CPB). Patients who met the study criteria were divided into two groups: those who received intraoperative ECMO support and those who did not. The indication for intraoperative ECMO was determined in the detection of hemodynamic instability after clamping the pulmonary artery and when faced with severe hypoxemia (SO2 < 90%) due to impaired gas exchange and intolerance of one-lung ventilation [8]. Demographic and clinical data, intraoperative data, postoperative complications, duration of mechanical ventilation (MV), length of stay (LOS) in intensive care and hospital, and mortality rates were recorded for both groups.

Anesthetic management

Premedication was not preferred due to low respiratory reserves. Since severe dyspnea may develop in the supine position, oxygen was delivered through a face mask in the semi-sitting position. Vascular access was established with two 16 G intravenous cannula. Ringer's lactate (LR) solution was used as a maintenance fluid. Continuous systemic arterial monitoring was achieved via a 5-lead electrocardiogram (ECG), pulse oximetry, and radial artery cannulation. The double-lumen tube (DLT) placement was confirmed with a fiberoptic bronchoscope (FOB). For intraoperative and postoperative systemic and pulmonary arterial pressure monitoring, two central venous routes, one for the Swan-Ganz catheter, were established through the right internal jugular vein following intubation. A bispectral index (BIS) (BIS™, Covidien, MN, USA) sensor was placed on the patient's forehead to determine the depth of anesthesia. Anesthesia was induced in all patients by titrating 1 mcg kg^{-1} fentanyl, 0.15 mg kg^{-1} midazolam, and 1–2 mg kg^{-1} propofol. When the BIS became stable between 40 and 50, 0.6 mg kg^{-1} rocuronium was administered to facilitate tracheal intubation. Following intubation, the O_2/air mixture (fraction of inspired oxygen, FiO_2: 0.5), 5 cm H_2O positive end-expiratory pressure (PEEP), tidal volume (TV) of 7–8 ml kg^{-1} (ideal body weight), and volume-controlled ventilation VCV were given. After switching to single-lung ventilation (SLV) following the transplantation of one lung, monitoring was continued in pressure-controlled ventilation (PCV) mode with titrated FiO_2 to maintain adequate arterial saturation (>92%), TV <6 ml kg^{-1}, moderate PEEP, and inspiratory pressure <20 cm H_2O. The respiratory rate was adjusted to maintain the end-tidal CO_2 pressure in the 35–45 mmHg range. During the maintenance of anesthesia, total intravenous anesthesia (TIVA) consisting of titrated remifentanil and propofol was administered. Besides, 0.2 mg kg^{-1} rocuronium was infused approximately every 45 min throughout the operation to keep BIS between 40 and 60. The oropharyngeal temperature was monitored. While removing the lungs and sequentially placing the new lungs, norepinephrine (0.05–2 mcg kg^{-1}min), which increases the systemic vascular resistance (SVR), was frequently administered to prevent hemodynamic fluctuations due to surgical manipulations or cold protective fluids filled into the thorax, especially during the pulmonary arterial and venous anastomoses. The patients were administered liquid infusion to maintain MAP >65 mmHg, heart rate at 120 beats per minute, and serum lactate level >2 mmol L. Erythrocyte suspension was administered to keep the hemoglobin level >10 g/dL. Cell salvage was used to recover blood loss. At the end of the surgery, the DLT was replaced with a single-lumen tube (SLT), and bronchoscopy was used to clear anastomotic lines and secretions. Before tube replacement, gastric contents were evacuated with a nasogastric or orogastric tube. The patients were transferred to the intensive care unit under propofol and remifentanil infusion and appropriate monitoring. Extubation was performed after the patient responded consciously and took deep breaths on verbal command in the ICU.

Surgical procedure

A clamshell incision was performed in all patients undergoing double-lung transplantation. In single-lung transplantation, a sternum-sparing anterior thoracotomy incision was performed in the supine position. Following the incision, the thoracic cavity adhesions were released, and the lungs were fully mobilized. Subsequently, the pulmonary artery and vein stumps were prepared for implantation. After the donor's lung arrived in the operating room, pneumonectomy was performed, starting with the lung with poorer pulmonary function. Meanwhile, the patient's hemodynamics, pulmonary arterial pressure (PAP), and contralateral lung pulmonary function were closely monitored until implantation, and ECMO was provided when necessary. Following the sequential implantation of the donor's lungs, the clamps were removed, cold ischemia was terminated, and pulmonary function was evaluated by ventilation of the lungs. After checking the vascular anastomosis site for bleeding, and the bronchial anastomosis site for air leak, the surgical procedure was completed by drain placement and chest closure.

ECMO procedure

The need for intraoperative ECMO is often due to pulmonary hypertension, hemodynamic instability, and the inability to tolerate one-lung ventilation [1]. When ECMO was required, heparinization was performed with an activated clotting time (ACT) range of 145–180. Nipro® Membrane Oxygenator (Affinity® NT Integrated CVR/Membrane Oxygenator, Medtronic, Minneapolis, MN) was used for ECMO support at 36°C and 1.5–2.4 L min m^2 flow rate. Central v-a ECMO was preferred. ECMO's prime volume composition included LR and other additives. The patients were admitted to the ICU with or without postoperative support devices (central or peripheral v-a ECMO).

Postoperative management

Early postoperative monitoring was a continuation of intraoperative monitoring. We targeted weaning the patients from mechanical ventilation at the earliest possible time to minimize ventilator-associated pneumonia and ventilator-associated lung injury. The amount of fluid to be administered was generally determined according to the restrictive approach to maintaining the oncotic pressure. Immunosuppressive therapy was started. We evaluated the patients as per the standardized definition of primary graft dysfunction by the International Society for Heart and Lung Transplantation (ISHLT), introduced in 2005 and updated in 2016 (Table 1) [9]. Therefore, we decided on the treatment modalities according to the patients' PaO2/FiO2 (P/F) ratios and chest radiographs at the postoperative 6th, 24th, 48th, and 72nd hours.

Table 1: The International Society for Heart and Lung Transplantation standardized definition of primary graft dysfunction

PGD stage	P/F ratio (mmHg)	Chest radiograph
0	>300	Normal
1	>300	Diffuse allograft infiltration/ pulmonary edema
2	200-300	Diffuse allograft infiltration/ pulmonary edema
3	<200	Diffuse allograft infiltration/ pulmonary edema

PGD: Primary graft dysfunction, P/F: PaO2/FiO2

Statistical analysis

Mean standard deviation, median, and minimum-maximum values were given as descriptive statistics for continuous data, and percentage values were given for discrete data. The Shapiro-Wilk test was used to examine the conformity of continuous data with normal distribution. In comparing continuous data in two groups, the t-test was used for normal distribution, and the Mann-Whitney U test was used for non-normal distribution. Chi-square and Fisher's Exact tests were used for group comparisons (cross tables) of nominal variables. Factors affecting entry to ECMO were analyzed by Multivariate Logistic Regression. Log-rank test was used in the survival analysis of the patients. IBM SPSS Statistics 20 program was used in the evaluations, and $P < 0.05$ was accepted as the statistical significance limit.

Results

Intraoperative ECMO support was required in 43 (51.9%) patients included in the study. Two patients who were bridged to transplantation with ECMO in the preoperative period and one patient who was supported by intraoperative CPB were excluded. Of the 84 patients included in the study, 67 (79.8 %) were male, and the mean age was 47.13 (13.51) (range, 15–67 years) years. The mean age of the ECMO group was significantly higher than the non-ECMO group (50.05 [12.85] and 44.35 [13.69] years, respectively, $P = 0.043$). Means of LAS and PAP in the ECMO group were significantly higher than those in the non-ECMO group (43.32 [14.01] and 38.25 [8.09], $P = 0.007$; 35.35 [16.77] and 28.63 [12.61], $P = 0.007$, respectively). There was no difference between the groups in terms of gender, body mass index (BMI), Charlson comorbidity index (CCI), transplant indications, and transplant types ($P > 0.05$) (Table 2).

Table 2: Baseline characteristics of lung transplant recipients with and without ECMO

	Total (n=84) Mean (SD) Median (min-max)		Non-ECMO (n=41) Mean (SD) Median (min-max)		ECMO (n=43) Mean (SD) Median (min-max)		*P*-value
Age, years	47.13 (13.51) 51 (15-67)		44.35 (13.69) 47 (15-64)		50.05 (12.85) 54 (19-67)		0.043*
BMI, kg/m2	22.22 (4.01) 22 (15-31)		21.81 (3.55) 21.32 (15.08-31)		22.62 (4.39) 22.5 (15-31)		0.359**
LAS	40.85 (11.72) 36.83 (31.90-90.36)		38.25 (8.09) 34.60 (31.90-63.20)		43.32 (14.01) 39.01 (32.32-90.36)		0.007*
CCI	1.80 (1.05) 1.5 (1-7)		1.88 (0.82) 2 (1-4)		1.72 (1.22) 2 (1-7)		0.104*
PAP, mmHg	31.07 (15.18) 28 (15-100)		28.63 (12.61) 25 (18-90)		35.35 (16.77) 30 (15-100)		0.007*
Indications	n	%	n	%	n	%	*P*-value
Bronchiectasis	12	14.3	7	17.1	5	11.6	0.080***
COPD	34	40.5	22	53.7	12	27.9	
IPF	18	21.4	6	14.6	12	27.9	
Cystic fibrosis	4	4.8	2	4.9	2	4.7	
Histiocytosis	3	3.6	1	2.4	2	4.7	
Silicosis	2	2.4	1	2.4	1	2.3	
Others	11	13.1	2	4.9	9	20.9	
Sex, Male	67	79.8	35	85.4	32	74.4	0.212***
Lung transplantation	n	%	n	%	n	%	*P*-value
Single	8	9.5	3	7.3	5	11.6	0.713***
Double	76	90.5	38	92.7	38	88.4	

BMI: Body mass index, LAS: Lung allocation score, CCI: Charlson comorbidity index, PAP: Pulmonary arterial pressure, COPD: Chronic obstructive pulmonary disease, IPF: Idiopathic pulmonary fibrosis, *Mann Whitney U test, ** Independent Samples t-test, *** Chi-Square/Fisher's Exact test

The mean intraoperative MAP of the ECMO group was significantly lower than that of the non-ECMO group (73.44 [6.69] and 77.55 [6.04] mmHg, respectively, $P = 0.001$). The mean intraoperative lactate of the ECMO group was significantly higher than that of the non-ECMO group (2.71 [1.30] and 2.48 [4.39], respectively, $P < 0.001$). The amount of blood and blood products used intraoperatively in the ECMO group was significantly higher than in the non-ECMO group ($P < 0.001$). The duration of mechanical ventilation of the ECMO group was significantly higher than that of the non-ECMO group (239.37 [371.59] and 87.63 [206.04] days, respectively, $P = 0.004$). Other variables are shown in Table 3. There was no significant

difference between the groups in terms of complications. The hospital mortality of the ECMO group was significantly higher than the non-ECMO group (11 [25.6%] and 3 [7.3%], respectively, P = 0.025) (Table 4). Overall survival rates were similar in lung transplant recipients with and without ECMO (P = 0.253) (Figure 1).

Table 3: Comparison of intraoperative and postoperative variables in lung transplant recipients with and without ECMO

	Total (n=84) Mean (SD) Median (min-max)	Non-ECMO (n=41) Mean (SD) Median (min-max)	ECMO (n=43) Mean (SD) Median (min-max)	*P*-value
MAP, mmHg	75.44 (6.67) 76.4 (55.1-88.7)	77.55 (6.04) 78.5 (55.1-87.1)	73.44 (6.69) 73.5 (60-88.7)	0.001*
Hematocrit, %	33.58 (3.78) 33.7 (24.9-40.5)	33.50 (3.60) 34.3 (26.2-39.1)	33.66 (3.98) 33 (24.9-40.5)	0.841**
pH	7.39 (0.06) 7.39 (7.22-7.55)	7.38 (0.05) 7.38 (7.24-7.54)	7.40 (0.06) 7.39 (7.22-7.55)	0.267**
Glucose, mg dl-1	158.68 (27.43) 157 (99-253)	158.01 (29.01) 151 (104-253)	159.31 (26.17) 163 (99-231)	0.271*
Lactate, mmol/L	2.59 (3.18) 2.05 (0.37-29.58)	2.48 (4.39) 1.50 (0.95-29.58)	2.71 (1.30) 2.55 (0.37-6.04)	<0.001*
Urine, ml	923.87 (732.53) 775 (60-4200)	917.07 (526.02) 800 (250-2500)	930.35 (892.64) 700 (60-4200)	0.270*
Crystalloid, ml	2137.50 (881.32) 2050 (400-4500)	1952.93 (877.82) 2000 (400-4500)	2284.88 (869.21) 2500 (500-4000)	0.117**
Colloid, ml	189.29 (223.89) 200 (0-1200)	209.76 (270.92) 200 (0-1200)	169.77 (168.37) 200 (0-700)	0.745*
FFP, U	12.24 (3.67) 11 (4-19)	9.45 (3.08) 9 (4-17)	12.91 (3.42) 13 (7-19)	<0.001**
RBCC, U	3.90 (2.88) 3 (0-12)	2.43 (2.34) 1 (0-9)	5.28 (2.67) 5 (0-12)	<0.001*
PC, U	0.27 (0.54) 0 (0-2)	0.05 (0.22) 0 (0-1)	0.47 (0.66) 0 (0-2)	<0.001*
Operative time, minutes	615.77 (98.45) 600 (435-1080)	599.51 (68.90) 600 (480-735)	631.28 (118.86) 615 (435-1080)	0.259*
Length of ICU stay, days	17.63 (17.23) 12 (3-96)	13.20 (8.26) 12 (6-51)	21.86 (22.10) 14 (3-96)	0.077*
Length of hospital stay, days	35.42 (22.44) 28 (0-120)	31.90 (17.48) 29 (7-119)	38.77 (26.09) 28 (0-120)	0.237*
Duration of MV, hours	165.31 (310.08) 28 (8-1680)	87.63 (206.04) 24 (10-1104)	239.37 (371.59) 72 (8-1680)	0.004*

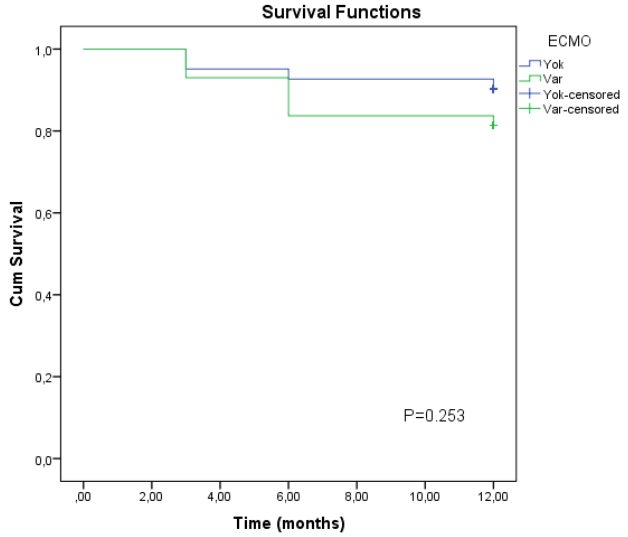
MAP: Mean arterial pressure, FFP: Fresh frozen plasma, RBCC: Red blood cell components, PC: Platelet concentrate, MV: Mechanical ventilation, *Mann Whitney U test, ** Independent Samples t-test

Table 4: Comparison of complication rates in patients with ECMO and patients without ECMO

	Total (n=84)		Non-ECMO (n=41)		ECMO (n=43)		*P*-value
	n	%	n	%	n	%	
Cardiovascular system	26	31	14	34.1	12	27.9	0.536*
PGD 3	15	17.9	4	9.8	11	25.6	0.058*
Neurological system	19	22.6	10	24.4	9	20.9	0.705*
Gastrointestinal system	3	3.6	0	0	3	7.0	0.241*
Bleeding/revision	12	14.3	4	9.8	8	18.6	0.247*
Acute kidney injury	15	17.9	5	12.5	10	23.3	0.186*
Mortality(Hospital)	14	16.7	3	7.3	11	25.6	0.025*
Mortality (one year)	12	14.3	4	9.8	8	18.6	0.247*

PGD: Primary graft dysfunction, *Chi-Square/Fisher's Exact test

Figure 1: Overall survival in lung transplant recipients with and without ECMO



Age, LAS, PAP, MAP, and lactate, which were thought to be associated with ECMO and were found to be significant in univariate analysis, were included in the Multivariate Logistic regression analysis to obtain a final model. As a result of the logistic model, intraoperative MAP was an effective risk factor. Other variables were not significant (Table 5).

Table 5: Logistic Regression model for preoperative and intraoperative risk factors affecting intraoperative ECMO

Variable	Regression Coefficient (SE)	OR	95 % CI		*P*-value
Age, years	-0.022 (0.022)	1.021	0.977	1.068	0.334
LAS	0.038 (0.027)	1.039	0.986	1.095	0.152
PAP, mmHg	0.034 (0.019)	1.035	0.998	1.074	0.068
Lactate, mmol/L	0.056 (0.072)	1.057	0.919	1.217	0.435
MAP, mmHg	-0.087 (0.040)	1.091	1.009	1.179	0.028

OR: Odds Ratio, CI: Confidence Interval, LAS: Lung allocation score, PAP: Pulmonary arterial pressure, MAP: Mean arterial pressure

Discussion

In this study, we aimed to determine the factors affecting the use of intraoperative ECMO in lung transplant patients and to evaluate the effect of ECMO use on morbidity and mortality. The rate of intraoperative ECMO use in the patients in our study was 51.9%. When the relationship between ECMO use and preoperative data was evaluated, age, LAS, and PAP were effective factors. Low intraoperative MAP and increased lactate levels were associated with ECMO use. In the logistic model, we determined that MAP is an effective risk factor for intraoperative ECMO use.

The widespread use of ECMO in lung transplantation occurred after Aigner et al. [10]. presented the first large case series in 2001, and its use as an intraoperative support device for complex cases, primary pulmonary hypertension (PPH), or patients who are not stable intraoperatively has increased over the past 15 years However, there are also studies reporting that more practices are needed before advocating ECMO as a standard of care to provide intraoperative support during LT [11]. It is known that ECMO support may cause complications, such as bleeding, revision, infection, and vascular injury, that may affect postoperative results and require more blood and blood product replacement. We use ECMO in our clinic for patients with preoperative ECMO requirements and intraoperative indications. We do not have routine intraoperative ECMO use. In this study, we observed that intraoperative ECMO support was higher in elderly recipients in accordance with the literature [1, 12]. With the expansion of lung transplant indications, lung transplantation is increasingly being applied to older recipients with various comorbidities. These recipients with high LAS scores prioritize transplant allocation and may require intraoperative ECMO due to their comorbidities. This study found that high LAS scores were effective in intraoperative ECMO support.

It has been reported that high PAP levels in lung transplantation are associated with ECMO requirements [13]. We also found that recipients requiring intraoperative ECMO had higher PAP levels. Patients with severe pulmonary hypertension often experience significant right heart failure. Hemodynamic instability caused by anesthesia induction and surgical manipulations can be balanced with ECMO support. Contrary to the literature [14], the indications for transplantation were not associated with the use of ECMO in this study. This may be because the patient population is relatively small.

Intraoperative ECMO decision is often made if PAP > 2/3 SAB, hemodynamic instability (MAP < 60 mmHg), hypoxia, and acidosis develop during the clamping of the pulmonary artery for 5–10 min [15]. In this study, intraoperative MAP values were significantly lower in patients with ECMO than in the group without ECMO. In addition, higher lactate levels were found in patients who used intraoperative ECMO.

Hoetzenecker et al. [10] showed that using preemptive ECMO in lung transplantation resulted in lower PGD rates and superior survival compared to transplantation without ECMO. However, they could only classify the PGD rates of patients who used intraoperative ECMO. They could not evaluate the postoperative prolonged ECMO group. A subsequent observational study reported that the intraoperative routine use of ECMO was associated with excellent PGD rates in lung transplant patients [7]. Contrary to the literature, PGD3 rates were higher in the ECMO group in this study, but this was not statistically significant. The fact that the patients we supported with ECMO in our clinic were more critical may have affected the results. Consistent with the clinic, the duration of mechanical ventilation was longer in the ECMO group.

It has been reported that the use of intraoperative ECMO in lung transplantation yields 100% superior results in terms of survival compared to the non-ECMO group [10]. In a study addressing intraoperative ECMO application, perioperative mortality was 11.1%, and 1-year survival was 81.5% in the ECMO group and 4.5% and 81.8% in the non-ECMO group [16]. Bermudez et al. [17] stated that there was no difference between ECMO and non-ECMO groups in terms of 1, 3, and 12 months and hospital mortality. In this study, the in-hospital mortality rate in the ECMO group was three times higher than in the non-ECMO group. When 1-year survival was evaluated, there was no difference between the two groups. We have already stated that the patients given ECMO support are more critical patients. It was observed that the survival of patients after undergoing the critical process was similar.

In this study, one of our limitations is the relatively small lung transplant patient population. Since it is a single-center and retrospective study, the inability to reach pulmonary artery pressure and oxygenation parameters at all intraoperative times is another important limitation of our study.

Conclusion

We show that age, LAS, and PAP elevation are preoperative indicators in determining intraoperative ECMO support in lung transplant patients. In addition, we found that lower MAP averages were evaluated at all times until intraoperative ECMO support was a predictive parameter in need for intraoperative ECMO. However, hospital mortality was higher in patients with ECMO, and survival after lung transplantation was similar in patients with and without ECMO after the acute phase. We believe multicenter studies with larger numbers of patients are needed to detect intraoperative ECMO determinants.

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Retrospective assessment of the association between co-morbid disease burden and biochemical parameters in hospitalized hypertensive COVID-19 patients

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Ethics Committee Approval
This study was approved by the Siirt University non-interventional research ethics committee (No: 2021/01.01).
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: Hypertension (HT) was examined as a risk factor affecting the progression of the 2019 novel coronavirus disease (COVID-19). In COVID-19 patients, it can be found in many co-morbid diseases, along with hypertension. It is not clear whether the co-morbid burden of the disease affects the prognosis in hypertensive COVID-19 patients and which biochemical parameters may be indicative of this. Therefore, this study was designed to determine the effect of co-morbid disease burden on biochemical parameters in hospitalized hypertensive COVID-19 patients.

Methods: After receiving approval from the University Ethics Committee, demographic, clinical, radiological, and laboratory data of 250 hospitalized hypertensive COVID-19 patients between May 2020 and Sept 2020 were screened. Patients with missing records and unclear history of hypertension drug use were excluded from the study. A total of 215 patients were included in the study. Patients were divided into four groups according to the co-morbidity status: (1) HT alone (Group HT0), (2) HT+ Diabetes Mellitus (DM) (Group HTDM1), (3) HT+one co-morbidity exclude DM (Group HT2), and (4) HT+at least two co-morbidities (Group HT3).

Results: We analyzed the data of 105 female and 110 male patients. Of the 215 patients whose data were evaluated in this study, 15 patients died. Two hundred people were discharged with recovery. The mortality rate was 7%. Of the hypertension patients, 34.9% had DM, 32.6% had coronary artery disease (CAD), 30.2% had chronic obstructive pulmonary disease (COPD), 16.3% had heart failure (HF), 23.3% had chronic kidney failure (CKD), and 9.3% had cerebrovascular disease (CVD). Twenty-five percent were smokers. Urea, creatinine, direct bilirubin (DBil), and Troponin-I values were significantly higher in the Group HT3 compared to the Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.002$ respectively). Glomerular filtration rate (GFR) and albümin levels were significantly lower in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ and $P < 0.001$, respectively). The logistic regression model was statistically significant ($\chi2(7) = 69.088$ and $P < 0.001$); advanced age, decrease in GFR and plateletcrit (PCT) levels, and increase in D-dimer and DBil levels were observed as predictive parameters of mortality in all hospitalized COVID-19 HT patients.

Conclusion: We determined that SARS-CoV-2 pneumonia patients with HT plus at least two co-morbidities were more serious than other patient groups in terms of organ damage and biochemical variables. In our study, we observed an increase in urea, creatinine, D-dimer, Dbil, and Troponin-I values and a decrease in GFR and albumin values as the co-morbidity burden increased in hypertensive COVID-19 patients. However, a decrease in GFR and hemogram PCT levels and an increase in D-dimer and DBil levels could be risk factors for mortality.

Keywords: COVID-19, Hypertension, CRP, Comorbidities, Troponin, Dimer

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Introduction

Coronavirus disease 2019 (COVID-19), which is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first discovered in Wuhan City, Hubei province, China, in December 2019 [1]. The World Health Organization proclaimed COVID-19 a pandemic on March 11, 2020, as soon as it met the epidemiological requirements (infection in more than 100,000 people in 100 countries) [2]. The virus is mostly spread by contaminated respiratory droplets and close contact with an infected individual. It is extremely infectious, and the incubation period can last up to 2 weeks [3]. The mean R0 of COVID-19 was shown to be around 2.68 (95% CI: 2.47–2.86). The risk of person-to-person transfer has been highlighted by an increasing number of epidemics of familial transmission [4]. Fever, dry cough, dyspnea, myalgia, lethargy, hypo lymphoma, and radiographic indications of pneumonia were the most prevalent signs of COVID-19. In extreme cases, complications [such as acute respiratory distress syndrome (ARDS), arrhythmia, shock, acute cardiac damage, secondary infection, and acute renal injury] and death may ensue [5].

A positive nasopharyngeal swab and respiratory pathogen nucleic acid test using high-throughput sequencing or real-time reverse transcriptase-polymerase chain reaction resulted in COVID-19 (RT-PCR) diagnosis. With better sensitivity, chest computed tomography (CT) imaging plays an important role in the surveillance and diagnosis of COVID-19 viral pneumonia [6]. Notably, it has been established that 2019-nCoV and SARS-CoV both enter cells through the same cell entry receptor, angiotensin-converting enzyme II (ACE2) [7]. Angiotensin receptor blockers (ARB) and ACE inhibitors (ACEi) may upregulate ACE2, increasing vulnerability to the virus, according to some evidence, as the ACE2 receptor is the route through which SARS-CoV2 enters the body. The lung-protective action of ACE2, an angiotensin II inhibitor, is potentiated by ACEi/ARB, according to previous investigations [8]. Medication affects ACE2 production, expression, and activity, with potentially significant implications for COVID-19 prevention, infection, severity, and therapy. Hypertension (HT) affects 1.39 billion people globally, with 349 million living in high-income nations and 1.04 billion in low- and middle-income countries. However, there are huge disparities in antihypertensive medication exposure worldwide; awareness, treatment, and control concern 67%, 56%, and 28% of patients in high-income nations, and 37%, 29%, and 7.7% of patients in low- and middle-income countries, respectively [9].

The European Society of Cardiology Council on Hypertension, European Society of Hypertension, and American Heart Association urge patients to continue on ACEi and ARB because no strong data support either a benefit or a risk [10]. Unfortunately, several studies have demonstrated that patients with underlying cardiovascular co-morbidities, such as HT and coronary artery disease (CAD), are more likely to get a severe COVID-19 infection that necessitates intensive care unit (ICU), have complications including ARDS, and ultimately die [11]. Adult inpatients with COVID-19 were also shown to have higher levels of age, lymphopenia, leucocytosis, lactate dehydrogenase (LDH), high-sensitivity cardiac troponin I, creatine kinase (CK), D-dimer, serum ferritin, IL-6, prothrombin time, creatinine, and procalcitonin [12].

Although there are many evaluations that HT and CAD adversely affect the prognosis of COVID-19, there are no publications in the literature showing how the prognosis is affected by additional co-morbid diseases (DM, CAD, COPD, HF, CVD, CKD) in hypertensive COVID-19 patients. The primary aim of this retrospective study was to evaluate the relationship between biochemical markers and groups separated by co-morbidity severity. The second aim was to determine the independent variables that could predict mortality by comparing the biochemical markers of those hypertensive COVID-19 patients who died and those that recovered.

Materials and methods

This study is a retrospective cohort study conducted with patients who had COVID-19 and also had HT and co-morbidities. After receiving approval from the Ethics Committee, demographic, clinical, radiological, and laboratory data of 250 hospitalized hypertensive COVID-19 patients were screened between May 2020 and Sept 2020. Patients with missing records and unclear history of hypertension drug use were excluded from the study. A total of 215 patients were included in the study. This study was approved by the Siirt University non-interventional research ethics committee (No:15.05.2020/06.01). Demographic, clinical characteristics, laboratory and radiological findings, and treatment protocols of the patients were obtained from hospital information system records. Information on demographic data, symptoms, pre-existing chronic co-morbidities, and laboratory results were collected. All data were checked by physicians who are experts in cardiology. The time from onset of illness to hospitalization was also recorded. All patients participating in this study were laboratory-confirmed COVID-19 patients, and the diagnostic criteria for COVID-19 were based on the positive detection of viral nucleic acids.

Leukocytes, neutrophils (NE), lymphocytes (LY), albumin, C-reactive protein (CRP), fasting blood glucose (FBG), LDH, urea, creatinine, sodium (Na), potassium (K), creatine kinase isoenzyme MB (CK-MB), total (TBil) and direct bilirubin (DBil), alanine aminotransferase (ALT), aspartate transaminase (AST), and D-dimer were determined for each patient. All medical laboratory data were measured by the clinical laboratory of Siirt State Hospital. HT disease was defined from the medical history of the patients.

Throat swab specimens from patients' upper respiratory tracts were kept in a viral-transport medium. The respiratory sample RNA isolation kit retrieved total RNA in less than 2 h. RT-PCR was used to look for SARS-CoV-2, as previously described.

The following criteria were satisfied by each COVID-19 patient: a history of epidemiology, fever or other respiratory symptoms, a typical viral pneumonia-related abnormality on a CT scan, and a positive RT-PCR result for SARS-CoV-2 RNA are all indicators of viral pneumonia. Patients were divided into four groups according to the co-morbidity status: (1) HT alone (Group HT0), (2) HT + Diabetes Mellitus (DM) (Group

HTDM1), (3) HT + one co-morbidity exclude DM (Group HT2), and (4) HT + at least two co-morbidities (Group HT3).

Statistical analysis

The statistical program SPSS for Windows, version 22.0, was used to conduct all statistical analyses (SPSS, Chicago, Illinois, USA). Continuous variables were presented as means and standard deviations, whereas categorical variables were specified as percentages. The distribution of continuous variables was examined for normality using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Differences in mean values between two groups were analyzed using the independent t-test and the Mann-Whitney test, and four groups were tested using the analysis of variance (ANOVA) test. When ANOVA revealed significant differences between means, the post hoc test, Games-Howell, was used to examine them. Additionally, binary logistic regression analyses were carried out. *P*-values < 0.05 were judged statistically significant.

Results

The study was conducted with 215 patients, of whom 105 were females and 110 were males. The enrolled patients were classified into four groups: Group HT0 (n: 63; 29.3%), Group HTDM1 (n: 42; 19.5%), Group HT2 (n: 25; 11.6%), and Group HT3 (n: 85; 39.5%). Fifteen of them died. Two hundred people were discharged with recovery. The mortality rate was 7%. All deceased patients were in Group HT3. Of the COVID-19 HT patients, 34.9% had diabetes mellitus (DM), 32.6% had CAD, 30.2% had chronic obstructive pulmonary disease (COPD), 16.3% had heart failure (HF), 23.3% had chronic kidney disease (CKD), and 9.3% had the cerebrovascular disease (CVD). The proportion of smokers was 25.6%. Of the COVID-19 HT patients, 165 were using ACE/ARB, and 50 were using non ACE/ARB HT drugs (Table 1). In addition, 15 patients who died had been using ACE/ARB class drugs. No deaths were observed in patients using non ACE/ARB drugs.

Table 1: General demographic and clinical characteristics of the COVID-19 HT patients

		mean (SD)
Age		63.79 (10.97)
		n (%)
Gender	Male	110 (51.2)
	Female	105 (48.8)
Co-morbidity groups	Group HT0	63 (29.3)
	Group HTDM1	42 (19.5)
	Group HT2	25 (11.6)
	Group HT3	85 (39.5)
Result	Deceased	15 (7)
	Discharged	200 (93)
DM	Yes	75 (34.9)
	No	140 (65.1)
CAD	Yes	70 (32.6)
	No	145 (67.4)
COPD	Yes	65 (30.2)
	No	150 (69.8)
HF	Yes	35 (16.3)
	No	180 (83.7)
CKD	Yes	50 (23.3)
	No	165 (76.7)
CVD	Yes	20 (9.3)
	No	195 (90.7)
Smoking	Yes	55 (25.6)
	No	160 (74.4)
HT Drug Class	ACE i /ARB	165 (76.7)
	Non ACE i /ARB	50 (23.3)

Age was significantly different between Group HT0, Group HTDM1, and Group HT3 ($P < 0.001$). FBG level was statistically significantly higher in Group HTDM1 than in Group HT0 and Group HT2 ($P < 0.001$ for all). Urea level was significantly higher in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ for all). Also, the urea level was higher in Group HT2 than in Group HT0 ($P = 0.009$). The creatinine level was significantly higher in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.05$ for all). Additionally, creatinine level was significantly higher in Group HT2 than in Group HT0 and Group HTDM1 ($P < 0.001$ for all). Glomerular filtration rate (GFR) level was significantly lower in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ for all). AST level was significantly higher in Group HT3 than Group HT2 ($P = 0.012$) and higher in Group HTDM1 than Group HT2 ($P = 0.029$). Na level was significantly lower in Group HTDM1 than in Group HT3 and Group HT2 ($P = 0.003$ and $P = 0.006$, respectively). The K level was significantly higher in Group HT3 than in Group HT0 ($P = 0.006$). Also, the K level was higher in Group HT2 and Group HTDM1 than in Group HT0 ($P < 0.001$ and $P = 0.003$, respectively). The TBil level was significantly higher in Group HT3 than in Group HTDM1 and Group HT2 ($P < 0.001$ for all). Also, the TBil level was higher in Group HT0 than in Group HTDM1 and Group HT2 ($P = 0.006$ and $P = 0.017$, respectively). The DBil level was significantly higher in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.001$ for all). The albumin level was significantly lower in Group HT3 than in Group HT0, Group HTDM1, and Group HT2 ($P < 0.05$ for all). CK-MB level was significantly higher in Group HT3 than in Group HTDM1 ($P = 0.035$). CRP level was significantly higher in Group HT3 ($P < 0.001$), Group HT2 ($P < 0.001$), and Group HTDM1 ($P < 0.001$) than Group HT0, respectively (Table 2).

Table 2: Comparision of laboratory parameters of four groups

Laboratory findings	Group HT0	Group HTDM1	Group HT2	Group HT3	*P*-value [a]
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age	59.71 (10.56)	61.19 (11.27)	57.80 (6.10)	69.86 (9.37)	<0.001
GFR (ml/min)	77.66 (13.44)	75.07 (8.37)	67.31 (14.03)	52.08 (21.25)	<0.001
FBG (mg/dL)	108.32 (38.76)	174.24 (104.34)	98.68 (8.91)	163.67 (83.79)	<0.001
CRP (mg/dL)	15.85 (17.33)	77.95 (71.76)	49.67 (37.30)	70.46 (55.01)	<0.001
Urea (mg/dL)	31.90 (8.51)	32.40 (9.25)	36.89 (5.46)	49.43 (17.28)	<0.001
Creatinine (mg/dL)	0.95 (0.16)	0.96 (0.14)	1.18 (0.22)	1.59 (1.08)	<0.001
TBil (mg/dL)	0.54 (0.34)	0.037 (0.18)	0.40 (0.06)	0.64 (0.35)	<0.001
DBil (mg/dL)	0.15 (0.11)	0.10 (0.08)	0.11 (0.03)	0.24 (0.18)	<0.001
ALT (U/L)	32.68 (27.02)	42.93 (34.67)	32.36 (24.18)	38.69 (47.97)	0.495
AST (U/L)	35.08 (23.07)	42.33 (20.98)	30.120 (13.99)	43.40 (29.10)	0.041
LDH (U/L)	254.13 (80.71)	305.12 (179.60)	283.08 (115.23)	259.80 (84.61)	0.095
Na (mmol/L)	137.29 (3.09)	136.40 (2.24)	139.04 (3.28)	138.19 (3.37)	0.002
K (mmol/L)	4.09 (0.45)	4.49 (0.60)	4.64 (0.22)	4.41 (0.70)	<0.001
CK-MB (U/L)	13.90 (7.85)	10.74 (6.57)	17.67 (13.50)	15.63 (13.56)	0.047
Albumin (g/dL)	40.37 (4.33)	41.16 (5.20)	40.08 (4.45)	36.39 (4.92)	<0.001

[a] One Way ANOVA test

Red blood cell (RBC) level was significantly lower in Group HT3 than in Group HT2 ($P = 0.005$). White blood cell (WBC) level was significantly higher in Group HT3 ($P < 0.001$) than Group HT0 and also higher in Group HT2 ($P = 0.012$) than Group HT0, respectively. Platelet (PLT) level was significantly higher in Group HTDM1 ($P = 0.005$) than Group HT0 and higher in Group HT2 ($P = 0.005$) than Group HT0, respectively. Also PLT level was higher in Group HT2 than in Group HT3 ($P = 0.040$). Plateletcrit (PCT) level was significantly higher in Group HTDM1 ($P = 0.027$) than Group HT0 and higher in Group HT2 ($P < 0.001$) than Group HT0, respectively. Also, the PCT level was lower in Group HT3 than in Group HT2 ($P = 0.022$). NE level was significantly higher in Group HT3 ($P < 0.001$) than Group HT0 and higher in Group HT2 ($P = 0.008$) than Group HT0, respectively. LY level was significantly lower in Group HT3 than in Group HT0 ($P = 0.010$). Hemoglobin

(HGB) level was significantly lower in Group HT3 ($P < 0.001$) than Group HT0 and lower in Group HTDM1 ($P < 0.001$) than Group HT0, respectively. Hematocrit (HCT) percentage was significantly lower in Group HT3 ($P = 0.010$) than Group HT0 and lower in Group HTDM1 ($P < 0.001$) than Group HT0, respectively. Also, the HCT percentage was significantly lower in Group HTDM1 than in Group HT2 ($P = 0.016$). D-dimer level was significantly higher in Group HT3 ($P < 0.001$), Group HT2 ($P = 0.003$), and Group HTDM1 ($P = 0.002$) than Group HT0 respectively. Troponin-I level was significantly higher in Group HT3 than Group HT0 ($P = 0.012$), Group HTDM1 ($P = 0.011$), and Group HT2 ($P = 0.010$), respectively (Table 3).

Table 3: Comparision of hemogram parameters, some coagulation factors and markers of four groups

Laboratory findings	Group HT0 Mean (SD)	Group HTDM1 Mean (SD)	Group HT2 Mean (SD)	Group HT3 Mean (SD)	*P*-value [a]
RBC (10^3/mL)	4.65 (0.37)	4.69 (0.71)	5.03 (0.67)	4.48 (0.73)	0.002
WBC (10^3/mL)	6.22 (1.87)	7.35 (3.27)	9.02 (4.04)	7.83 (2.26)	<0.001
PLT (10^3/mL)	221793.6 (74195.3)	293761.9 (120449.5)	327120 (136688.6)	245011.8 (93931.8)	<0.001
MPV (fl)	9.88 (1.02)	10.17 (2.42)	10.03 (1.92)	9.93 (0.88)	0.767
PCT (%)	0.22 (0.07)	0.27 (0.09)	0.31 (0.11)	0.24 (0.09)	<0.001
NE (10^3/mL)	3.78 (1.39)	4.71 (2.97)	6.48 (3.76)	5.62 (1.98)	<0.001
LY (10^3/mL)	1.88 (0.55)	1.90 (0.99)	1.61 (0.92)	1.54 (0.78)	0.020
HGB (g/dL)	13.39 (1.16)	11.61 (1.59)	12.540 (1.61)	11.89 (2.05)	<0.001
HCT (%)	41.95(3.39)	38.45 (4.01)	42.168 (5.07)	39.39 (6.31)	<0.001
D-dimer (mg/L)	635.24 (440.58)	994.69 (509.87)	1141.60 (611.43)	1594.39 (1300.38)	<0.001
Troponin I (ng/mL)	0.0196 (0.021)	0.016 (0.012)	0.011 (0.010)	0.403 (1.122)	0.002

[a] One Way ANOVA test

When comparing COVID-HT patients who died versus those who were discharged according to age ($P < 0.001$), urea ($P < 0.001$), creatinine ($P = 0.046$), DBil ($P < 0.001$), Troponin-I ($P = 0.036$), D-dimer ($P = 0.031$), and hospitalization day ($P < 0.001$), all parameters were higher in the deceased group than the discharged group. On the other hand, GFR ($P < 0.001$), LDH ($P = 0.008$), HGB ($P = 0.013$), PLT ($P = 0.021$), PCT ($P = 0.040$), and LY ($P = 0.005$) levels were lower in deceased group than discharged group (Table 4). The logistic regression model was statistically significant ($\chi2(7) = 69.088$, $P < 0.001$) and decreases in PCT and GFR levels, increases in D-dimer and DBil levels, and advanced age were assessed as predictive factors for mortality (Table 5).

Table 4: Comparison of some biochemical and clinical data of deceased and discharged patients

	Deceased Median (Min-Max)	Discharged Median (Min-Max)	*P*-value [a]
Age	76 (71-83)	63 (39-87)	<0.001
Urea (mg/dl)	47.08 (40.66-68.48)	36.38 (17.12-92.02)	<0.001
Creatinine (mg/dl)	1.13 (1.07-1.22)	1.05 (0.61-4.54)	0.046
GFR (ml/min)	56.82 (43.13-59.77)	69.83 (10.41-100.96	<0.001
LDH (U/L)	210 (106-259)	248.5 (104-751)	0.008
DBil (mg/dl)	0.43 (0.05-0.58)	0.12 (0.03-0.64)	0.010
HGB (g/dl)	11.4 (10.8-12.6)	12.65 (8-15.8)	0.013
HCT (%)	39.5 (37.7-44.9)	39.95 (26.8-49.9)	0.914
PLT (10^3/mL)	178 (139-287)	251.5 (79-541)	0.021
PCT (%)	0.161 (0.137-0.304)	0.246 (0.092-0.436)	0.040
LY	1 (0.72-1.85)	1.79 (0.49-4.10)	0.005
Troponin I (ng/ml)	0.028 (0.014-0.660)	0.020 (0-4.79)	0.036
D-dimer (mg/L)	1190 (993-1320)	794.5 (245-5140)	0.031
Hospitalization day	15 (5-17)	7 (2-15)	<0.001

[a] Mann Whitney U test

Table 5: Predictors of mortality in binary logistic regression model

	B	SE	Wald	*P*-value [a]
GFR (ml/min)	-0.182	0.076	5.668	0.017
Age	0.506	0.189	7.197	0.007
D-dimer (mg/L)	0.008	0.003	7.235	0.007
DBil (mg/dl)	18.374	7.643	5.779	0.016
Troponin I (ng/ml)	-0.237	0.533	0.197	0.657
PCT %	-39.751	15.109	6.922	0.009
Comorbidity groups	2.611	2.395	1.188	0.276

[a] Binary Logistic Regression

Discussion

In our study, we observed an increase in urea, creatinine, D-dimer, Dbil, and troponin values and a decrease in GFR and albumin values as the co-morbidity burden increased in hypertensive COVID-19 patients. According to data from a different meta-analysis, HT was independently linked to a considerably higher incidence of critical COVID-19 and in-hospital COVID-19 mortality [13]. The severity of sickness, ICU hospitalization, death, and other organ damage was several times greater in COVID-19 patients with cardiac injuries than in infected individuals without them [14]. It is concluded that HT worsens the severity of COVID-19 due to underlying endothelial dysfunction and coagulopathy. Due to ACE2 downregulation, COVID-19 may exacerbate HT problems. The use of ACEIs or ARBs in the treatment of hypertensive individuals with COVID-19 might be advantageous [15]. In addition to the effect of HT on ACE-2 receptors alone, the co-morbidity burden may enable the virus to enter the cell more easily and damage the cell by influencing the ACE-2 receptor expression and providing the release of viral proprotein convertase [16]. As the co-morbidity burden increased in our patients, the deterioration in renal (urea, creatine and GFR), hepatic (DBil and albumin), and cardiac (Troponin-I) biochemical markers may have been due to these effects of co-morbidities. According to one investigation, prior exposure to ACEIs or ARBs was not related to a higher risk of hospitalization or all-cause death from COVID-19 infection [17]. For this reason, it can be thought that the use of ACEIs and ARBs may be beneficial in terms of prognosis as co-morbidities increase in hypertensive COVID-19 patients.

In previous studies, it has been stated that the presence of Type 2 DM is a risk factor for poor prognosis in COVID-19 infection. The disruption of insulin secretion from the pancreas due to the direct cytotoxic effect of the virus and the glucocorticosteroid group drugs taken may cause hyperglycemia. It is thought that hyperglycemia also increases the penetration of the virus by causing hyperglycosylation of ACE-2 receptors, which is the natural receptor of the virus and may cause more serious infection with increasing virulence [17]. In studies performed on COVID-19 patients with and without Type 2 DM, it was found that the group with Type 2 DM was more prone to severe disease than the group without DM, and inflammatory markers (CRP, ferritin, LDH, procalcitonin, and D-dimer) were significantly higher in this group [18]. In our study, when we compared the DM group (Group HTDM1) with the non-DM co-morbidities group (Group HT2) in hypertensive COVID-19 patients, we did not observe any significant difference in inflammatory markers (CRP, LDH and D-dimer). Observation of significant increases in inflammatory markers in Group HT3, where co-morbidity is higher, reveals that DM should be considered together with other additional disorders, not alone. Major cardiovascular risk factors and other co-morbidities (HT, DM, obesity, immunosuppression and end-stage kidney disease) increase the risk of dying in patients with COVID-19. The presence of two or three co-morbid diseases showed a stronger association with mortality than each co-morbid disease alone compared to the absence of them [20].

Similarly, another study showed that COVID-19 mortality risk sharply increased in patients with two or more co-

morbid diseases (obesity, DM, HT, and CAD) in Mexico [21]. In a retrospective study in Egypt, patients with DM, liver cirrhosis, HT, hepatitis C virus (HCV), and CKD tended to have more severe COVID-19; it has been suggested that it may be associated with ALT, AST, CRP, serum ferritin levels, FBG, segmented % and neutrophil/lymphocyte ratio (NLR) [22]. In another study on COVID-19 mortality, mortality for patients in the older age group and those patients who were admitted to the ICU was higher. Additionally, six laboratory measurements had a favorable correlation with the likelihood of dying: WBC count, NE, CK-MB, CRP, urea, and LDH [23].

In a study comparing laboratory parameters according to the severity of pneumonia involvement in CT, it was observed that COVID-19 had a worse prognosis in male patients and patients with HT and CAD, while no difference was found in terms of disease severity in patients with DM and COPD. In addition, it has been suggested in this study that the relationship between D-dimer and ferritin may indicate the severity of COVID-19 [24]. In our study, however, the increase in Troponin-I was significantly higher in Group HT3 (HT and at least two co-morbidities) compared to all other groups, and D-dimer values were found to be significantly higher as the co-morbidity increased. At the same time, these two parameters were significantly higher in patients who died, in hypertensive COVID-19 patients with a high co-morbid disease burden. It makes us think that it would be useful to evaluate Troponin-I and D-dimer together in the prognosis of COVID-19 patients. The fact that DM and CAD were higher than other diseases in our study group may have been responsible for the increase in Troponin-I and D-dimer, which was observed in hypertensive COVID-19 patients as co-morbidity increased, especially by causing silent ischemia in the coexistence of the two diseases.

In our study, it was seen that low GFR might be predictive in terms of mortality. Especially the hemodynamic changes experienced during viral sepsis, the nephrotoxic effects of the treatments used in co-morbid patient groups, and the development of acute tubular damage due to systemic inflammation suggest that low GFR may be a mortality indicator related to the severity of the disease. In this respect, fluid management, administration of anti-inflammatory and antiviral drugs, and avoidance of acute tubular damage by close hemodynamic monitoring can play a vital role, especially in patients with impaired renal function [25].

An endogenous byproduct of heme catabolism, known as bilirubin, is a protective bioactive molecule with potent antioxidant and anti-inflammatory properties and other critical physiological activities [26]. In our study, it was seen that DBil might have a predictive role in mortality. The use of ACE2 receptors expressed in the liver and bile ducts by SARS-CoV2 to increase viral replication may cause direct cytotoxicity. Again, with an immune-mediated mechanism, severe inflammation may cause cell damage in the liver and biliary tract [27]. These two mechanisms may be potential mechanisms of DBil increase in hypertensive COVID-19 patients with high co-morbidity, which we demonstrated in our study.

In a study comparing the COVID-19 pneumonia group to the control group, there was no discernible difference between the PCT value of advanced COVID-19 patients and mild COVID-19 patients, while the PCT value was discovered to have been considerably lower in the COVID group as compared to the control group [28]. In our study, decreased PCT value was determined as a predictive factor in HT COVID-19 patients, especially in mortality. In a study by Gao et al. [29] on hemogram parameters in septic shock patients, PCT values and a decrease in PLT were shown to be associated with mortality. On the other hand, D-Dimer is a well-known biomarker that has an important place in predicting the prognosis of COVID-19 and shows COVID-related coagulopathy [30]. We also showed that high D-dimer levels are associated with mortality. In this respect, using D-dimer and PCT to predict prognosis may be more effective in clinical decision-making, especially in patients with a high co-morbidity burden with hypertensive COVID-19 patients.

Our study has some limitations. First, hypertensive COVID-19 patients who were hospitalized were included in the study. Different results can be obtained in outpatients. Secondly, since our study was designed in a retrospective style, only patients using drugs for HT could be included from the records. Different results could be achieved with prospective, randomized, multicenter, and longer-term studies. A final limitation is that independent outcomes and variables may be affected in hypertensive COVID-19 patients, depending on metabolic status.

Conclusion

In this study, we determined that SARS-CoV-2 pneumonia patients with hypertension plus at least two co-morbidities were more serious than other patient groups in terms of organ damage and biochemical variables. In our study, we observed an increase in urea, creatinine, D-dimer, Dbil, and Troponin-I values and a decrease in GFR and albumin values as the co-morbidity burden increased in hypertensive COVID-19 patients. However, a decrease in GFR and hemogram PCT levels and an increase in D-dimer and DBil levels could be risk factors for mortality. Studies in larger patient numbers by different research groups are needed to contribute to these findings.

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A novel method for assessing the condition of the cervix before labor induction: Cervical length/thickness ratio

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Ethics Committee Approval
Ethics Committee approval was taken from the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee, 2011-KAEK-25 2019/07-15.
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: Due to the increasing cesarean rates globally, new methods for supporting vaginal delivery and induction of successful vaginal delivery are still being developed. We aimed to obtain an easy-to-use method that can predict the effectiveness of cervical ripening agents before labor induction. So, we presented the effects on labor by measuring the thickness of the cervix and the cervical length/thickness ratio ultrasonographically.

Methods: In this prospective cohort study, we evaluated 183 pregnant between 37 and 41 weeks of gestational age and will apply vaginal delivery induction. Before oxytocin induction, we applied 10 mg dinoprostone vaginally to women whose cervix was stiff. We started labor induction with oxytocin when regular uterine contractions or dilatation occurred. We used the Bishop Scoring System for favorable cervix defining. Then, we compared the groups with successful and unsuccessful cervical ripening regarding cervical length and thickness parameters.

Results: The mean cervical thickness of the pregnant women with successful cervical ripening was 34.5 (7.5) mm before treatment, while the mean values of the unsuccessful group were 29.2 (9.1) mm ($P < 0.001$). The cervical length did not differ between the two groups (31.6 [8.2] vs. 32.5 [6.8], $P = 0.44$), while the cervical length/thickness ratio was lower in the group with successful ripening (0.9 [0.38–2], $P < 0.001$). Cervical length/thickness ratio was the highest predictor of the favorable cervix with dinoprostone. Each 1 unit decrease in the length/thickness ratio of the cervix increases the preparation of the cervix for induction by 0.25 times ($P = 0.04$). A successful response to dinoprostone can be obtained if the cervical length/thickness ratio is <1.06 mm ($P < 0.001$).

Conclusion: In conclusion, assessing the cervix's condition before labor induction by measuring the cervical length/thickness ratio may be a good predictor of cervical ripening activity.

Keywords: Cervix uteri, Cervical length, Ultrasonography, Cervical thickness

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Introduction

During pregnancy, the cervix has extensive remodeling, resulting in softening, shortening, and dilation (a process referred to as ripening) to allow delivery. Sudden transformations result in preterm birth. Cervical softening, which begins soon after conception and advances throughout pregnancy, is an essential change [1, 2]. The current clinical approach for assessing the cervix involves a subjective evaluation of cervical immobility as soft, medium, and firm categories based on digital examination [1].

The cervical condition affects the induction time and the vaginal delivery process in pregnant women for whom we are planning labor induction. If the cervical condition is not favorable, a period of cervical ripening is usually expected before induction to shorten the induction time and maximize the possibility of vaginal delivery. Although cervical status at induction suggests the chance of cesarean delivery, it does not predict whether avoiding induction of labor and managing the patient with anticipation will result in a higher chance of vaginal delivery [3, 4].

The two primary methods for cervical ripening are mechanical interventions [4] (such as balloon catheterizing) and using pharmacologic agents (such as prostaglandins) [3]. A universal definition for favorable or unfavorable cervix has not yet been established. Many clinicians consider a Bishop score < 6 indicative of an unfavorable cervix and the need for a ripening agent, while others utilize a lower threshold [5].

There is no specific practice for the best agent to use for cervical ripening. Both mechanical and pharmacologic agents are acceptable. The choice should be based on clinicians' preferences and experience unless there is a contraindication for the agent or technique [6,7]. Balloon catheters have few adverse effects and are a potentially irritated vaginal procedure for catheterization. It is easier to access than prostaglandin agents. In contrast, an advantage of prostaglandins is that they promote myometrial contractility, reducing the need for oxytocin to increase or induce labor. Contrarily, a disadvantage of using prostaglandins is the possibility of excessive uterine activity, leading to fetal heart rate (FHR) abnormalities. However, neither the theoretical advantage nor the disadvantage in clinical studies resulted in differences in clinically significant outcomes (e.g., cesarean delivery, neonatal morbidity) [6-9].

Once a ripening agent starts, it generally continues until the cervix is favorable. Prostaglandins stimulate the biophysical changes that lead to cervical ripening and growth in myometrial contractility [10].

While discussions continue about the application preparations of the Dinoprostone (PGE-2) ovule, which is commonly used in cervical maturation and induction of labor induction [11, 12], articles on the future use of this agent are also published [13]. There are no clear objective criteria regarding the efficacy and use of dinoprostone, which is still universally used as a cervical ripening agent. Although the pre-treatment Bischop score is being evaluated, the evidence for efficacy remains low.

In our experience, we frequently use the Dinoprostone ovule for cervical ripening before labor induction. However, we categorize the cervix only as soft or stiff in the pre-treatment examination. There is a need for an objective, accessible, and easy-to-use method that can predict dinoprostone treatment efficacy. We measured the thickness of the cervix before treatment and aimed to show at which measurement intervals dinoprostone treatment results in positive vaginal delivery outcomes. In this respect, we presented the first study in the literature as an article.

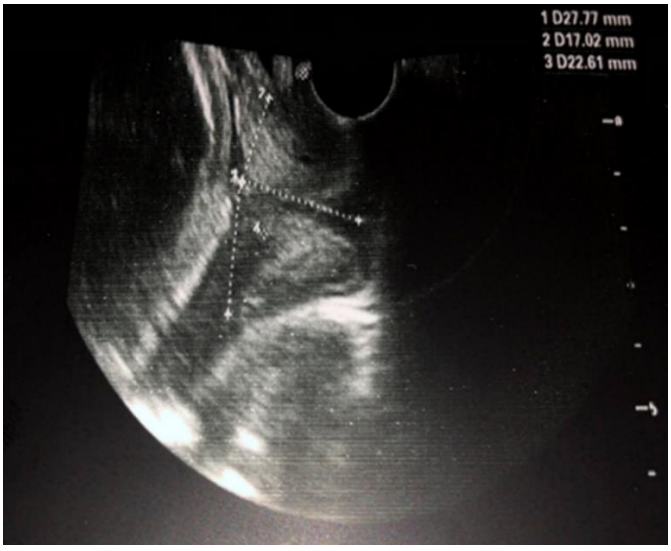
Materials and methods

In this article, we compiled the analysis of 183 pregnant women from 37–41 weeks from January 2020 to November 2020. We conducted this study in Bursa Yüksek İhtisas Training and Research Hospital, Gynecology and Obstetrics department. The Bursa Yüksek İhtisas Training and Research Hospital ethics committee approved the study (2011-KAEK-25 2019/07-15). The gestational week of all pregnant women included in the study was calculated according to the first-trimester ultrasound, which was correlated with their last menstrual period. Women with fetal macrosomia (>4500 grams), fetal anomaly, previous uterine surgery, short stature (less than 150 cm), occiput posterior fetal position, history of dystocia, and maternal comorbid conditions were excluded from the study.

While performing the essential evaluations (e.g., fetal biometric parameters, estimated fetal weight) before labor induction, we also evaluated the cervix ultrasonographically. We performed cervical length and thickness measurements. We also evaluated cervical maturity by performing a vaginal examination on each pregnant woman.

We observed the sagittal plane using transvaginal ultrasound for cervical length and thickness measurements by placing the probe in the anterior fornix and obtaining the sagittal plane with rotation. We obtained cervical length by measuring the distance between the internal and external cervical os [14-16]. In addition, we measured the outer cervical diameter, in other words, the distance of the cervical canal to the anterior and posterior cervical lips in the same plane, and named this cervical thickness [17-19] (Figure 1).

Figure 1: Cervical thickness measurement figure



Before oxytocin induction, we applied 10 mg of dinoprostone ovule vaginally in sustained release form to pregnant women with a stiff cervix, without dilatation and effacement. When regular uterine contractions started and dilatation of 4 cm occurred or after 12 h, the suppository was removed from the vagina. After a 1-h break, we switched to labor induction with

oxytocin. During this period, the ovule was immediately removed in cases of fetal tachysystole or distress or bleeding from maternal spontaneity [5].

Then, we followed up on the latent, active, and second phases of labor. The latent phase of labor was expressed as the time from the onset of labor to 6 cm cervical dilation. The active phase of labor started at 6 cm of cervical dilation. A 4-h threshold for diagnosing labor arrest may be acceptable. The time from full cervical dilation to the delivery of the baby also formed the second stage [20]. We noted the duration of these phases and the fetal head's expulsion by performing digital examinations at recommended intervals [21]. We analyzed the relationship between prolongation in labor processes and arrest situations with ultrasonographic cervical measurements. We defined labor with protraction or arrest in the active or second phase as labor dystocia. We performed Bishop scoring for defining the favorable cervix and considered 6 points and above as successful cervical ripening [22].

Statistical analysis

A Windows-based SPSS 22.0 statistical analysis program was used (SPSS Inc., USA). We examined variables via visual (histograms, probability plots) and analytical methods (Shapiro-Wilk's and Kolmogorov-Smirnov test) to determine whether they were normally distributed. Variables are specified as mean (standard deviation) (X [SD]), the mean difference between groups, 95% confidence interval (95%CI), median (minimum-maximum [min-max]), frequency (n), and percentage (%). Student *t-test* and Mann-Whitney U test compared normally distributed and undistributed variables. Pearson and Spearman's tests were conducted to show relationships between normally and non-normally distributed or ordinal variables. The level of significance was $P \leq 0.05$. For the multivariate analysis, the possible factors identified in previous analyses were further entered into the logistic regression analysis to determine independent predictors of study outcomes. Hosmer-Lemeshow goodness of fit statistics was for evaluating model fit. A 5% type-1 error level was accepted to infer statistical significance. The diagnostic values of cervical thickness and length measures in predicting successful vaginal delivery, labor dystocia, and cesarean delivery were examined by ROC curve analysis. The sensitivity, specificity, and positive and negative predictive values were presented when a significant cut-off value was observed. While evaluating the area under the curve, a 5% type-1 error level was used to accept a statistically significant test variable's predictive value.

Results

In this study, we included 183 pregnant women after exclusion criteria. While the median value of their age was 25 years, the mean week of gestation was 39 weeks and 3 days. In the first evaluation, the mean cervix length values measured ultrasonographically were 31.6 (8.2), and the mean thickness of the cervix was 34.5 (7.5) mm. The mean cervical length/thickness ratio was 0.95 (0.3). In the digital examination, 37.8% of the pregnant women had a hard cervix, 31.1% had a medium, and 31.1% had a soft cervix. While the median latent phase duration of these pregnant women to whom we applied labor induction was 8 h (1.45-24), the active phase duration was 30 min (10-340). While the number of pregnant women ready for induction and achieved adequate patency after dinoprostone was 127 (69.4%), 56 (30.6%) pregnant women could not obtain adequate cervical dilatation. While 124 (67.8%) of the pregnant women were vaginally straight, the rest were subjected to cesarean section (Table 1).

Table 1: Descriptive analysis table according to demographic and clinical characteristics of pregnant women

Characteristics of patients (n=183)	Median (min-max) / Mean (SD)
Age (year)	25 (18-40) #
Parity	1 (0-8) #
Gestational Age (week + day)	39+3 (37-42) #
Labor induction indications (n; %)	Non-reactive NST (50; 27.3)
	Prelabor membrane rupture (29; 15.8)
	Surmaturation (48; 26.2)
	Oligohydramnios (56; 30.6)
Cervical Length (mm)	31.6 (8.2)*
Cervical Thickness (mm)	34.5 (7.5)*
Cervical Length/Thickness Ratio	0.95 (0.3)*
Cervical Consistency (n; %)	Soft (57; 31.1)
	Medium (57; 31.1)
	Firm (69; 37.8)
Dilation (cm)	No (101; 55.2)
	1-2 cm (82; 44.8)
Latent phase duration (hour, minute) (n=169)	8 (1, 45-24) #
Active phase duration (minute) (n=127)	30 (10-340) #
Second stage duration (n=127)	10 (5-90) #
Labor induction indications (n; %)	Non-reactive NST (50; 27.3)
	Prelabor membrane rupture (29; 15.8)
	Surmaturation (48; 26.2)
	Oligohydramnios (56; 30.6)
Adequate cervical ripening	No (56; 30.6)
after treatment (n; %)	Yes (127; 69.4)
Labor (n; %)	Vaginal delivery (124; 67.8)
	Cesarean (59; 32.2)
Cesarean indications (n; %)	Fetal distress (22; 12)
	Labor dystocia (37; 20.2)

Min: minimum, max: maximum, SD: standard deviation, # Descriptive analyses were presented using median (min-max), * for non-normally distributed, and (n; %) for categorical variables. mm: millimeter, n: frequency, % percentage

We performed a correlation analysis between the length and thickness of the cervix and the labor process. Accordingly, the length, thickness, or ratios of the cervix, which we evaluated prenatally, were not correlated with the duration of labor or labor stages. The latent, active phase and second stage duration did not significantly correlate. On the other hand, while the age of the pregnant women was negatively correlated with the thickness of the cervix ($P = 0.004$), the cervical length/thickness ratio was positively correlated ($P < 0.001$) (Table 2).

Table 2: Correlation analysis table of cervical length and thickness data with birth parameters in nulliparous women

	Cervical length		Cervical thickness		Length/Thickness ratio	
	r	*P*-value	r	*P*-value	r	*P*-value
Age	0.16	0.104	-0.28	0.004	0.358	<0.001
Gestational Age	-0.12	0.22	0.003	0.97	-0.103	0.29
Latent phase duration	-0.55	0.62	-0.22	0.044	0.13	0.23
Active phase duration	-0.063	0.63	-0.22	0.094	0.015	0.91
Second stage duration	-0.99	0.45	-0.022	0.87	-0.069	0.601

r: correlation coefficient, $P < 0.05$ was considered significant (Spearmen test)

We divided the pregnant women into two groups: successful and unsuccessful cervical ripening after dinoprostone. There was no difference between the two groups regarding the volunteers' age and gestational week. There was a difference between the two groups regarding the number of births. The thickness of the cervix, which was evaluated ultrasonographically before the treatment, revealed a difference between the two groups ($P < 0.001$). Accordingly, the mean cervical thickness of the pregnant women with successful cervical ripening was 34.5 (7.5) before treatment, while the mean values of the unsuccessful group were 29.2 (9.1). In addition, cervical length did not differ between the two groups ($P = 0.44$), while the cervical length/thickness ratio was significantly lower in the group with successful maturation ($P < 0.001$) (Table 3).

Table 3: Comparison of ultrasonographic and demographic parameters in terms of cervical ripening

	Successful (n=127) X (SD) / Median (min-max)	Non successful (n=56) X (SD) / Median (min-max)	Mean difference (95%CI) / U	*P*-value
Cervical length*	31.6 (8.2)	32.5 (6.8)	0.89 (-1.40 - 3.20)	0.44
Cervical thickness*	34.5 (7.5)	29.2 (9.1)	-5.32 (-6.8 - -2.8)	<0.001
Cervical length/thickness ratio#	0.9 (0.38-2)	1.1 (0.5-2)	2181	<0.001
Age (year) #	25 (18-40)	28 (18-38)	3198	0.27
Parity#	1 (0-8)	0 (0-7)	2370	<0.001
Gestational Age (week + day) #	39 (37-42)	39 (37-42)	3480	0.81

X: mean, SD: standard deviation, %: percent, min: minimum, max: maximum, CI: Confidence interval, U: U value. Descriptive analyzes are presented using (X [SD]) and median (min-max) for normally distributed and non-normally distributed, respectively. Student's t-test *$P < 0.05$ and Mann-Whitney U test #$P < 0.05$ were considered significant.

We performed binary logistic regression analysis to determine the most valuable parameter to affect cervical ripening. Accordingly, the cervical length/thickness ratio was the highest predictor of adequate maturation of the cervix with dinoprostone. Each 1 unit decrease in the length/thickness ratio of the cervix increases the preparation of the cervix for induction by 0.25 times ($P = 0.04$) (Table 4).

Table 4: Binary logistic regression table for cervical thickness and length/thickness ratio in terms of cervical ripening success

Cervical ripening	Parameters	B	Wald	OR	95% CI	*P*-value
Successful	Cervical thickness	0.035	1.4	1.03	0.97-1	0.23
	Cervical length/thickness	-1.38	4.1	0.25	0.7-0.94	0.04

CI (95%); confidence interval, OR: estimated relative risk. Wald: test statistic value. Binary logistic regression was used because the dependent variable consisted of 2 groups. The reference category was taken as the unsuccessful ripening. Parameters found significant in the previous analysis were included in the analysis. Hosmer-Lemeshow model fit was $P < 0.05$.

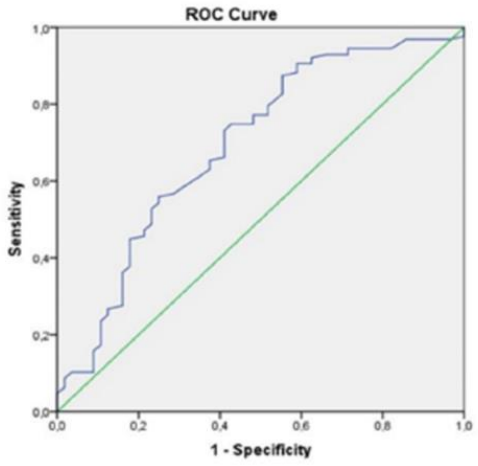
Using the ROC (receiver operating characteristics) curve, we analyzed the chance of predicting the length/thickness ratio of the cervix in successful cervical ripening with dinoprostone treatment. We determined a cut-off value for the cervix length/thickness ratio according to the ROC curve and the area under the curve table (AUC) (Table 5), and the cervical length/thickness parameter had a diagnostic value in predicting successful cervical ripening. As a result, if the cervical length/thickness ratio is <1.06 mm ultrasonographically, a successful and significant response to dinoprostone can be obtained with 73.2% sensitivity and 60.1% specificity ($P < 0.001$) (Table 5) (Figure 2).

Table 5: ROC analysis table in terms of cervical length/thickness ratio threshold value in the prediction of successful dinoprostone therapy

Area Under Curve (AUC)	*P*-value	Cut-off	Sensitivity	Specificity	PPV	NPV
0.693 (0.607 – 0.780)	<0.001	1.06	73.2%	60.1%	80.2%	58.1%

CI: Confidence Interval, PPD: Positive predictive value, NPV: Negative predictive value

Figure 2: Receiver operating characteristic (ROC) analysis chart of predicting the length/thickness ratio of the cervix in successful cervical ripening with dinoprostone treatment



Discussion

In this article, we reviewed the study in which we correlated the effectiveness of vaginal dinoprostone therapy for cervical ripening with cervical length and thickness. Before labor induction, we apply the dinoprostone vaginal ovule as a standard for the cervix to mature sufficiently. We evaluate with cervical examination before this therapy. However, an objective examination or examination method that can show the effectiveness of treatment is not yet available. By evaluating the cervix ultrasonographically before labor induction, we showed that the increase in the thickness of the cervix and the decrease in the cervical length/thickness ratio is predictive of successful dinoprostone treatment in terms of adequate maturation. We showed the cervical length/thickness ratio as the most valuable parameter. Thus, we obtained an objective pre-diagnosis method to prepare the patient for vaginal delivery planned and labor induction. This study will be preliminary in the literature with these findings.

The purpose of cervical ripening is to ease the process of cervical softening, thinning, and dilating with a resultant decrease in failed induction and induction to delivery time. Cervical remodeling is a critical component of the pregnancy process. Collagen degradation, rearrangement, changes in glycosaminoglycans, cytokine release, and increased white blood cell infiltration occur. If induction is indicated and the status of the cervix is unfavorable, agents for cervical ripening may be chosen [5]. The status of the cervix can be determined by the Bishop pelvic scoring system [22].

The currently known and accepted methods for cervical ripening are mechanical cervical dilators and synthetic prostaglandin E1 (PGE1) and prostaglandin E2 (PGE2) treatments [23, 24].

Boulvain et al. [25] showed that in pregnant women with an unfavorable cervix and scheduled for an induction, initial mechanical dilatation is associated with a lower cesarean delivery rate than oxytocin alone. There is insufficient data to evaluate the effectiveness of mechanical methods when compared with prostaglandins [5, 25, 26].

Food and Drug Administration (FDA) approves Misoprostol, a synthetic PGE1 analog, and Dinoprostone, PGE2 preparations, for cervical ripening before labor. Dinoprostone has two forms: a gel containing 0.5 mg of dinoprostone and a vaginal insert containing 10 mg of dinoprostone [5]. Vaginal prostaglandins used for cervical ripening increase the chance of delivery within 24 h but do not reduce the rate of cesarean delivery and increase the risk of uterine tachysystole with associated FHR changes compared with placebo or oxytocin alone [5, 27].

The Bishop score is the cervical assessment method and is still most commonly used in the United States [22]. It seems to be a more available tool than cervical length measurement [28] or fetal fibronectin [29] for assessing the cervical status or predicting successful induction.

Lauterbach et al. [30] performed a 4-year study in nulliparous pregnant women with a Bishop score <5. Accordingly, they compared the results between groups by applying a balloon catheter or vaginal dinoprostone to two groups of patients for cervical ripening. Accordingly, the duration of vaginal delivery was shorter in pregnant women who received a cervical balloon

dilator. Bagory et al. [31], in a retrospective study of two years, did not find a significant relationship between misoprostol and dinoprostone treatments in terms of the effect of cervical ripening on vaginal delivery. Garg et al. [32] compared Misoprostol+Foley catheter and Dinoprostone+Foley catheter combinations for cervical ripening in delivery outcomes. In this study, delivery times and outcomes did not differ between the two groups. Chen et al. [7] have a meta-analysis study covering 17,387 pregnant women in 2015. This study compared the efficacy of Foley catheter, misoprostol, and dinoprostone treatments for cervical ripening in labor induction. As a result, no superiority could be shown between the three methods.

Evaluation of the cervix length has been the main subject of many studies in the literature. Numerous studies have reported that an especially short cervix is a sign of premature birth risk [33-37]. In addition, studies are showing the significant effect of cervical length on labor induction and delivery time [38-40]. Park et al. [41] showed that sonographic cervical length was more successful than Bishop's score in predicting the success of labor induction with prostaglandin or oxytocin in their study. Laenciana et al. [42] published that measuring cervical length by transvaginal ultrasonography is a better predictor of successful labor induction than the Bishop score. Cubal et al. [43], in their published study, show that the Bishop score and cervical length are good indicators of successful labor induction, especially in nulliparous women.

While there are many articles about cervical length and its effect on labor, we found no study of cervical thickness. The expression of cervical thickness was previously defined by taking a sagittal section in only one study and was used to calculate the cervical volume. This study showed that cervical volume measurement did not benefit compared to cervical length measurement for predicting preterm birth [44].

As a result of our analyses, measuring the length and thickness of the cervix before using dinoprostone for maturation can result in successful ripening and preparation for induction. The thickness of the cervix is easy to measure and evaluate, as shown in literature examples [1, 17, 44, 45], and can be standardized with more studies. This research is a novel and preliminary study regarding methods and results.

Limitations

Our study had some limitations. The number of pregnant women could have been higher, only nulliparous pregnant women could have been studied, and the data related to delivery duration could have been analyzed. Also, since the score distribution of pregnant women was narrow and there was insufficient data, we could not compare the Bishop score with cervical ultrasonographic parameters. In addition, the number of vaginal deliveries decreased slightly due to pregnant women for whom we decided to have an emergency cesarean section due to the weakening of fetal well-being in the early period after dinoprostone or at the beginning of induction. We also excluded pregnant women who could not obtain an optimal ultrasonographic image due to overall obesity.

In a longer-term study with more pregnant women, the prediction of cervical thickness, especially the duration of labor, the time between induction and delivery, and the cesarean section can be compared.

Conclusion

In this article, we found it meaningful to measure the length and thickness of the cervix ultrasonographically before dinoprostone ovule treatment. The increase in the thickness of the cervix or the decrease in the cervical length/thickness ratio, which we will evaluate before labor induction, may indicate that cervical ripening may be facilitated.

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The correlation of clinical status and imaging findings in patients with chronic low back pain

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Ethics Committee Approval
The study protocol was approved by the Izmir Katip Celebi University clinical research ethics committee (approval date: 27/09/2018, approval number: 108).
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: Chronic low back pain (LBP) is a common health problem that negatively affects quality of life. A multidisciplinary approach is recommended in treating chronic LBP. In the literature, we could not find any study examining the relationship between clinical status, activities of daily living, angular measurements in the lumbar region, and spondylosis level in patients with LBP. We aimed to reveal whether there is a relationship between the severity of the clinical condition and these angular measurements. In addition, there are opposing views in the literature about the relationship between obesity and LBP, and we planned to investigate this issue in our study. We aimed to investigate the correlation between clinical, functional evaluations, and radiographic findings in patients with chronic LBP and examine the relationship between these variables and gender and educational level. We also determine the effects of age, body mass index (BMI), and waist circumference on these variables.

Methods: The research was designed as a cross-sectional, uncontrolled study. Seventy patients aged 18–65 years with chronic LBP and VAS (Visual Analog Scale) values ≥ 3 were included. Patients were grouped by gender and educational level. Lumbar lordosis angle (LLA), sacral inclination angle (SIA), and Kellgren-Lawrence (K-L) grade were recorded. VAS, Oswestry Disability Index (ODI), Back Pain Functional Scale (BPFS), and Katz Activities of Daily Living (Katz-ADL) scores were calculated. Pearson correlation analysis determined the normal distribution status of the variables. Spearman's correlation analysis evaluated the linear relationship between ODI and BPFS and LLA and SIA continuous variables. A p-value of < 0.05 was considered statistically significant.

Results: A total of 70 patients (47 females and 23 males) with chronic LBP were included in the study. Mean BMI (28.2 [6.1] kg/m^2) and waist circumference (95.7 [12.7] cm) of the patients were above normal ranges (normal BMI: 18.5–24.99 kg/m², normal waist circumference: < 80 cm for women, < 90 cm for men). Katz-ADL ($P = 0.006$) and BPFS scores ($P = 0.027$) were lower, and LLA ($P = 0.042$) was higher in women than men. The BPFS score was lower in the low-level education group than in the high-level education group ($P = 0.004$). There was a positive correlation between age and SIA ($P = 0.028$, r = 0.262), and between age and K-L grade ($P < 0.001$, r = 0.633). A positive correlation was also observed between BMI and K-L grade ($P = 0.001$, r = 0.395) and waist circumference and K-L grade ($P < 0.001$, r = 0.442).

Conclusion: No correlation was found between functional clinical scales and radiographic findings in patients with chronic LBP. Increasing age, BMI, and waist circumference were associated with more severe radiographic osteoarthritis of the lumbar spine, whereas female gender and low educational level were related to lower functional levels. Further extensive studies, including a larger number of patients, are needed to clarify our results.

Keywords: Low back pain, Lumbar lordosis, Lumbar spondylosis, Obesity

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Introduction

Low back pain (LBP) is defined as pain, muscle tension, and stiffness, with or without leg pain, in the area between the lower edge of the 12th rib and the lower gluteal fold at the proximal thigh [1].

The biomechanics of the lumbar spine is crucial in LBP cases. Various studies have investigated the relationship between changes in the angle of the lumbar spine and back pain [2, 3]. A previous study examined the lumbar lordosis angle (LLA), sacral inclination angle (SIA), lumbosacral angle (LSA), and sacral horizontal angle (SHA) in acute and chronic LBP patients, as well as the correlation between spinal stability and these angles [3]. Some studies show that specific exercise programs affect these angular measurements [4, 5].

Therefore, this study aimed to investigate the correlation between LLA, SIA, osteoarthritis level of the lumbar region, and functional clinical scales in chronic LBP patients. Secondary outcomes were the relationship between gender and educational level with functional clinical scales and radiographic findings and the effects of waist circumference, body mass index (BMI), and age parameters on these variables. Especially the emergence of this relationship will guide us in our treatment decision. If a significant relationship was detected between the severity of the patient's clinical condition and angular measurements, it would have been useful to give specific exercises to improve these angles (LLA, SIA). On the other hand, if the increases in BMI and waist circumference made the clinical condition worse, weight control or the prevention of obesity would be more critical for these patients.

Materials and methods

The study was single-centered, clinical, uncontrolled, and cross-sectional. Participants were informed about the study, and their written informed consent was obtained. The protocol was performed per the ethical standards in the 1964 Helsinki Declaration and approved by the Izmir Katip Celebi University clinical research ethics committee (approval date: 27/09/2018, approval number: 108).

Participants

The sample size was calculated with the NCSS/PASS program. Using the data of a previous study [6], it was predicted that the correlation between the lumbar lordosis angle in the extension position and the Sacral inclination angle in individuals with chronic LBP would be r = 0.40, reaching at least 61 people for 90% power, type 1 error level: 5% (2-way).

This study included 70 patients admitted to the Physical Medicine and Rehabilitation outpatient clinics of Izmir Katip Çelebi University Atatürk Education and Research Hospital between October 2018 and February 2019. Inclusion criteria were the subjects aged between 18–65 years, the duration of LBP > 12 weeks, and the VAS value ≥ 3. Exclusion criteria were a history of trauma, malignancy, uncontrolled endocrine disorders, fibromyalgia syndrome, inflammatory rheumatic diseases, acquired or congenital malformations (spondylolisthesis, spondylolysis), inflammatory rheumatic diseases, previous spinal surgery, disc pathologies that cause radicular symptoms and neurological deficits, and pregnancy.

Study design

The patients were grouped according to gender and educational level. There were three groups according to educational level (illiterate/primary school, high school, and university graduates). Radiographic measurements were measured by two different doctors at different times and averaged. Questionnaires were also given to the patient and asked to fill in. Regardless of the groups, the relationships between functional clinical scales and radiographic findings of the patients were evaluated, and the effects of BMI, waist circumference, and age on these variables were determined. Then, it was investigated whether there was any difference between groups regarding functional clinical scales and radiographic findings.

Assessment methods

1. Demographic information: The patients' age, BMI, waist circumference, marital status, educational level, and socioeconomic level were recorded.

2. Evaluation of pain: Visual Analog Scale (VAS).

3. Functional Level Measurement: Oswestry Disability Index, Back Pain Functional Scale, and Katz Activities of Daily Living Scales were used to evaluate functional level. Validity and reliability studies of these scales for Turkish society have been conducted [7-9].

4. Radiographic evaluation of the spine: 2-view lumbosacral spine radiographs were used to measure the lumbar lordosis angle, sacral inclination angle, and Kellgren-Lawrence classification grade. These measurement methods have also been used in similar studies [10, 11].

Statistical analysis

Statistical analysis was performed with the SPSS (Statistical Package for Social Sciences) 21.0 program. The number, percentage, mean, and standard deviation values were calculated in descriptive analyses.

Pearson correlation analysis determined the normal distribution status of the variables. Statistical analysis of independent Sample t-test, Mann Whitney U, and Kruskal Wallis H (post hoc Bonferroni corrected Mann Whitney U) tests were performed comparing two groups' regular variables according to their suitability for normal distribution. T-test determined whether the difference between the mean values of the two groups was significant, and the F (ANOVA- Analysis of Variance) test whether the difference between the mean values of more than two groups was significant.

Spearman correlation analysis evaluated the linear relationship between ODI and BPFS and LLA and SIA continuous variables [12]. The correlation was accepted as very weak when the correlation coefficient (r) was < 0.3, weak when r = 0.3–0.5, moderate when r = 0.5–0.7, and strong when r > 0.7. A *P* -value of < 0.05 was considered statistically significant.

Results

A total of 70 patients (47 females and 23 males) with chronic LBP were included in the study. The sociodemographic characteristics of the patients are presented in Table 1.

Mean VAS, ODI, Katz ADL, BPFS, LLA, SIA, and Kellgren-Lawrence grades of the patients are shown in Table 2.

Table 1: Sociodemographic characteristics of patients

		n (%)
Education	Illiterate/primary school	37 (52.9%)
	High school	20 (28.6%)
	University	13 (18.6%)
Martial status	Married	47 (67.1%)
	Single	17 (24.3%)
	Widow/widower	6 (8.6%)
Income rate	2000 ₺ or less	54 (77.1%)
	2000-4000 ₺	12 (17.1%)
	4000-8000 ₺	4 (5.7%)

₺: Turkish lira

Table 2: Descriptive statistics

	Number	Minimum	Maximum	Mean	SD
Age	70	20	65	43.6	13.28
BMI	70	15.94	43.7	28.23	6.14
Waist C.	70	72	127	95.76	12.71
VAS	70	4	10	6.41	1.91
ODI	70	2	27	14.43	5.84
Katz ADL	70	5	6	5.81	0.39
BFPS	70	13	56	36.21	10
LLA	70	12.0	62.3	35.8	10.34
SIA	70	27.5	62.3	44.23	8.18
K-L Grade	70	1	3	1.94	0.74

BMI: Body Mass Index, Waist C: Waist Circumference, VAS: Visual Analog Scale, ODI: Oswestry Disability Index, ADL: Activities of Daily Living, BPFS: Back Pain Functional Scale, LLA: Lumbar Lordosis Angle, SIA: Sacral Inclination Angle, K-L: Kellgren-Lawrence SD: Standard deviation

The patients were grouped by gender, and it was investigated whether there was any difference between both groups' functional clinical scales and radiographic findings (Table 3). When comparing the groups according to educational levels, the BPFS score was significantly lower in the Illiterate/Primary school group than in the High school and University groups (P = 0.004) (Table 4).

Table 3: Comparison of VAS, ODI, Katz ADL scale, BPFS, LLA, SIA and K-L by gender

	Gender		
	Female (n = 47) mean(SD)	Male (n = 23) mean(SD)	*P*-value
VAS	6.45 (1.92)	6.35(1.95)	0.333*
ODI	15.09(5.37)	13.09(6.65)	0.181**
Katz ADL	5.72(0.452)	6.0(0.0)	0.006*
BPFS	34.38(9.88)	39.96(9.37)	0.027**
LLA	37.56(9.52)	32.23(11.23)	0.042**
SIA	45.12(7.38)	42.42(9.55)	0.198**
K-L	2.0(0.69)	1.83(0.83)	0.813*

VAS: Visual Analog Scale, ODI: Oswestry Disability Index, ADL: Activities of Daily Living, BPFS: Back Pain Functional Scale, LLA: Lumbar Lordosis Angle, SIA: Sacral Inclination Angle, K-L: Kellgren-Lawrence Classification, SD: standard deviation,*Mann Whitney U, **Student t- test

Table 4: Comparison of VAS, ODI, Katz ADL scale, BPFS, LLA, SIA and K-L by educational level

	Educational level			
	Illiterate/primary school (n= 37) mean(SD)	High school (n=20) mean(SD)	University (n= 13) mean(SD)	*P*-value
VAS	6.68(2.02)	6.55(1.96)	5.46(1.27)	0.550*
ODI	15.86(6.09)	12.50(6.07)	13.31(3.59)	0.085**
Katz ADL	5.76(0.44)	5.80(0.41)	6.00(0.0)	0.195*
BPFS	32.57(10.24)	40.55(8.90)	39.92(6.97)	0.004**
LLA	36.86(8.9)	33.27(10.7)	36.72(13.4)	0.436**
SIA	44.59(7.0)	42.67(9.42)	45.61(9.40)	0.562**
K-L	2.08(0.72)	1.80(0.834)	1.77(0.60)	0.256**

VAS: Visual Analog Scale, ADL: Activities of Daily Living, BPFS: Back Pain Functional Scale, LLA: Lumbar Lordosis Angle, SIA: Sacral Inclination Angle, SD: standard deviation, K-L: Kellgren-Lawrence Classification, ODI: Oswestry Disability Index,*Kruskal Wallis, **ANOVA

The relationship between the functional clinical scales and radiographic measurements of the patients is presented in Table 5, and no correlation was found between these variables. The relationships between age, BMI, and waist circumference with functionality and radiographic measurements are shown in Table 6.

Table 5: Correlation of LLA, SIA and K-L with VAS, ODI, Katz ADL and BPFS

	LLA		SIA		K-L	
	r	*P*-value	r	*P*-value	r	*P*-value
VAS	-0.082	0.449*	-0.144	0.235*	0.120	0.324*
ODI	0.114	0.346**	-0.033	0.785**	0.183	0.130*
Katz ADL	-0.088	0.468*	-0.090	0.459*	-0.187	0.121*
BPFS	-0.188	0.118**	0.052	0.670**	-0.220	0.068*

VAS: Visual Analog Scale, ADL: Activities of Daily Living, BPFS: Back Pain Functional Scale, LLA: Lumbar Lordosis Angle, SIA: Sacral Inclination Angle, K-L: Kellgren-Lawrence Classification, ODI: Oswestry Disability Index, *Spearman correlation, **Pearson correlation

Table 6: Correlation of VAS, ODI, Katz ADL scale, BPFS, LLA, SIA and K-L with age, BMI and waist circumference

	Age		BMI		Waist circumference	
	r	*P*-value	r	*P*-value	r	*P*-value
VAS	0.009	0.942*	-0.140	0.248*	-0.226	0.60*
ODI	-0.022	0.854**	0.047	0.700*	0.009	0.941**
Katz ADL	-0.198	0.100*	-0.172	0.155*	-0.234	0.051*
BPFS	-0.081	0.503**	-0.120	0.322*	-0.043	0.726**
LLA	0.170	0.160**	-0.017	0.889*	-0.044	0.715**
SIA	0.262	0.028**	0.029	0.809*	0.025	0.835**
K-L	0.633	<0.001*	0.395	0.001*	0.442	<0.001*

BMI: Body Mass Index, VAS: Visual Analog Scale, ADL: Activities of Daily Living, BPFS: Back Pain Functional Scale, LLA: Lumbar Lordosis Angle, SIA: Sacral Inclination Angle, K-L: Kellgren-Lawrence Classification, ODI: Oswestry Disability Index,*Spearman correlation, **Pearson correlation

Discussion

This study aimed to investigate whether there was any correlation between functional clinical scales and radiographic findings in patients with chronic LBP. However, we could not find any correlation in-between.

Ayvat et al. [13] investigated the risk factors that trigger LBP by examining patients' characteristics, such as age, gender, marital status, occupation, educational levels, smoking, and alcohol consumption. This study reported significant correlations between low educational level, low economic level, heavy work, and smoking with LBP but did not find any correlation between LBP and gender. Similarly, we found that BPFS scores were significantly lower for those with lower educational attainment. However, in our study, the Katz ADL Scale and BPFS scores were significantly lower in women than men.

Our results showed that the mean values of BMI and waist circumference of the patients were higher than normal values for both genders (normal BMI: 18.5–24.99 kg/m², normal waist circumference: < 80 cm for women, < 90 cm for men) [14]. The relationship between obesity and LBP has been investigated in many other studies. A study investigating pain localization, the most prevalent age group, and the frequency of physical therapy sessions in obese and non-obese subjects with LBP showed that obesity and age had no direct influence on back pain, but they could prolong healing [15]. Chowdury et al. [16] found a direct association between BMI and LBP severity in another study. In addition, our study found that osteoarthritis grade was positively correlated with waist circumference and BMI values.

Among radiographic measurements, we found that LLA was higher in women than men, concordant with the literature [6]. The mean LLA of patients in our study was 35.8 (10.3), significantly below the normal range showing a decrease in lumbar lordosis. In this regard, the study of Murray et al. [17], in which they evaluated 301 patients, reported that both hypolordosis and hyperlordosis in both genders were correlated with degenerative joint disease.

Amonoo-Kuofi [6] reported that SIA increases in men and decreases in women towards the end of the second decade, but between the 3rd and 5th decades, it increases in women and increases after a brief decrease in men. A decline in SIA was noted in both genders after the fifth decade. However, a weak positive correlation was found between age and SIA in both genders in our study. Another variable that increased with age was Kellgren-Lawrence grade of lumbar vertebrae, and a moderate positive correlation was found in-between. Different views have been reported on this issue in the literature. The positive correlation between age and osteoarthritis level, which is

the more common opinion, was supported by the results of our study.

The study of Ashraf et al. [11], in which they assessed 150 patients, noted a correlation between Kellgren-Lawrence level and ODI in female patients. In our study, we could not find any correlation between Kellgren-Lawrence grade and functional clinical scales, including ODI.

There are some limitations of this study. A major limitation is the lack of a control group. Second is the relatively small number of participants.

Conclusion

To conclude, in this study, we revealed that obesity is associated with both LBP and the level of spondylosis in the lumbar region. We would like to emphasize the importance of lifestyle changes and weight control in treating chronic LBP.

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Research article

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Evaluation of neurological and cardiac development of newborn infants born to mothers infected with COVID-19

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Ethics Committee Approval
This study was approved by İzmir Bakırçay University, Ethical Committee on Noninvasive Clinical Research (Date:24.06.2021, Number: 4329-3380).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: In the coronavirus disease 2019 (COVID-19) pandemic, which has been affecting the world for the last 2 years, pulmonary, cardiovascular, and neurological adverse effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported. These negative influences entail a risk for fetal progress. In this study, by performing a detailed clinical evaluation, postnatal ultrasonography, and echocardiography, we aimed to investigate potential neurological and cardiac complications of newborns born to pregnant women infected with COVID-19.
Methods: This prospective and cross-sectional study was conducted between January and July 2021. Newborn infants (0–28 days postpartum) born to mothers with proven COVID-19 infection by positive RT-PCR test during pregnancy were enrolled. Fetal cardiac development was evaluated by a pediatric cardiologist with an echocardiographic examination. Fetal neurologic evaluation was performed by a pediatric neurologist using both neurologic examination and transfontanelle ultrasonography (TFUS). Infants were reevaluated every 2 months until 6 months of age.
Results: Thirty-three female and 32 male infants born to 64 pregnant women, one being a twin birth, were included in the study. Seven women developed COVID-19 infection in the first trimester, 11 in the second trimester, and 46 in the third trimester. Neurological examination and TFUS were normal in all newborns except one with microcephaly. The etiologic cause could not be detected in this infant, and his neurodevelopment was normal in the follow-up. The cardiac examination did not reveal any significant disorders. Eleven infants failed the standard "Auditory Brainstem Response" (ABR) hearing screening test, so a second test was performed. Only two infants required further investigation after the second test.
Conclusion: We did not observe any neurologic and cardiologic teratogenic effects associated with COVID-19 infection during pregnancy.

Keywords: Newborn, COVID-19, Neurodevelopment, Cardiac functions

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Introduction

Infections during pregnancy threaten the health of both the mother and the developing fetus [1]. Viral intrauterine infections transmitted from the maternal genitourinary system and other infections can be detected in approximately 2.5% of all live births [2]. The effect of intrauterine infections on the fetus varies according to the infectious agent, gestational week, and maternal immune response. These infections may cause prematurity, intrauterine growth retardation, stillbirth, or severe congenital malformations [1-4]. The newborn infant may be completely asymptomatic or show subclinical or clinical symptoms soon after birth. The effects of some infections can be detected as systemic complications in long-term follow-up. However, the most important reasons for neonatal morbidity and mortality remain neurologic and cardiac complications [3-4]. In the last 2 years, during the coronavirus disease 2019 (COVID-19) pandemic affecting over 17 million people worldwide and over 5 million people in our country, pulmonary, cardiovascular, and neurological side effects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus are clearly stated [4-6, 7, 8]. These adverse effects may pose a risk to fetal growth. However, there is limited data on this infection's fetal and maternal outcomes [6-9]. In our country, there are studies on the clinical course of the disease in the neonatal period [9, 10].

This study investigates potential neurologic and cardiac complications of newborns born to mothers infected with COVID-19.

Materials and methods

This prospective cross-sectional study was conducted between January and July 2021. This was the time when COVID-19 infection was most common in our country. Newborn infants (0–28 days postpartum) born to mothers with proven COVID-19 infection by positive RT-PCR test during pregnancy were enrolled. Physical examinations of the infants were performed immediately after birth. Fetal cardiac development was evaluated by a pediatric cardiologist with an echocardiographic examination. Fetal neurologic evaluation was performed by a pediatric neurologist. TFUS was performed for all infants. Infants were reevaluated every 2 months until they were 6 months old. Infants with abnormal cardiac or neurologic clinical or radiological evaluation were examined concerning their preliminary diagnosis.

This study was approved by İzmir Bakırçay University, Ethical Committee on Noninvasive Clinical Research (Date:24.06.2021, Number: 4329-3380).

Statistical analysis

Statistical analysis was performed with IBM SPSS 25.0 package program. All statistical tests were two-sided. The Kolmogorov-Smirnov test was used to check the normality assumption. Values were expressed as mean (SD) or median (min-max) as appropriate. According to the distribution type of the variable, a comparison of independent means was performed with the Mann-Whitney U test or Student's t-test, whereas a comparison of dependent means was performed with the paired Student's t-test or Wilcoxon test. Categorical variables were expressed as frequency and related percentage values and were compared by the Chi-square test or Fisher's exact test. Spearman correlation analysis was carried out to assess the relationship between the degree of high serum unconjugated bilirubin level and heart rate variability parameters. *P*-values < 0.05 were considered statistically significant.

Results

Sixty-five infants born to 64 COVID-19 infected pregnant women, one being a twin birth, were evaluated. Of these infants, 33 (51%) were female, and 32 (49%) were male. Seven (11%) women were diagnosed with COVID-19 infection in the first trimester and 46 (72%) women in the second trimester. After the initial diagnosis, 57 women were followed in the outpatient departments, and seven (11%) were hospitalized. Only one patient required intensive care. While two hospitalized women were diagnosed in the first trimester and required emergency treatment, five were diagnosed after 36 weeks of gestation. Antiviral treatment with favipiravir was administered to all hospitalized women, except for two women diagnosed in the first trimester. None of the pregnant women followed in the outpatient clinics received treatment. There was no correlation between the trimester at which the diagnosis was made and the week of gestation at which the delivery took place ($P = 0.13$).

Sixteen (25%) of 65 newborns were hospitalized in the neonatal intensive care unit (NICU). Seven (43%) of the hospitalized infants had respiratory problems. Other causes of hospitalization were prematurity, early-onset neonatal sepsis, and feeding problems. Only one (1.5%) infant in the whole study group showed positive RT-PCR test from nasopharyngeal swab samples taken within the first 24 h after birth. Most neurological examination results were normal, except for physiological hypotonia in one infant and familial microcephaly in another. These two infants showed normal neurodevelopment. We did not have any patients with hearing loss.

Echocardiographic examination in the first week revealed patent ductus arteriosus (PDA) in 33 newborns (51%), patent foramen ovale (PFO) in 32 newborns (49%), and tricuspid valve insufficiency in three newborns (4.6%), ventricular septal defect (VSD) was found in three newborns (4.6%), atrial septal defect (ASD) in two newborns (3%), and peripheral pulmonary stenosis (PPS) in two newborns (3%). In the follow-up, all PDAs closed spontaneously compatible with physiological development.

Discussion

No transplacental infection was observed in studies evaluating newborns born to COVID-19 infected mothers. Placenta cultures were negative in all cases. However, during vaginal delivery, exposure of the infant to both stools and respiratory secretions of infected mothers is possible. In the recent literature, most infected pregnant women are diagnosed in the third trimester [6]. In newborns whose PCR test is positive from a nasopharyngeal swab immediately after birth, there is a possibility of this contamination by the postpartum, intrauterine, or transplacental route and the distinction cannot be made definitively. However, the absence of an increase in the frequency of congenital anomalies and dysmorphic features in newborn infants born to infected mothers suggests that this

transition occurs mostly during birth or that the transplacental transition does not affect the baby. Only one newborn in our study had PCR positivity, which we thought was due to contamination during delivery. Although this patient had transient tachypnea in the first few days of life, she recovered quickly enough to be discharged from the NICU on postnatal day 7.

Complications of SARS-CoV-2 infection during pregnancy are defined as premature rupture of membranes (PPROM), preterm birth, preeclampsia, hypertension, and gestational diabetes mellitus (GDM) [6, 7]. In our study, GDM was found in five pregnant women, PPROM in two, and placental dysfunction and abnormal flow in four.

Complications observed in infants of COVID-19 infected women include respiratory distress syndrome, transient tachypnea of the newborn, congenital pneumonia, early or late-onset neonatal sepsis, low birth weight, diffuse intravascular coagulation, birth asphyxia, and perinatal death [7, 8]. In our study, there were 20 preterm (31%) and five term neonates with transient tachypnea, four infants with early-onset neonatal sepsis, and three infants with indirect hyperbilirubinemia.

Congenital heart disease (CHD) is the most common congenital anomaly in the neonatal period and is responsible for 28% of all major congenital anomalies. Various septal and valve anomalies were detected in ten newborns in our study. However, this condition was not more common than in the general population.

Neurological involvement is in the form of headaches and anosmia in most adults. However, the evaluation of COVID-19 exposure in newborn infants can only be in terms of observing intrauterine effects, dysmorphology, seizures, tone, and consciousness. No neurological abnormalities were observed except familial microcephaly in one patient and physiological hypotonia in another.

A multicenter study including 125 newborns from our country reported 26% prematurity and 13% low birth weight [7]. In our study, it was noticed that all infants of mothers with COVID-19 infection in the first trimester, when organogenesis is most active, were born to full-term, and these infants did not have any neurological and cardiological problems. Two infants of mothers with COVID-19 infection in the second trimester were born as a middle (medium)-preterm. In our study, we found no evidence of an increase in preterm birth or vertical transmission with COVID-19.

As a result, in our single-center and limited study, no teratogenic impact related to intrauterine COVID-19 infection was determined. But in case of a possible correlation, new large-scale studies are needed.

Limitation

This is a single-center, time-limited, and case number-limited study.

Conclusion

This study could not demonstrate a teratogenic effect of COVID-19 infection.

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Does uterus volume affect the total laparoscopic hysterectomy outcomes?

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Ethics Committee Approval
Ethics Committee approval was taken from the University of Health Science Adana City Training and Research Hospital Ethical Committee, 20.05.2020 and no:872.
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: Increased uterus weight, high body mass index (BMI), and history of abdominal surgeries increase the risk of complications in total laparoscopic hysterectomy (TLH), similar to other types of surgery. However, there are conflicting reports about improving technology. This study aimed to retrospectively investigate the clinical features and postoperative results of TLH cases regarding uterine volume performed for benign reasons in our clinic.

Methods: In this retrospective cohort study, 252 patients were included. The demographic data of all patients, including BMI, pre-operative uterine volumes, operation times, number of cesarean sections, history of lower abdominal operation, indications, pre-operative and postoperative hemoglobin differences, complications, length of hospital stay, and final pathologies were reviewed. The uterine volume was measured using the prolate ellipsoid formula before surgery, using the maximum length and anteroposterior and transverse diameters of the uterine corpus. The normal uterine volume with these measurements (8 cm long, 4 cm high, and 5 cm wide) was estimated as 83.2 cm^3. The patients were classified into two groups according to uterine volume (Group 1 Normal volume ≤83.2 cm^3 and Group 2 uterine volume >83.2 cm^3). Surgical outcomes of patients were compared between groups.

Results: Two-hundred-fifty-two women were included in the study. The mean uterine volumes of groups 1 and 2 were 53.66 cm^3 (2.25) and 296.33 cm^3 (6.25), respectively. In group 1, the mean operation time was 111.14 (6) min, compared to 118.2 (3.06) min in group 2; there was no significant difference (P = 0.164). The mean postoperative hospital stays of groups 1 and 2 were 3.21 (0.15) and 3.34 (0.09) days, respectively, and there was no significant difference (P = 0.706). The mean blood loss values of groups 1 and 2 were 1.34 g/dl (0.19) and 1.16 g/dl 0.06), respectively.

Conclusion: According to our results, TLH is a safe method even in patients with a larger uterus; operating time, blood loss, and postoperative hospital stays did not differ according to uterine volume.

Keywords: Laparoscopic hysterectomy, Uterine volume, Surgery outcome

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Introduction

Hysterectomy is one of the most common gynecologic operations performed worldwide for indications such as abnormal uterine bleeding, uterine leiomyoma, uterovaginal prolapse, endometriosis, adenomyosis, and pelvic inflammatory disease [1]. It has been shown in the literature that laparoscopic hysterectomy is better than abdominal hysterectomy in terms of intraoperative blood loss, postoperative analgesic requirement and wound infection, faster recovery time, return to daily activities, and avoidance of large abdominal scarring [2]. Total laparoscopic hysterectomy (TLH) has become a well-tolerated and effective technique with the modern laparoscopic instruments and the development of surgical techniques [3]. According to the results of the ACOG guideline, it was emphasized that laparoscopic hysterectomy could be applied when vaginal hysterectomy is contraindicated or inappropriate [2]. In each clinic, the first and most appropriate method is selected without harming the patient, with the effect of variables such as the surgeons' laparoscopy experience and the patient's characteristics [4]. This study aimed to retrospectively evaluate the clinical features and postoperative results of TLH cases in terms of uterine volume performed for benign reasons in our clinic. This was the first study comparing pre-operative estimated uterine volume by ultrasonography and TLH outcomes in the literature.

Materials and methods

This retrospective study included 252 women who underwent TLH with benign indications at the University of Health Science Adana City Training and Research Hospital between December 2017 and February 2020. The study's ethical approval was obtained from the local ethics committee of the University of Health Science Adana City Training and Research Hospital (872/2020). Demographic data of all patients were reviewed, including body mass index (BMI) and pre-operative uterine volumes, operation times (from the beginning to the awaking up from anesthesia), indications, pre-operative and postoperative hemoglobin differences, endometrial biopsies, complications, length of hospital stay, and final pathologies. The number of cesarean sections and history of lower abdominal operations were all recorded.

Pre-operative pelvic ultrasonographic measurements of each patient before hysterectomy were taken by at least two doctors. The patients were taken in lithotomy position with an empty bladder. Aloka ProSound Alpha 6 ultrasound with a 3–9 MHz transvaginal probe and a 2–6 MHz abdominal probe was utilized. The calculations of the uterine volume were performed by length (L), width (W), and anteroposterior (AP) diameters. AP length was obtained from a sagittal scan parallel to the midline axis of the body and length by measuring from the internal os of the cervix to the top of the fundus or mass in the same visualizing plane. Then, the vaginal probe is rotated parallelly to the coronal axis to visualize the widest transverse line and to find the width of the uterine corpus. A single expert physician performed all the examinations independently and performed three consecutive measurements during the scanning of individuals. The uterine volume was calculated by measuring the uterine corpus's maximum length, AP, and width measurements and using the formula for the volume of a prolate ellipsoid: $V = 0.52 \times (L \times AP \times W)$ [5]. The average dimensions of the normal uterus in women of reproductive age are approximately 8 cm long, 4 cm high, and 5 cm wide, while that of multiparous women is larger than in nulliparous women, by approximately 1 cm in each dimension [6]. Using these measurements, we calculated the normal uterine volume as 83.2 cm^3. The participants were divided into two groups according to uterine volume. Group 1 is patients with the uterine volume ≤83.2 cm^3 and Group 2 is the patients with uterine volume >83.2 cm^3. Surgical outcomes of patients were compared between groups.

General anesthesia was used in all surgeries with a pneumoperitoneum in the lithotomy position. An umbilical trocar (10 mm) and three 5-mm lower abdomen trocars (two ipsilateral ports and one assistant port) were inserted using the TLH port technique. Clermont Ferrand's uterine manipulator was inserted in all cases. After inspection of the abdominal and pelvic organs, a hysterectomy was started. The bladder peritoneum was dissected, and the infundibulo pelvic or ovarian ligaments were coagulated and cut. The uterine arteries were ligated. The uterosacral ligaments were coagulated and cut. The cardinal ligaments were coagulated and transected. Monopolar energy was used for colpotomy. Ligasure and bipolar energy were used for other sections.

After removing the uterus along the vagina, the vaginal cuff was sutured with laparoscopic suturing (Vicryl 1-0). After hemostasis was achieved, insertion sites of the trocars were sutured. Skilled laparoscopic gynecologic surgeons performed all surgeries. Written informed consent was taken one night before surgery, including antibiotic prophylaxis and bowel preparation.

Statistical analysis

The Kolmogorov-Smirnov test was used for the normality of variables. Normal variables were defined as the mean (standard deviation) and 95% confidence interval. The Spearman correlation test was used to find the relationship between continuous variables. Statistical Package for the Social Sciences, version 20 (SPSS Inc.), was used for the statistical analysis. *P*-values < 0.05 was considered statistically significant.

Results

The patients' clinical characteristics are shown in Table 1. Two-hundred-fifty-two patients were enrolled for this research. The mean age of participants was 49.26 (7.56) years, and the mean body mass index was 30.17 (5.33) kg/m^2. The mean gravida and parity were 4.11 (2.36) and 2.34 (1.94), respectively. Seventy-one women (28.2%) had one or more previous Caesarean sections, and 14 women (5.6%) had a previous laparotomy.

Table 1: Clinical characteristics of patients.

	n = 252
Age (years) mean (SD)	49.26 (7.56)
Gravida (n) mean (SD)	4.11 (2.36)
Parity (n) mean (SD)	2.34 (1.94)
Body mass index (kg/m^2) mean (SD)	30.17 (5.33)
Pre-operative hemoglobin (g/dl) mean (SD)	12.11 (1.45)
Postoperative hemoglobin (g/dl) mean (SD)	10.91 (1.51)
Previous low abdominal surgery, *n* (%)	14 (5.6)
Previous cesarean section, *n* (%)	71 (28.2)

SD: Standart deviation

Table 2 shows the Surgical outcomes of patients. Two-hundred-fifty-two TLH were performed with the indications as follows: myoma uteri (15, 6%), abnormal bleeding (160, 63.5%), endometrial hyperplasia (54, 21.4%), and others (23, 9.1%). Major complications were bladder injury in three women, bowel injury in one woman, stomach injury in one woman, and vascular injury in one woman. Conversion to laparotomy was performed in one patient due to vascular injury.

Table 2: Surgical outcomes of patients

	n = 252
Indications (n, %)	
Myoma uteri	15 (6)
Abnormal bleeding	160 (63.5)
Endometrial hyperplasia	54 (21.4)
Others	23 (9.1)
Endometrial biopsy (n, %)	
Normal	152 (60.3)
Myoma uteri	1 (0.4)
Endometrial polyp	51 (20.2)
Simple hyperplasia without atypia	32 (12.7)
Simple atypical hyperplasia	7 (2.8)
Complex hyperplasia without atypia	6 (2.4)
Complex atypical hyperplasia	3 (1.2)
Major complications (n, %)	
Bladder injury	3 (1.2)
Stomach injury	1 (0.4)
Bowel injury	1 (0.4)
Vessel injury	1 (0.4)
Conversion to laparotomy (n, %)	1 (0.4)
Final pathology (n, %)	
Normal	89 (35.3)
Myoma uteri	68 (27)
Endometrial polyp	43 (17.1)
Adenomyosis	41 (16.3)
Simple hyperplasia without atypia	8 (3.2)
Simple atypical hyperplasia	1 (0.4)
Complex hyperplasia without atypia	2 (0.8)

The mean uterine volume of 252 patients was 241.74 cm^3 (14.11). Compared with the uterine volume and operation time, there were no significant differences (116.65 [2.73] min, P = 0.644) and no significant differences were found between uterine volume and blood loss (1.2 [0.06] g/dl, P = 0.116) or postoperative hospital stay (3.31 [0.8] days, P = 0.813). The mean uterine volume of group 1 and group 2 were 53.66 cm^3 (2.25) and 296.33 cm^3 (16.25) ml, respectively. In group 1, the mean operation time was 111.14 (6) min and 118.2 (3.06) min in group 2; no significant difference was found (P = 0.164). The mean postoperative hospital stays of group 1 and 2 were 3.21 (0.15) and 3.34 (0.09) days respectively (P = 0.706). The mean blood loss values of groups were 1.34 (0.19) and 1.16 (0.06) g/dl, respectively. The surgical outcomes according to uterine volume cut-off are shown in Table 3.

Table 3: Surgical results according to uterine volume

	Group 1 n = 55	Group 2 n = 197	*P*-value
Operative time (min), mean (SD)	111.14 (6)	118.2 (3.06)	0.164
Postoperative hospital stay (days), mean (SD)	3.21 (0.15)	3.34 (0.09)	0.706
Blood loss (g/dl)	1.34 (0.19)	1.16 (0.06)	0.553

Blood loss: Difference of post- and pre-operative hemoglobin, SD: Standard deviation.

No cancer was detected in any of the pathology results of the cases.

Discussion

This study reports no significant difference between pre-operative uterine volume and TLH surgical outcomes, such as blood loss, operating time, and postoperative hospital stay. It was thought that patients with larger uteruses could have more risks. Since TLH allowed good image quality at large magnification and easy access to deep tissues with improved technology, no significant difference between groups was found. Our findings show that TLH is not a risk factor regarding uterus volume for surgical outcomes.

It was well known that increased uterus weight, high BMI, and history of abdominal surgeries, the increased risk of complications in TLH, similar to other types of surgery [7]. However, there were conflicting reports in the literature regarding technology improvement. Moreover, surgeons and skills differ in regions related to facilities.

Twinjstra et al. [8] aimed to estimate the various risk factors, like uterus weight, BMI, abdominal surgery history, laparoscopic hysterectomy types, and the number of surgeons for outcome in laparoscopic hysterectomy. It was a 1-year cohort analysis conducted with laparoscopist gynecologists. These authors reported that as experience increases, surgical time shortens, and blood loss and complications decrease. However, they also mentioned that there was not a guaranteed result because of variability in experience among individuals and independent surgical skills [8].

In a retrospective study, the authors evaluated TLH outcomes in 504 patients and compared the results to categorizing patients with or without previous cesarean sections [9]. These authors did not find any significant difference between the groups concerning parity, duration of operation, hospital stay, or pre and postoperative hemoglobin levels [9]. They concluded that TLH could be performed safely in the previous caesarean section (CS) group. However, Seo et al. [10] showed longer operating times and a higher rate of conversion to laparotomy in patients with a history of abdominal surgery. The results were explained by common adhesiolysis in that group of patients (145/331). Also, there were significant differences in two or more surgeries in adhesiolysis compared to one previous surgery.

A study evaluated the effect of BMI on TLH outcomes [11]. The authors divided the patients (183 total) according to the following BMI ranges: <18.5 kg/m^2 "underweight", 18.5-25 kg/m^2 "normal weight", 25–30 kg/m^2 "overweight", ≥30 "obese" kg/m^2, respectively. Also, they reported significantly longer operation times and more perioperative complications in obese patients. In our study, the mean BMI was 31 kg/m^2. Since obesity was common in our area, no difference was observed between the groups.

Multiple studies have investigated TLH results based on uterine dimensions (weight) [4, 12, 13]. In all studies, the uterus was weighted (without ovaries) after being removed vaginally before sending the pathology. Terzi et al. showed a cut-off value of 300 g for an increased operation time [13]. O'Hanlan et al. [4] divided the groups according to uterine weights (less or greater than 250 g). These authors reported that although operating times and blood loss increased significantly (but by a very modest amount) with the increasing size of the uterus, TLH was safe and applicable regardless of uterine weight.

Kung et al. [14] evaluated the uterine volume estimated by ultrasonographic uterine measurements (three dimension-ellipsoid formula) and compared the reported pathologic measurements. These authors showed that uterine volume could be converted to uterine weight *in vivo* before surgery. The measurements consisted of the length of the uterus from the dome to the cervix, width, and the largest cross-sectional anteroposterior diameter. The mean volume of the uterus was

302 cm^3, which referred to 271 g actual uterus weight. Uterus measurements were routinely measured by transvaginal ultrasonography in our clinic as ellipsoid formula (anteroposterior diameter × longitudinal diameter × transverse diameter × 0.5236) and recorded to files before surgery.

Gerges et al. [15] investigated the relationship between pre-operative uterine volume and prediction of morcellator usage in TLH. They used the ellipsoid formula and Virtual Organ Computer-aided AnaLysis (VOCAL™) for pre-operative measurements. They concluded that morcellation was not required in patients with uterus volumes less than 120 mL at 3D-US. We did not use morcellation in our clinic. Therefore, the mean volume of a normal uterus was selected as a cut-off.

Limitations and strengths

This study has some limitations. First, it was a retrospective study, and also we did not measure the vaginal volume which could affect the operation time by alternating the time for uterine removal from vagina. Second, depending on the surgeon's experience, the TLH preference in our clinic may have been performed in certain sizes of the uterus, in line with the habits.

The comparison of uterine volume estimated by ultrasonography and surgery outcomes was the major strength of our study. Further prospective studies addressing TLH outcomes, including pre-operative uterine size and vaginal measurement, should be planned.

Conclusion

In conclusion, TLH was performed safely in patients with larger than normal uteruses. Operating time, blood loss, and postoperative hospital stays did not differ significantly regarding uterine volume.

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The effectiveness of major ozone autohemotherapy in the treatment of fibromyalgia syndrome

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Ethics Committee Approval
This study was approved by the Kocaeli Derince Education and Research Hospital Ethics Committee (Project no: 2020-161)
Clinical trial registration number: NCT05034770
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: Fibromyalgia syndrome (FMS) is a disease that seriously affects the quality of life. Although many modalities are used in treatment, there is still no common protocol. The aim of this study was to evaluate the effectiveness of major autohemotherapy (MAH) with ozone, which has come into use in recent years.

Methods: The retrospective cohort study included 45 male and female patients who were admitted to the Physical Medicine and Rehabilitation (PMR) outpatient clinic of Private Medar Hospital between January 2017 and October 2020 and were treated with MAH for a diagnosis of FMS. Evaluations were made before and after the last session of treatment using a visual analog scale (VAS), the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form Health Survey-36 (SF-36). The scores of the patients were compared.

Results: Posttreatment VAS and FIQ scores decreased significantly (P = 0.014, P = 0.022 respectively) compared to pretreatment. After treatment, SF-36; PF, PH, EP, Fatigue, EW, SF, Pain, GH, HC scores increased significantly ($P < 0.05$ for all) compared to before treatment. The use of analgesics after treatment decreased significantly (P = 0.033) compared to before treatment.

Conclusion: MAH applied twice a week is an effective and practical method in the treatment of FMS.

Keywords: Fibromyalgia, Ozone, Hemotherapy, Oxidative stress, Pain

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Introduction

Fibromyalgia Syndrome (FMS) is a rheumatological disease characterized by widespread pain, fatigue, sleep disturbance, abnormal pain processing, and often psychological distress [1]. FMS generally affects women between the ages of 20-55 years and its prevalence in the whole population is 1.78% with a predominant ratio of women to men [2]. It has a very high personal and social impact and seriously impairs the quality of life of the patient [3].

Since the etiopathogenesis has not yet been clarified and the problems differ from patient to patient, there is currently no single, effective treatment method that provides full recovery of FMS. The treatments applied aim to reduce symptoms and maintain and improve quality of life and functions [4]. Methods using a single treatment modality cannot provide full effectiveness in FMS patients, and it is thought that the most effective method in clinical practice is multidisciplinary treatment [5]. Therefore, considering the patient's symptoms, applying both pharmacological and non-pharmacological approaches together would be an appropriate treatment approach [6].

Major ozone autohemotherapy (MAH), which is a simple and applicable method in the treatment of inflammatory and degenerative diseases related to the musculoskeletal system, has attracted attention in recent years. It differs from other treatment methods, because it is inexpensive, has almost no side-effects if applied correctly, offers a systemic treatment option, and is successfully applied in clinics. In MAH, the anti-inflammatory, anti-oxidative capacity activation and immunomodulation effects of ozone are utilized. Studies on the use of ozone therapy in musculoskeletal diseases started in the late 1980s with Verga [7] and Riva Sanseverino [8], and the number of studies have gradually increased. The highest level of evidence for the effects of ozone is in discogenic radiculopathies and osteoarthritis, especially in the knee [9].

From a scan of the literature, it can be seen that there have been limited studies in which ozone injections are applied in the treatment of FMS patients. Although positive effects have been observed in these studies, it has been emphasized that studies with greater patient numbers are needed.

The aim of this study was to determine the effectiveness of MAH in FM treatment with evaluations based on pain, quality of life, and FIQ scores.

Materials and methods

The study included 45 male and female patients who presented at the Private Gölcük Medar Hospital Physical Therapy and Rehabilitation outpatient clinic between January 1, 2017 and October 15, 2020, and underwent MAH for the diagnosis of FMS.

The study inclusion criteria were defined as patients diagnosed with FMS (examined by a PMR specialist and diagnosed with FMS according to the American College of Rheumatology (ACR) 1990 and 2010 classification criteria), aged 18-60 years, and provided a signed voluntary consent form to participate in the study [1, 10].

Patients with inflammatory rheumatic disease, primary psychiatric disease, pregnancy or a history of substance abuse, and patients who did not complete the ten-session treatment program were excluded from the study.

This study was approved by the Kocaeli Derince Education and Research Hospital Ethics Committee (Project no: 2020-161) and was carried out in compliance with the institutional guidelines and principles of the Declaration of Helsinki.

At the beginning of the study, a record was made for each patient including age, height, body weight, education level, smoking and alcohol habits, systemic diseases, duration of complaints, and medical treatment used for FMS. During the study, patients continued on their usual medication. All participants were assessed with a visual analog scale (VAS), the Fibromyalgia Impact Questionnaire (FEA) and SF-36 scales before and after treatment. It was recorded whether they used analgesics (paracetamol, NSAID) in the presence of pain. Exercise practices were also noted for patients who exercised regularly at least two days a week.

Evaluation of pain: The general pain status of the patients was evaluated with VAS [11]. Patients rated the intensity of pain on a scale from "0" (no pain) to "10" (worst possible pain).

Functional Evaluation: The Turkish version of the FIQ was used to evaluate the quality of life and functional status of the patients [12]. FIQ is a disease-specific tool for assessing the impact of fibromyalgia, and there is high evidence of its use in controlling the course of the disease [13, 14]. In this scale, ten different characteristics are measured, including physical functioning, the number of days patients felt well, the number of days patients were unable to work, work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety and depression. With the exception of well-being, low scores indicate recovery or less affliction. The FIQ was completed by the patient and has a maximum score of 100.

Short Form Health Survey-36: The level of health-related quality of life was determined using the Short Form-36 (SF-36). This is the most widely used general quality of life scale and has proven Turkish validity and reliability [15]. It measures nine scales: physical functioning (PF), role physical (RP), pain (P), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) mental health (MH) and health change (HC). High scores in all the subscales of the SF-36 reflect a better quality of life, and lower scores indicate deterioration in quality of life.

Application of major ozone autohemotherapy: In one session for each patient, the following were used: one bottle of vacuum sterile citrate, one blood collection set, one serum set, one intravenous cannula, and one ozone filter and one injector (50 cc) to remove ozone from the device. A blood sample of 100 mL was taken from the patient and prepared outside the body by enrichment with ozone at the right dose (10-50 GAMA) with special systems. The blood was then administered back to the patient at the recommended rate of 60-90 drops per minute. A total of ten sessions of MAH were applied as two sessions per week for five weeks [16].

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS v 27.0 software. In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency, and ratio values were used. The conformity of variables to normal distribution was assessed with the

Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data, and the Wilcoxon test was used for dependent quantitative data. Spearman correlation analysis was used. A value of $P < 0.05$ was considered statistically significant.

Results

The demographic data of the patients and the median values of the outcome measures are shown in Table 1.

Table 1: Demographic features and median values of outcome scores of FMS patients

		Values	
Age (years) mean (SD)		51.2	10.6
Gender	Female	41	91.1%
n %	Male	4	8.9%
Height (cm) mean (SD)		163.3	9.1
Weight (kg) mean (SD)		71.5	12.8
BMI (kg/m^2) mean (SD)		26.9	4.3
		n	%
Level of education	Primary school	19	42.2%
	High school	14	31.1%
	University	12	26.7%
Marital status	Single	2	4.4%
	Widowed	9	20.0%
	Married	34	75.6%
Smoking habit	(-)	34	75.6%
	(+)	11	24.4%
Alcohol consumption	(-)	38	84.4%
	(+)	7	15.6%
Exercise Habit	(-)	37	82.2%
	(+)	8	17.8%
Drug use for FMS	(-)	18	40.0%
	(+)	27	60.0%
Systemic disease	(-)	21	46.7%
	(+)	24	53.3%
Analgesic usage	No	17	37.8%
	Once a week	5	11.1%
	Everyday	23	51.1%
		Mean	SD
Ozone dose		32.9	3.8
VAS		6.3	1.4
FIQ		57.9	13.7
PF		67.6	15.8
RP		53.3	25.9
RE		54.1	28.7
VT		43.9	13.1
MH		57.1	13.6
SF		51.4	23.7
BP		35.7	15.9
GH		57.4	16.3
HC		41.7	16.0

SD: standard deviation, BMI: body mass index, VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change

The posttreatment VAS score decreased significantly ($P = 0.014$) compared to pretreatment. The posttreatment FIQ score decreased significantly ($P = 0.022$) compared to pretreatment. After treatment, the SF-36 PF, RP, P, GH, VT, SF, RE, MH and HC scores increased significantly ($P < 0.05$ for all) compared to pretreatment. The level of analgesic use after the treatment decreased significantly ($P = 0.033$) compared to the pretreatment level. (Table 2)

The rate of change in VAS, FIQ, RP, P, GH, VT, SF, RE, MH and HC scores did not differ significantly between males and females after treatment ($P > 0.05$ for all). The posttreatment PF score increase in males was significantly ($P < 0.05$) higher than in females (Table 3).

The rate of change in VAS, FIQ, PF, RP, P, GH, SF, RE, MH, and HC scores after treatment did not differ significantly ($P > 0.05$ for all) between those who exercised and those who did not. The VT score increase in the exercising group was significantly ($P = 0.038$) lower than in the non-exercising group (Table 4).

Table 2: Comparison of analgesic use and outcome scores of patients before and after treatment

		Min	Max	Median	Mean	SD	*P*-value	
VAS								
Before Treatment		4.0	10.0	6.0	6.3	1.4	0.014	w
After Treatment		0.0	7.0	2.0	2.4	1.7		
FIQ								
Before Treatment		24.2	82.6	59.7	57.9	13.7	0.022	w
After Treatment		5.6	58.2	22.3	24.3	12.8		
PF								
Before Treatment		40.0	95.0	65.0	67.6	15.8	0.028	w
After Treatment		45.0	100.0	80.0	77.8	13.1		
RP								
Before Treatment		0.0	100.0	50.0	53.3	25.9	0.018	w
After Treatment		0.0	100.0	75.0	67.2	26.0		
RE								
Before Treatment		0.0	100.0	66.7	54.1	28.7	0.030	w
After Treatment		0.0	100.0	66.7	64.5	27.9		
VT								
Before Treatment		20.0	70.0	45.0	43.9	13.1	0.002	w
After Treatment		25.0	75.0	45.0	49.6	13.8		
MH								
Before Treatment		24.0	84.0	64.0	57.1	13.6	0.002	w
After Treatment		24.0	84.0	64.0	63.7	12.9		
SF								
Before Treatment		12.5	100.0	50.0	51.4	23.7	0.011	w
After Treatment		25.0	100.0	62.5	57.5	17.4		
BP								
Before Treatment		10.0	67.5	35.0	35.7	15.9	0.016	w
After Treatment		12.5	100.0	67.5	71.4	18.3		
GH								
Before Treatment		25.0	90.0	55.0	57.4	16.3	0.034	w
After Treatment		40.0	90.0	60.0	63.4	13.6		
HC								
Before Treatment		25.0	75.0	50.0	41.7	16.0	0.024	w
After Treatment		25.0	75.0	50.0	57.7	15.7		
Analgesic usage					n	%	*P*-value	
Before Treatment	*No*				17	37.8%	0.033	N
	Once a week				5	11.1%		
	Everyday				23	51.1%		
After Treatment	*No*				28	62.2%		
	Once a week				8	17.8%		
	Everyday				9	20.0%		

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, W: Wilcoxon test, n: McNemar test

Table 3: Comparison of pre- and posttreatment outcome scores between males and females

Pre-Post Treatment Change %	Female Mean	Female SD	Female Median	Male Mean	Male SD	Male Median	*P*-value	
VAS	-64.0%	26.0%	-66.7%	-57.3%	26.0%	-64.6%	0.660	m
FIQ	-59.9%	17.6%	-65.1%	-49.1%	20.6%	-57.0%	0.232	m
PF	15.7%	21.9%	11.8%	54.6%	50.0%	40.3%	*0.034*	m
RP	30.9%	51.3%	0.0%	37.5%	47.9%	25.0%	0.628	m
RE	36.7%	77.0%	0.0%	-8.3%	16.7%	0.0%	0.206	m
VT	16.7%	40.0%	0.0%	45.0%	90.0%	0.0%	0.892	m
MH	18.0%	45.2%	0.0%	18.1%	30.5%	8.3%	0.947	m
SF	30.3%	64.0%	0.0%	46.4%	74.3%	25.0%	0.724	m
BP	159.9%	214.5%	89.5%	200.0%	122.5%	200.0%	0.144	m
GH	14.8%	28.9%	7.7%	23.2%	20.5%	18.1%	0.266	m
HC	51.0%	63.7%	40.0%	87.5%	85.4%	75.0%	0.308	m

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, m: Mann-Whitney U test

Table 4: Comparison of pre- and posttreatment outcome scores between groups that exercised regularly and those who did not

Pre-Post Treatment Change %	Exercises (-) Mean	Exercises (-) SD	Exercises (-) Median	Exercises (+) Mean	Exercises (+) SD	Exercises (+) Median	*P*-value	
VAS	-63.0%	23.8%	-66.7%	-65.2%	35.3%	-75.0%	0.512	m
FIQ	-59.1%	17.8%	-61.7%	-58.3%	19.5%	-62.1%	1.000	m
PF	19.4%	25.6%	14.3%	18.1%	35.0%	2.8%	0.259	m
RP	30.2%	45.1%	0.0%	37.5%	74.4%	0.0%	0.634	m
RE	31.5%	75.7%	0.0%	37.5%	74.5%	0.0%	0.596	m
VT	23.6%	49.2%	0.0%	-1.3%	3.5%	0.0%	0.038	m
MH	21.9%	47.6%	0.0%	0.0%	0.0%	0.0%	0.086	m
SF	39.2%	68.6%	20.0%	-2.5%	7.1%	0.0%	0.051	m
BP	182.6%	223.1%	100.0%	74.9%	58.6%	49.1%	0.118	m
GH	18.0%	30.5%	7.7%	4.2%	5.9%	0.0%	0.114	m
HC	60.5%	67.9%	50.0%	25.0%	46.3%	0.0%	0.137	m

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, m: Mann-Whitney U test

The rate of change in VAS, FIQ, PF, RP, P, GH, VT, SF, RE, MH, and HC scores did not differ significantly ($P > 0.05$ for all) after treatment between those using and not using drugs for FMS (pregabalin, gabapentin, duloxetine, selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant) (Table 5).

Table 5: Comparison of pre- and posttreatment outcome scores between groups that used and did not use drugs for FMS

Pre-Post Treatment Change %	Drug use for FM (-) Mean	SD	Median	Drug use for FM (+) Mean	SD	Median	*P*-value	
VAS	-68.2%	25.8%	-71.4%	-60.2%	25.7%	-62.5%	0.285	m
FIQ	-60.7%	19.0%	-65.5%	-57.8%	17.4%	-59.4%	0.517	m
PF	15.3%	17.7%	14.8%	21.7%	31.9%	11.8%	0.814	m
RP	25.9%	34.4%	0.0%	35.2%	59.3%	0.0%	1.000	m
RE	49.1%	88.0%	0.0%	21.2%	63.1%	0.0%	0.347	m
VT	23.1%	49.8%	0.0%	16.6%	43.2%	0.0%	0.472	m
MH	26.5%	43.9%	3.1%	12.4%	43.7%	0.0%	0.051	m
SF	44.4%	80.0%	0.0%	23.4%	50.9%	0.0%	0.933	m
BP	96.2%	84.6%	61.1%	208.3%	250.7%	107.7%	0.131	m
GH	20.7%	35.0%	8.4%	12.1%	22.6%	7.7%	0.565	m
HC	63.3%	63.9%	50.0%	48.1%	67.2%	0.0%	0.283	m

VAS: visual analog score, FIQ: Fibromyalgia Impact Questionnaire, PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: body pain, GH: general health, HC: health change, m: Mann-Whitney U test

Discussion

The aim of this study was to reveal the efficacy of MAH in the treatment of FMS by evaluating its effect on quality of life, functional status, and pain of the patients.

FMS is known to be much more common in females, and of the 45 patients included in this study, 41 (91.1%) were female and 4 (8.9%) were male [2].

In a study published in 2019, in which MAH was applied to 20 FMS patients, there was reported to be a significant decrease in the number of trigger points, FIQ scores, and oxidative stress markers in the blood, as well as an increase in sleep quality and mental awareness [17]. In the current study, there was also a statistically significant decrease in the FIQ score after treatment compared to the pretreatment scores.

In another study published in 2019, which included 65 FMS patients, MAH was applied to 55 patients and rectal ozone was applied to 10 patients. The results were evaluated with the numeric rating scale (NRS) and Fatigue Severity Scale (FSS). Posttreatment, a significant decrease in NRS, and scores was observed in 45 (70%) of the patients [18]. In the current study, the posttreatment VAS scores decreased significantly compared to pretreatment. This result was also reflected in the significant decrease in the use of analgesics in the posttreatment period.

No previous studies have investigated the efficacy of ozone therapy in FMS that has evaluated quality of life with SF-36. Tirelli et al. applied MAH to 30 patients and rectal ozone to 10 patients with FMS, and reported a decrease of more than 50% in the NRS and FSS scores in 80% of patients [19].

In a case report published in 2017, MAH was applied twice a week to a 45-year-old female patient with FMS. In the components of the Fibromyalgia Survey Questionnaire, the Widespread Pain Index decreased from 15 to 7, and the Symptoms Severity Scale from 7 to 1 at the end of 12 sessions [20].

The etiopathogenesis of FMS is still unclear, so a number of causes and mechanisms are still cited, one of which is that oxidative stress may play a role [21]. Therefore, MAH has gained a place in the treatment of FMS due to its antioxidant effect. Ozone rapidly transforms into molecular oxygen and oxygen radicals in biological environments, creating a moderate level of oxidative stress in the body. In this way, ozone is perceived as an oxidative threat in the body, which results in the stimulation of enzymes working in antioxidant defense systems. Moderate oxidative stress activates nuclear factor erythroid 2-related factor-2 (Nrf-2) and this triggers the transcription of antioxidant response elements (ARE). However, severe oxidative stress causes an inflammatory response by activating nuclear factor kappa B and ultimately tissue destruction by increasing cyclooxygenase 2, prostaglandin E2 and cytokine production [12].

The key point in ozone therapy is the regulation of the oxidative stress level [22]. As a result, ozone therapy has an antioxidant effect at the appropriate dose. The ozone dose should be sufficient to produce an acute, clear, and temporary oxidative stress. Lower doses cause a placebo effect, and higher doses cause toxicity [23]. Therefore, it is very important to set ozone doses correctly. Despite attempts to determine the optimal dose and safe range from the results of animal studies on ozone-oxygen concentrations, application volumes and the number of applications, a common consensus could not be achieved. However, the general opinion is that applications are started at low concentrations and the concentration is increased if necessary [24].

In the current study patients the treatment was started at a low dose (15-20 gamma) and gradually increased. The treatment was then continued at the dose at which the patient's complaints were minimized (40-50 gamma). The mean ozone dose was 33.5 (32.8 [3.8]) gamma and no side-effects were observed in any of the patients included in this study.

Three new clinical trials involving fibromyalgia patients were included in the 2017 Cochrane review, evaluating the role of physical activity and exercise in the treatment of chronic pain.

Despite the low level of evidence in the review, it was concluded that physical activity and exercise were beneficial at a mild to moderate level in terms of reducing the severity of pain and improving physical functions in general, as well as improving the quality of life with few undesirable effects [25]. In the current study, the increase in vitality score was significantly lower in the exercising group than in the non-exercising group.

Conclusion

MAH has been widely used in recent years, especially in chronic pain syndromes. We also observed positive and significant results in the treatment of FMS in our study. The most important limitation of this study was the absence of a control group and long-term follow-up results. No randomized controlled study could be found in the literature that has investigated the efficacy of ozone therapy in FMS patients. In addition, there is no common approach regarding the ozone dose to be applied in FMS. There is, therefore, a need for further randomized controlled studies with longer follow-ups and the creation of a general approach to dosage to be able to further illuminate the place of ozone therapy in FMS.

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Are blood parameters assessed before taking frozen sections useful in gynecological oncology?

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Ethics Committee Approval
Ethics Committee approval was taken from the Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee, 2011-KAEK-25 2022/08-21.
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: Inflammatory processes are often implicated in oncology, and inflammatory markers and indices have been much studied in this context. In gynecological surgery, frozen sections have proven valuable in decision-making. Here we aim to identify laboratory parameters that correlate with frozen section results and thus develop new indices in neoplastic decision-making.
Methods: In this retrospective cross-sectional study at Bursa Yüksek İhtisas Training and Research Hospital, we evaluated 139 patients diagnosed with adnexal mass and endometrial intraepithelial neoplasia. We divided the patients whose frozen sections were reported as malignant, borderline, or benign into three groups and compared the pre-operative complete blood parameters.
Results: The mean age of our patients was 57.3 (11.5) years, and frozen section reports were benign in 33 (23.7%), borderline in 43 (30.9%), and malignant in 63 (45.3%) patients. The mean corpuscular volume and mean platelet volume values were different, and this difference was significant between borderline and malignant groups in post-hoc analyses (P = 0.04 and P = 0.03, respectively). While the percentage of lymphocytes was lower in malignant groups, the percentage of neutrophils was higher (P = 0.01 and P = 0.03, respectively). According to post-hoc analysis, the percentage of neutrophils differs between benign and malignant groups (P = 0.05). The difference in lymphocyte percentage was significant between benign-borderline and benign-malignant groups (P = 0.02, P = 0.05; respectively). The blood neutrophil/lymphocyte ratio was higher in the malignant groups compared to the other two groups (P = 0.02). We used the Multi Linear Regression Analysis method to analyze the factors that play a role in predicting the frozen outcome as malignant. Accordingly, the model with the best performance used lymphocyte percentage, neutrophil/lymphocyte ratio, and Ca-125 parameters (P = 0.03).
Conclusion: This study indicates that inflammatory markers may give a clue about the character of the neoplastic mass before oncology surgery. Thus, we can make new contributions to the surgical and clinical approach in the literature by developing new malignancy indices.

Keywords: Frozen section, Gynecological oncology, Complete blood count, Lymphocyte, Neutrophil

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Introduction

Intraoperative pathological examination is an important part of surgical oncology for many reasons and is supportive in terms of gross evaluation. It can protect the patient from a possible second procedure by ensuring that appropriate surgical procedures are performed. The frozen section approach has been reported to have sensitivity and specificity values of up to 90–100% [1, 2].

The frozen section ensures sampling of the correct material to determine the tumor and degree of spread to plan surgery and assess clearance margins at the surgery [3]. In gynecologic cancers, the frozen section choices and findings can vary depending on the cancer genital tract subsite. Although frozen section histology may be done on the sentinel lymph node for cervical cancer, complete lymphadenectomy remains a universal standard. On the other hand, tumor size, grade, and depth of invasion are all findings from frozen section histology of endometrial cancer that can be utilized to determine the extent of staging procedure necessary. For ovarian cancer, frozen section histology is critical for women who are being taken for cytoreductive or staging surgery without a pre-operative cancer diagnosis [1, 4–6].

In routine histological examination, tissues are usually preserved by fixation in formaldehyde or another solution during the day and must go through many stages for evaluation. In the frozen section approach, these steps for intraoperative diagnosis are modified to shorten the process. Frozen sections are intensive welding procedures and require the skill and experience of the pathologist and good communication with the broader team [3, 7].

There is an essential variation in the use of frozen sections for diagnosing pelvic masses, and frozen is not universally used for diagnosis [3, 8]. The surgeon can use protective options or continue surgery when a borderline tumor is diagnosed. In any case, the frozen section results are compared with the diagnosis in the paraffin section. Other methods, like malignity indexes, serum markers, and imaging studies, can diagnose malignancy preoperatively [6, 9–11].

A frozen section is also recommended during hysterectomy in endometrial neoplasms or hyperplasia, especially in atypia subgroups [12, 13].

Frozen sections dramatically impact the care of gynecological oncology patients. Frozen sections allow for intraoperative evaluation to distinguish benign from malignant tumors during surgery. Frozen section diagnosis in gynecological oncology is sufficiently sensitive and specific for clinical use. Generally, the false-negative and false-positive rates are low [14]. In this study, we aimed to evaluate the predictive effect of the patient's laboratory parameters in frozen results in surgery candidates for freezing.

Materials and methods

We conducted this retrospective cross-sectional study at Bursa Yüksek İhtisas Training and Research Hospital, University of Health Sciences, Department of Obstetrics and Gynecology, Bursa, Turkey. Our study groups consisted of patients with endometrial or ovarian masses, for whom we applied frozen section between 2017 and 2020 and whose malignant-benign distinction was not made before surgery. We divided the patients whose frozen section results were reported as malignant, borderline, or benign into three groups and compared the pre-operative whole blood parameters. Ethics approval was obtained by the committee of Bursa Yüksek İhtisas Training and Research Hospital with the number 2011-KAEK-25 2022/08-21.

Patients with incomplete pre-operative complete blood count data, a previous history of other cancer, a history of splenectomy, a history of chemotherapy and radiotherapy, a history of steroid use, a history of chronic systemic disease, and patients with documented vitamin B12 or folate deficiencies were excluded from the study.

We analyzed 139 patients diagnosed with adnexal mass and endometrial intraepithelial neoplasia. Hemoglobin values, white blood cell, platelet, neutrophil, lymphocyte, mean erythrocyte volume, mean platelet volume, and erythrocyte distribution volume were evaluated in the last month before surgery. In addition, NLR, which is the number of neutrophils divided by the number of lymphocytes, and PLR, which is the number of platelets divided by the number of lymphocytes, were assessed. We investigated the relationship between frozen and advanced pathology results using statistical methods.

Statistical analysis

Windows-based SPSS 22.0 statistical analysis program (SPSS Inc., USA) was used for appropriate statistical analysis. Variables were examined visually (histograms, probability charts), and analytical methods (Shapiro-Wilk test) were used to determine whether the data showed normal distribution. In descriptive analyzes, variables were defined as mean (standard deviation) (X [SD]), the mean difference between groups, 95% confidence interval (95% CI), median (minimum-maximum [min-max]), U value, frequency (n), and percentage (%). The student t-test and Mann-Whitney U tests compared normally distributed and non-normally distributed variables in the two-group analysis. ANOVA and Kruskal-Wallis tests analyzed variables involving more than two groups. Tukey tests were used in cases where variances were homogeneously distributed from post hoc tests, and Games-Howell tests were used in cases where they were not homogeneously distributed for the double group analysis of the results that were significant in multiple analyses. Homogeneity of variances was evaluated by the Levene test. *P*-value < 0.05 was considered significant.

Results

Demographic and laboratory characteristics and descriptive analysis of the patients are given in Table 1. One-hundred-thirty-nine patients were included in the study. The mean age of our patients was 57.3 (11.5) years. Mean hemoglobin values were 12.4 (1.6) g/dl, and the median red blood cell distribution width was 13.7. The median neutrophil percentage was 63.5%, while the median lymphocyte percentage was 26.9%. Frozen results of our patients were reported as benign in 33 (23.7%), borderline in 43 (30.9%), and malignant in 63 (45.3%). Postoperative final pathology results were generally correlated with frozen results, and 34 patients were reported as benign, 33 as borderline, and 72 as malignant. The gross pathology of one patient whose frozen result was found to be

borderline was benign, and nine patients were reported as malignant (Table 1).

Table 1: Descriptive analysis table of patient characteristics and laboratory data

Characteristics and Laboratory data	Frozen section (n=139)
	Mean (SD) / Median (min-max)
Age*	57.3 (11.5)
Hemoglobin (g/dl)*	12.4 (1.6)
Mean corpuscular volume (fl)	85.1 (60.5-98)
Mean platelet volume (fl)	9 (6.9-12.6)
Red cell distribution width (%)	13.7 (11.6-19.7)
Neutrophil percentage (%)*	63.5 (38.5-95.9)
Lymphocyte percentage (%)*	26.9 (2.4-47.2)
White blood cell (mcl)	7.550 (3.920-25.980)
Platelets (mcl)	277.000 (148.000-672.000)
Creatinine (mg/dl)	0.79 (0-3.6)
Alanine Transaminase (ALT) (u/l)	14 (0-157)
Aspartate Transaminase (AST) (u/l)	19 (0-89)
Plasma glucose level (mg/dl)	106 (76-503)
Fibrinogen (milligram)	385 (246-741)
Ca 125 (u/ml)	50.6 (0.8-512.9)
Ca 19-9 (u/ml)	24.9 (0.0-336)
Neutrophil/Lymphocyte Ratio	2.4 (0.8-23.3)
Frozen Result (n;%)	Benign (33; 23.7)
	Borderline (43; 30.9)
	Malign (63; 45.3)
Gross Pathology Result (n;%)	Benign (34;24.5)
	Borderline (33; 23.7)
	Malign (72; 51.8)

g/dl: gram/deciliter, fl: femtolitre, ml: milliliter, u:unit, mcl: microliter,%: percent, cm: centimeter, SD: standard deviation, min: minimum, max: maximum. Descriptive analyses were performed using mean and standard deviation, marked as *, for normally distributed data, and median and minimum-maximum values (median (min-max)) for non-normally distributed data.

In Table 2, we compared the pre-operative laboratory data of all three groups according to the frozen result. While hemoglobin values did not differ significantly between the groups (P = 0.58), mean corpuscular volume and mean platelet volume values were statistically different (P = 0.04 and P = 0.03, respectively). While the mean corpuscular volume differed between the borderline and malignant groups, the mean platelet volume was significantly different between the benign and borderline groups (P = 0.042 and P < 0.01, respectively). While the percentage of lymphocytes was lower in malignant groups, the percentage of neutrophils was higher and statistically significant (P = 0.01 and P = 0.03, respectively). In pairwise comparisons, the percentage of lymphocytes was significantly different between benign, borderline, and malignant groups (P = 0.02 and P = 0.05, respectively). While the blood neutrophil/lymphocyte ratio was significantly higher in the malignant groups compared to the other two groups, the median neutrophil/lymphocyte ratio was 3 in these groups (P = 0.02). One of the cancer markers, the Ca-125 value, was statistically significantly higher in malignant groups compared to the other two groups (P = 0.01). The remainder of the analysis is summarized in Table 2.

We used the Multi Linear Regression Analysis Enter method and MCV, MPV, Neutrophil, Lymphocyte, Ca-125 and NLR variables to analyze the factors that play a role in predicting the result of the frozen section. According to the results obtained, the model with the best performance (correlation with frozen section malignant findings) was: -0.115 (Lymphocyte percentage [%]) + 0.08 (Ca-125) + 0.175 (Neutrophil/Lymphocyte Ratio) (R2: 0.364, P = 0.03) (Table 3).

Table 2: Comparison analysis table in terms of laboratory data of all three groups

	Benign (n=33) Mean (SD) Median (min-max)	Border (n=43) Mean (SD) Median (min-max)	Malign (n=63) Mean (SD) Median (min-max)	*P*-value Comparison of Three groups Benign vs Border Benign vs Malign Border vs Malign
Age*	55.9 (12.8)	58.3 (12.2)	56.6 (10.5)	0.65
Hemoglobin (g/dl)*	12.5 (1.3)	12.5 (1.3)	12.2 (1.8)	0.58
Mean corpuscular volume (fl)	86.4 (60.5-96.5)	86.5 (60.5-98)	83.9 (66.3-90.2)	0.04 0.98 0.22 0.042
Mean platelet volume (fl)	9.5 (7.2-12.6)	8.3 (6.9-11.8)	9.2 (7.1-11.6)	0.03 <0.01 0.18 0.09
Red cell distribution width (%)	13.3 (11.6-19.7)	14 (12.5-19.7)	13.8 (11.6-17.6)	0.54
Neutrophil percentage (%)	58.8 (40.4-90.3)	62.3 (38.5-96)	66.7 (40.4-89.9)	0.03 0.22 0.05 0.96
Lymphocyte percentage (%)	31.2 (7-47.2)	26.7 (2.4-40.2)	24 (9.2-47.2)	0.01 0.02 0.05 0.80
White blood cell (mcl)	6.8 (3.9-25.9)	8 (4-20)	7.7 (3.9-15.4)	0.31
Platelets (mcl)	277 (181-672)	272 (148-558)	283 (155-452)	0.59
Creatinine (mg/dl)	0.82 (0.6-1.1)	0.79 (0.1-3.6)	0.8 (0.1-1.4)	0.75
Alanine Transaminase (ALT) (u/l)	14 (5-157)	13 (1-114)	17 (1-64)	0.09
Aspartate Transaminase (AST) (u/l)	19 (1-88)	17 (1-46)	19 (1-39)	0.77
Plasma glucose level (mg/dl)	105 (76-503)	106 (83-229)	103 (77-258)	0.81
Fibrinogen (milligram)	346 (176-654)	344 (189-712)	355 (167-491)	0.46
Ca-125	36.6 (7-291)	27.4 (5.4-124)	75.3 (7.7-512.9)	0.01 0.31 0.03 0.07
Ca-19-9	19.6 (0.7-136)	36.7 (0.1-196.7)	75.7 (35.7-336)	0.05 0.80 0.96 0.57
Neutrophil/Lymphocyte Ratio	1.8 (0.8-12.9)	2.1 (0.8-20.1)	3 (1.3-23.3)	0.02 0.31 0.04 0.96

Descriptive analyses were performed using mean and standard deviation, marked as *, for normally distributed data, and median and minimum-maximum values (median (min-max)) for non-normally distributed data. *P*-value < 0.05 was considered significant (*: One Way ANOVA, Others: Kruskal Wallis).

Table 3: Multiple linear regression to predict malignancy after frozen section in gynecology

	B	*P*-value	OR
Lymphocyte percentage (%)	-0.115	0.04	0.89
Ca-125	0.08	0.03	1.008
Neutrophil/Lymphocyte Ratio	0.175	0.036	0.839

B: Standardized regression coefficient. OR: odds ratio. *P*-value < 0.05 was considered significant.

Discussion

In oncological surgeries, the frozen section is a valuable method that is globally accepted and directs surgery today. It is a surgical method recommended and frequently used in gynecology, especially in the approach to adnexal masses and hyperplasia surgeries with endometrial atypia. The perioperative malignant-benign distinction is valuable for in-patient management, avoiding unnecessary surgical burdens or preventing a second surgery later.

In this study, we examined whether whole blood parameters, which are easy to analyze before surgery, could be associated with a possible frozen result in gynecological surgeries. We decided to use a frozen section. Mean corpuscular volume, mean platelet volume, neutrophil percentage, lymphocyte percentage, and neutrophil/lymphocyte ratios in whole blood were significantly correlated with frozen results. As there are many examples in the literature [15–19], these parameters, which play a role in the inflammatory process, had data that could provide clues in the differentiation of benign-borderline-malignant during surgery. We found that blood lymphocyte ratio, Ca-125, and neutrophil/lymphocyte ratio values have the most significant findings regarding the parameters that are the most predictive feature of the malignancy

indicator. The findings in this study will be valuable to those planning future studies on this topic.

Many studies show that the progression of patients with endometrial cancer may be related to cancer-related risk factors and laboratory parameters. Ekici et al. [20] showed that preoperatively elevated white blood cells may be associated with advanced endometrial cancer. Matsuo et al. [21] showed that increased monocyte levels might be associated with poor prognosis in endometrial cancer. Metindir et al. [22] also showed that low hemoglobin levels might be associated with poor endometrial cancer prognoses. Heng et al. [23] stated that there might be a relationship between thrombocytosis and endometrial cancer in terms of poor prognosis. Haruma et al. [24] and Cummings et al. [25] also stated that an increased neutrophil/lymphocyte ratio might be associated with advanced endometrial cancer. An article published in 2021 reported that lymphocyte values are associated with endometrial cancer prognostic factors [26].

Zhao et al. [27], in a meta-analysis of 3467 patients, concluded that the neutrophil/lymphocyte ratio might be a prognostic factor of ovarian cancer. In addition, Sanna et al. [28] stated that the neutrophil/lymphocyte ratio might be a predictive marker of the response to neoadjuvant chemotherapy in advanced serous ovarian cancers. Williams et al. [29] published an article in 2014 and mentioned the neutrophilic marker in ovarian cancer. Accordingly, increased neutrophil/lymphocyte ratio was identified as a risk factor for aggressive ovarian cancer. Neutrophils reflected the immediate release of neutrophilic growth factor and CA-125 from the tumor and correlated with CA-125 values.

It is now known that inflammation and inflammatory cells play an essential role in malignant neoplasms, poor prognosis, and response to treatment [30–32]. Since the relationship between cancer and inflammation was first reported, many studies have been conducted on this subject. Today, we know that many cells we evaluate with complete blood count play a role in the chronic inflammatory pathway.

We consider the evaluation of complete blood parameters and inflammatory markers, which are easy to evaluate and cost-effective before surgery, can give a clue before the neoplastic case approach. Finding new malignancy indices and new markers that can be correlated with frozen or gross pathological examination will provide insight into the clinical approach in gynecological oncology. Studies related to this issue are published frequently and typically support this situation.

In this study, we found that frozen reports in gynecologic oncologic surgery may be associated with some pre-operative inflammatory markers. Especially when lymphopenia, high CA-125, and high neutrophil/lymphocyte ratio are evaluated together, this may provide a clue about the malignancy potential of the case. We believe that these data should form a basis for more comprehensive studies. Meta-analyses are needed with a much larger number of other parameters, patients with different demographics, and a more comprehensive range of oncologic cases.

Limitations

Our study has limitations. It was a retrospective single-center analysis with a relatively small patient number. Also, a selection bias may exist, and the surveillance duration was relatively short.

Conclusion

Based on our findings, we propose that complete blood count and inflammatory parameters, taken before gynecological oncology surgery, may provide clues about the prognostic components of the disease and the type of neoplasia. Complete blood lymphopenia and a high neutrophil/lymphocyte ratio may be associated with a higher probability of gynecologic malignancy.

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Characteristic and management of pediatric arachnoid cysts: A case series

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Abstract

Background/Aim: Arachnoid cysts (ACs) are the collection of fluid, which is similar in composition to cerebrospinal fluid, within the congenitally duplicated arachnoid membrane. ACs are clinically silent lesions, but sometimes they can manifest themselves with headache, convulsion, focal neurological deficits, cognitive decline, torticollis, and macrocephaly. Although the appropriate surgical approach is less clear, there is a consensus on the need for surgical treatment in symptomatic ACs. This study aims to reveal the advantages and disadvantages of cystoperitoneal shunt and microsurgical fenestration techniques.

Methods: One hundred ninety-one consecutive patients from 1 month to 15 years old with AC were evaluated for suitability. Sixteen patients who underwent surgery were included in the study. Medical records of the patients with AC managed at our institutions were retrospectively collected and analyzed. Sixteen of 191 patients underwent surgical treatment via craniotomy for microsurgical cyst fenestration (CF) and cysto-peritoneal shunting (CS). CF was performed with partial cyst wall excision in all patients.

Results: Seizure was the most common presentation in the patients, followed by headache and trauma, respectively. In our series the most common indications of the surgery were increased intracranial pressure (IICP). CF was performed in nine patients, and CS was performed in seven as the primary treatment. CS-related complications, such as infection (n = 2), dysfunction (n = 2) and intraabdominal abscess (n = 1) were the most commonly observed complications. No infections were observed after CF, but subdural hematoma was observed in one child.

Conclusions: Although the most common symptoms in cases with arachnoid cysts are headache, rare symptoms, such as torticollis, may exist. Due to this, clinicians should reveal the cyst-complaint relationship first. Given the increased complications of CS, in addition to shunt independency and being free from shunt-related complications, the microsurgical CF with wide excision of the membranes seems to be the more preferable surgical option.

Keywords: Arachnoid cysts, Conservative management, Craniotomy, Cysto-peritoneal shunting, Microsurgical cyst fenestration

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Introduction

Arachnoid cysts (ACs) are the collection of fluid, which is similar in composition to cerebrospinal fluid within the arachnoid membrane. It is thought to result from splitting or duplication of the primitive arachnoid membrane in early embryonal life [1, 2]. These benign congenital cystic lesions occur in 2.6% of children [3, 4]. The incidence of ACs is reported to be about 1% of intracranial space-occupying lesions. Males are involved in more than two-thirds of the cases and there is an increased incidence on the left side [5].

ACs most frequently arise in the supratentorial space, especially in the middle cranial fossa, followed by the convexity and suprasellar regions. Only 10% of ACs arise in the posterior fossa [1, 4].

In general, ACs are clinically silent lesions. Sometimes they can manifest themselves with clinical symptoms and signs, such as headache, convulsion, focal neurological deficit, and cognitive decline like intellectual disabilities and torticollis [6-10]. In addition to these, thinning of the adjacent bone and macrocephaly may also be seen. These clinical manifestations depend on the location, size and mass effect of ACs [8-12].

Although the appropriate surgical approach is less clear, there is a consensus on the need for surgical treatment in symptomatic ACs [12-15]. In symptomatic ACs, the treatment options vary from open craniotomy and endoscopic approaches to cystoperitoneal shunts and stereotactic aspirations [12, 14-17]. In asymptomatic ACs, conservative management has been proposed and prophylactic surgery is generally not recommended. For these patients, a close radiological and clinical follow-up is of great importance [2, 4, 18].

This study aims to reveal the advantages and disadvantages of the cystoperitoneal shunt and microsurgical fenestration techniques.

Materials and methods

PatieIn this study, we evaluated the clinic, radiologic, demographic findings, and therapeutic approaches and prognoses of children with arachnoid cysts. We have aimed to evaluate the clinical and radiological course of the disease as well as the impact of clinical symptoms and radiologic findings of children with ACs to best determine the treatment modalities. We have also compared the results of two different surgical approaches in the enrolled children. One hundred ninety-one consecutive patients with AC diagnosed and treated in the Department of Neurosurgery, Erciyes University Medical Faculty from August 2012 to June 2014 were included in the study. Medical records of all pediatric patients with ACs who underwent surgical treatment and were conservatively managed at our institution were analyzed.

The data collected included age, gender, neurologic symptoms and signs, associated abnormalities, psychomotor status, surgical intervention, complications, electroencephalography findings, radiologic findings, and follow-up. Patients with secondary ACs due to infection or trauma were excluded from the study.

All patients were evaluated preoperatively using computed tomography (CT) and/or magnetic resonance imaging (MRI) scans. Postoperatively all patients had regular follow-up clinical and radiological evaluations. The mean follow-up period was 61 months (range, 14-136 months).

Informed consent forms from the patients' parents were obtained for all patients.

Cranial CT

All of the patients underwent a low dose non-enhanced multi-detector cranial CT (Toshiba Aquilion One 320 slice CT, Toshiba Medical Systems, Otawara, Japan) (120 kV, 10mA). None of the patients were sedated.

Cranial MRI

Patients younger than age five were sedated with midazolam (intranasal 0.1-0.2 mg/kg, Dormicum, Roche, Istanbul, Turkey) for brain MRIs. Patients five years old and older underwent brain MRIs without sedation in the supine position. A total of 191 patients underwent a routine pediatric brain MRI examination (1.5 T Philips Intera, Philips Medical System, Best, The Netherlands and 1.5 T Siemens Aera, Siemens Medical Solutions, Erlangen, Germany) in our institution. Our pediatric brain MRI protocol included T1-W axial-sagittal, T2-W axial-coronal, T2-W FLAIR axial, DWI and ADC images. The slice thickness varied from 4 mm to 5 mm.

Sixteen (9 males and 7 females aged from 1 month to 15 years old) out of 191 patients underwent surgical treatment via craniotomy for microsurgical cyst fenestration (CF) and cystoperitoneal shunting (CS). CF was performed with partial cyst wall excision in all the patients. We performed CS in one patient whose parents refused the CF operation. Three of the seven patients in the CS group had been operated via CS in other centers before admission to our department. In all of the 16 patients in surgical group sulcal obliteration, shifting of adjacent vascular structures, adjacent cortex depression or ventricle effacement or enlargement, and midline shift were observed.

We performed CF in nine patients and CS in seven as a primary treatment. In three of the seven cases who underwent CS, we performed CF due to shunt-related complications (two instances of shunt revision, two cases of shunt dysfunction, one shunt infection with intraabdominal abscess, and one case of meningitis).

Statistical analysis

Statistical analyses were performed with R [R project (2014). R (Version 3.1.1), computer software, retrieved from https://www. r-project.org). To summarize the data obtained from the study, descriptive statistical data are presented as mean (standard deviation) and median (range) for continuous variables based on data distribution. Categorical variables are summarized as count and percentage.

Results

The median (min-max) age of the patients (121 male and 70 female) was 5.0 years (ranging from 1 month to 18 years) for both genders. Seizure was the most commonly presented symptom and indication for MRI in the patients, and headache and trauma followed respectively. In this study of 191 children under 18 years of age with AC, indications for MRI are given in Table 1.

Figure 1 (a, b, c, d, e, f): 17-month-old boy with torticollis: A giant arachnoid cyst with right cerebellar hypoplasia is shown on T1-W (a), T2-W (b) axial and T2-W (c) coronal images. Cyst size reduction and no brainstem compression are seen on the postoperative late control T1-W (d), T2-W (e) axial and T2-W (f) coronal images of the case.

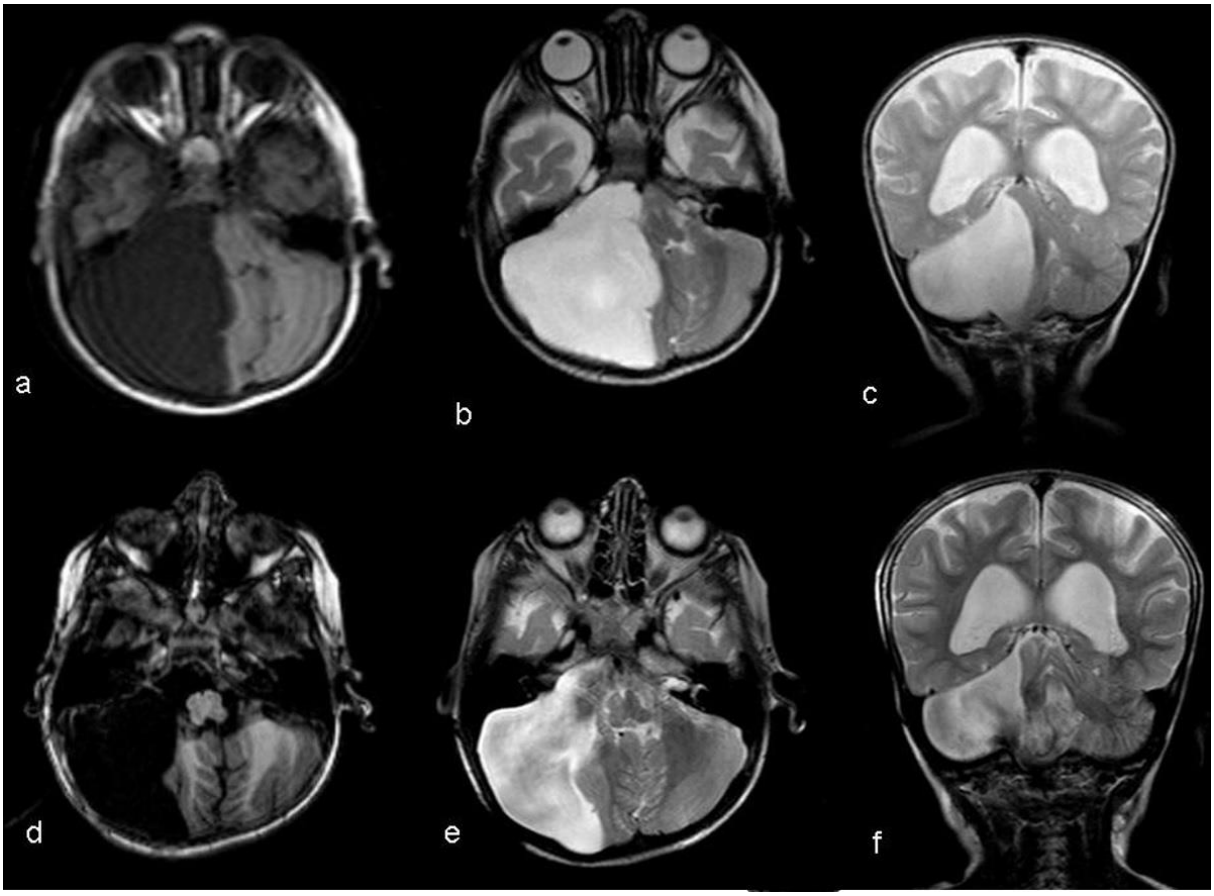

Figure 2 (a, b, c, d): 11-month-old boy: A giant arachnoid cyst at left frontotemporal region, which compresses the left lateral ventricle and causes a midline shift is demonstrated on T1-W (a) sagittal and T2-W (b) coronal images (arrows). After the CF, the cyst regressed totally but still remains at left temporal region on T1-W (c) sagittal and T2-W (d) coronal images (arrows).

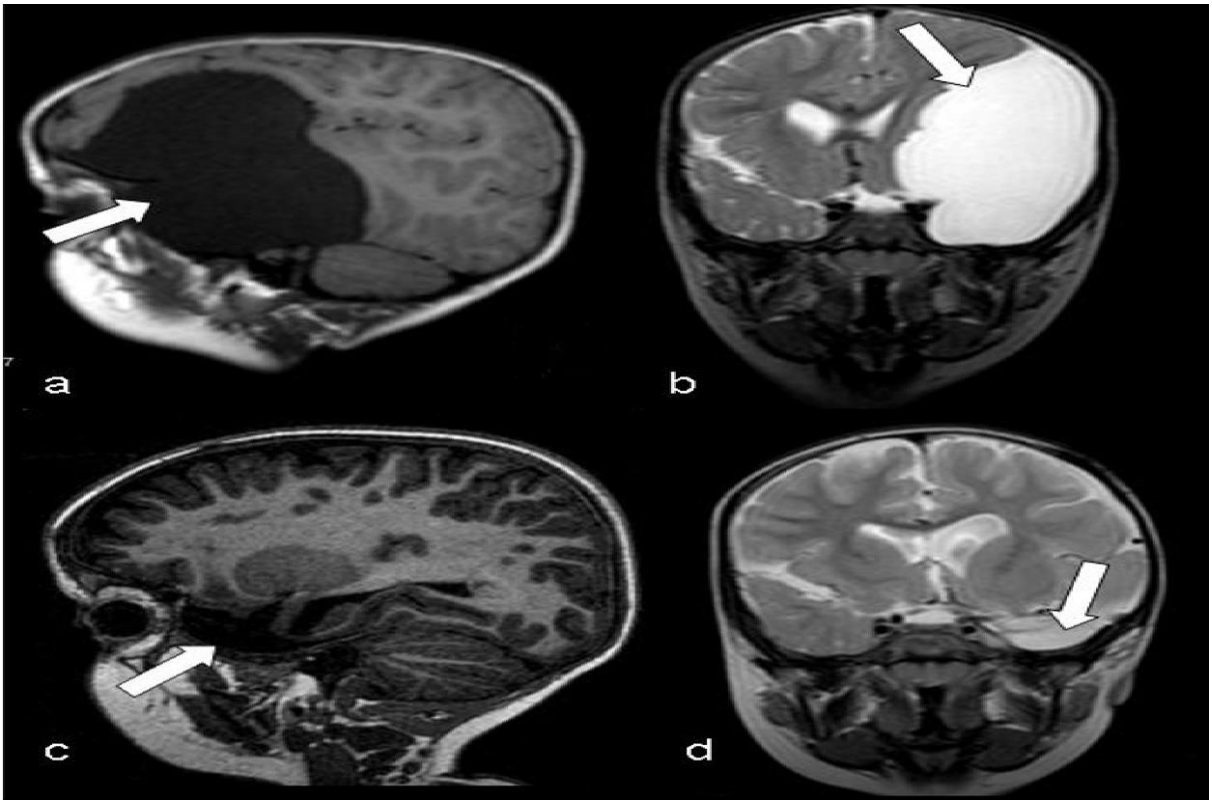

Table 1: Initial presentation symptoms of 191 children with arachnoid cysts

Indication	No	Case %
Concern for seizure	74	38.9
Headache	34	18.0
Trauma	16	8.0
Headache with vomiting and ataxia	11	6.0
Cognitive dysfunction or developmental delay	12	6.2
Signs related to the eye	12	6.2
Pitosis 1		
Strabismus 9		
Nistagmus 2		
Gait Disturbance	9	5.0
Macrocephaly	8	4.1
Abnormal and involuntary movement	5	3.0
Vertigo	4	2.1
Pituitary/endocrine issues	1	0.05
Cutaneous lesion	2	1.0
Torticollis	1	0.05
Other (detected in fetal MRI)	2	1.0

One hundred thirty-four of the ACs were supratentorial (70.2%) and 57 were infratentorial (29.8%). The left hemisphere was more often affected (n = 80). Lesion locations are given in Table 2. During the follow-up period, even though there were no clinical complaints and neurological symptoms in 175 of 191 cases with ACs, spontaneous resolution in AC was observed in 6 patients. However, in 17 cases, there was a slight growth in their cysts, but no clinical or neurological findings were observed.

Table 2: Location of arachnoid cysts in 191 pediatric patients with arachnoid cysts

Lesion location	Total No.	% Cases
Anterior fossa	12	6.3
Middle fossa	96	50.3
Left temporal 61		
Right temporal 29		
Bilateral 6		
Posterior fossa	52	27.3
Left cerebellar 15		
Right cerebellar 25		
Cisterna magna 12		
Cerebellopontine angle	4	2.1
Convexity	1	0.05
Ventricular region	11	6.0
Bilateral lateral ventricle 2		
Right lateral ventricle. 4		
Left lateral ventricle 1		
3rd ventricle 3		
4th ventricle 1		
Basal cisterns	8	4.2
Sellar/suprasellar region	1	0.05
Interhemispheric region	6	3.2
Total	191	

Anterior fossa → right frontotemporoparietal n:1, frontotemporal n:4 (2 right, 2 left), right frontoparietal n:1, frontal n:6 (5 right, 1 left)

During the study period, only 8.4% of the patients with AC (16/191) underwent surgery via microsurgical CF and/or a CS procedure. This included 9 males and 7 females with a mean age at the time of surgery of 57.8 months (ranging from 1 month to 15 years). Of the 16 ACs, 12 were in the supratentorial and 4 were in the infratentorial location.

Table 3: Clinical and imaging details and surgical indications for 16 pediatric patients with arachnoid cyst who underwent surgical treatment

Case No	Age/Sex	Sign/Symptom	Cyst Location	Cyst Size (mm) Initial	Surgical indications	Surgical Procedure	Cyst Size (mm) Postoperative	Complication CS / CF	Clinical Improvement
1	17 m/M	Torticollis	PF	64×74×55	Torticollis	CF	41×52×60	none	No Torticollis
2	31 m/M	Convulsion	Right LV	40×30×35	Hydrocephaly	CS, CF	30×18×27	Shunt Dysfunction / none	Normalized skull skull growth rate
3	122 m/F	Convulsion, Ataxia	PF	68×62×41	Brainstem Compression, MEC	CF	68×52×43	none	No Ataxia
4	94 m/M	Headache, self- harm	Interhemispheric	78×42×69	MEC	CF	70×20×50	/CSDH	No headaches
5	38 m/F	Macrocephaly	PF, Occipital	132×110×143	Hydrocephalus	CS	94×94×124	SDHy	Normalized skull skull growth rate
6	1 m/M	Macrocephaly	Left LV	57×65×63	Hydrocephalus	CS	34×58×41	SDHy	Normalized skull skull growth rate
7	56 m/M	Strabismus	3rd ventricle	37×42×42	Strabismus, Hydrocephalus	CF	31×21×52	none	Normalized skull skull growth rate No Strabismus
8	17 m/F	Strabismus	3rd ventricle, prepontine–interpedincular cisterna	31×34×25	Strabismus, Hydrocephalus	CF	31×21×32	none	Normalized skull skull growth rate No Strabismus
9	156 m/F	Polydips ia, gait disturbance, vertigo,	Prepontine cisterna, suprasellar	32×30×33	Hydrocephalus, Brainstem Compression	CS	20×26×15	Meningitis / none	No Polydipsia and gait disturbance
10	7 m/M	Vomiting, irritability	interhemispheric	60×50×45	Hydrocephalus	CS	30×20×33	none	Normalized skull skull growth rate No Vomiting
11	21 m/M	Macrocephaly, vomiting	Left Frontotemporal	70×58×98	MEC, macrocephaly	CF	33×36×17	none	Normalized skull skull growth rate No Vomiting
12	8 m/F	Macrocephaly	Right LV	79×65×65	Hydrocephalus, macrocephaly	CS, CF	71×30×64	Shunt dysfunction / none	Normalized skull skull growth rate
13	82 m/F	Headache, Fainting	PF	52×42×46	MEC	CF	29×31×28	none	No headaches and fainting
14	84 m/M	Headache, blurred vision, vomiting, papilledema	Right Frontotemporo-parietal	76×49×43	MEC	CF	38×21×12	none	Symptoms of IICP improved
15	180 m/F	Headache, vomiting, papilledema, confusion	Ambient cisterna	35×31×19	MEC, Hydrocephalus	CS, CF	10×14×11	Shunt infection, intra abdominal abscess / none	No headaches and fainting
16	11 m/M	Headache, vomiting	Left Frontotemporal	85×61×59	MEC	CF	26×20×16	none	No headaches and vomiting

m: Month, M: Male, F: Female, PF: Posterior fossa, LV: Lateral Ventricle, CF: Cyst fenestration, CS: Cyst shunting, CSDH: chronic subdural hematoma, SDHy: subdural hygroma, MEC: Mass effect of the cyst

In two patients less than one year of age who were administered CF, we did not come across any complications. The result was both clinically and radiologically a success. A 17-month-old boy with torticollis and a right cerebellar arachnoid cyst (Figure 1) and an 11-month-old boy with a giant arachnoid cyst at the left frontotemporal region (Figure 2) were given as sample cases.

There were no deaths in our series. No infections were observed after CF, but we did meet with subdural hematoma in one case, which was treated surgically. Shunt-related complications, such as infection and dysfunction, were the most common complications in the included patients. Additionally, we found subdural hygroma in two patients treated with CS. These were managed conservatively.

In our series, the most common indications of the surgery were IICP due to mass effect of the cyst (n = 6) or hydrocephalus (n = 9) that was related to AC. The other indications included strabismus (n = 2), brain stem compression (n = 2), macrocephaly (n = 2) and torticollis (n = 1), respectively. No patients were operated on with an indication of cyst size alone. Clinical, surgical, and imaging details of 16 pediatric patients with AC who underwent surgical treatment are given in Table 3.

Discussion

The most common locations of ACs are reported to be middle cranial fossae (80%) and posterior cranial fossae (10%), whereas convexity lesions constitute only 5% of all [1, 13]. In our series, 134 of the ACs were supratentorial (70.2%), and 57 were infratentorial (29.8%).

ACs are CSF collections usually incidentally found on MRI/CT and usually do not enlarge. Even so, they rarely disappear spontaneously. In our series, spontaneous resolution in AC was observed in six patients. Most ACs are static, typically clinically silent but have the potential to enlarge and surgical intervention is absolutely required when sufficient cyst enlargement occurs. Asymptomatic and incidental cysts do not require treatment or should not be treated surgically, but they should be followed up regularly. All authors agree that symptomatic ACs, which are presented with IICP, intractable seizures, and focal neurological deficits should be treated surgically [14, 18].

In our series the most common indications of the surgery were IICP due to mass effect of the cyst or hydrocephalus that was related to AC. The other indications of the surgery included strabismus, brain stem compression, and torticollis, respectively.

Seizure may not always be an indication for surgical intervention when originated from the dysmorphic cortex beneath the seizure or originated from a different region of the brain [16]. Although the most common presentation in 191 patients was seizure, there were only two patients with seizure complaints in the surgical group, whose indication was not related to the seizure but hydrocephalus and brain stem compression due to ACs. No patients were operated on due to intractable seizures in our series.

Although neurological symptoms exist, clinicians should exactly correlate nonspecific symptoms with AC, because ACs can present themselves with uncommon symptoms, such as torticollis in a 17-month-old boy in our series. This patient completely recovered from torticollis after the surgery. In the surgical group of our study, all the complaints of the patients were examined regardless of whether they were correlated with AC. Most of the complaints were related to IICP due to hydrocephalus and/or mass effects of the cyst.

The choice of the most appropriate surgical approach to the treatment of pediatric arachnoid cysts remains widely debated [12-14]. The treatment options vary from microsurgical resection of the cyst wall, fenestration of the cyst to the ventricle or cisternal space with open craniotomy or endoscopic approaches to CS [19, 20]. However, each treatment modality has some advantages and disadvantages. Nevertheless, CS placement seems easier, and it is possible to achieve high rates of cyst elimination with this treatment. However, CS carries the additional risk of shunt-dependent complications, such as shunt infection, shunt failure, unexpected hemorrhage, and over drainage. Additionally shunt-related complications may occur at any time in life [5].

Both of the open craniotomy and endoscopic procedures for cyst excision or fenestration have the advantage of leaving the patient shunt independent [11, 13, 15]. However, surgical techniques require a slow learning process and the learning curve should be completed before using them as the first line of treatment [16]. In addition, it is difficult to fenestrate the cyst into a CSF cistern or ventricle and to perform cyst wall resectioning using this technique. Overall, the rate of radiological resolution of the cyst has been reported to be lower in endoscopic approaches.

Another important disadvantage of this procedure is controlling unexpected profuse bleeding due to difficulties in instrument use and insufficiency in view. These problems are not encountered in microsurgery [4, 17]. In addition, the location of the cyst may impose significant risk to surrounding structures, as is the case with suprasellar or posterior fossa cysts [4]. CF procedure is not always effective, and cyst recurrence has been reported [13, 20]. It has some complications including meningitis, hemiparesis, subdural hematomas, seizure, and even death [4, 19].

Because surgical therapy is more effective in children, it is recommended that ACs that show poor communication between the cyst and the subarachnoid spaces should be treated as early as possible with regard to reversible brain growth in childhood [11].

The results in patients under one year of age who were administered CS were radiologically and clinically successful in this series. Nevertheless, in an eight-month-old patient, due to recurrent shunt problems, we had to perform CF. In two patients less than one year of age who were administered CF, we did not come across any complications. The results were both clinically and radiologically successful. Even though a relatively high surgical failure rate was previously reported in pediatric patients under one year of age [18], due to the success of the procedure in this age category, we are of the opinion that in patients under one year of age, CF is possible to be performed.

Both subdural hygromas and subdural hematomas have been previously reported after the treatment of ACs in children,

whether microsurgical or endoscopic [17, 20]. In the patients treated with CS, we observed shunt infection in two patients, shunt dysfunction in two, and subdural hygroma in another two. In only one of the cases treated with CF did we observe acute subdural hematoma. No infection was experienced. The rate of complications in our series, especially infection in the CF group, was significantly less than in the CS group.

Late follow-up imaging data showed nearly complete resolution of the cyst in 12.5% of the 16 patients. In addition, there was a significant reduction in size in 50% of cases, while 37.5% of the cysts slightly decreased. In one patient, although the cyst size was decreased in early control, it was found to be in similar dimensions in late control. We concluded that the reason for this might have been the insufficient fenestration of the cyst or the closure of fenestration. Even the radiological improvement was not observed or the cyst did not change in size. Clinical symptoms of IICP in the cases, such as headache (n = 4) and vomiting (n = 4), were improved and normalized skull growth rate was obtained in eight patients. Other improved symptoms included ataxia (n = 1), torticollis (n = 1), strabismus (n = 2), gait disturbance (n = 1), polydipsia (n = 1) and fainting (n = 2). There was no exact correlation between radiological and clinical improvements.

Although it has been previously reported that patients who show radiological improvement do not always demonstrate clinical improvement [18], the patients who showed radiological improvement always demonstrated a corresponding improvement of clinical symptoms in the presented patients. Although we observed a recurrence of the size after surgery, we speculate that these procedures are clinically effective, since the symptoms and complaints of the patients clearly improved.

However, a weakness of this study is that it consisted of a small number of surgical cases. Due to this, generalizability of the results is difficult.

Conclusion

Although the most common symptoms in cases with arachnoid cysts are headache, rare symptoms, such as torticollis, may exist. Due to this, clinicians should reveal cyst-complaint relationship first.

This study aimed to reveal the advantages and disadvantages of cystoperitoneal shunt and microsurgical fenestration techniques.

Cystoperitoneal shunting is likely to be a technically easier surgical treatment modality in children. However, lifelong shunt dependency and a lifelong risk of shunt-related complications are the serious disadvantages of this treatment modality. The microsurgical fenestration into more than one space of the cyst with wide excision of the membranes is a preferable option for surgical treatment.

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Medical students' views on the distance education practices of the neuroanatomy course during the pandemic

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Ethics Committee Approval
The ethical approval was given by the Hamidiye Scientific Research Ethics Committee (21/185). 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: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019. This highly contagious and pathogenic coronavirus causes acute respiratory disease pandemic coronavirus disease 2019 (COVID-19). More than 1.2 billion students in 186 countries are currently affected by school closures due to the COVID-19 pandemic. Educational activities, including clinical medical education, were also stopped during the pandemic. To maintain the continuity of medical education, distance learning approaches were developed, including online/offline teaching methods. Within the scope of this training, the effect of distance learning on students' experience of neuroanatomy teaching was investigated.

Methods: The study sample included 61 students who agreed to participate. The data of the students who accepted to participate in the study were obtained via a questionnaire form created using the "Attitude Scale towards Distance Education". The questionnaire was uploaded to the forms section of the Microsoft Teams program, and the link address was sent to all students who took the Neuroanatomy course from the International Faculty of Medicine 2nd year students via e-mail.

Results: Most students (n = 44, [72.1%]) stated that they could access the internet without any problems, while others had problems. Some students (n = 10; 83.6%) had to share their remote connection devices with their family members during distance education. Some students (n = 9, [14.8%]) had to use mobile phones for homework and exams. Less than half of the students (n = 27, [44.3%]) responded that 3 h per week neuroanatomy teaching was sufficient; most (n = 34, [55.7%]) responded that this was insufficient ($P < 0.01$). Many of the students who took the distance learning neuroanatomy course (n = 27, [44.3%]) believe that the course has contributed to their professional development ($P < 0.01$). During distance education, active participation of the classmates – by turning on their microphones – increased the students' motivation (n = 53, [88.3%]).

Conclusion There were difficulties in understanding the neuroanatomy lectures delivered by distance education. The Turkish students had greater problems in understanding relative to the international students, who were much more focused. Students will likely derive greater benefit from doing the neuroanatomy course face to face.

Keywords: Attitude scale, Anatomy, COVID-19, Pandemic

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Introduction

Widespread changes have occurred in our society, accompanying the global response to the coronavirus disease 2019 (COVID-19) outbreak [1]. Schools and universities in Turkey have been closed to encourage social distance. The impact of this change on medical education has been immense. The effect of basic medical sciences education in the first 3 years of medical school on students who will become physicians is essential in terms of patient knowledge [2]. On the other hand, anatomy education has been separated from laboratory conditions due to the transfer of teaching activities to the online environment [3]. Currently, there is disappointment among medical students transitioning to a complete distance education paradigm.

Neuroanatomy is a challenging sub-anatomy subject for medical students, addressing the complex structures of the three-dimensional relationships of the neuronal system and difficult clinical integration [4]. In the absence of contact teaching, such as dissection room sessions, and the removal of extrinsic motivations such as exams, it is easy to see how undergraduate neuroanatomy training was particularly vulnerable during the COVID-19 pandemic.

To minimize the negative impact, it is necessary to provide neuroanatomy resources that are easily accessible, support an inner interest, and are supported by appropriate pedagogy to positively impact knowledge [5]. Students may continue to work independently during long periods of isolation with high-inner interest.

Online learning platforms are currently used by universities to support the learning of students in neuroanatomy and to expand free educational resources [6]. Online platforms now have a wide variety of functions. This way, lecture-discussion rooms are created for small group discussions by organizing online lectures. Interactive materials, such as quizzes or patient-based case studies, are also used. Alternatively, student information is supported by pre-recorded content such as screen video recordings by organizing mini-courses.

Online learning provides medical students the flexibility and option to carry out self-learning at home at convenient times [7]. This also allows medical students to control their time on a subject. Thus, the students prevent information overload and allow them to allocate more time to the areas they struggle with. To minimize the cognitive load, it is important that the instructional design of screen video recordings is in line with the principles of the cognitive theory of multimedia learning. Cognitive load is placed on studying memory while processing information for learning and is particularly important in an information-rich subject, such as neuroanatomy [5]. Therefore, it is crucial to consider online resources to be effective in increasing knowledge acquisition and maintaining student engagement. Along with the participation of the students in the course process, their opinions also play a key role in improving the lecture [8].

In this study, the views of Turkish and international students in our faculty about the distance education of the neuroanatomy course were evaluated. The results will contribute to efforts to improve the functioning of challenging lessons, such as neuroanatomy.

Materials and methods

Research type

Here we investigate the attitudes of medical students studying at the University of Health Sciences, International Faculty of Medicine, towards distance education in neuroanatomy lectures. Ethical approval was obtained from the Hamidiye Scientific Research Ethics Committee, the scientific ethics committee of the university (accepted in 2021 and numbered as 21/185).

Research universe and sample

The study universe consisted of the University of Health Sciences, Faculty of International Medicine, and Turkish and International students studying in semester 2. The study sample included 91 students who agreed to participate in this study. These students were 76 (83.5%) women and 15 (16.5%) men. Eighty-one students (89.0%) were Turkish Republic citizens, and ten (11.0%) were international students.

Data collection type

The data of the students who accepted to participate in the study were obtained with a questionnaire form created using the "Attitude Scale towards Distance Education". This questionnaire form was prepared, the gender of the student and how it provides communication with the lecturers. Communication options included "I can communicate by phone", "text message", "email when I need it" and "teachers are unavailable". In neuroanatomy education, the online follow-up level of all courses and the device elements were questioned by combining the distance education method during the pandemic process. In addition, students' views on the efficiency of theoretical courses and their attitudes towards distance education were also asked.".

Attitude Scale towards Distance Education

The "Attitude Scale towards Distance Education" developed by Agir et al. [9] has two sub-dimensions and consists of 21 items. It was developed as a 5-point Likert scale: (1) (strongly disagree) to (5) (strongly agree). The measurement tool contains seven negative items (11, 12, 13, 14, 15, 17, 19) whose values should be reversed in data analysis. The lowest score that can be obtained from the scale is 21, while the highest score is 105 [9].

Online data collection

Informed consent was obtained from the students. The students' names remained confidential. The questionnaire was uploaded to the forms section of the Microsoft Teams program, and the link address was sent to all students who took the Neuroanatomy course from the International Faculty of Medicine 2nd year students via e-mail.

Statistical analysis

The distribution of the students' responses participating in the study was analyzed with the number and percentage in the SPSS 22.0 package program. The students' answers differed according to their demographic information and were analyzed using the Chi-square test. Statistical techniques, such as percentage, frequency, t-test, and One-Way Analysis of Variance (ANOVA), were used to analyze the sub-problems. In addition,

the correlation of the scale with the 17 questions added was examined with the Pearson test. $P < 0.05$ was considered significant.

Results

Student attendance

Sixty-one students (38 female [62.3%]) participated in the survey study. Most (75.4%) were international students (n = 46, 24.6%) and 15 were Turkish Republic citizens. Responding to the question about what device was used for distance education, 54 (88.5%) answered that they connected using a computer and seven (11.5%) connected with a tablet.

The question asked whether there was a problem with free access to the internet in the place where students live. Students (n = 44, [72.1%]) stated that they could access the internet without any problems, while others (n = 44, [72.1%]) had problems. Some students (n = 10, [83.6%]) had to share their remote connection devices with their family members during the distance education process. Some students (n = 9, [14.8%]) had to use mobile phones for homework and exams. Most students (n = 34, [55.7%]) responded that the 3 h per week of neuroanatomy lessons was insufficient.

To the question that sharing the lecture videos beforehand had a positive effect on learning the neuroanatomy lesson, students (n = 44, [72.1%]) answered that this situation had a positive effect. Many of the students who took the distance learning and neuroanatomy course (n = 27, [44.3%]) responded that they believe this contributed to their profession ($P < 0.01$).

Students (n = 37, [60.7%]) stated that actively participating in the neuroanatomy lecture by turning on the microphone during the lesson contributed to the course's learning. In distance education, the fact that the instructor's camera was constantly on during the lesson increased students' interest (n = 55, [90.2%]). During distance education, active participation of the classmates by turning on the microphone increased students' motivation (n = 53, [88.3%]).

It has been observed that international students find distance education more effective than Turkish students ($P < 0.01$). Also, attending lessons from abroad find distance education more effective than in Turkey ($P < 0.01$). All the obtained findings were classified and displayed in the description table (Table 1). Information about the neuroanatomy course is shown in Table 2. Descriptive statistical analysis of the students was classified in Table 3.

Table 1: Description of student conditions

	f	%
Gender		
Woman	38	62.3
Male	23	37.7
Nationality		
Turkish	15	24.6
International	46	75.4
Device		
Computer	54	88.5
Tablet	7	11.5
Attendance		
Turkey	46	75.4
Abroad	15	24.6
I have constant and smooth access to the internet.		
No	17	27.9
Yes	44	72.1
During distance education, I must share my device with family/home members.		
No	51	83.6
Yes	10	16.4
I must use my cell phone for homework and exams.		
No	52	85.2
Yes	9	14.8

Table 2: Condition of neuroanatomy lectures

Hours of the neuroanatomy lesson were sufficient for distance education from the pandemic process.	f	%
No	34	55.7
Yes	27	44.3
Sharing the theoretical and laboratory lecture videos beforehand had a positive effect on learning neuroanatomy		
No	17	27.9
Yes	44	72.1
I think learning neuroanatomy with distance education methods will contribute to my profession.		
No	34	55.7
Yes	27	44.3
I could repeat the lecture notes the same day after the lesson topic was taught.		
No	41	67.2
Yes	20	32.8
I could answer the questions the lecturer asked during the neuroanatomy distance education course.		
No	21	34.4
Yes	40	65,6
Being active in the lesson by turning on my microphone during the lesson contributed to my learning about neuroanatomy.		
No	24	39.3
Yes	37	60.7
The fact that the instructor's camera was always on during the lesson increased my interest in the lesson		
No	6	9.8
Yes	55	90.2
Active participation of my classmates in the class by turning on their microphones during the lesson increased my motivation.		
No	7	11.7
Yes	53	88.3

Table 3: Descriptive statistical analysis of the students, *$P < 0.05$

	Mean (SD)		*P*-value
Woman	68.89 (16.08)		0.428
Male	72.26 (5.77)		
Turkish	61.07 (17.16)		0.010*
International	73.13 (14.48)		
Computer	70.19 (15.89)		0.977
Tablet	70 (17.45)		
Turkey	66.43 (15.29)		0.001*
Abroad	81.6 (12.20)		
I have constant and smooth access to the internet.			
No	68.29 (18.20)		0.573
Yes	70.89 (15.11)		
During distance education, I must share my device with family/home members.			
No	72.53 (14.47)		0.008*
Yes	58.1 (18.24)		
I must use my cell phone for homework and exams.			
No	71.04 (14.53)		0.306
Yes	65.11 (22.84)		
Hours of the neuroanatomy lesson were sufficient for distance education from the pandemic process.			
No	64.88 (14.89)		0.003*
Yes	76.81 (14.87)		
Sharing the theoretical and laboratory lecture videos beforehand had a positive effect on my learning neuroanatomy			
No	63.94 (17.71)		0.057
Yes	72.57 (14.68)		
I think learning neuroanatomy with distance education methods will contribute to my profession.			
No	62.59 (14.83)		<0.001*
Yes	79.70 (11.67)		
I could repeat the lecture notes the same day after the lesson topic was taught.			
No	68.83 (15.99)	-0.937	0.353
Yes	72.9 (15.83)		
I could answer the questions the lecturer asked during the neuroanatomy distance education course.			
No	65.81 (15.83)	-1.567	0.123
Yes	72.45 (15.68)		
Being active in the lesson by turning on my microphone during the lesson contributed to my learning about neuroanatomy.			
No	71.88 (18.83)	0.673	0.504
Yes	69.05 (13.88)		

SD: standard deviation

Discussion

There are several ways in which online learning can be structured and implemented. The online platform can be designed as a complete reconstruction of the curriculum or in addition to other envisaged activities. A complete online curriculum provides structured learning and allows students to measure progress and set goals, an important element of intrinsic motivation [10]. The downside of recreating online activities for a whole curriculum value is taking time and planning that is not covered by this emergency.

Methods of promoting inner interest through online platforms include case studies and gamification. Patient-based case studies motivate learning by reminding the student of the value and interest that learning neuroanatomy has in future careers [5]. Online learning approaches, although structured, can be a versatile way to engage medical students in their learning. The role of the educator is to consult with the relevant pedagogy to ensure that online learning tools are well equipped to provide students with a clear learning path throughout the curriculum [11].

Although online teaching and learning have been practiced for years, the effects were unsatisfactory. Teachers refused to use unconventional online teaching tools. The data investigated the factors affecting student motivation in online teaching tools [12]. Motivating teachers to change their teaching approach or style is one of the biggest obstacles. The research examined successful online teaching practices and found that teachers' "themselves" and their participant roles in the online environment were essential [13].

On the other hand, many students were not used to using online learning platforms to study. Studies have reviewed practices for providing effective online teaching and learning to students. Technology and communication competencies are key factors that increase student satisfaction and retention, but motivation and availability in online learning are key issues for student engagement [14, 15]. Practical scenarios, video lectures, self-assessment activities, and exercises to integrate theory and practice, including learning activities, were recommended to educators to improve the online learning presence of the students [16, 17].

Despite the difficulties associated with distance education, the students stated that the neuroanatomy course hours were sufficient. In addition, they believe that learning neuroanatomy, even from a distance, will have a positive effect at the time of specialization. Finally, another challenge is that students have to share their educational tools with households throughout the entire distance education process. This situation may cause them to delay the lessons.

Understandably, concerns arise when only online teaching is used. However, it has been shown that students with a blended learning experience combining online and face-to-face teaching have better knowledge [18].

Educators and students navigated new education systems and adapted existing teaching and learning methods to the evolving educational environment. Balancing home and work may now have minimal physical segregation and include childcare for some. With additional clinical responsibilities, educators may have limited time to create content and could sometimes complete the transformation of courses from face-to-face training to fully virtual experiences. Course managers may encounter educators unfamiliar with newly applied technologies in medical education [19].

In response to the coronavirus epidemic, distance learning was one of the solutions for the education sector. Higher education institutions around the world reviewed the feasibility of online learning to minimize its impact on students' academic progress while face-to-face lectures were suspended.

The immediate impact of the COVID-19 outbreak on burnout, work engagement, and surgical training in the Netherlands was measured. This study demonstrated a significant impact of the first months of the COVID-19 outbreak on the Dutch surgical trainee program, with a significant reduction in surgical exposure and training [20]. This study emphasized the need for adequate guidance for all surgical residents and the potential extension of the surgical training program.

Changes in institutions were the transition to formative end-of-year exams regardless of achievement. Researchers have hosted the Soton-BrainHub website with social media accounts. This included animated videos about neuroanatomy, head and neck anatomy, cranial nerve examination videos, and recorded lectures. The Soton-BrainHub YouTube channel received 69,000 views in April 2020, a 61% increase over the monthly average in 2019 [5]. This was an example of the growing demand for online licensing neuroanatomy resources.

Documents detailed an approach to redesigning the clinical learning system, which includes a description of the learners and the environment, the pedagogical principles guiding the approach, and the technological tools used in practice. In addition, the available literature on this topic was researched, and an assessment of the work to date was presented [21]. Recommendations for future guidelines for postgraduate medical education online have been presented.

Limitation

The low number of participants in this study is a limitation but was unavoidable due to the pandemic. The large number of students attending the course allowed us to analyze only this number. This study could be repeated on a larger scale. In future research, we will conduct face-to-face lectures and compare students' perceptions relative to those using distance learning. Afterward, an assessment may be required for other anatomy courses, both face-to-face and online. Cooperating with different universities and increasing the number of samples is necessary.

Conclusion

In conclusion, it was found that there were difficulties in understanding neuroanatomy lectures with distance education. It was determined that Turkish students had greater problems in understanding while international students were much more resilient. Conducting the neuroanatomy course face to face will support a better understanding of the systems, especially from a clinical point of view.

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Research article

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What is the role and importance of temperature measuring devices in finger replantation surgery?

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Ethics Committee approval was taken from the the University of Health Sciences, Basaksehir Cam and Sakura City Hospital ethical committee (date: 22.06.2022, decision number: 2022.06.192).
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Abstract

Background/Aim: Post-operative circulation monitoring is very important in replantation surgery. Vascular pathologies that occur can be detected and undergo intervention as a result of strict follow-up protocols, thus increasing success rates. Although many alternative methods for circulation monitoring are available, no gold standard for such monitoring exists. This study aimed to find a more reliable and easier method by comparing different temperature measurement methods to facilitate the follow-up of patients who underwent finger replantation after the operation.
Methods: This study was designed as a retrospective case series study. It was conducted between January 2017 and December 2019. Eighteen patients who presented with flexor zone 2 finger amputations and who had undergone replantation surgery were included in the study. The cases were randomly divided into two equal groups. While the finger temperature of the patients in the first group was measured with an indoor/outdoor temperature device, the measurement was obtained using a non-contact infrared thermometer in the second group.
Results: In our study, the mean age of group 1 was 44.33 years, and the mean age of group 2 was 45. Eleven fingers from nine patients in the group 1 and 10 fingers in 9 patients in the group 2 were replanted. All amputated finger replantation were performed. The patients stayed in the hospital for five days, were followed, and treated. The success rate based on living fingers was 54.54% in group 1 and 60% in group 2. The mean measured finger temperatures were 34.12 and 35.76 ℃ in groups 1 and 2, respectively. In group 1, the mean time of measurement was calculated as 4 min 31 s. In the group 2, the mean time of measurement was calculated as 1 s. In the study, two measurement tools were used to determine fingertip temperatures in the two similar groups.
Conclusion: In our study, we found that infrared non-contact temperature measuring devices are both reliable and useful as a heat meter in the follow-up of finger after the replantation operation.

Keywords: Finger replantation, Temperature measuring devices, Follow-up

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Introduction

Today, with the developments in microsurgery and the increase in number of trained surgeons, microsurgery and finger replantation operations can be performed in all major hospitals. Postoperative care is as important and essential as surgical success in replantation surgeries. Unfortunately, physicians working outside of big cities do not have the chance to establish a microsurgery team, and usually only one or two surgeons can work on a provincial basis. The viability and circulatory status of the replanted fingers are generally followed by capillary filling, finger color, turgor, arterial Doppler, measurements of the filling pressure of the pulp, or simply puncturing the fingertip with a needle and measuring bleeding levels [1]. It is obvious that surgeons cannot be at a patient's side continuously. A nurse with good experience in microsurgery case follow-up procedures monitors capillary filling, finger skin temperature, skin color, turgor, and tissue fullness, which are indicators of finger circulation after replantation surgery, and warns the surgeon when necessary. In cases in which frequent nursing rotations occur in the ward, the need to simplify these findings, learn to evaluate the condition of the finger, and facilitate decision-making is present. Capillary filling, finger color and temperature are easily measurable findings, but they are subjective. Measuring finger temperature during follow-ups yields the most accurate information about circulation in the finger [2]. It is not possible to follow up without understanding the use of different temperature measuring devices and correct measurement methods. This study aimed to find a more reliable and easier method to monitor finger temperature by comparing different temperature measurement methods to facilitate the follow-up of patients who underwent finger replantation after the operation [3]. It was seen that no current literature concerning this topic is available, and it is thought that our study with current temperature measuring instruments will contribute to the replantation-related literature.

Materials and methods

This study was conducted retrospectively between January 2017 and December 2019 after approval from the local ethics committee was received. The study was dated 22.06.2022 and numbered 2022.06.192. The data were collected by the researcher. Between January 2017 and December 2019, 18 patients who had presented with flexor zone 2 finger amputation and undergone replantation surgery were included in the study. The cases were randomly divided into two equal groups. While the finger temperature of the patients in the first group was measured with an indoor/outdoor temperature device (Figure 1), the measurement was made with the non-contact infrared thermometer used routinely in the hospital in the second group (Figure 2). Informed consent was obtained from all individual participants included in the study and complied with the 1964 Helsinki Declaration and comparable ethical standards.

Figure 1: Measurement of finger replantation temperatures with contact probe in group 1

Figure 2: Measurement of finger replantation temperatures with infrared thermometer in group 2

Technical information of devices

1. The indoor/outdoor humidity and temperature measuring device has dimensions of 100 mm × 100 mm × 20 mm with a weight of 98 g. The object measures the temperature of the surfaces between −50~70 °C and measures the body temperature and the temperature of the contact surface with the outdoor temperature measuring probe. It measures the ambient humidity in the range of 10% to 99%. Temperature accuracy s ±1°C, humidity accuracy ±5% relative humidity (rh), temperature resolution 0.1 °C, and humidity resolution 1% rh. The measurement time is not specified.

2. The non-contact infrared thermometer has dimensions of 110 mm × 53 mm × 162 mm (L*W*H) and weight of 147g (battery excluded). It measures the temperature of the object surfaces between 0 and 118°C and measures the body temperature in the area in which it is marked. Measurement time is ≤ 0.8 seconds. Sensitivity is 0.1 °C.

Other circulatory findings, primarily the temperature of our patients, to whom we gave the same treatment and care, were also evaluated during this process. The patients were routinely hospitalized for five days during which time finger temperature, color, and capillary filling were checked every hour. For the two groups with similar characteristics, temperature measurements were obtained from the same body area every hour, the circulation of the patients was monitored, and notes were taken. the patients' temperature measurements always came above 32 °C. It was also considered that the air temperature in the city, including summer, is below 30 ºC, and the temperature of the hospital is around 22 ºC. The mean finger temperature of the patients was calculated by taking the average of all measurements. The duration of the measurements was made by placing the finger pulp sideways in the first group, the largest

possible contact surface was created, and the measurement was then obtained. In the second group, the measurement was made with the finger pulp in the middle of the thermometer measurement window.

Statistical analysis

Data were analyzed using SPSS Version 20.0. For categorical variables, data were summarized as frequencies and percentages. No assumptions were made for missing data. Those variables that showed a statistically significant difference in the univariate analysis were included in the multivariate analysis at $P < 0.05$. The results are presented as odds ratios (ORs), 95% confidence intervals (CIs), and corresponding *P*-values.

Results

In our study, injury characteristics and individual characteristics were similar and homogeneous in the two groups. In our study, the mean age of group 1 was 44.33 years (20.2), and the mean age of the group 2 was 45 (21.5). One female patient was in group 1 and two female patients were included in group 2. Seven right and two left hand injuries were reported in group 1, and six right and three left hand injuries in group 2. Eleven fingers from nine patients in group 1 and 10 fingers in 9 patients in group 2 were replanted. The number of amputations included five index fingers, three ring fingers, one thumb, one middle finger, and one little finger in the group 1, and three middle fingers, three little fingers, two ring fingers, one thumb, and one index finger in the group 2. All amputated fingers underwent replantation surgery. The patients stayed in the hospital for five days and were followed and treated. Circulation was monitored and detected in the replanted fingers of the patients and was followed until the day of discharge. At the first follow-up session, stump revision was performed on necrotic fingers, which were found to have no circulation in the finger. The success rate was 54.54% in group 1 and 60% in the group 2 based on the number of living fingers. The mean measured finger temperature was 34.12 (0.2) °C in group 1 and 35.76 (0.9) °C in group 2. In group 1, the mean time of measurement was calculated as 4 min 31 s. In group 2, the mean time of measurement was calculated as 1 s (Tables 1, 2). Contact measurement temperature was controlled by non-contact measurement in four randomly selected patients in group 1. Accordingly, it was observed that the contact measurement was between 0.9 and 2.1 °C and showed an average of 1.64 °C underestimation. This finding was interpreted as an effect of the cylindrical metal probe because one surface of the metal probe touches the finger, while the larger surface does not; it is also affected by low ambient temperatures.

Table 1: Group 1 measurements with external contact measuring device

Age	Gender	Finger	Temperature	Measurement time	Success Status
24	Male	Ring	34.3	4 min	Unsuccessful
26	Female	Index middle Ring	34.0	4 min 10 s	Unsuccessful Successful
44	Male	Little	34.3	4 min 30 s	Successful
45	Male	Index	34.7	5 min	Unsuccessful
18	Male	Index	34.6	4 min 15 s	Successful
60	Male	Index	32.0	5 min 5 s	Successful
68	Male	Ring	34.2	5 min 40 s	Successful
74	Male	Index	34.8	4 min	Successful
40	Male	Thumb	34.2	4 min 25 s	Successful

Table 2: Group 2 measurements obtained with an infrared non-contact measuring device

Age	Gender	Finger	Temperature	Measurement time	Success Status
65	Male	Little	35.2	0.8 s	Unsuccessful
51	Male	Ring	35.3	0.8 s	Unsuccessful
19	Male	Middle	35.9	0.8 s	Unsuccessful
51	Male	Thumb	36.2	0.8 s	Successful
23	Male	Index middle	35.8	0.8 s	Unsuccessful
55	Female	Ring	35.9	0.8 s	Successful
44	Male	Little	35.2	0.8 s	Successful
62	Female	Little	36.1	0.8 s	Successful
35	Male	Middle	36.3	0.8 s	Successful

Discussion

The first replantation surgery was performed by the team of Ronald Malt in 1962 with brachial artery repair on a 12-year-old who needed arm replantation at the proximal humerus level. Following this case, Kleinert revascularized the partial finger amputation in 1963, and Zhong Wei Chen replanted an amputation at the distal forearm level of a machinist patient under loop magnification. The first finger replantation was performed by Komatsu and Tamai in 1965. After these successful surgeries, the subject of monitoring these limbs and revision in case of arterial or venous insufficiency began to be discussed [1, 2].

The first thermometer dates to Ancient Greek history and works according to the principle of expansion of air from heat. They discovered the “air thermoscope”, a temperature measuring device that traps air. The medical thermometer was also invented by Galileo Galilei toward the end of the 1500s and called the “water thermoscope”. An Italian physician made a mm gradation on the thermometer of that day and began to accurately measure the temperature of the patients. The ue of infrared temperature measuring devices became widespread after The American Society for Nondestructive Testing accepted it as a standard test in 1992 [2].

The temperature of the replanted finger and the temperature of the adjacent control finger were monitored in a 1977 study, and three poor prognostic criteria were identified: (1) the temperature of the replanted finger between the fingers by more than 2.5 °C lower than the other, (2) the temperature of the replanted finger is below 30 °C for more than 1 h, and (3) the replanted finger was below 30 °C when no apparent problem existed. During the hospitalization period, the finger temperature of our patients was at least 32 °C and the highest was 36.3 °C. Since problems developed after discharge in unsuccessful cases, it is not possible to give a valid reason for such an occurrence [1].

In a 1982 article by Okutsu (in Japanese), it was reported that as a result of temperature measurements and follow-ups starting in 1974, they warmed the limb with an electric blanket to provide peripheral circulation after replantation surgery and free tissue transplants [2]. They found that the critical temperature for circulation is 32 °C, and if the replant temperature is below this temperature, blockage in the vessels occurs. They stated that the temperature was the same as the armpit temperature in 80% of the replantation patients and 90% of the free tissue transplants. Based on these limits, they developed a device consisting of a thermistor and a resistance bridge to be used in microsurgery case follow-ups. The device consisted of the thermistor and the device in contact with the flap or finger. They set the device to 32.1 (0.3) °C so that when the temperature was above this value, the blue light would light up,

and when the temperature dropped below the set degree, both the red light would light up, and it would make a buzzing sound. According to Okutsu, clinical examination findings, such as skin color of the finger and capillary filling are subjective [2]. Hence, he stated that these parameters are not always reliable. In our cases, the patients were followed up with an interval of 1 h between evaluations, and the temperature did not fall below 32 °C during the hospitalization period in any of the patients.

In the study of Lu et al. in 1984, 153 of 154 replantation surgeries that were above 32 °C survived [3]. Necrosis occurred in 22 of 26 cases at 32 °C and below. To investigate the critical temperature for successful surgeries, the best temperature for finger survival between 31 and 33 °C was investigated at 0.1 °C intervals. They reported that a skin temperature of 32 °C and above after the finger replantation operation was the best prognostic finding. This study revealed that finger temperature monitoring is effective in replant survival and is the best indicator of circulation.

Aihara et al. [4] described the use of an adherent skin surface temperature indicator by evaluating it in their study in 1993. This method, in which the circulation is understood based on a color indicator, is not available in every country and has an extra cost. The biggest shortcoming is that the adjusted color change scale does not give clear temperature information.

Along with technological developments, the use of more sophisticated devices, such as laser Doppler flowmeter and implantable Doppler also in use. In the review by Karina et al. [5], the methods preferred by surgeons in developed countries were investigated: “It showed that in the United States, 151 surgeons interested in microsurgery preferred the monitoring technique, while 56.1% used hand Doppler, 22% implantable Doppler, and 16.6% tissue oximetry. Similarly, it showed that less than 20% of 148 microsurgery surgeons in the UK routinely used such devices in clinical evaluation. However, the implantable Doppler system, Laser Doppler flowmetry (LDF) and Near-infrared spectroscopy (NIRS) are methods that are reported to detect flap failure earlier than conventional methods. Therefore, these appear to be the best monitoring techniques for most flaps at this time. Moreover, implantable Doppler and microdialysis showed a successful usage in embedded flaps. However, head-to-head comparisons of different monitoring techniques are required to better and more thoroughly evaluate which technique or combination of techniques is most appropriate for each flap type.” As can be understood from the quote, these methods are more expensive and more complex.

In our study, we sought an easy-to-teach and safe method for surgeons who cannot follow patient follow-up with a hand Doppler or other methods due to other duties in the hospital and due to the low number of surgeons in developing countries.

In a study by Smith et al., measured temperature and oxygen saturation in the dorsal middle phalanx in replanted fingers in the middle and both ends of the alternating flap in free flap surgery using a Copenhagen radiometer and Clark-type electrode equipment by adhering the electrodes with adhesive tape [6]. No information about this method in patients with advanced age finger replantation and free flap, chronic obstructive pulmonary disease (COPD), or similar patients with low oxygen saturation in the blood is available. However, it would be very difficult to obtain these measurements in Ishikawa subzones and flexor zone 2, since the electrodes cannot be adhered to such a small area. Difficulties in applying this method in replants that are constantly bleeding exist. In our study, contact and non-contact temperature measurements may vary according to a patient’s condition, and these devices can be inexpensive and easy to use. Uncomplicated follow-up methods can be performed and measured by the nurse without the need for a physician to be present.

Working with a wireless thermometer on intact fingers, Ruopsa et al. [7] stated that this type of thermometer may be useful, but no study has been done regarding its use in replantation surgeries or injured tissue. It does not give any information and experience about clinical applications. In this study, we revealed the difference between fever measurement methods and emphasized which parameters should be considered when using one method in cases in which the other method is not available, not as a way to emphasize the use of one method over the other.

We saw that the infrared non-contact temperature meter, which we used in the follow-up of the patients, showed lower temperature when it was not used in the correct area. Therefore, during surgery, the skin on the arterial anastomosis trace was marked, and the temperature was measured from that area. It was understood that the measurements with the contact probe measuring the outdoor temperature can differentiate temperatures by 1.63 °C on average. Furthermore, the average time to measure temperature with this method was 4 min 31 s. It was necessary to wait an extra 20–30 s to make sure the thermometer showed the final temperature. Since capillary filling and finger color are subjective findings, they are not always reliable as Okutsu [2] stated. Measuring temperature is the best objective finding. In our study, hourly measurements were not below 32 °C, and revision surgery was not required. In the literature, no current article on our research topic could be found. The discussion was made with the publications that are available and whose data are still considered up-to-date.

Limitations

The limitation of this study was the small sample size.

Conclusion

In our study, we found that infrared non-contact temperature measuring devices are both reliable and useful. The usage of non-contact infrared thermometers guided by red light will show more accurate temperature in marked replant follow-up. Contact temperature measuring instruments can be used as an alternative and can be kept in mind as a device that measures less than 1.63 °C temperature. As a result of this study, it was understood that it can be easily learned to measure the skin-marked replant temperature with a non-contact thermometer.

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Evaluation of intravenous zoledronic acid-induced acute-phase response in the emergency department

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Ethics Committee Approval
The ethical approval was obtained from Derince Training and Research Hospital Clinical Research Ethics Committee (date: 10/10/2019, decision number: 2019-89).
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: A temporary influenza-like condition, called acute-phase reaction (APR), is commonly observed with intravenous (IV) administration of nitrogen-containing amino bisphosphonates, such as zoledronic acid (ZOL). This single-center study aimed to evaluate the incidence of APR symptoms after intravenous (IV) ZOL administration in patients with postmenopausal osteoporosis who were admitted to emergency department (ED).

Methods: In this cross-sectional study, 107 osteoporotic patients who were diagnosed with post-menopausal osteoporosis (bone mineral density T-score equal to or below −2.5 with/without prevalent fractures) and who had an ED admission in the first 72 h after intravenous injection of ZOL were included in the study. The patient's pre-treatment blood sample measurements, presenting symptoms (such as fever, fatigue, hyperpyrexia, headache), family history, previous medical treatment, and adverse effects caused by osteoporosis drugs, in addition to information on co-morbidities and comedications were obtained from clinical records.

Results: One-hundred seven osteoporotic patients (19.56%) patients experienced APR and were admitted to the ED after IV-ZOL administration. The mean age was 64.58 (11.15) years (n = 107). The three most commonly reported symptoms were diffuse musculoskeletal symptoms, influenza-like illness, and gastrointestinal symptoms (34.5%, 21.5%, and 18.5%, respectively). Seventy percent of the patients who presented to the ED with APR symptoms were prescribed drugs only, and 30% of the patients received treatment specific for their symptoms in the ED. Most of the diffuse musculoskeletal symptoms consisted of myalgia (22.4%). A positive correlation between the onset time of APR symptoms and the number of IV bisphosphonate (BP) doses was found ($r = 0.597$; $P = 0.032$).

Conclusion: Our study indicates that as the number of IV-ZOL administrations increase yearly in patients with osteoporosis, symptom onset time occurs later. A linear relationship was found between the number of drug applications and the duration of symptoms. Also, the incidence of APR following IV-ZOL administration was 19% in the osteoporotic patient population who presented to the ED or to other clinics according to the symptoms.

Keywords: Zoledronic acid, Acute-phase response, Postmenopausal osteoporosis, Emergency department

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Introduction

Osteoporosis is a common bone disease that represents vertebral and hip fragility fractures associated with an increase in morbidity and mortality [1, 2]. Over a lifetime, it is considered that 30% of women and 15% of men will be exposed to a fracture associated with osteoporosis [3, 4]. Thus, early diagnosis of patients at risk and suitable treatment in affected patients is compulsory [2, 3].

Bisphosphonates (BP), synthetic analogues of bone mineralization, and regulator pyrophosphates have been associated with remarkable clinical increases in bone mineral density, suppression of bone-turnover markers, and reduction of vertebral fractures [5–7]. Both types of compounds both effective, well-tolerated drugs that are considered as a standard treatment choice for osteoporosis, and available in both oral and intravenous (IV) formulations [8]. Amino-bisphosphonates (alendronate, ibandronate, risedronate, and zoledronate), which contain nitrogen in their structure, inhibit farnesyl diphosphate synthase. This inhibition results in impedance of cell signaling [9] and rapid production of pro-inflammatory cytokines, such as tumor necrosis factor and interleukin 6 (TNF-α and IL-6) [10].

The temporary influenza-like condition caused by a transient increase of proinflammatory cytokines is called acute-phase reaction (APR), which is rarely observed with oral administration, but commonly observed after intravenous (IV) administration of nitrogen-containing amino bisphosphonates, such as zoledronic acid (ZOL) or ibandronic acid [11]. APR appears to be caused by the rapid and transient release of proinflammatory cytokines from circulating T-cells [11]. It frequently occurs in the first dose of treatment within 24 to 72 h after IV administration, and its intensity gradually decreases after subsequent doses of IV BP treatment [12–14]. APR manifests with fatigue, malaise, low-grade fever, myalgia, and arthralgia symptoms, which resolve within 3 to 14 days [8, 15–17]. Symptoms disappear usually without treatment or sometimes with the use of anti-inflammatory or antipyretic drugs [18].

ZOL is a potent, novel bisphosphonate that is administered via a IV route once per year [19]. It was approved in August 2007 for the treatment of postmenopausal osteoporosis [10]. APR symptoms, such as fever and a flu-like syndrome, are frequently observed after IV administration of ZOL [20]. Based on safety data from clinical trials performed in different countries, the incidence of APR varies between 46.8% and 54.3% after a patient receives an IV injection of ZOL [17, 21]. It is thought that race may be a significant factor in the development of APR. Non-Japanese Asians and Pacific Islanders have the highest risk [13]. In a postmenopausal osteoporosis study performed with a small patient population in Turkey, APR was observed in 2 of 38 (5.2%) patients who received IV ZOL [22].

When the literature was analyzed, a few studies were found addressing APR from different countries and populations. Although growing awareness of post-treatment IV BP-associated APR in postmenopausal osteoporosis among the general public around the world is ongoing, we have little knowledge about the incidence of APR in the Turkish osteoporotic patient population.

Therefore, this present single-center study aimed to evaluate the incidence of APR symptoms after IV ZOL treatment in patients with postmenopausal osteoporosis. The second aim was to determine the awareness, knowledge, and treatment skills of emergency department (ED) physicians in terms of APR symptoms.

Materials and methods

Study design and population

In this cross-sectional, single-center study, we analyzed data from patients who were admitted to the ED of State Hospital between September 1, 2019, and September 1, 2020 due to symptoms of APR after IV administration of ZOL. The records of patients who were diagnosed with postmenopausal osteoporosis from internal medicine, physical therapy, and orthopedic clinics and prescribed IV ZOL were obtained from the hospital program named “SARUS”. Also, the patient’s pre-treatment blood sample measurements, presenting symptoms (such as fever, fatigue, hyperpyrexia, headache), family history, previous medical treatment and adverse effects caused by osteoporosis drugs, in addition to information on co-morbidities and comedications were available from clinical records of the SARUS hospital program. Health records and drug reports for the last six months were obtained by examining the ‘Med-eczane’ and ‘E-nabız’ systems.

The measured laboratory parameters included several indicators: (1) serum calcium, phosphate, and creatinine; (2) serum alkaline phosphatase (ALP); (3) serum 25-hydroxyvitamin D (25[OH]D); (4) serum parathyroid hormone (PTH); (5) C-reactive protein (CRP); (6) white blood count (WBC); and neutrophil and lymphocyte counts and neutrophil/lymphocyte ratio (NLR). Patients with a baseline level of 25(OH)D above 30 ng/mL were considered as vitamin D normal, those with a level between 20 and 29 ng/mL were considered as vitamin D insufficient, and patients with levels below 20 ng/mL were deemed to be deficient [23].

Acute-phase response is defined as the presence of fever (body temperature > 38°C) or the presence of at least one other APR symptom. Also, symptoms considered to be very similar were grouped (for example, pyrexia and raised body temperature were pooled as fever, myalgia, cramps, arthralgia, bone and musculoskeletal pain were pooled as diffuse musculoskeletal pain, nausea, vomiting, dyspepsia, anorexia and decreased appetite were pooled as gastrointestinal issues, headache, dizziness, fatigue, vertigo, nasopharyngitis and malaise were grouped as a flu-like syndrome, and uveitis, episcleritis, conjunctivitis, eye inflammation, eye irritation, eye pruritus and ocular hyperemia were pooled as eye inflammation).

Patients who were diagnosed with postmenopausal osteoporosis as defined by the available disease definition suggested by the World Health Organization as an aerial bone mineral density (BMD) T-score at or below −2.5 that was assessed using dual-energy X-ray absorptiometry (DXA) with/without prevalent fractures and who had an ED admission in the first 72 h after IV injection of ZOL were included in the study.

A physician blinded to the study telephoned the patients who met the criteria for inclusion in the study and questioned

whether or not they had been admitted to the emergency department after IV-zol treatment. If the patients replied "yes", the physician inquired about the types of symptoms on admission in the first 72 h after a ZOL injection. Another physician blinded to the study entered the data and clinical data assessments for the diagnosis of APR.

Patients who were not admitted to the ED after IV injection and received supportive treatment at home or patients who admitted after 72 h after the injection were excluded from the study. Patients were also excluded if they had one more of several conditions: (1) any bone and mineral disorders other than osteoporosis (such as osteogenesis imperfecta, multiple myeloma, hyperparathyroidism, Paget's disease, fibrous dysplasia, metastatic bone tumors), (2) if they were regularly using anti-inflammatory medicines, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressives for rheumatologic disorders; (3) if they had previously used parathyroid hormone, strontium, or sodium fluoride; (4) if they used or were using anabolic steroids for the last six months; and (5) if they were diagnosed as having any other organic pathology that could explain their symptoms. Also, patients with repeated ED or symptom-associated outpatient admissions within three days and patients who did not want to answer APR questions, and/or patients whose data cannot be obtained from "E- nabız" or 'Med-eczane' systems were excluded from the study.

Ethical approval

The local Ethics Board approval was taken from the study Derince Training and Research Hospital Clinical Research Ethics Committee (date: 10/10/2019, decision number: 2019-89) and The study was performed in accordance with principles of the Declaration of Helsinki.

Outcomes

In this study, our primary outcome was to determine the frequency and variety of symptoms of patients who were diagnosed with osteoporosis who were admitted to the ED with APR syndrome after IV ZOL administration. The second outcome of our study was to investigate knowledge, awareness, and treatment skills concerning ZOL-induced APR of ED physicians.

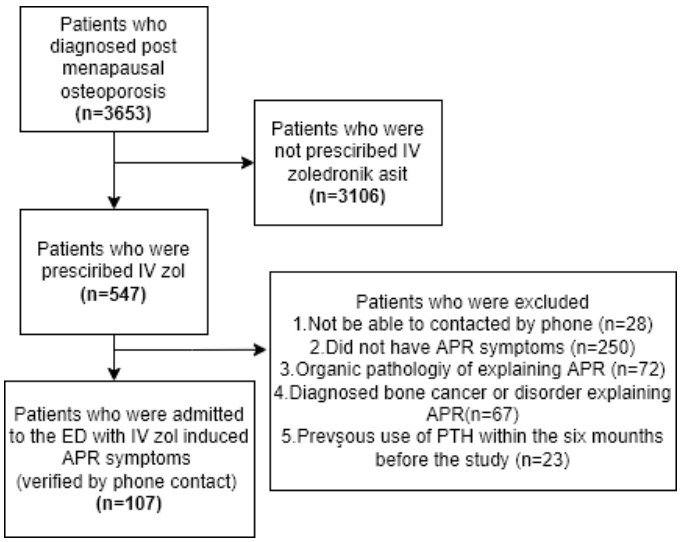
Statistical analysis

Statistical analysis was mainly performed using the Predictive Analysis Software (PASW) statistical software (version 18.0; SPSS™, Chicago, IL). Data for quantitative variables were described as mean (standard) error of the mean. Data for categorical variables were described as numbers and/or percentages. Correlations between variables were evaluated using Spearman's correlation test. All tests were two-tailed, and $P < 0.05$ was considered significant. The sample size of the study was calculated using the G*Power 3.1 program. Reaching 80% power and adding a 20% patient loss, 100 patients had been planned to be included in the study with data obtained from the previous study [13].

Results

A total of 3653 patients who were diagnosed as having postmenopausal osteoporosis in the Internal Medicine, Physical Therapy, or Orthopedic clinics of the state hospital between September 1, 2019, and September 1, 2020, were included in the study. Five-hundred forty-seven (14.97%) out of 3653 patients were prescribed IV ZOL. Four-hundred forty patients were excluded because they could not fulfil the inclusion criteria; thus, 107 patients were included in the final analysis (Figure 1).

Figure 1: Flow chart



First, these 107 patients (19.56%) patients experienced APR symptoms and were admitted to the ED after IV-ZOL administration. All patients were women, and their mean age was 64.58 (11.15) years. BMD t-score of the lumbar spine was lower than the femur neck t-score (−2.5 [0.62] versus 1.96 [0.75]). In 33.3% of the patients, symptoms of APR started on the first day of IV administration. Ninety-nine patients (92.5%) had no previous history of oral bisphosphonate use. APR symptoms were observed in 69 (64.5%) patients after the first dose of IV ZOL.

The patient's data of prior IV BP therapy, age, BMD t-scores, laboratory parameters in serum, and white blood cell (WBC) counts, and percentage of patients previous IV or oral BP use are presented in Table 1. Except for 25(OH)D values, counts of serum parameters and WBCs were determined to be within normal limits. 25(OH)D levels were found to be 29.23 (16.54) ng/mL and within the insufficiency range of 20 to 29.9 ng/mL.

Table 1: Baseline characteristics of the study population of 107 patients

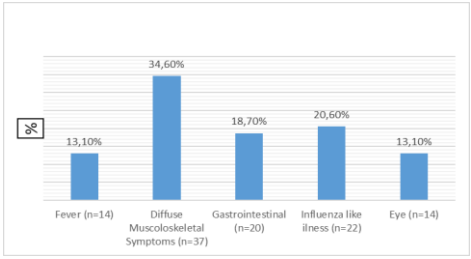
	Mean (SD)	Median	Min–Max
Age(years)	64.58 (11.15)	63	45–90
Bone Mineral Density			
Lumber vertebrae L1-L4 (t-score)	-2.5 (0.62)	2.6	0.3–4.2
Femur neck (t-score)	-1.96 (0.75)	2.1	0.1–3.5
Lab parameters in serum			
25OH-D ng/mL	29.23 (16.54)	25	4.7–85.8
Calcium mg/dL	9.32 (0.49)	9.3	8–10.4
PTH pg/mL	67.02 (36.23)	62	29.5–342
ALP U/L	68.95 (18.04)	69	27–105
Phosphate mg/dL	3.42 (0.55)	3.42	1.7–4.63
Creatinine mg/dL	0.77 (0.19)	0.75	0.02–1.58
CRP mg/dL	0.72 (1.03)	0.46	0.08–9.4
Lab parameters in white blood cell counts			
WBC µL	6519.31 (1621.82)	6500	1930–9940
Neutrophil µL	3875.04 (1424.81)	3590	1150–8570
Lymphocyte µL	1997.67 (794.10)	1900	340–4100
N/L ratio	1012.20 (6060.33)	1.94	0.68–44075
	n (%)		
The onset time of APR symptoms			
First day	36 (33.3)		
Second Day	35 (32.4)		
Third Day	36 (33.3)		
Previous history of BP use (oral)			
Yes	8 (7.5)		
No	99 (92.5)		
The number of IV BP administration			
1st	69 (64.5)		
2nd	30 (28)		
3rd	8 (7.5)		

*Normal range of 25(OH)D: 14-60 ng/mL, Calcium (Ca) 8.8-10.6 mg/dL, PTH: 12-88 pg/mL, ALP: 30-120 U/L, Phosphate (P): 2.3-4.7 mg/dL, Creatinine (Cr): 0.6-1.1 mg/dL, CRP: 0-0.5 mg/dL, WBC: 4-10 $x10^3$/µL, Neutrophils: 2-7 $x10^3$/µL, Lymphocyte: 0.8-4 $x10^3$/µL. h: hours, WBC: white blood count; CRP: C-reactive protein, ALP: alkaline phosphatase, PTH: parathyroid hormone, 25(OH)D:25-hydroxyvitamin D3, N/R ratio: Neutrophil/Lymphocyte ratio; Min: minimum, Max: Maximum

Seventy-eight (72.9%) patients had no fractures, but 22 (20.6%) patients had one, and seven (6.5%) patients had more than one fracture associated with osteoporosis. NSAIID drugs had been prescribed together with IV-ZOL in 99 (89.7%) of the women's treatment regimens.

The three most frequently reported symptoms were diffuse musculoskeletal symptoms, influenza-like illness, and gastrointestinal symptoms (34.5%, 21.5%, and 18.5.%, respectively). Eye symptoms and fever were seen in equal ratios. They were the two least common symptoms (13.1%) as shown in Figure 2.

Figure 2: Distribution of the main acute-phase response (APR) symptoms



Most of the diffuse musculoskeletal symptoms consisted of myalgia, and most of the influenza-like illness symptoms consisted of nasopharyngitis (22.4% and 13.1%, respectively) as shown in Table 2.

Table 2: Occurrence of acute-phase response symptoms within three days of IV-ZOL treatment

	n (%)
Fever	14 (13.1)
Diffuse Musculoskeletal Symptoms	37
Myalgia	24 (22.4)
Arthralgia	13 (12.1)
Gastrointestinal	20
Dyspepsia	13 (12.1)
Gastroenteritis	6 (5.6)
Nausea	1 (0.9)
Influenza-like Illness	22
Headache	3 (2.8)
Malaise	2 (1.9)
Vertigo	4 (3.7)
Nasopharyngitis	13 (13.1)
Eye	14
Eye inflamation	6 (5.6)
Allergic conjunctivitis	8 (7.5)

Seventy percent of the patients who presented to the ED with APR symptoms were prescribed drugs only, and 30% of the patients received treatment specific to their symptoms in the ED (Table 3).

Table 3: Treatment skills of emergency department physicians

	n (%)
Prescribed drugs only	70 (65.4)
Antipyretic drugs	11 (10.3)
Paracetamol tablets	3 (2.8)
Pseudoephedrine tablets	6 (5.6)
Paracetamol+Codeine phosphate	2 (1.9)
NSAIDs	26 (24.3)
Ibuprofen tablet	6 (5.6)
Dexketoprofen trometamol tablet	8 (7.5)
Diclofenac sodium tablet	3 (2.8)
Ibuprofen gel	2 (1.9)
Diclofenac sodium gel	6 (5.6)
Dexketoprofen trometamol gel	1 (0.9)
Steroids	3 (2.8)
PPI	10 (9.3)
Antivertigo drugs	2 (1.9)
Antispasmotic drugs	4 (3.7)
Intraocular treatments (droplets, creams)	14 (13.1)
Symptomatic treatment in the ED	37 (34.6)
IM injection	11 (10.3)
Diclofenac ampule	8 (7.5)
Prednisolone ampule	3 (2.8)
IV injection	24 (22.4)
Paracetamol vial	5 (4.7)
Metoclopramide ampule	11 (10.3)
Metamizole sodium	8 (7.5)
Nasal treatments	2 (1.9)

ED: Emergency Department, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: Proton pump inhibitors, IM: intramuscular injection, IV: intravenous injection

The three most frequently prescribed drug types were NSAIDs, proton pump inhibitors (PPIs), and antipyretics (24.3%, 10.3%, and 9.3%, respectively).

We found a positive correlation between the onset time of APR symptoms and the number of IV BP doses (P = 0.032) and a negative weak correlation between serum 25(OH)D levels and the onset time of APR. No correlation between BMD scores of lumbar vertebrae and femur, age, lymphocytes, and N/R ratio (P = 0.78) was found (Table 4).

Table 4: Correlation analysis between BMD scores, age, the number of IV BP dose, lymphocytes, NLR, and APR and serum 25(OH)D levels

	The onset time of APR r*	Serum 25OH-D levels r*
The onset time of APR	N/A	-0.223**
Serum 25(OH)D levels	-0.223**	N/A
Lomber vertebrae L1-L4 (t-score)	0.045	-0.038
Femur neck (t-score)	0.106	-0.231
Age	0.01	-0.145
The number of IV BP dose	0.597**	-0.077
Lymphocyte	-0.102	0.042
N/R ratio	-0.054	-0.071

* r Spearman's correlation coefficient, ** P = 0.032 (statistically significant), N/A: Not applicable

Discussion

In this study, we first aimed to investigate the characteristics of patients with osteoporotic symptoms who presented to the ED with APR after IV-ZOL administration and which treatments were administered to these patients by the physicians in the ED. An important finding of study was that the number of IV-ZOL administrations increased yearly in patients with osteoporosis in this Turkish study population, and the time of the appearance of APR symptoms emerged in later. Also, as the second result of our study, we found that the rate of patients who presented to the ED with symptoms of APR after IV-ZOL administration in the osteoporotic patient population was 19%.

Data from clinical trials indicate that the incidence of APR varies between 4.9% and 54.9% [24, 28]. A lower APR incidence was found in patients using IV-IBN and oral BP (4.9% and 5.6%, respectively) [24, 25]. The incidence of APR symptoms was greater in patients with osteoporosis treated with IV-ZOL (41.5%,42.4%, 46.8%, 54.3%, and 54.9% respectively) [13, 17, 21, 26–28]. Due to the lack of a precise definition of APR, the authors based their definitions on a different variety of symptoms when these studies were analyzed [28]. Also, it is easy to follow-up symptoms in studies designed prospectively. Symptom inquiries via phone and informing patients about the symptoms that may be experienced after IV administration by clinicians may contribute to a higher reported incidence of APR in these studies [13, 17, 28]. The relatively low rate in our study may be attributed to reasons. In addition, in a study of 87 patients with similar race, the incidence of APR was found as 5.2% [22]. We are of the opinion that the 19% incidence of APR in the Turkish population should be supported by further prospective studies.

It is confirmed that APR incidence showed a dramatic decline after the second and third infusions [13]. Additionally, previous BP use is known to be one of the protective factors against APR [27]. The present study, whose results parallel the above studies, indicates that as the number of IV-ZOL doses administered increases, the onset of time APR symptoms gradually increases. In other words, a correlation between an increased number of IV doses and the onset time of symptoms

can be found. This situation can also be interpreted as the increase in the number of IV-ZOL doses leads to an increase on patient awareness of APR symptoms, and those whose symptoms do not decrease even after using symptomatic treatment at home may present to the ED.

The present study indicates another relationship between the APR symptom onset time and serum 25OH-D levels. Although we found a weak correlation between these two parameters, the onset time of APR symptoms was earlier in patients with lower serum 25OH-D levels. Amino bisphosphonates, IV-ZOL in particular, can produce an APR by stimulating a transient release of pro-inflammatory cytokines from activated monocytes, macrophages, and γδ-T-cells [18]. It was revealed that IV ZOL treatment induced γδ-T cells to mature toward an interferon (IFN)-γ-producing cell type, which may induce release of more acute-phase proteins, such as CRP and elastase. [18, 29]. Furthermore, 25(OH)D is a potent immunomodulator that plays a role in the inhibitory action on adaptive immunity through inhibiting T cell proliferation, mainly the γδ-T cells that produce IFN-γ and interleukin (IL)-2 and activate macrophages [30, 31].

We are of the opinion that with the decrease in serum 25(OH)D levels, the inhibitory effect on T-cells may be eliminated, and also the positive impact on the increase of T cells of IV-ZOL may be supported. From this point of view, we conclude that in patients with low serum 25(OH)D levels, early and severe APR symptoms resulting in an increase in pro-inflammatory cytokine release may occur after IV-ZOL treatment. The findings of our study did not verify a strong relationship between 25(OH)D levels and the onset time of APR. Further randomized, controlled trials are needed to clarify this relationship based on a strong rationale.

In the present study, we defined APR as a rise in body temperature to > 38 °C or the presence of at least one other APR symptom. Using these conservative criteria, we found that the leading sign of APR was diffuse musculoskeletal symptoms consisting of myalgia and arthralgia, which were reported by 34.5% of the entire patient population with APR symptoms. Consistent with our results, an open-label prospective study found that musculoskeletal symptoms were the most common group among APR symptoms (68.1%) [27].

In contrast to our results, previous trials performed with IV-ZOL have determined the leading sign of APR was fever, ranging from 17.2% to 54.9% [13, 17, 28]. The lack of a clear definition of APR may have created this difference between studies. Additionally, we believe that symptoms of fever may have been detected relatively less in our study population due to deficiencies in vital sign records during the outpatient admission process into the ED.

The APR treatment strategy is another issue to be addressed; in a randomized-controlled study, treatment with acetaminophen or ibuprofen safely and effectively relieved the symptoms of postmenopausal women with osteopenia after a single dose of IV-ZOL [32]. The probability of having APR after IV-ZOL administration may be decreased by using a combination of acetaminophen an another anti-inflammatory agent (commonly paracetamol or ibuprofen) after dosing and continuing for the next three days [13, 15, 33].

We found that paracetamol was prescribed in 9.4% and ibuprofen in 5.6% of patients when all patients admitted to the outpatient or treated in the ED were examined, and our results are in agreement with these studies [13, 17, 32, 33]. We found that pseudoephedrine tablets and metamizole sodium ampules were given more in the antipyretic drugs group, and dexketoprofen trometamol tablets and diclofenac ampules were administered more in the NSAID group.

We suppose that the reason why wide variety of NSAIDs and antipyretic drugs are preferred instead of paracetamol or ibuprofen in the treatment of APR may be due to a number of factors: (1) ED physicians do not consider patients' symptoms as APR, (2) they do not have sufficient awareness about the symptoms and treatment of APR, and (3) patients are not treated by the same physicians.

We indicate that prospective, multicenter, and controlled studies involving data from a large cohort of patients are needed to confirm our findings concerning the relationship between APR onset time, IV-BP dose, and 25(OH)D.

To the best of our knowledge, the present study is one of the first studies to reveal the incidence of APR in a Turkish osteoporotic population. Also, we consider that this study is the first of several steps toward conducting more extensive studies to address the relationship between the onset of APR symptoms and the dose of IV BP and 25(OH)D, and to examine the treatment patterns of physicians in the ED.

Strengths and limitations

This present study's results should be considered within the bounds of its strengths and limitations. First, errors may arise from the incomplete recording of the clinical data, which might not have been eliminated because our retrospective findings are based on data collected from clinical reports. Second, due to the lack of a control group, the exact incidence of APR is uncertain. Third, because our study was not multicenter, it may have been biased in determining the incidence of APR. Finally, in our study, we included the pre-treatment blood samples of the patients. Blood samples could not be obtained from all patients at the time of onset of APR and the first month post-treatment, so this information could not be included. Collecting blood samples from before treatment, at APR onset time, and first-month post-treatment may help in clarifying the relationship between 25(OH)D, IV BP dose, and APR onset time of symptoms.

Conclusion

Our study indicates that as the number of IV-ZOL administrations increases yearly in patients with osteoporosis, symptom onset time occurs later. A linear relationship was found between the number of drug applications and symptom duration. Also, the incidence APR following IV-ZOL administration was 19% in the osteoporotic patient population who presented to the ED or other clinics according to the symptoms. The mechanisms underlying the IV-ZOL dose number and the onset time of APR warrants further investigation.

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