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Our experiences with carotid artery endarterectomy operations

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ABSTRACT

Aims: In this retrospective study, we aimed to present our experiences with patients undergoing carotid endarterectomy (CEA) operations.

Methods: Between January 2011 and January 2021, a total of 88 patients (27 female, 61 male, mean age; 68.9±8.7 and 41-88 years old) who underwent CEA were included in the study. Patients' files were reviewed. Bilateral CEA was performed in 2 of the patients. The complaints and demographic characteristics of the patients are shown in Table 1 and Table 2, respectively. Coronary artery bypass grafting (CABG) was also performed in 10 (8 of them simultaneously and 2 of them 1 month later) of the patients. In one of these simultaneously operated patients, aortic valve replacement was performed in addition to CEA and CABG. On the other hand, the operation was terminated due to the development of intraoperative sudden cardiac arrest in 2 patients.

Results: Polytetrafluoroethylene patch, biological patch, dacron patch, and great saphenous vein patch were used in 1, 1, 3, and 40 patients, respectively, while the CEA site was primarily closed in 43 patients. Characteristic features of the CEA operations are shown in Table 3. Also, complications of CEA surgery are shown in Table 4. In-hospital mortality was detected in 3 patients.

Conclusion: The early results of our CEA operations are in line with the literature.

Keywords: Carotid endarterectomy, carotid artery occlusion, stroke

INTRODUCTION

Extracranial carotid artery stenosis which is caused by atherosclerotic plaque usually exists in carotid artery bifurcation. It is the progressive narrowing disease of the carotid arteries day by day. Thus, it gradually reduces the blood flow to the brain. Since carotid artery stenosis causes stroke due to ischemic infarction, it has the potential to seriously worsen the patient's quality of life.¹

In the present time, as the population gets older, carotid artery stenosis becomes a more important and common problem.² It can cause devastating effects in patients. When a stroke happens, the developing symptoms vary depending on the affected area and occur due to hypoperfusion and embolism.¹ It is known that stroke is the second most common cause of cardiovascular death and the most common cause of fatal neurological event.³ Carotid endarterectomy (CEA) is a surgical procedure to remove the endothelium and atherosclerotic plaque from the inner wall of the carotid artery.⁴ CEA operation which is a highly important surgical procedure reduces the incidence of stroke in patients with critical carotid stenosis.⁵

In this study, we aimed to present our experiences with

patients undergoing CEA operations. Patients' complaints, comorbid conditions, surgical techniques and CEA results were investigated.

METHODS

Between January 2011 and January 2021, a total of 88 patients (27 female, 61 male, mean age; 68.9±8.7 years; range 41-88 years old) who underwent CEA were included in this single-centre, retrospective study. Data were collected using the patient records. The study protocol was approved by the Samsun Training and Research Hospital Ethics Committee (Date: 24.02.2021, Decision No: 2021/4/8). The study was conducted in accordance with the principles of the Declaration of Helsinki. When the patient with asymptomatic ($\geq 70\%$ stenosis) or symptomatic ($\geq 50\%$ stenosis) carotid artery stenosis was admitted to our clinic, the patient was interrogated preoperatively and prepared for the operation. Treatment of comorbid diseases was also started.

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The complaints and demographic characteristics of the patients are shown in Table 1 and Table 2, respectively.

Table 1. Complaints of the patients

Complaints of the patients	Number	Percentage (%)
Hemiplegia or hemiparesis	27	30.6
Vision lost (Amaurosis fugax)	3	3.4
Dizziness and balance disorder	34	38.6
Syncope	7	7.9
Amnesia	1	1.1
Transient ischemic attack	5	5.6
Speech disorder	5	5.6
Stubborn headaches	1	1.1

Table 2. The demographic characteristics of the patients.

Characteristics of the patients	Number	Percentage (%)
Diabetes Mellitus	7	7.9
Smoking	19	21.5
Hyperlipidemia	8	9.0
Hypertension	18	20.4
Coronary artery disease without any coronary artery intervention history	12	13.6
Obesity	1	1.1
Chronic obstructive lung disease	7	7.9
Heart failure	1	1.1
Peripheral artery disease	10	11.3
Chronic renal failure	4	4.5
Alzheimer's disease	1	1.1
Bilateral carotid artery disease	11	12.5
Hypothyroidism	3	3.4
Hyperthyroidism	1	1.1
Male	61	69.3
Female	27	30.7
History of CABG	6	6.8
History of coronary artery stenting	4	4.5
Epilepsy	1	1.1
Age (mean $\pm$ SD years)	68.9 $\pm$ 8.7	

CABG: coronary artery bypass grafting, SD: standard deviation.

Surgical Technique

The patients were operated on under general anaesthesia except for three patients who were operated on under local anaesthesia and sedation. As a prophylactic antibiotic, 1 gram of cefazolin sodium was administered intravenously at the beginning of the operation. With the exception of one patient (a 44-year-old female patient with aesthetic concerns underwent a transverse incision), a standard longitudinal incision parallel to the sternocleidomastoid muscle was performed. When autologous great saphenous vein (GSV) was used as a vein patch, the harvesting of GSV was performed as well.

Internal, external, and common carotid arteries were explored and suspended with Silastic slings after incision. Cross-clamps were placed as usual after 1 ml (5000 IU) of heparin was administered intravenously. Cross-clamp time was 36.3 $\pm$ 9.7 minutes, and heparin neutralization was not performed. A carotid shunt was not used except in 2 patients. Conventional

CEA was performed and then polytetrafluoroethylene (PTFE) patch, biologic patch, dacron graft patch and GSV patch were used in 1, 1, 3, and 40 patients, respectively. In contrast, the CEA site was primarily closed in 43 patients. Cross-clamps were released. A hemovac drain was placed in the CEA incision site. In all patients, incisions were managed for bleeding and were completely closed. Characteristic features of the CEA operations are shown in Table 3.

Table 3. Characteristic features of the CEA operations

Characteristic features of operations	Number	Percentage (%)
Great saphenous vein patch	40	45.4
Dacron graft patch	3	3.4
PTFE graft patch	1	1.1
Biologic graft patch	1	1.1
Primary closure	43	48.8
Left side CEA	42	47.7
Right side CEA	44	50.0
Bilateral CEA	2	2.2
Local anaesthesia and sedation	3	3.4
General anaesthesia	85	96.6
Longitudinal incision	87	98.9
Transverse incision	1	1.1
Carotid shunt application	2	2.2
Cross clamp time (mean $\pm$ SD minutes)	36.3 $\pm$ 9.7	

SD: Standard deviation, CEA: Carotid endarterectomy, PTFE: Polytetrafluoroethylene

While the patients who received local anaesthesia and sedation were transferred to the ward, the others who received general anaesthesia continued to be followed up in our intensive care unit after surgery. Then they were also transferred to the ward when their general condition improve and their vital signs became stable.

In one patient, oral warfarin sodium was initiated on day 1 after the surgery with low-molecular-weight heparin (LMWH) therapy and overlapped until the desired INR reached (between 2,0-3,0), the LMWH was discontinued later. The exception of that patient, all patients were treated with LMWH and a single antiplatelet drug after the extubation on the day of surgery and they were treated with dual antiplatelet therapy subsequent days. Patients who could not be extubated on the same day (8 patients) received antiplatelet drugs via a nasogastric tube. Patients who underwent surgery were called to the outpatient department for follow-up.

Statistical Analysis

In this study, statistical analysis was performed using the Microsoft Excel version 2013 software (Microsoft Corp., WA, USA). Descriptive data were expressed in mean $\pm$ standard deviation (SD), median (minimum-maximum) or number and frequency.

RESULTS

Bilateral carotid artery stenosis was detected in 11 patients. One and two had a history of carotid artery stenting (CAS) and CEA, respectively. In two patients with bilateral critical carotid artery stenosis among these patients, bilateral CEA was performed with an interval of two weeks. In these patients, priority was given to the symptomatic side. As well, left-sided CEA was performed

in 42 patients and right-sided CEA was performed in 44 patients. On the other hand, sudden unexpected cardiac arrest developed intraoperatively in 2 patients during exploration of the carotid arteries and cardiopulmonary resuscitation (CPR) was performed. The operation was terminated after response to CPR. They were discharged after being advised to apply to neurology and cardiology clinics.

While 6 of the patients had a history of coronary artery bypass grafting (CABG), 4 patients had a history of coronary stent placement, one had mitral valve repair due to mitral insufficiency. CABG was also performed in 10 patients (CABG was simultaneously performed in 8 of them and CABG was performed in 2 of them 1 month later after CEA). In one of these simultaneously operated patients, aortic valve replacement was performed in addition to CEA and CABG. Apart from these patients, it was determined that 12 more patients received medical treatment for coronary artery disease and 1 patient for congestive heart failure and rhythm problems. This latter patient also had an ICD and this ICD was temporarily stopped preoperatively. It was activated as a result of the cardiology consultation again before the patient's discharge.

Postoperative atrial fibrillation and sinus tachycardia were observed in 5 patients and 1 patient, respectively. These rhythm abnormalities and hypotension responded to drug treatment. Also, postoperative myocardial infarction (MI) was detected in 6 patients and medical treatment was applied in 5 patients, while percutaneous coronary intervention (coronary artery stent implantation) was performed in the last patient who had a history of coronary artery disease.

Hematoma at the CEA incision site was observed in 6 patients in the early postoperative period, 3 of them were re-operated and hematoma drainage was performed with bleeding control. On the other hand, the hematoma was observed at the GSV harvest site (the saphenectomy site) in 5 patients, 1 of them was re-operated and hematoma drainage was performed. The hematomas that did not require intervention were resolved over time with medical treatment.

Twenty-seven patients had preoperative hemiplegia and new monoplegia of the upper extremity developed in the two of them (2.2%) in the early postoperative period. Also, a new epileptic seizure developed in the early postoperative period in 1 (1.1%) patient and this patient was treated with medicines that were arranged by neurology consultation.

In 5 patients with a history of hypertension, the antihypertensive treatments they received in the early postoperative period were not sufficient, and it was necessary to switch from dual drug therapy to triple antihypertensive therapy. In addition, newly detected hypertension developed postoperatively in one patient.

Cranial nerve injury was noted in 7 patients in the early postoperative period. In 3 patients, the tongue slipped to the ipsilateral side while the tongue was protruding from the mouth, and these patients had varying degrees of hoarseness, difficulty speaking, difficulty chewing and swallowing. These patients recovered within six months. In addition, two patients were found to have transient dysphagia, and one of them also had transient hypoesthesia in the ipsilateral angle of the mandible. Other findings of nerve damage were transient hoarseness and transient ipsilateral drooping of the lower half of the lip along with pallor in the nasolabial sulcus and were observed in one patient each. Unlike the others, these patients recovered within three months. Postoperative complications are shown in Table 4.

Table 4. Postoperative complications

Postoperative complications	Number	Percentage (%)
Transient ischemic attack	1	1.1
Monoplegia	2	2.2
Atrial fibrillation	5	5.6
Acute renal failure	2	2.2
New onset epileptic seizure	1	1.1
Postoperative myocardial infarction	6	6.8
Prolong entubation	5	5.6
Wound infection	1	1.1
Cranial nerve injury	7	7.9
Postoperative hypertension (new onset/ uncontrolled)	1/5	1.1/5.6
Hematoma (carotid artery site/ saphenectomy site)	6/5	6.8/5.6
Sinus tachycardia	1	1.1

In-hospital mortality was detected in 3 patients (3.4%). Postoperative MI caused death in two patients. The first of these patients had a history of CABG, the second had undergone combined CABG and CEA surgery. Postoperative diffuse cerebral infarction, left hemiplegia, development of pneumonia and respiratory failure caused death in the last patient.

DISCUSSION

Extracranial internal carotid artery stenosis accounts for 15 to 20% of ischemic strokes, depending on the population studied.⁶ When it is detected, surgical indication criteria should be interrogated. Then if a CEA operation is indicated according to current guidelines, surgery should be planned as soon as possible.

It is known that CEA is now widely performed in patients with carotid artery stenosis throughout the world. CEA is an effective operation designed to prevent the development of stroke.⁷ In addition, Chaturvedi et al.⁶ pointed out that CEA is the most common operation performed for this purpose. It has been reported that an aggressive surgical approach to carotid bifurcation atherosclerosis is superior to nonsurgical therapy in symptomatic and selected asymptomatic patients if low perioperative mortality, stroke and morbidity rates are achieved.⁸ Atherosclerotic plaque properties and the narrowness of carotid arteries is evaluated by colour flow Doppler ultrasound (US), computed tomography angiography (CTA), magnetic resonance (MR), magnetic resonance angiography (MRA) and digital subtraction angiography (DSA).⁹ Carotid artery stenosis was diagnosed by the carotid artery and vertebral artery colour flow Doppler US and then CTA was used to make a decision of the surgical intervention in our clinic. On the other hand, it has been found that some patients with symptomatic or asymptomatic are referred by neurologists to us after the diagnosis of carotid artery stenosis.

The majority of patients (48 patients; 54.5%) were symptomatic but some of these had had more than one symptoms. The most common symptom was dizziness and balance disorder (38.6%). Hemiplegia or hemiparesis was detected in 27 patients (30.6%). Asymptomatic critical carotid stenosis was detected in 10 patients (11.3%) during the preparation of CABG operation. Also, asymptomatic critical carotid artery stenosis was detected in the routine examination of some patients who applied to our outpatient clinic with complaints not related to carotid artery stenosis.

The use of patch angioplasty following CEA is controversial.¹⁰ Aslım et al.¹¹ suggested a patch should be used if standard CEA is to be performed, as primary closure of the carotid artery may result in a higher rate of restenosis in the carotid arteries. On the other hand, it has been reported that routine patching of larger carotid arteries may not be necessary and that selective patching based on distal internal carotid diameter can give equivalent results for patch and non-patched patients while minimising the requirement for patching.¹⁰ Also, patch angioplasty can be associated with complications, such as patch rupture and catastrophic haemorrhage.¹⁰ Thus patching does not benefit all patients and may be better employed selectively.¹⁰ The development of infection in graft patch use is another important complication. It has been reported that graft infection after carotid endarterectomy is extremely rare in the latest Peripheral Artery and Vein Diseases-National Treatment Guideline.¹² On the other hand, no patient with applied patch was found to have wound infection in the area of carotid incision in our clinic but one patient was found to have a wound infection at the leg incision (GSV harvest site). This patient received medical treatment and the wound healed without surgical intervention.

In the CEA operation, some surgeons preferred a patch usage for CEA site closure avoiding restenosis but others preferred primary closing technique caused by complications of usage of a patch. There was no standardization for this in our clinic. Choosing of surgical technique was made by the surgeon in the operation. Because of this, subgroup analysis according to closure types of CEA was not performed (patients with patch plasty versus primarily closed patients).

The cross-clamp times in patients with primary closure and patch plasty closure were detected as 28.9 ± 6.7 minutes and 39.9 ± 15.5 minutes, respectively. However, it was thought that the operations were performed by different surgeons in our clinic might be playing a role in this difference and therefore the statistical analysis was not performed.

Hematoma can be seen after the CEA operations. In this study, carotid artery site hematoma and saphenectomy site hematoma were detected as 6.8% and 5.6%, respectively. Hematoma formation at the CEA site requiring surgical revision has been reported to range from 0.7-3.4%.¹² On the other hand, we detected this ratio as 3.4%. Heparin was not neutralized by protamine sulfate in our CEA operations to prevent perioperative clotting of the carotid arteries. However, we think that the hematomas which are seen in our patients after CEA could be caused by this condition. Another reason for the development of hematomas in our patients may be the early initiation of anticoagulant and antiaggregant therapy in the early postoperative period.

It is known that some authors operate their patients without shunt during surgery, while others routinely perform their operations with shunt usage. On the other hand, Ünal¹³ reported that shunt use is preferred selectively and shunt usage was required in 31 (7%) of a total 417 patients who underwent CEA operation. In our clinic, while no shunt was used in patients with sufficient back bleeding from the internal carotid artery, the shunt (Javid's shunt) was used in two patients with internal carotid artery stump pressure below 40 mm Hg.

There is still no consensus on concurrent surgical treatment and sequential surgical treatment in the coexistence of carotid and coronary artery disease.^{12,14} Some authors reported that combined interventions of CEA and CABG can be performed

with acceptable morbidity and mortality when severe carotid stenosis is associated with advanced, symptomatic coronary artery disease.^{15,16} On the other hand, Borger et al.¹⁷ reported in their meta-analysis that the combined CABG and CEA may be associated with a higher risk of stroke or death than staged procedure. Furthermore, Saraç et al.¹⁸ pointed out that a general opinion, supported by different studies, suggests that simultaneous CEA and CABG carry a cumulative complication risk and high cardiovascular event rates. When symptoms of coronary artery disease coexist with carotid artery disease, we generally preferred to perform CEA operation simultaneously with CABG. In addition, 2 of them underwent CABG 1 month later after the CEA operation. These two patients had symptoms of carotid artery disease and coronary artery disease had been found incidentally during preparation for CEA surgery.

On the other hand, postoperative MI was detected in 6 patients who were decided not to need CABG regarding coronary artery disease during the preparations before CEA surgery. In 5 of them, drug treatment for coronary artery disease was performed after CEA surgery, while in one of them a coronary stent was placed by percutaneous coronary intervention.

Cranial nerve injuries are seen in about 8% of CEA operations during or early postoperative periods.^{12,19} In various studies, it is reported that the hypoglossal, vagus, and fascial nerves were most commonly involved.¹⁹ The most injured nerve in our patients was the nervus hypoglossus (hypoglossal nerve). The good thing is that most of the injuries are temporary.¹⁹ The other injured nerves were superior laryngeal nerve (external branch of vagus nerve), peripheral section of fascial nerve, cutaneous auricular nerve which is sensory branch of glossopharyngeal nerve and glossopharyngeal nerve. The overall rate of cranial nerve injury observed in our patients was 7.9% and these were resolved in 3 to 6 months.

It has been reported the risk of seizures is less than 1% and it can be seen within the first month after CEA surgery in patients with intense ischemic findings.²⁰ In our study, a new epileptic seizure developed in 1 patient (1.1%) in the early postoperative period.

Depending on the definition used, postoperative hypertension can affect up to two-thirds of patients undergoing CEA and is associated with preoperative hypertension.²¹ New onset hypertension was seen in 1 patient and uncontrolled hypertension with preoperative antihypertensive medications was seen in 5 patients in the early postoperative period in our patients. In addition, postoperative hypertension was controlled with preoperative antihypertensive drugs in 13 patients. On the other hand, postoperative hypotension could also be seen after the CEA.²¹

Stroke developing in the early postoperative period, has been reported to be associated with manipulations causing microemboli during CEA (cross-clamping, closure of the artery, shunt placement).¹² Borst et al.²² reported that the intraoperative stroke rate was 0.7% and in sixteen (2.7%) operations related strokes appeared after a symptom-free interval of between 2 hours and three days 18 hours. We found that new monoplegia was developed in 2 patients (2.2%).

It is known that the treatment of carotid stenosis consists of the best medical treatment and carotid revascularization, including CEA and CAS.²³ CAS is a new approach alternative to surgical CEA.²⁴ Hıdıroğlu et al.²⁵ reported that CEA today is accepted as the standard treatment for patients with carotid artery stenosis but endovascular methods and carotid artery stenting could also be chosen in these patients. It has been pointed out that CAS is an alternative treatment method for

patients at high surgical risk for CEA.^{26,27} Also, CAS attracts lots of attention since it is a less invasive intervention than CEA surgery.²⁵ On the other hand, we think that patient preference is also important in deciding on a treatment modality for carotid artery stenosis at the present time.

However, our study has some limitations. Firstly, this study is a retrospective study. Secondly, we have a small sample size. Indeed, CAS is routinely performed by doctors of cardiology and invasive neurology at our hospital, so, is a relatively limited number of patients we have encountered and performed CEA. Thirdly, and finally, long-term outpatient follow-up could not be performed by us because this follow-up was performed by neurologists.

Patients who will undergo CEA operations have generally various comorbid factors that could affect the result of the operation. Knowing and treating the morbidities preoperatively in these patients can significantly increase the success of these operations. Furthermore, unpredicted lots of complications could happen postoperatively. Early treatment of these complications when detected can reduce mortality and morbidity.

CONCLUSION

The early results of our CEA operations are in line with the literature. In addition, based on our clinical experience, we think that patients who will undergo CEA operations due to carotid artery stenosis should be meticulously prepared for surgery and should be followed up and treated closely in the perioperative period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Samsun Training and Research Hospital Ethics Committee (Date: 24.02.2021, Decision No: 2021/4/8).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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The effect of general anesthesia applied during cesarean section on newborn bilirubin

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ABSTRACT

Aims: Today, delivery is often performed as normal spontaneous vaginal delivery (NSVD) and cesarean section operations. Deliveries with NSVD mostly take place in the delivery room without the need for additional anesthetic agents. General anesthesia and regional anesthesia techniques are applied in cesarean section operations. In this study; the aim of this study was to examine the effect of general anesthesia on newborn bilirubin and to compare it with the bilirubin level of babies born without general anesthesia with NSVD method.

Methods: Between March 2022 and September 2022, 152 patients over the age of 18 with term pregnancy NSVD and elective cesarean section without complications were randomly included in the study. Cases diagnosed with liver and biliary tract disease, systemic liver and biliary tract effective drug use, Dcoombs (+) and COVID 19 (+) clinics were excluded.

Results: Of the patients included in our study, 75 (49.3%) were given general anesthesia and 77 (50.7%) delivered with NSVD without general anesthesia. It was determined that the first hour bilirubin and the fourth hour bilirubin values were significantly higher ($p<0.05$, $p=0.001$) in the general anesthesia group compared to the group that did not receive general anesthesia. In the group that did not receive general anesthesia, the APGAR 5th min score was found to be significantly ($p<0.05$, $p=0.027$) higher than the general anesthesia group. APGAR 1 min value did not differ significantly ($p>0.05$) between the anesthesia-free and general anesthesia groups. Neonatal weight, head circumference, and infant height did not differ significantly between the groups that did not receive general anesthesia and those who did not receive general anesthesia ($p>0.05$).

Conclusion: Between general anesthesia and non-anesthesia groups; it has been determined that the bilirubin value measured in babies born by cesarean section under general anesthesia is higher. It seems that it may be more beneficial to avoid systemic effective practices as much as possible and to disseminate NSVD.

Keywords: Anesthesia, cesarean section, neonatal bilirubin

INTRODUCTION

Birth is known to be one of the most challenging experiences most mothers have in their lifetime. While NSVD can often be performed without anesthesia; in some obstetric patients, anesthesia may be required in various interventional procedures, especially in cesarean section.¹ Cesarean section operation is performed with general anesthesia and regional anesthesia methods. General anesthesia application in obstetric surgery started in 1847 with the use of ether at birth.² While trying to provide only one person's safety and optimal conditions in anesthesia applied in most surgeries and surgical applications; in the cesarean section, the safety of the mother and the baby affected by any changes in the mother must also be ensured, and precautions should be taken accordingly.³ In the 1960s and 1970s, while attention was drawn to the correlation between the rates of binding of drugs to serum bilirubin and their secretion

into breast milk, on the other hand, there were studies on the effects of drugs used in pre-pregnancy, especially the liver and biliary tract, and the effects of drugs used in childbirth and anesthesia.^{4,5} In these studies, the regional anesthesia techniques used, the drugs used in these techniques, the transfer of anesthetic gases to the baby via the uteroplacental circulation and their effects on the newborn are noteworthy.^{6,7,8} The purpose of this study; to evaluate the effect of general anesthesia applied during cesarean section on the level of bilirubin on the newborn.

METHODS

After getting approval from the İstanbul Medipol University Clinical Researches Ethics Committee with the date 17.02.2022 and decision number 153, followed in the obstetrics and

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gynecology clinic; the data of babies who were delivered with NSVD between March 2022 and September 2022 and who were born with ASA 1 electively under general anesthesia after cesarean section were analyzed prospectively. The groups were divided into 2 groups as those who received general anesthesia (n=75) and those who did not receive anesthesia (n=77). During the induction phase of general anesthesia, 2 mg/kg propofol and 0.5 mg/kg rocuronium were administered as standard, and no anesthetic agent was administered to those who gave birth with NSVD. The newborns' 1st and 5th minute APGAR scores, birth weight, height, head circumference, 1st hour and 4th hour bilirubin levels were evaluated by recording transcutaneously.

COVID (+) and DCoombs (+) cases were excluded. Emergency cases, drug use affecting the systemic hepatic biliary tract, pregnancies under the age of 18 and non-term pregnancies were excluded from the study. This study was conducted in accordance with the principles of the Declaration of Helsinki. Consent was obtained from all patients included in the study.

Statistical Analysis

IBM SPSS version 28 (IBM Co., Chicago, USA) was used for statistical analysis of the data. The normal distribution of the variables was checked with the Kolmogorov-Smirnov test. Descriptive statistical

methods (mean, standard deviation) were used. Mann-Whitney U test and chi-square test were used to compare quantitative and qualitative data. Statistical significance level was defined as $p < 0.05$.

RESULTS

The ages of the patients did not differ significantly ($p > 0.05$) between the non-anesthesia and general anesthesia groups. The height, weight, and BMI value of the patients did not differ significantly ($p > 0.05$) between the non-anesthesia and general anesthesia groups. The week of gestation did not differ significantly ($p > 0.05$) between the non-anesthesia and general anesthesia groups. The number of births did not differ significantly ($p > 0.05$) between the non-anesthesia and general anesthesia groups. The rate of comorbidities did not differ significantly ($p > 0.05$) between the non-anesthesia and general anesthesia groups. The rate of drug use in the general anesthesia group was significantly higher than in the non-anesthesia group ($p < 0.05$, $p = 0.005$) (Table 1).

APGAR 1 min value did not differ significantly ($p > 0.05$) between the anesthesia-free and general anesthesia groups. The APGAR 5th min value in the general anesthesia group was significantly ($p < 0.05$) lower than the group that did not

Table 1. Information about pregnant

	Min-Max	Medyan	Ort.±ss/n-%
Age	20.0-41.0	29.0	30.0±4.3
Height (cm)	150.0-186.0	167.0	166.9±5.1
Weight (kg)	60.0-96.0	73.0	73.4±7.3
BMI	21.0-33.9	26.3	26.4±2.8
Gestation week (wk)	30.0-42.0	39.0	38.8±1.2
Number of births	1.00-4.0	2.0	1.9±0.78
Comorbidities			
(-)		116	75.8%
(+)		37	24.2%
GDM		5	3.3%
Varicose vein disease		6	3.9%
HT		10	6.5%
Asthma		7	4.6%
Anxiety		3	2.0%
Thyroid disease		2	1.3%
Vertigo		2	1.3%
Rheumatoid arthritis		1	0.7%
Ulcerative colitis		1	0.7%
Drug use	(-)	131	85.6%
	(+)	22	14.4%
Type of birth	NSVD	77	50.7%
	Cesarean section	75	49.3%
APGAR 1 min	7.0-10.0	9.0	8.5±0.70
APGAR 5 min	8.0-10.0	10.0	9.5±0.61
Newborn weight (gr)	2325-4700	3270	3288±380
Height (cm)	44.0-55.0	51.0	50.8 2.0
Head circumference (cm)	31.0-39.0	35.0	34.8 1.5
1 hour bilirubin	0.10-2.6	0.90	0.98±0.57
4 hour bilirubin	0.30-3.1	1.7	1.7±0.73
DCoombs	(-)	152	99.3%
	(+)	1	0.7%
Suspected COVID 19	(-)	153	100%
	(+)	0	0.0%

BMI: Body mass index, GDM: Gestational diabetes mellitus

receive anesthesia. The newborn weight, height, and head circumference values did not differ significantly ($p>0.05$) between the anesthesia-free and general anesthesia groups. In the general anesthesia group, 1st hour bilirubin and 4th hour bilirubin values were significantly higher than the group without anesthesia ($p<0.05$, $p=0.001$) (Table 1). The Dcoombs rate did not differ significantly ($p>0.05$) between the anesthesia-free and general anesthesia groups. Between maternal and baby blood groups; There was no significant difference in blood group distribution (Table 2). The rate of Suspicion of COVID 19 did not differ significantly ($p>0.05$) between the non-anesthesia and general anesthesia groups (Figure).

Table 2. Blood groups distribution

	n	%
Maternal blood group		
O-	8	5.2%
O+	52	34.0%
A-	5	3.3%
A+	60	39.2%
AB+	1	0.7%
B-	5	3.3%
B+	22	14.4%
Baby blood group		
O-	7	4.6%
O+	46	30.1%
A-	12	7.8%
A+	52	34.0%
AB+	4	2.6%
B-	1	0.7%
B+	31	20.3%

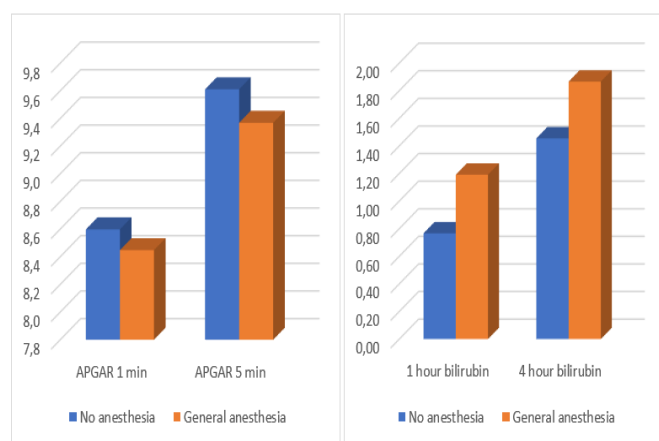


Figure. Apgar and bilirubin values

DISCUSSION

Birth is one of the vital processes that has not lost its importance for centuries and maintains its popularity. Most of the time, the mode of delivery is determined by clinicians according to both the anatomical and clinical conditions of the patient and the fetus. With the increase in cesarean section operations worldwide and in our country in recent years, the anesthesia method applied in cesarean section operations and its effects on the newborn have become an important issue.

Since the 1970s, we have come across publications that draw attention to the relationship between the applied anesthesia method and neonatal jaundice. At the beginning of the subjects that are especially emphasized in the studies are the deliveries with or without anesthesia, the transfer of anesthetic drugs to the baby via the umbilical cord and their effects on the newborn.⁹

Studies investigating the effects of volatile anesthetic drugs on bilirubin levels and liver functions have also been conducted, and it seems that more studies are needed in this area.^{10,11} In a study in which newborn bilirubin levels with general anesthesia and NSVD were compared, 24-hour serum bilirubin values were found to be high, although not statistically significant.¹² El Kabbany et al.¹³ there is a current study reporting that maternal general anesthesia has a negative effect on newborn bilirubin. In our study, we found that the 1st hour bilirubin and 4th hour bilirubin values in the general anesthesia group were significantly higher than the group that did not receive anesthesia ($p<0.05$, $p=0.001$).

In another study, newborn heart rate was significantly lower in the general anesthesia group, and the 1st minute APGAR scores were found to be significantly lower in the general anesthesia group, and the 5th minute APGAR scores were found to be similar.¹⁴ In our study, although the APGAR 1st minute scores did not differ significantly between the general anesthesia group and the group that did not receive anesthesia; APGAR 5th min value was found to be significantly ($p<0.05$) lower in the general anesthesia group.

In one of the remarkable studies, a significant relationship was found between cesarean section and anesthesia and newborn bilirubin, while in another similar study, researchers could not detect a relationship between delivery type and newborn bilirubin levels.¹⁵ In a study, newborn weight did not show a significant difference in 160 cases (32% regional, 68% general anesthesia) in a comparison according to the anesthesia method in cesarean deliveries.¹⁶ In our study, there was no statistically significant difference between the two groups in terms of newborn weight, height and head circumference ($p>0.05$).

CONCLUSION

As a result, in our study, the bilirubin values of the newborns who underwent general anesthesia were found to be higher than the newborns who were born with NSVD without anesthesia. Making normal delivery more common is seen as beneficial, new randomized studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medipol University Faculty of Medicine Research and Application Hospital Clinic Ethics Committee (Date: 17/02/2022, Decision No: 153).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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ESR1 rs2234693 might be associated with TMD risk in the Turkish population, but not rs9340799

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ABSTRACT

Aims: The gender and age distribution of temporomandibular disorder (TMD) suggest a possible role for the female hormonal axis in the pathogenesis. The goal of this study was to evaluate if estrogen receptor (ESR1) gene variants contribute to TMD susceptibility in the Turkish population.

Methods: A total of 270 people, 130 of whom were TMD patients and 140 healthy controls, were included in the study. The ESR1 PvuII (rs2234693) and XbaI (rs9340799) variants were genotyped using the polymerase chain reaction based restriction fragment length polymorphism (PCR-RFLP). The results were evaluated statistically.

Results: There were 110 women (81.48%) and 25 men (18.52%) in the patient group. We found there was a significant association between rs2234693 T/C, C/C genotypes and TMD ($p=0.007$). Also, the C allele was more prevalent in patients compared to controls ($p=0.002$). A statistically significant association was observed when the patients were compared with the controls according to TT versus TC+CC ($p=0.002$). There was no statistical significance between the patient and control groups in terms of rs9340799 genotype and allele distribution. Then we evaluated the relationship between genotype distributions and clinical characteristics. Both males and females had the highest rs2234693 T/C genotype ($p=0.049$). The majority of people with bruxism, bruxomania, and bruxism plus bruxoma carried the rs2234693 T/C genotype ($p=0.025$).

Conclusions: Our results showed that ESR1 rs2234693 might be associated with TMD risk in the Turkish population, but not rs9340799.

Keywords: Temporomandibular disorder, estrogen receptor alpha, variant, PCR-RFLP

INTRODUCTION

Temporomandibular disorder (TMD) covers clinical conditions affecting the temporomandibular joint (TMJ) and related structures. Preauricular pain, masticatory muscles, limitation of mandibular range of motion, noise during mandibular movement, headache, and facial pain are common symptoms.¹ Although the exact etiology of TMD is not fully elucidated, trauma, occlusal imbalances, psychological factors, parafunctional habits (e.g., bruxism), and systemic factors [e.g., rheumatoid arthritis (RA)] may be involved in TMD. It is a disorder that affects approximately 7-15% of the adult population. TMD is 1.5-2 times more common in women than in men.² Other inflammatory diseases, such as RA and osteoarthritis, are more common in women than men. The fact that women were more sensitive to experimental pain than men suggested that gender differences might play a role in pain sensation. TMD pain, which tends to occur after puberty, is more prominent during the reproductive years.³ According to

gender and age distribution, a possible link between the female hormonal axis, or estrogen level, and the pathogenesis of TMD is considered.⁴

Estrogen, the main female hormone, is produced endogenously during reproductive age. Estrogen acts through estrogen receptors, estrogen receptor-alpha ($ER\alpha$), and beta ($ER\beta$), which are encoded by the *ESR1* and *ESR2* genes, respectively. These receptors, which directly affect the expression of many target genes, are called dependent transcription factors.⁵ Many data points suggest that this pathway plays a crucial role in several immune-related responses.⁶ Estrogen receptors are highly expressed in bone and bone marrow. Wang et al.⁷ demonstrated with a three-dimensional (3D) culture model that mechanical overload significantly suppressed the level of $ER\alpha$ in chondrocytes. This pressure and mechanical loading increased hypertrophy and osteogenic transition. In animal studies, it

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has been shown that estrogen deficiency causes structural changes in the TMJ.⁸ Expression of *ESR1* in chondrocytes, stromal cells, and osteoblasts indicates that bone and cartilage can be regulated by the *ESR1* gene.⁵ The *ESR1* gene located on the long arm of chromosome 6 (6q25.1). There are many polymorphisms in this gene. Especially PvuII (rs2234693) and XbaI (rs9340799) variants, which are frequently seen in intron 1 of the *ESR1* gene, can affect ER α gene expression through changes in the binding and action of transcription factors.⁹ In studies examining the relationship of these variants with osteoarthritis, the findings are controversial.^{10,11}

Therefore, we aimed to evaluate whether *ESR1* gene variants (rs2234693 and rs9340799) contribute to TMD susceptibility in the Turkish population.

METHODS

Subjects

One hundred thirty patients with TMD (110 females and 25 males: mean age: 30.97 $\pm$ 11.59) were included in the present study. Patients were chosen from those who were diagnosed with TMD in the Department of Medical Genetics in the Giresun University. The diagnosis of TMD was made according to the diagnostic criteria published in 2014.¹² Subjects with TMJ surgery and trauma, RA, fibromyalgia, or other systemic musculoskeletal disorders, past or present neurological and/or psychiatric disorders, investigational drug or device use, opioid drug use, or pregnancy were excluded from either group. A total of 140 unrelated healthy age-matched controls (88 females and 52 males: mean age: 34.48 $\pm$ 10.43) were included in the study. These control cases had no previous history of TMD. Both groups were of Turkish origin. The principles outlined in the Declaration of Helsinki were followed. The Kanuni Training and Research Hospital Ethics Committee approved the study (Date: 13.01.2016, Decision No: 2016/09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Genotyping

DNA extraction was performed using a commercial kit from two mL of venous blood taken from the groups. Genotyping of *ESR1* rs2234693 and rs9340799 variants was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis using the method described previously.¹³ After amplification, the 1374 bp PCR product was digested with PvuII and XbaI restriction enzymes. Digestion products were separated on a 2% agarose gel. 982 and 392 bp fragments were detected when the G allele was present at position -351, and 937 and 437 bp fragments were detected when the C allele was present at position -397. 25% of samples were reworked to avoid inconsistencies in results.

Statistical Analysis

Statistical Package for the Social Sciences 22.0 IBM (NY, USA) was used for statistical analysis in the evaluation of the data in the study. The percentage frequency of categorical variables was used. The mean standard deviation was used to express continuous variables. In group comparisons, the chi-square test for categorical variables, the independent sample t-test for continuous variables, and the one-way Anova test were used.

RESULTS

In our study, we compared 135 patients [110 females (81.48%), 25 males (18.52%)] and 140 controls in terms of *ESR1* rs2234693 and rs9340799. The genotype and allele distribution of *ESR1* rs2234693 and rs9340799 in the patient and control groups are shown in Table 1.

Table 1. Genotype distribution and allele frequencies of rs2234693 and rs2234693 in patients and controls				
rs2234693 (PvuII)	Patient group n:135 (%)	Control group n:140 (n)	p	OR (95%CI)
Genotypes				
T/T	45 (33.33)	72 (51.43)	0.007	
T/C	62 (45.93)	51 (36.43)		
C/C	28 (20.74)	17 (12.14)		
TT: TC+CC	45 (33.33): 90 (66.67)	72 (51.43): 68 (48.57)	0.002	2.12 (1.30-3.45)
TT+TC: CC	107 (79.26): 28 (20.74)	123 (87.86): 17 (12.14)	0.097	1.73 (0.90-3.34)
Alleles				
T	152 (56.30)	195 (69.64)	0.002	1.75 (1.24-2.49)
C	118 (43.70)	85 (30.36)		
rs9340799 (XbaI)	Patient group n: 135 (%)	Control group n: 140 (n)	p	OR (95%CI)
Genotypes				
A/A	59 (43.70)	52 (37.14)	0.137	
A/G	58 (42.96)	76 (54.29)		
G/G	18 (13.33)	12 (8.57)		
AA: AG+GG	59 (43.70): 76 (56.30)	52 (37.14): 88 (62.86)	0.268	0.76 (0.47-1.23)
AA+AG: GG	117 (86.67): 18 (13.33)	128 (91.43): 12 (8.57)	0.205	0.61 (0.28-1.32)
Alleles				
A	176 (65.19)	180 (64.29)	0.825	1.04 (0.73-1.48)
G	94 (34.81)	100 (35.71)		

Statistically significant values are shown in bold.

ESR1 rs2234693

The *ESR1* rs2234693 genotype distribution was statistically different between TMD patients and controls. The rs2234693 T/C and C/C genotypes were higher in the patient group compared to the control group (p=0.007). The T/T genotype was more prevalent in controls than in patients. A statistically significant association was observed when the patients were compared with the controls according to TT versus TC+CC [p=0.002, OR (CI 952.12 (1.30-3.45)]. Also, the C allele frequency was more prevalent in patients compared to controls (p=0.002, OR=1.78, 95% CI=1.24-2.49).

ESR1 rs9340799

The prevalence of genotypes A/A, A/G, and G/G, profiles for the rs9340799 was 43.70%, 42.96%, and 13.33%, respectively, in patients, and 37.14%, 54.29%, and 8.57%, respectively, in the control group. We found no statistical significance between the patient and control groups in terms of rs9340799 genotype distribution (p=0.137). There was no significant difference in terms of rs9340799 allele frequency (p=0.825, OR=1.22, 95%CI=0.73-1.32).

Then we analyzed the relationship between the *ESR1* rs2234693 and rs9340799 genotype distribution and clinical characteristics,

including age, gender, disease age, family history, pain, teeth grinding or bruxism, increased pain when chewing or talking, pain severity, eating difficulties, a click sound from the chin, jaw locking, loudness, pain region, pain persistence, TMJ disorder, muscular muscle symptoms, headache, Schiffman

associated structure, and TMD criteria. Both males and females had the highest rs2234693 T/C genotype ($p=0.049$). In the subjects with bruxism, bruxomania, and bruxism plus bruxomania, there was mostly the rs2234693 T/C genotype ($p=0.025$). Results are presented in [Table 2](#) and [Table 3](#).

Table 2. The relationship between rs2234693 (PvuII) genotype distribution and patient characteristics

Characteristics	Total n=135 (%)	T/T n=45 (%)	T/C n=62 (%)	C/C n=28 (%)	P
Age, X $\pm$ SD	30.97 $\pm$ 11.59	32.40 $\pm$ 12.81	31.11 $\pm$ 11.50	28.36 $\pm$ 9.52	0.350
Gender, n (%)	Male	25 (18.52)	5 (20.00)	17 (68.00)	0.049
	Female	110 (81.48)	40 (36.36)	45 (40.91)	
Disease age, n (%)	0-1 year	63 (46.67)	19 (30.16)	31 (49.21)	0.211
	1-5 years	39 (28.89)	10 (25.64)	18 (46.15)	
	5 years and above	33 (24.44)	16 (48.48)	13 (39.39)	
Family history, n (%)	Yes	79 (58.52)	29 (36.71)	35 (44.30)	0.594
	No	56 (41.48)	16 (28.57)	27 (48.21)	
Presence of pain, n (%)	Yes	117 (86.67)	42 (35.90)	52 (44.44)	0.266
	No	18 (13.33)	3 (16.67)	10 (55.56)	
Teeth grinding or bruxism, n (%)	No	55 (40.74)	21 (38.18)	24 (43.64)	0.025
	Bruxism	11 (08.15)	3 (27.27)	8 (72.73)	
	Bruxomania	21 (15.56)	9 (42.86)	11 (52.38)	
	Bruxism+ Bruxomania	48 (35.56)	12 (25.00)	19 (39.58)	
				17 (35.42)	
Increased pain when chewing or talking, n (%)	Evet	91 (67.41)	32 (35.16)	38 (41.76)	0.355
	No	44 (32.59)	13 (29.55)	24 (54.55)	
Pain severity, X $\pm$ SD	4.36 $\pm$ 2.53	4.58 $\pm$ 2.26	4.29 $\pm$ 2.57	4.18 $\pm$ 2.89	0.772
Eating difficulties n (%)	Yes	64 (47.41)	25 (39.06)	28 (43.75)	0.356
	No	71 (52.59)	20 (28.17)	34 (47.89)	
Click sound from the chin, n (%)	Yes	112 (82.96)	36 (32.14)	54 (48.21)	0.494
	No	23 (17.04)	9 (39.13)	8 (34.78)	
Jaw locking, n (%)	Yes	31 (22.96)	8 (25.81)	16 (51.61)	0.597
	No	104 (77.04)	37 (35.58)	46 (44.23)	
Loudness, X $\pm$ SD	3.96 $\pm$ 2.46	4.07 $\pm$ 2.46	4.00 $\pm$ 2.33	3.68 $\pm$ 2.79	0.794
Pain region, n (%)	No pain	10 (07.41)	2 (20.00)	5 (50.00)	0.807
	Muscle pain	18 (13.33)	8 (44.44)	7 (38.89)	
	Joint region	44 (32.59)	15 (34.09)	22 (50.00)	
	Joint and muscle pain	63 (46.67)	20 (31.75)	28 (44.44)	
Pain persistence, n (%)	Continually	35 (25.93)	16 (45.71)	14 (40.00)	0.385
	Periodically	90 (66.67)	27 (30.00)	43 (47.78)	
	No	10 (07.41)	2 (20.00)	5 (50.00)	
Tmj disorder, n (%)	Yes	125 (92.59)	39 (31.20)	60 (48.00)	0.143
	No	10 (07.41)	6 (60.00)	2 (20.00)	
Masticatory muscle symptoms, n (%)	Yes	81 (60.00)	27 (33.33)	34 (41.98)	0.331
	No	54 (40.00)	18 (33.33)	28 (51.85)	
Headache, n (%)	Yes	67 (49.63)	26 (38.81)	30 (44.78)	0.296
	No	68 (50.37)	19 (27.94)	32 (47.06)	
Schiffman associated structure, n (%)	Yes	2 (01.48)	0 (00.00)	2 (100.00)	0.303
	No	133 (98.52)	45 (33.83)	60 (45.11)	
TMD criteria n (%)	TMD TMJ disorder	16 (11.85)	3 (18.75)	10 (62.50)	0.421
	Masticatory muscle	6 (04.44)	3 (50.00)	1 (16.67)	
	1 and 2 together	46 (34.07)	13 (28.26)	21 (45.65)	
	1 and 3 together	39 (28.89)	15 (38.46)	19 (48.72)	
	2 and 3 together	4 (02.96)	3 (75.00)	1 (25.00)	
	1, 2, and 3 together	24 (17.78)	8 (33.33)	10 (41.67)	
				6 (25.00)	

TMD: Temporomandibular disorder, TMJ: temporomandibular joint. Statistically significant values are shown in bold

Table 3. The relationship between rs9340799 (XbaI) genotype distribution and patient characteristics

Characteristics		Total n=135 (%)	A/A n=59 (%)	A/G n=58 (%)	G/G n=18 (%)	p
Age, X±SD		30.97± 11.59	30.31±11.49	31.64±12.14	31.00±10.61	0.826
Gender, n (%)	Male	25 (18.52)	11 (44.00)	11 (44.00)	3 (12.00)	0.976
	Female	110 (81.48)	48 (43.64)	47 (42.73)	15 (13.64)	
Disease age, n (%)	0-1 year	63 (46.67)	27 (42.86)	26 (41.27)	10 (15.87)	0.927
	1-5 years	39 (28.89)	17 (43.59)	17 (43.59)	5 (12.82)	
	5 years and above	33 (24.44)	15 (45.45)	15 (45.45)	3 (09.09)	
Family history, n (%)	Yes	79 (58.52)	34 (43.04)	38 (48.10)	7 (08.86)	0.132
	No	56 (41.48)	25 (44.64)	20 (35.71)	11 (19.64)	
Presence of pain, n (%)	Yes	117 (86.67)	48 (41.03)	53 (45.30)	16 (13.68)	0.268
	No	18 (13.33)	11 (61.11)	5 (27.78)	2 (11.11)	
Teeth grinding or bruxism, n (%)	No	55 (40.74)	24 (43.63)	25 (45.45)	6 (10.91)	0.249
	Bruxism	11 (08.15)	5 (45.45)	4 (36.36)	2 (18.18)	
	Bruxomania	21 (15.56)	14 (66.67)	6 (28.57)	1 (04.76)	
	Bruxism+	48 (35.56)	12 (25.00)	19 (39.58)	17 (35.42)	
Increased pain when chewing or talking, n (%)	Yes	91 (67.41)	37 (40.66)	41 (45.05)	13 (14.29)	0.587
	No	44 (32.59)	22 (50.00)	17 (38.64)	5 (11.36)	
Pain severity, X±SD		4.36± 2.53	4.14± 2.66	4.67±2.45	4.11±2.37	0.470
Eating difficulties n (%)	Yes	64(47.41)	30 (46.88)	27 (42.19)	7 (10.94)	0.663
	No	71 (52.59)	29 (40.85)	31 (43.66)	11 (15.49)	
Click sound from the chin, n (%)	Yes	112 (82.96)	46 (41.07)	50 (44.64)	16 (14.29)	0.383
	No	23 (17.04)	13 (56.52)	8 (34.78)	2 (08.70)	
Jaw locking, n (%)	Yes	31 (22.96)	15 (48.39)	11 (35.48)	5 (16.13)	0.618
	No	104 (77.04)	44 (42.31)	47 (45.19)	13 (12.50)	
Loudness, X±SD		3.96±2.46	3.71±2.57	4.17±2.41	4.06±2.31	0.592
Pain region, n (%)	No pain	10 (07.41)	5 (50.00)	4 (40.00)	1 (10.00)	0.340
	Muscle region	18 (13.33)	11 (61.11)	4 (22.22)	3 (16.67)	
	Joint region	44 (32.59)	18 (40.91)	23 (52.27)	3 (06.82)	
	Joint region and muscle pain	63 (46.67)	25 (39.68)	27 (42.86)	11 (17.46)	
Pain persistence, n (%)	Continuously	35 (25.93)	18 (51.43)	15 (42.86)	2 (05.71)	0.467
	Periodically	90 (66.67)	36 (40.00)	39 (43.33)	15 (16.67)	
	No	10 (07.41)	5 (50.00)	4 (40.00)	1 (10.00)	
Schiffman TMJ disorder, n (%)	Yes	125 (92.59)	52 (41.60)	57 (45.60)	16 (12.80)	0.091
	No	10 (07.4)	7 (70.00)	1 (10.00)	2 (20.00)	
Schiffman masticatory muscles, n (%)	Yes	81 (60.00)	37 (45.68)	30 (37.04)	14 (17.28)	0.122
	No	54 (40.00)	22 (40.74)	28 (51.85)	4 (07.41)	
Schiffman headache, n (%)	Yes	67 (49.63)	30 (44.78)	29 (43.28)	8 (11.94)	0.891
	No	68 (50.37)	29 (42.65)	29 (42.65)	10 (14.71)	
Schiffman associated structure, n (%)	Yes	2 (01.48)	0 (00.00)	1 (50.00)	1 (50.00)	0.099
	No	133 (98.52)	59 (44.36)	57 (42.86)	17 (12.78)	
TMD criteria n (%)	TMJ disorder	16 (11.85)	6 (37.50)	9 (56.25)	1 (06.25)	0.500
	Masticatory muscle	6 (04.44)	5 (83.33)	0 (00.00)	1 (16.67)	
	1 and 2 together	46 (34.07)	18 (39.13)	20 (43.48)	8 (17.39)	
	1 and 3 together	39 (28.89)	17 (43.59)	19 (48.72)	3 (07.69)	
	2 and 3 together	4 (02.96)	2 (50.00)	1 (25.00)	1 (25.00)	
	1, 2, and 3 together	24 (17.78)	11 (45.83)	9 (37.50)	4 (16.67)	

TMD: Temporomandibular disorder, TMJ: temporomandibular joint.

DISCUSSION

One of the most common causes of chronic pain in the orofacial region is TMD.¹⁴ Gender is an important determinant of health. It plays a role in the pathophysiology of various

dental diseases, including TMD and pregnancy-associated gingivitis.¹⁵ Although the results are controversial, it is reported that women are 2-3 times more likely to develop TMD than men.¹⁶ It is considered that this difference is due to excessive

articular flaccidity, trauma, age, and behavioral, hormonal, genetic, anatomical, and psychosocial reasons. It was reported that subjective symptoms and clinical characteristics of TMD patients show distinct tendencies according to different age groups.¹⁷ Hormonal fluctuations during pregnancy and during the menstrual cycle have been shown to cause painful sensations in patients with TMD.^{18,19} Jedynak et al.²⁰ reported that TMD is common in women with menstrual disorders (92.3%). They declared that women with TMD symptoms should be questioned about female hormone disorders.

Estrogen is important in development and homeostasis for both sexes, although relative levels vary. Estrogens do not only affect the female reproductive system, they can also affect the functioning of the whole body. Estrogens in the blood affect the metabolism of other tissues and organs by binding to plasma proteins. Estrogens can exert their effects on cells with a direct or indirect effect on gene expression through receptors located on cell membranes as well as nuclear estrogen receptors.²⁰ Estrogens have the ability to influence monocytes and macrophages by regulating the production of proinflammatory cytokines (interleukin-1, interleukin-2, and TNF- α). It has been reported that 10 nM estradiol treatment reduces the promoter activity and gene expression of proteoglycan 4, which is required for joint lubrication in baboon disc fibrochondrocytes.²¹ 17- β estradiol induces the production and destruction of matrix metalloproteinases (MMP9 and MMP13) in TMJ fibrocartilage.^{19,22} Abdrabuh et al.²³ demonstrated that some TMJ structures, including the articular disc and condylar cartilage layer, are disrupted after estrogen deficiency. In one study, the prevalence of TMD was found to be 2-3 times lower in pregnant women with reduced estrogen than in non-pregnant women.²⁴ In a study investigating the relationship between TMD pain and periods of the menstrual cycle, it was stated that TMD pain is highest at times when estrogen is lowest, but rapid estrogen change may also be associated with increased pain.²⁵ One method to assess the role of estrogen in TMD is to examine its prevalence in postmenopausal women taking hormone replacement therapy (HRT). A study observed a significant increase in the prevalence of TMD in postmenopausal women taking HRT.²⁶ However, other studies have found no significant difference in the prevalence of TMD in postmenopausal women taking HRT compared to those receiving no treatment.^{27,28} Some studies have shown that TMD mostly affects women of childbearing age, suggesting that these high estrogen levels aggravate the disease.²⁹ Two studies showed that orofacial pain was significantly reduced during the third trimester of pregnancy³⁰ and increased postpartum.¹⁸ This suggests that TMD pain is reduced by high estrogen levels.

Several single nucleotide polymorphisms (SNPs) have been identified in the *ESR1* gene. rs2234693 and rs9340799, two of the most studied SNPs, are located in the first intron of *ESR* and are in strong linkage disequilibrium with each other.³¹ It has been suggested that these variants affect *ESR1* expression and activation and alter the action of estrogen. The rs2234693 C and rs9340799 G alleles in *ESR1* were associated with higher gene expression and more positive estrogen-induced effect.³² In women, overexpression of the *ESR* in the TMJ indicates excessive joint laxity. The clinical picture is likely to be affected by *ESR* polymorphisms.³³ These variants appear to be markers for bone mineral density and cardiovascular disease in women.³⁴ Additionally, these variants are thought to play a role in estrogen-related diseases such as breast cancer, osteoporosis,

endometriosis, and familial early ovarian dysfunction.³⁴ In our previous study, we showed that *ESR1* rs2234693 and rs9340799 are effective in the development of common fibromyalgia and some clinical features in women.³⁵ Quinelato et al.³⁶ reported that the *ESR1* rs2273206 T/T genotype was associated with an increased risk of developing TMJ pain. In an animal study, *ESR2* rs1256049 was associated with disc displacement and arthralgia in adult rats.³⁷ Bonato et al.³⁸ reported that the rs1676303 T/T and rs6574293 G/G genotypes were associated with TMD. The A/A genotype of *ESR1* rs1643821 was found to be a risk factor for dysfunctional worsening after orthognathic surgery.³⁹

In this study, we investigated the effect of *ESR1* rs2234693 and rs9340799 on TMD development in the Turkish population. To the best of our knowledge, this is the first study to examine the relationship between TMD and *ESR1* gene variants in our country. We found that the rs2234693 C allele is a risk factor for the development of TMD. This suggested that patients were exposed to high *ESR1* expression. Also, there was a significant association in terms of TT vs. TC+CC (Table 1). We then compared the genotype distributions of these variants with the demographic and clinical characteristics of the patients. Homozygous genotypes were more common in females, while heterozygous genotypes were more common in males for rs2234693. The majority of our patients with bruxism, bruxomania, and bruxism plus bruxomania carried the rs2234693 T/C genotype (Table 2). However, the genotype distribution of both variants was not significantly associated with other clinical characteristics.

Our study has some limitations. It is important that female patients do not have hormone level information and that their menstrual cycle is not questioned.

CONCLUSION

TMD is a disease of complex origin. In this study, we showed for the first time in our country that *ESR1* rs2234693 is a factor that may predispose to joint degeneration. Determining the relationship between TMD and these variants is important for elucidating the molecular structure of TMD.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was obtained from Kanuni Training and Research Hospital Ethics Committee (Date: 13.01.2016, Decision No: 2016/09).

Informed Consent: Written informed consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

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Author Contributions: All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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Coagulation parameters and prognosis in COVID-19 patients

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ABSTRACT

Aims: There are many factors that affect morbidity and mortality in COVID-19. Coagulopathy is thought to be one of the important mechanisms in COVID-19 mortality. In this study, it was aimed to investigate coagulation factors and their relationship with prognosis in COVID-19.

Methods: Patients diagnosed with COVID-19 were retrospectively reviewed in our hospital. The patients' demographic data, laboratory data on admission to the hospital, intensive care admissions, and surveillance were recorded. Patients were divided into two groups; Group 1 is non-critical patients followed up in the clinic, Group 2 is critical patients who need treatment in the intensive care unit.

Results: 403 patients followed up for COVID-19 were analyzed. It was determined that the average age of the patients in Group 1 was statistically significantly lower than those in Group 2. (1: 45.28±15.31 vs. 2: 60.15±15.72, respectively, $p<0.001$). It was observed that the rates of HT, DM, CHD, and COPD in Group 2 were statistically significantly higher than Group 1 ($p<0.05$). While APTT values were similar in both groups, D-Dimer values were significantly higher in Group 2. As QSOFA, SIC, DIC, and coagulation marker scores increased, the percentage of patients with death increased significantly ($p<0.05$). Age, HT, COPD, PT, and high fibrinogen levels were found to increase the mortality risk rates statistically ($p<0.05$).

Conclusion: It was determined that the most important factors determining mortality in COVID-19 are COPD and HT. APTT and D-dimer values were not found to be a prognostic factor in terms of mortality. However, PT, fibrinogen, and age are poor prognostic factors and can be used to predict mortality requiring intensive care.

Keywords: COVID-19, coagulopathy, prognosis, mortality

INTRODUCTION

Human coronavirus is a pathogen of the respiratory system that causes mostly mild upper respiratory tract infection. The viral epidemic called COVID-19 caused by SARS-CoV-2, the new coronavirus of zoonotic origin that started in China, in 2019, spread rapidly worldwide with its wide range of clinical symptoms, from asymptomatic to death. has resulted in millions of cases worldwide.¹

In COVID-19 infection, leukopenia, lymphopenia, neutrophilia, hypoalbuminemia, hyponatremia can often be seen, while increase in levels of biochemical parameters such as D-dimer, ferritin, creatine kinase, troponin, lactic dehydrogenase (LDH), C-reactive protein (CRP), myoglobin.²⁻⁵ The erythrocyte and platelet count usually maintains normal levels until the later stages of the disease. The procalcitonin level is typically normal in most patients.^{3-6,7} It has been reported that the overall mortality rate varies in age groups between 2.3% and 12.8%, and the development of coagulopathy increases mortality.⁷⁻⁹

There is considerable variability in the extent of the effects of COVID-19 on coagulation parameters and their correlation with disease severity and mortality. Coagulopathy induced by COVID-19 (CIC) causes morbidity and mortality different from sepsis-induced coagulopathy (SIC).^{2,5} While intravascular coagulation (DIC) is more common with bleeding in SIC, micro and macro vascular thrombosis and latent DIC frequently occur with CIC, and anticoagulation plays a major role in treatment.^{4,5,10} In this study, we tried to reveal the effect of SARS-CoV-2 infection on coagulation parameters, the severity of COVID-19, disease progression, and mortality in patients we followed up.

METHODS

The study was approved by the Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 08/07/2020 Decision No: 2135). All procedures were carried

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out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Following the approval of the local ethics committee, patients who received inpatient treatment between March 2020 and June 2020 at Keçiören Training and Research Hospital, which has been serving as a pandemic hospital since the outbreak began, and the diagnosis of COVID-19 was confirmed by RT-PCR test, were retrospectively screened. Patients with negative RT-PCR tests and diagnosed with COVID-19 due to clinical findings and computed tomography findings were excluded from the study. Demographic data of the patients, laboratory values at hospital admission, intensive care admissions, and surveillance were recorded. Patients were divided into two groups and analyzed; Group 1 is non-critical patients followed up in the clinic (no need for intensive care). Group 2 is critical patients who need treatment in the intensive care unit.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation and categorical data as numbers and percentages. In the intergroup analysis of continuous variables, normality analyzes were performed using the Kolmogorov-Smirnov Goodness of Fit Test. T-Test was used for the intergroup analysis of data that conformed to the normal distribution, and Mann Whitney U test was used for the analysis of non-compliant data. Comparisons of categorical data were made with the Chi-Square Test (Fisher's Exact Test when necessary). Risk factors and odds ratio values for intensive care need due to COVID-19 were determined by Binary Logistic Regression Analysis. Analyzes were done with IBM SPSS (Statistics Package Program for Social Sciences) version 24.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was taken as $p < 0.05$.

RESULTS

While the average age of 403 patients who were followed up at the pandemic hospital due to COVID-19 was 46.50 ± 15.86 years, a statistically significant difference was found between the groups (60.15 ± 15.72 for Group 2, 45.28 ± 15.31 for Group 1; $p < 0.001$). The body mass index (BMI) values of the patients in Group 2 (29.98 ± 5.55 vs 27.60 ± 5.20) and the length of hospital stay (18.88 ± 16.47 vs. 8.99 ± 3.47 , $p = 0.02$) were statistically significantly higher compared to the patients in Group 1. It was determined that 55.9% of the patients in group 1 were female, whereas 69.7% of the patients in group 2 in need of intensive care were male ($p = 0.005$). No significant difference was found in terms of smoking and pregnancy ($p = 0.614$, $p = 1.000$, respectively) (Table 1).

The rates of hypertension (HT), diabetes mellitus (DM), chronic heart disease (CHD), and chronic obstructive pulmonary disease (COPD) (45.5%, 27.3%, 21.2%, and 27.3%, respectively) in patients in Group 2 were compared to patients in Group 1 (23.4%, 13.0%, 6.4%, and 5.7% respectively) were found to be statistically significantly higher ($p < 0.05$). There was no significant difference in terms of chronic kidney disease (CKD) rates ($p = 0.216$). The rates of 'severe' and 'critical' pneumonia in group 2 patients (42.4% and 45.5%, respectively) were found statistically significantly higher than Group 1 patients (4.2% and 0.6%, respectively) ($p < 0.001$ respectively) at

hospital admission. While all of Group 1 patients (100.0%) were discharged with recovery, 27.3% of Group 2 patients died ($p < 0.001$), while the COVID-19 fatality rate was found to be 27.3% in intensive care patients (Table 2).

Table 1. Comparison of groups in terms of some socio-demographic and clinical characteristics

	Group 1 (Clinic Patients) (n=370)	Group 2 (ICU Patients) (n=33)	Total (n=403)	p
Age (year) (Avg $\pm$ Ss)	45.28 $\pm$ 15.31	60.15 $\pm$ 15.72	46.50 $\pm$ 15.86	0.013*
BMI (kg/m ²) (Avg $\pm$ Ss)	27.60 $\pm$ 5.20	29.98 $\pm$ 5.55	27.79 $\pm$ 5.26	0.020**
Length of stay in the hospital (day)	8.99 $\pm$ 3.47	18.88 $\pm$ 16.47	9.90 $\pm$ 6.59	0.002**
Smoking (n, %)				
No	307 (85.0%)	27 (81.8%)	373 (84.8%)	0.614***a
Yes	54 (15.0%)	6 (18.2%)	4 (15.2%)	
Pregnancy (n, %)				
No	340 (98.8%)	33 (100.0%)	373 (98.9%)	1.000***a
Yes	4 (1.2%)	0 (0.0%)	60 (1.1%)	
Gender (n, %)				
Female	207 (55.9%)	10 (30.3%)	217 (53.8%)	0.005***
Male	163 (44.1%)	23 (69.7%)	186 (46.2%)	
Total	370 (100.0)	33 (100.0)	403 (100.0)	

* T Test ** Mann whitney U test *** Chi-square test (aFisher's exact test)

In intensive care patients in Group 2, the median values of CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), lactic dehydrogenase (LDH), fibrinogen, D-dimer, ferritin, creatinine, troponin, sedimentation, and urea were statistically significantly higher than in Group 1 patients ($p < 0.05$), platelet values were found to be significantly lower ($p < 0.05$) (Table 3).

In our study, while 3 or more coagulation markers were not observed in any "living" patient, they were found in 25% of the patients with "ex". Three or more SIC criteria were found to be 1.5% in survivors, 62.5% in those who were dead, and DIC criteria were found in 1.5% in surviving patients and 25% in patients who are ex. It was found that as the QSOFA, SIC, DIC, and Coagulation marker scores increased, the percentage of patients who died significantly increased (Table 4).

According to univariate logistic regression analysis for risk factors for mortality due to COVID-19; Age, HT, COPD, PT, and high fibrinogen levels were found to increase the mortality risk rates statistically ($p < 0.05$). It was found that a 1 unit increase in age increased the need for intensive care by 1.13 times (OR=1.130, 95% CI=1.068-1.197). It was determined that the most important factors increasing the mortality risk were the presence of COPD (OR=18.385, 95% CI=4.633-72.953) and the presence of HT (OR=3.832, 95% CI=1.008-14.576). Age, PT, and fibrinogen levels were found to increase mortality 1-1.1 times (Table 5). D-dimer levels were not detected as a risk factor for mortality (OR=1.001, 95% CI=1.000-1.001).

Table 2. Comparison of groups according to comorbid disease rates

	Group 1 (Clinic Patients) (n=353)	Group 2 (ICU Patients) (n=33)	Total (n=403)	p
Hypertension (n, %)				
No	265 (76.6%)	18 (54.5%)	283 (74.7%)	0.010**
Yes	81 (23.4%)	15 (45.5%)	96 (25.3%)	
DM (n, %)				
No	301 (87.0%)	24 (72.7%)	325 (85.8%)	0.035**
Yes	45 (13.0%)	9 (27.3%)	54 (14.2%)	
CHD (n, %)				
No	322 (93.6%)	26 (78.8%)	348 (92.3%)	0.008**
Yes	22 (6.4%)	7 (21.2%)	29 (7.7%)	
CKD (n, %)				
No	335 (97.7%)	31 (93.9%)	366 (97.3%)	0.216**
Yes	8 (2.3%)	2 (6.1%)	10 (2.7%)	
COPD (n, %)				
No	333 (94.3%)	24 (72.7%)	357 (92.5%)	<0.001**
Yes	20 (5.7%)	9 (27.3%)	29 (7.5%)	
Total	353 (100.0)	33 (100.0)	386 (100.0)	
Presence of pneumonia (n, %)				
No	114 (34.23%)	2 (6.1%)	116 (31.7%)	<0.001*
Mild	203 (61.0%)	2 (6.1%)	205 (56.0%)	
Severe	14 (4.2%)	14 (42.4%)	28 (7.7%)	
Critical	2 (0.6%)	15 (45.5%)	17 (4.6%)	
Treatment Result (n, %)				
Discharged with healing	370 (100.0%)	19 (57.6%)	389 (96.5%)	<0.001*
Exitus	0 (0.0%)	9 (27.3%)	9 (2.2%)	
Referral to another hospital (Unknown outcome)	0 (0.0%)	5 (15.2%)	5 (1.2%)	
Total	370 (100.0)	33 (100.0)	403 (100.0)	
* Chi-Square Test (aFisher's Exact Test)				

* Chi-Square Test (aFisher's Exact Test)

Table 3. Comparison between and within groups of COVID-19 cases followed in intensive care and ward in terms of cytokine levels

	Group 1 (Clinic Patients) (n=370)	Group 2 (ICU Patients) (n=33)	p
	Median (min-max)	Median (min-max)	
HGB	13.8 (5.2-18.1)	14.1 (10.1-16.9)	0.433*
WBC	5400 (2300-20800)	5600 (3700-26700)	0.211*
Lymphocyte	1490 (117-28400)	1120 (370-22800)	0.314*
Platelet	208000 (15000-616000)	166500 (25000-391000)	0.011*
CRP	6.3 (0.2-218.8)	51.02 (5.98-508)	<0.001*
ALT	21 (6-400)	24 (3-118)	0.139*
AST	23 (1-1020)	33 (15-101)	<0.001*
PT	10.5 (0.94-28.7)	11.6 (1.05-16.9)	0.001*
aPTT	24.8 (0.8-38.7)	25 (1.2-36.7)	0.780*
LDH	199 (17-520)	328.5 (122-1523)	<0.001*
Fibrinogen	318 (54-683)	439 (85-696)	0.001*
D-dimer	370 (0-4800)	520 (40-3890)	0.004*
Ferritin	66.8 (1-1486)	160.5 (10-975)	0.010*
Creatinine	0.85 (0.53-13.7)	1 (0.6-11)	0.009*
Troponin	2.72 (0.7-198.9)	8.11 (2.5-72.1)	<0.001*
Sedimentation	24 (1-107)	47 (9-80)	<0.001*
Urea	27.8 (3-74)	34.2 (7-188)	0.002*

* Mann whitney U test

Table 4. Comparison of Qsofa and coagulation markers in deceased and surviving patients

	Living Patients (n=133)	Ex Patients (n=8)	Total (n=141)	p
Qsofa (n, %)				
0	104 (78.2%)	2 (25.0%)	106 (75.2%)	<0.001* ^a
1	27 (20.3%)	2 (25.0%)	29 (20.6%)	
2	2 (1.5%)	3 (37.5%)	5 (3.5%)	
3	0 (0.0%)	1 (12.5%)	1 (0.7%)	
SIC (n, %)				
0-2			134 (98%)	<0.001* ^a
3-5	131 (98.5%)	3 (37.5%)	12 (8.5%)	
	2 (1.5%)	5 (62.5%)		
DIC (n, %)				
0-2	131 (98.4%)	6 (75.0%)	110 (78%)	0.001* ^a
3-4	2 (1.5%)	2 (25%)	4 (2.8%)	
Coagulation markers (n, %)				
0-2	133 (100%)	6 (75%)	139 (98.6%)	<0.001* ^a
3-5	0 (0%)	2 (25%)	2 (1.4%)	
Total	133 (100.0)	8 (100.0)	144 (100.0)	
* Chi-square test (aLinear-by-Linear Association)				

* Chi-square test (aLinear-by-Linear Association)

Table 5. Univariate logistic regression analysis for risk factors for the need for intensive care due to COVID-19

Risk Factors	B	SE	OR (Exp β)	95% CI	p
Age	0.123	0.029	1.130	1.068-1.197	<0.001*
HT					
No	1.343	0.682	1.0		
Yes			3.832	1.008-14.576	0.049*
COPD					
No	2.912	0.703	1.0		<0.001*
Yes			18.385	4.633-72.953	
PT	0.152	0.064	1.164	1.027-1.320	0.018*
Fibrinogen	0.07	0.03	1.007	1.001-1.013	0.023*
D-dimer	0.001	0.00	1.001	1.000-1.001	0.020*

*Binary logistic regression test (Enter method)

**OR=Odds ratio, CI=Confidence interval, SE=Standard error

DISCUSSION

As a result of our study, it was observed that the majority of critically ill patients in need of intensive care were older, had higher BMIs, and had additional systemic diseases such as HT, DM, and COPD. When laboratory tests were examined, it was found that platelet values were lower, D-Dimer, fibrinogen, PT, LDH, and CRP values were higher in patients requiring intensive care. It was seen that the most important factors determining mortality were the presence of COPD and HT. PT, fibrinogen, and increased age were found to be poor prognostic factors.

Coagulation parameters can be affected at different levels in the COVID-19 clinic, depending on the severity of the disease. Among these parameters, D-dimer, fibrinogen, and fibrin split products (FSP) increase significantly, while PT, aPTT may be normal or slightly prolonged. Although thrombocytopenia is uncommon, it appears in the later days of the disease in parallel with the severity of the disease.¹¹

In their study in which Tang et al.¹⁰ associated coagulopathy with poor prognosis in the first months of the pandemic, they found that D-dimer and fibrinogen, as well as prolonged PT, aPTT values, and thrombocytopenia were observed in COVID-19 patients at the first admission. In subsequent studies, it was emphasized that the platelet counts were higher than other coronavirus infections.¹² During the follow-up in a series of 50 patients in an ICU in Ireland, high D-dimer and fibrinogen values, platelet counts, and PT were found to be normal.¹³ Since the disease is not recognized, the implications of Tang are thought to be due to the patients being admitted to the hospital with a more serious clinic and late.

D-dimer, one of the coagulation parameters, is the degradation product of cross-linked fibrin showing increased thrombin formation and fibrin melting by plasmin.¹⁴ However, increased D-dimer levels are also common in acutely ill individuals with a range of infectious and inflammatory diseases. COVID-19 related D-dimer has been reported to increase at the level of 0.9 mg /L in 36% of cases.^{6,7} In critically ill patients, D-dimer levels are frequently higher compared to cases with a mild clinical course and are inversely proportional to survival.^{4,6,14} Zhou et al.^{6,7} showed that 24% of living patients in their study had D-dimer above 1 mg/L, whereas 81% of mortal cases had D-dimer higher than 1 mg/L and increased gradually.

Similarly, Tang et al.¹⁰ showed that the D-dimer was higher than 3 mg/L in more than 85% of COVID-19 cases with death. In addition, although the threshold value of D-Dimer measurements in showing coagulation cannot be determined exactly, studies have recognized that D-Dimer measurements are also valuable in identifying individuals who could potentially benefit from anticoagulation treatment.^{5,10,14} In our study, as a result of univariate logistic regression analysis, the D-Dimer value was not evaluated as a prognostic factor predicting intensive care admission. However, in the first admission tests, D-dimer values were found to be statistically significantly higher in critical patients who required ICU admission compared to patients followed in the clinic.

Fibrinogen is the most specific test for DIC diagnosis (100%), but its sensitivity is low (22%).^{5,15} In the International Society of Thrombosis and Hemostasis (ISTH) guidelines, recommended as one of the overt DIC diagnostic parameters.^{5,16,17} Fibrinogen is often elevated in patients with sepsis but may be low in severe cases of DIC. Fibrinogen levels are monitored at 4.55 g/L and above in most COVID-19 patients. The degree of fibrinogen elevation, which is strongly associated with interleukin (IL)-6 level, has not been shown to be consistently associated with mortality.^{5,10} However, progressive reduction in fibrinogen level has been associated with poor prognosis but has been shown that it occurs in later stages of the disease, and it is measured less than 1g/L in approximately 29% of patients who died. With these detections, fibrinogen does not appear to be useful in early detection of poor progression in COVID-19. In our study, in critically ill patients who need to be followed up in the intensive care unit, fibrinogen levels were found to be statistically significantly higher than those followed in the clinic. According to regression analysis, the OR value of 1.007 makes fibrinogen a weak predictor of poor prognosis.

PT elevation is among the DIC diagnostic criteria determined by ISTH and PT is used for the diagnosis of overt DIC.^{5,16,17} Unlike traditional sepsis, the PT is normal or slightly prolonged in most patients in COVID-19, prolonged PT is detected in 5% of COVID-19 cases.^{3,5} However, significant PT prolongation has been shown in critical and dying cases of COVID-19.^{4,5,7} In the study of Tang et al.¹⁰, mean PT values were found to be 1.9 seconds longer in mortal COVID-19 cases. In addition, they reported that approximately 48% of mortal cases showed prolonged PT prolongation in the course of the disease for more than 6 seconds. Therefore, the level of PT helps clinical follow-up and evaluation of the course of the disease, especially in severe cases. Progressive prolongation of PT is considered a predictor of poor prognosis and mortality.⁵ In accordance with the literature, in our study, it was found that patients with long PT measurements at first admission required more intensive care (OR 1.164) and were found to be a poor prognosis indicator.

aPTT is often elevated in the severe form of DIC yet, it is not included in criteria for diagnosing overt DIC by ISTH.^{15,16} Unlike traditional sepsis, aPTT is usually normal in COVID-19 patients, and aPTT prolongation occurs only in 6% of patients.^{3,5} aPTT were not different in critically ill patients and no significant correlation with disease progress was shown.^{4,5,10} In our evaluations, no significant difference was found between critical and non-critical patients in terms of aPTT values. Therefore, aPTT has not been evaluated as an indicator of poor prognosis in COVID-19.

In patients who progress to DIC, thrombocytopenia is common and often means clinical decompensation and organ dysfunction. However, in the COVID-19 clinic, the platelet count is usually normal or slightly decreased and thrombocytopenia is occurred in 12-36% of patients with a platelet count below $100 \times 10^9/L$ in 5% of cases.^{3-6,10} In a meta-analysis of 1779 COVID-19 patients, male patients with severe COVID-19 infection found more thrombocytopenia than women with mild clinical course.¹¹ Severe thrombocytopenia has been reported with the progression of the disease in COVID-19 patients resulted in death. In our study, although the course of platelets was investigated during the treatment process, the first platelet values on admission to the hospital were found to be significantly lower in critical patients who needed follow-up at ICU compared to clinical patients, and it was found to be consistent with the literature. In our study, platelet values at the first admission to the hospital were found to be significantly lower in critically ill patients requiring follow-up in the ICU compared to clinical patients. In our study, the course of platelet amount during treatment was not included in discussion. Consistent with literature, PLT levels at hospitalization were found to be significantly lower in patients who needed ICU.

DIC is an acquired syndrome that triggers intravascular activation of coagulation causing organ dysfunction by causing microvascular damage.¹⁵⁻¹⁸ DIC is seen in 30-50% of patients with severe sepsis.^{19,20} Thrombosis and bleeding it causes result in organ dysfunction. DIC can be overt or latent. Latent DIC cannot be easily noticed since it is caused by an instability between activation and inhibition of the coagulation system and occurs with thrombus rather than bleeding. Overt DIC, that caused by significant irregularity in the coagulation system, results in widespread microvascular thrombosis, bleeding, and consumption coagulopathy and is easier to diagnose.^{1,5,18,19} Unlike sepsis-associated coagulopathy in coagulopathy due to COVID-19, most patients do not have DIC, and it is interpreted as clinical latent DIC in detected cases. Therefore, the development of DIC in COVID-19 patients often occurs with vascular thrombosis. This is a late sign for all possible medical interventions that could reverse the underlying process in treatment.⁵ In our study, two (22.2%) of the cases who died met the DIC criteria, and no evidence of bleeding was observed in the clinic in both cases.

In Tang's study, DIC was detected in 71.4% of the cases who died, and the average time from admission to DIC was reported as 4 days.¹⁰ Although thromboembolic events are generally seen with the increase in the severity of the disease, a case admitted to the hospital with acute splenoportal mesenteric vein thrombosis with elevated CRP, d-dimer has been reported.²¹ Detection of diffuse alveolar damage and microvascular thrombus in patients who died in postmortem autopsy studies reveals the effect of coagulation disorders on prognosis in covid-19.²²

The COVID-19 epidemic in our country started in March 2020, and the health system reacted quickly to combat the epidemic, awareness of the disease was created in our society, and the follow-up process began with early application to health centers. However, scientific research on the disease process is also planned.²³⁻²⁶ An important reason why we found the rate of DIC to be low in our study may be that, thanks to the strong health system in our country, patients were admitted early and the patients were observed in a light clinic.

Hadid et al.⁵ noted that with a few key differences, severe CIC in its late stages can progress like sepsis-induced coagulopathy (SIC). Significant thrombocytopenia, occurring in 22-58% of patients with SIC, is either absent or very mild in most COVID-19 patients with CIC.^{5,27} Again, in these patients, mostly PT and aPTT are detected as normal or slightly long, while the prevalence of hypofibrinogenemia is less than classical sepsis.⁵ These differences may explain the rarity of bleeding in COVID-19 patients.^{5,14} On the other hand, it is stated that the disproportionate high level of D-dimer with respect to changes in coagulation parameters frequently seen in COVID-19 reflects a significant increase in thrombin production and fibrinolysis. However, since DIC is not typically seen in COVID-19, it is thought that organ damage during this process may be limited to certain organs such as the lungs and kidneys.⁵

In our study, it is known that severe pneumonia, which is the strongest marker of poor prognosis in triage, has distinctive features compared to traditional pneumonia. COVID-19 patients have been found to develop an unregulated host response that causes excessive release of inflammatory cytokines and chemokines. The release of these molecules induces a macrophage activation syndrome-like pathway that triggers cytokine storm, which initiates or further increases pulmonary coagulopathy and microvascular thrombosis.^{5,28}

In addition to the SIC (PT, Platelet, SOFA), DIC (Platelet D-dimer, PT, Fibrinogen) scoring recommended by ISTH during the hospitalization of the patients, the coagulation criteria recommended in the guideline of the ministry (platelet <100.000 , PT >3 sec, APPT >5 sec, fibrinogen <150 mg, D-dimer $>4-6$ times) was followed. As a result of our study, it was found that the percentage of patients who died increased significantly as the scores of QSOFA, SIC, DIC, and coagulation markers increased.

CONCLUSION

The fact that our study covers the beginning period of the pandemic and data from a single center can be considered as a limitation. However, analysis of laboratory parameters and risk factors is important in understanding the clinical course of the disease and will guide future studies. During this period, all patients diagnosed with COVID-19, including patients with mild clinical symptoms, were hospitalized and isolated, and the patients were taken under clinical observation. In a study conducted in this population, coagulation parameters were found to be a weak marker to show a poor prognosis. Rather than evaluating the coagulation parameters as isolated, having a coagulation marker score of 3 or above is seen as a stronger indicator in predicting a poor prognosis. In order to reveal the effectiveness of coagulation parameters in predicting intensive care need and mortality, it is necessary to conduct studies in larger series of the later stages of the pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 08.07.2020, Decision No: 2135).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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How much did the February 6 earthquakes affect a distant hospital?

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ABSTRACT

Aims: In the earthquakes that took place in Kahramanmaraş on 06.02.2023, a large number of casualties and injuries were observed. Organizations and healthcare personnel providing healthcare services in the earthquake regions have significantly lost their functions and there have been disruptions in the provision of healthcare services. In this study, we analyzed the patients who applied due to being affected by the earthquake in Kastamonu, one of the provinces far from the epicenter of the earthquake.

Methods: The records of 135 patients who admitted to Kastamonu Training and Research Hospital Emergency Medicine Clinic with the diagnosis of earthquake damage between 7-16 February 2023 were examined. They were divided into two groups: patients with trauma and other non-traumatic complaints. Demographic data, complaints, requested tests, final diagnoses, consultation and hospitalization status of the patients were recorded.

Results: While 50 patients applied with complaints of trauma caused by the earthquake, 85 patients applied to the emergency department due to diseases other than trauma. 10 of these patients were hospitalized and the others were discharged. It was observed that soft tissue trauma was the most common diagnosis in applications for trauma reasons, and upper respiratory tract infection was the most common diagnosis for non-traumatic reasons.

Conclusion: In our study, since we were a hospital far from the center of the earthquake, there were no patient applications on the first day, and since the patients arrived over the days, no problems arose during the triage and intervention stages.

Keywords: Earthquakes, emergency medicine, trauma

INTRODUCTION

Turkey is one of the countries where earthquakes are common and many large earthquakes have occurred until today. On 06.02.2023, at 04:17 and 13:24 local time in Türkiye, two earthquakes with a magnitude of Mw 7.7 and Mw 7.6 occurred, the epicenters of which were Pazarcık (Kahramanmaraş) and Elbistan (Kahramanmaraş), respectively. Both earthquakes were felt very strongly in Kahramanmaraş, Hatay, Adıyaman, Gaziantep, Malatya, Kilis, Diyarbakır, Adana, Osmaniye, Şanlıurfa and Elazığ, causing loss of lives and heavy damage.¹ Aftershocks, which were seen in large numbers, also increased the number of damage and injured and became a reason for the people to leave the region.

In the two-month period after the earthquake, the death toll was declared as more than 50 thousand and it is estimated that this number will increase even more. Although the number of injured could not be determined exactly, apart from injuries, the quality of life of many people was

obviously affected due to homelessness and harsh weather conditions. Organizations providing health services and health personnel in earthquake regions have also lost their functions to a great extent and there have been disruptions in the provision of health services. For these reasons, patients were attempted to be transferred to hospitals in the provinces that were not affected by the earthquake, and the injured who left the earthquake area applied to hospitals in other provinces.

Kastamonu is a province located 707 km from the epicenter of the earthquake, but due to the large number of injured and homeless people, many people were transported here by their own means and by the state. After the earthquake, hospitals in the nearby provinces usually cover the majority of the injured, but the excessive patient load seen after the 6 February earthquakes also affected very distant provinces. In this study, we analyzed the patients who presented due to earthquake effects in Kastamonu, which is one of the distant provinces.

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METHODS

The study protocol was approved by the Local Ethics Committee of Kastamonu University Medical Faculty (Date: 19/04/2023, Decision No: 2023-KAEK-35). Patients who presented to the hospital in the 10-day period after the earthquake were retrospectively screened from the hospital automation system. The records of 135 patients who presented to the Emergency Medicine Clinic of Kastamonu Training and Research Hospital between 7-16 February 2023 with the diagnosis of earthquake damage were examined. The patients were divided into two groups as those with trauma and non-traumatic complaints. Patients' demographic data, complaints, ordered investigations, final diagnosis, consultation and hospitalization status were recorded. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The obtained data were entered into Microsoft Excel 2007 (Microsoft Corporation, Redmond, CA) and analyzed using SPSS (v20; IBM, Armonk, NY). Descriptive statistics were given as number (n), percentage (%) and mean.

RESULTS

The first presentation to our hospital due to damage from the earthquake was on February 7. It was seen that a total of 135 patients presented in the 10 days between 7-16 February. Of the patients, 81 were female and 54 were male, and the mean age was 41 years. While 132 of the patients presented to our hospital on their own, three patients were brought to the emergency room by ambulance from places such as dormitories and nursing homes in our city where the injured people were placed after the earthquake. Demographic data of the patients are shown in Table 1.

Table 1. Demographic data of the patients

	Trauma (n=50)	Non-traumatic (n=85)
Female	32 (64%)	49 (58%)
Male	18 (36%)	36 (42%)
Mean age (years)	41.37	
Presentation		
Ambulance	2 (4%)	1 (1.1%)
Outpatient	48 (96%)	84 (98.9%)

While presentations due to trauma were more commonly observed in the first days after the earthquake, admissions for other reasons increased in the following days. The reasons for the presentations of the patients according to the days are shown in Figure.

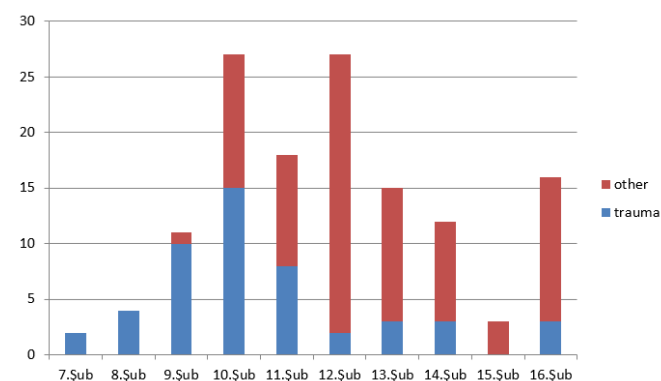


Figure. Analysis of patients admitted with trauma and other reasons after the earthquake by days

While a total of 50 patients presented with the complaint of trauma caused by the earthquake, 85 patients presented to the emergency department due to diseases other than trauma. Ten of these patients were hospitalized and the others were discharged. It was observed that soft tissue trauma was the most common diagnosis in trauma-related admissions, and upper respiratory tract infection was the most common among non-traumatic causes. Complaints of admission, diagnoses, consultation and hospitalization status are shown in Table 2.

Table 2. Patients' diagnoses, consultation and hospitalization requirements

	Trauma (n=50)	Non-traumatic (n=85)
Extremity fractures	7 (14%)	-
Lumbar fractures	2 (4%)	-
Soft tissue trauma	41 (82%)	-
Pneumonia		5 (5.8%)
Upper respiratory tract inf.		34 (40%)
Drug supplement		6 (7%)
Other		40 (47%)
Consultation	9 (18%)	7 (8.2%)
Orthopedics	7 (14%)	-
Neurosurgery	2 (4%)	-
Thoracic diseases	-	3 (3.5%)
Cardiology	-	1 (1.1%)
Internal medicine	-	1 (1.1%)
Gynecology	-	2 (2.3%)
Psychiatry	-	1 (1.1%)
Hospitalization	5 (10%)	5 (5.8%)
Orthopedics	4 (8%)	-
Neurosurgery	1 (2%)	-
Intensive care unit	-	1 (1.1%)
Thoracic diseases	-	2 (2.3%)
Internal medicine	-	1 (1.1%)
Psychiatry	-	1 (1.1%)

The investigations ordered for the patients who presented to the emergency department with the diagnosis of damage from the earthquake are also shown in Table 3. While investigations were ordered in almost all of the trauma patients (94%), 67% of the patients who presented for non-traumatic reasons were not ordered any examination.

Table 3. Investigations ordered for the patients

	Trauma (n=50)	Non-traumatic (n=85)
X-ray	30 (60%)	7 (8.2%)
CT	18 (36%)	9 (10.5%)
USG	1 (2%)	1 (1.1%)
Blood	12 (24%)	20 (23.5%)
No order	3 (6%)	57 (67%)

DISCUSSION

Earthquake is a large scale natural disaster that affects a large population in a wide geography and has medical, economic and social consequences. Two earthquakes with a magnitude of 7.7 and 7.6 Mw, which occurred in Pazarcık and Elbistan districts of Kahramanmaraş on February 6, 2023, caused loss of lives and destruction in 11 provinces in the vicinity. The

earthquake caused high levels of loss of lives and properties in 11 provinces including Adana, Adıyaman, Diyarbakır, Elazığ, Gaziantep, Hatay, Kahramanmaraş, Kilis, Malatya, Osmaniye and Şanlıurfa.²

Kastamonu is a province quite far from Kahramanmaraş, the epicenter of the earthquake. However, the high number of injuries due to the earthquake caused people to go to almost all provinces of the country, as staying in the earthquake zone became because of the aftershocks and housing problems. It is observed that 135 patients presented to the Kastamonu Training and Research Hospital Emergency Service in the first 10 days after the earthquake. The number of patients admitted daily has increased by around 13-14 on average, but since the average number of admissions to the emergency service is already 500-600, it seems that there is no an increase that will affect the intensity of the emergency service.

One of the largest studies to investigate earthquake trauma was conducted after the Hanshin-Awaji Earthquake in Japan. Examination of the presentations made to 95 hospitals revealed that the most common traumas caused by earthquakes were extremity and spine traumas. Soft tissue trauma was reported in 35%.³ In our study, the most common reason for presentation in trauma-related admissions was extremity injuries, and soft tissue trauma was diagnosed in the vast majority of these patients (82%). Only seven patients had a fracture in the extremity, and two patients had a lumbar fracture. Ten percent of the patients admitted with trauma were hospitalized. This result confirms the opinion that cases with major trauma refer to closer centers due to the distance of Kastamonu province from the earthquake epicenter.

Chest trauma was the most common cause of death from trauma in the young population.⁴ However, in a study conducted after the 1999 earthquake, the highest rate of post-earthquake deaths was due to abdominal trauma by 27.3%.⁵

In another study revealing the problems experienced in the emergency services after the earthquake, it was reported that 70.4% of the injured who were brought to the emergency department after the earthquake had simple minor injuries that were not of vital importance.⁶ In our study, there were no life-threatening patients admitted due to trauma because of the distance of our province.

In a study conducted after the Van earthquake, it was reported that 754 (47.7%) of 1582 patients who presented to the emergency department with earthquake-related injuries were admitted on the 1st day of the earthquake.⁷ It was reported in the same study that while 149 of the patients were referred to hospitals outside the province, 301 were admitted to the wards and the most hospitalizations (n=84, 28%) were in the orthopedics and traumatology clinic. In the Gujarat earthquake in India, orthopedic injuries were prominent in 234 (51%) of the 534 injured.

In our study, while no patient was admitted on the first day of the earthquake, the first patient was presented on 7 February. In the first days of the earthquake, presentations were mostly due to trauma, but in the following days, health problems such as struggling to survive outside and other diseases due to winter conditions, and the inability of those with chronic diseases to take their medications were also observed. Of the 135 patients who presented to us, 50 were due to trauma and 85 were due to other non-traumatic diseases. In our study, the highest rate of hospitalization was in the orthopedics and traumatology clinic with 8%. The lower rate of hospitalization to the orthopedics

and traumatology clinic in our study than in the literature can be explained by the higher number of patients presenting for non-traumatic reasons.

Considering the presentations with non-traumatic reasons, it was observed that 34 (40%) patients presented with upper respiratory tract symptoms and were discharged with a prescription. The winter season, when the earthquake occurred, increased the incidence of such diseases due to the fact that people stayed in cold weather for a long time as a result of the destruction and low self-care. Hospitalization was made for five of the 85 patients who presented for reasons other than trauma, and this number did not create much of a burden for our hospital.

X-ray was ordered for 30 patients and computed tomography for 18 patients during the diagnosis processes of patients who applied due to trauma. The vast majority (67%) of the patients who applied for non-traumatic reasons were examined and prescribed on an outpatient basis without ordering an investigation.

One of the most important problems experienced after major earthquakes is that the panic and uncertainty in the earthquake region cause disruptions in the first response and triage process, and as a result, the emergency services can be exposed to a patient load far above their capacity.⁹ In our study, since we were a hospital far from the earthquake center, there were no patient admissions on the first day, and there was no problem in the triage and intervention stages, as the patients came in days. The records of the persons affected in such disaster events should also be kept properly. Necessary sensitivity has been shown in this regard.

In another study that analyzed the lessons learned from the Marmara and Van earthquakes, it was emphasized that the number of deaths and injuries was related to the adequacy of preparedness and early intervention rather than the severity or magnitude of the earthquakes.¹⁰ Therefore, adequate preparations must be made in all clinics, especially emergency services.

CONCLUSION

Our country is in a geography where earthquakes are frequent and the probability of recurrence of such disasters is quite high. It is very important to raise awareness against the number and variety of injuries that may occur after an earthquake, as well as measures such as building the structures on solid ground and resistant to earthquakes. It is also obvious that our health system and emergency services, which are the units that will make the first interventions, should be developed on disaster medicine and the trainings on this subject should gain continuity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The necessary approval was received from the Kastamonu University Clinical Researches Ethics Committee (Date: 19.04.2023, Decision No: 2023-KAEK-35).

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors declare no conflict of interest.

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Author Contributions: MK designed and wrote manuscript, MK and FMKG made the literature search and supervised the conduct of data collection, FMKG critically revised the manuscript.

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Ultrasound-guided neuromonitoring methods in the intensive care unit

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ABSTRACT

Ultrasonography (USG) is a non-invasive, portable, bedside, reproducible, radiation-free, inexpensive, and easily accessible imaging method. It provides morphological and functional information. It allows for diagnosis, monitoring, and guiding treatment. The usage areas of USG in the ICU are broad. In interventional procedures (thoracentesis, vascular interventions, percutaneous tracheostomy), evaluation of lung pathologies (pneumothorax, pleural effusion, pulmonary edema, consolidation, A-line, B line), diaphragm evaluation, abdominal imaging (trauma, kidney, liver), diagnosis and follow-up of deep vein thrombosis and the assessment and follow-up of fluid resuscitation (IVCI) and neuromonitoring. USG-guided neuromonitoring can detect stenosis or occlusion of intracranial arteries, monitor the development of patients with vasospasm after subarachnoid hemorrhage, detect cerebral embolism, evaluate the cerebral collateral system, and determine brain death. It can also indirectly calculate intracranial pressure (ICP) and cerebral perfusion under USG guidance.

Keywords: Ultrasound, intensive care unit, neuromonitoring, intracranial pressure, optic nerve sheath diameter, transcranial doppler

INTRODUCTION

Ultrasonography (USG) is an imaging method based on the detection and conversion of ultrasound waves reflecting from tissue surfaces of different densities and converting them into images (Pulse-Echo). The introduction of USG technology into clinical use was in the 1950s. The use of USG in intensive care units has gained popularity in the last 20 years.

USG is a valuable tool because of its ability to quickly and efficiently identify or rule out specific pathologies. In the literature, especially in studies conducted in intensive care units, USG has been defined as the stethoscope of the 21st century for the evaluation of many organs.¹⁻³

The goals of USG protocols for the critically ill are to be a part of the physical examination of the critically ill, to reduce complications in interventional procedures in the intensive care unit, and to predict changes in the treatment decision and treatment process.

USG is a non-invasive, portable, bedside, reproducible, radiation-free, inexpensive, and easily accessible imaging method. It provides morphological and functional information. It allows for diagnosis, monitoring, and guiding treatment. Although it has disadvantages, it has many significant advantages.

Advantages:

- Easily accessible
- Easy to apply

- Cheap
- Does not cause severe discomfort to the patient
- No risk of ionizing radiation
- Can be applied at the bedside
- Can be repeated at frequent intervals
- Does not require opaque material
- Provides functional, morphological, and physiological information
- Often crucial in the assessment of vascular flow
- Cross-sectional modalities typically only show vascular patency, whereas USG can detect flow direction, velocity, and waveform

The usage areas of USG in the ICU are broad. In interventional procedures (thoracentesis, vascular interventions, percutaneous tracheostomy), evaluation of lung pathologies (pneumothorax, pleural effusion, pulmonary edema, consolidation, A-line, B line), diaphragm evaluation, abdominal imaging (trauma, kidney, liver), diagnosis and follow-up of deep vein thrombosis and the assessment and follow-up of fluid resuscitation (IVCI) and neuromonitoring.⁴⁻⁶

USG-guided neuromonitoring can detect stenosis or occlusion of intracranial arteries, monitor the development of patients

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with vasospasm after subarachnoid hemorrhage, detect cerebral embolism, evaluate the cerebral collateral system, and determine brain death. It can also indirectly calculate intracranial pressure (ICP) and cerebral perfusion under USG guidance.

EVALUATION OF INTRACRANIAL PRESSURE

The average intracranial pressure value is 7-15 mmHg, and ICP >20 mmHg is a high ICP. It has been reported that increased intracranial pressure is associated with increased mortality and morbidity.⁷ Increased intracranial pressure (ICP) can result from various cerebral conditions, such as stroke, bleeding, malignancy, and trauma. Timely diagnosis and treatment of high ICP can prevent dramatic consequences such as cerebral ischemia and herniation and reduce mortality.

Invasive methods (intraventricular and intraparenchymal monitors) are still the gold standard in diagnosing and following increases in ICP. However, such complications as infection, bleeding, parenchymal damage, and misplacement may develop. It also requires neurosurgery expertise. Non-invasive alternative methods are recommended to be used to evaluate ICP; cranial CT and cranial MRI are the measurements of changes in tympanic membrane displacement, intraocular pressure, venous ophthalmic dynamometry, transcranial doppler and optic nerve sheath diameter (ONSD).⁸

Although non-invasive techniques such as computed tomography (CT) and magnetic resonance (MRI) can be used, these techniques are expensive, require time to achieve results, and cannot be applied at the bedside. Therefore, in unstable patients in the intensive care unit (deep hypoxia, hypotension, etc.), problems may be encountered during patient transport, limiting accessibility.⁹

This article will explain ONSD and transcranial Doppler, which can be measured by USG in intensive care neuromonitoring.

OPTIC NERVE SHEATH DIAMETER

The optic nerve is still surrounded by the dural sheath at the point where it emerges from the intracranial space into the orbital cavity. Therefore, the subarachnoid area surrounding the optic nerve is adjacent to the intracranial subarachnoid area. The anatomical relationship between the optic nerve and the subarachnoid space causes enlargement of the optic nerve sheath through the CSF in cases of increased intracranial pressure. Thus, optic nerve sheath diameter can provide information about ICP.^{10,11}

According to the modified Dandy criteria, papilledema is a criterion for diagnosing idiopathic intracranial hypertension.¹² As papilledema is optic disc edema caused by high ICP transmitted through the optic nerve sheath, the increase in ONSD must occur before the development of papilledema. Therefore, ONSD helps to recognize increased ICP earlier than the presence of papilledema. Recently, the measurement of optic nerve sheath diameter (ONSD) has grown as a non-invasive, accurate, safe, reproducible, and low-cost method to evaluate ICP.

In comparative studies, ONSD among patients with high ICP was significantly higher than among patients with normal ICP. Several studies have demonstrated a correlation between invasively measured ICP and ultrasonographic ONSD diameter (ONSD) measurements, with 95% sensitivity and

92% specificity for detecting high ICP. In addition, ONSD can be measured using CT and MRI, but the accuracy of measurements made with these two methods is lower than those made with USG.^{13,14}

In the study conducted by Lee et al.¹⁵, patients with better outcomes were found in patients with an ONSD <5mm in post-cardiac arrest. They reported that it may help estimates. In their study, Chelly et al.¹⁶ found high ONSD associated with poor prognosis and increased mortality in cardiac arrest patients. Robba et al.¹⁷ reported that ICP changes were correlated with ONSD changes in their meta-analysis. In addition, in this meta-analysis, ONSD was also correlated with ICU mortality.¹⁷ In another study by Robba et al.¹⁸, patients with traumatic brain injury were followed up with ONSD, and it was reported that it was correlated with invasive ICP. In this study they developed a formula with ONSD for non-invasive measurement of ICP in their study ($nICPONSD = 5 \times ONSD - 14$ ($nICPONSD$ in mmHg, $ONSD$ in mm)). In addition, the same study reported that ONSD was correlated with intensive care mortality and was an independent predictor of mortality.

Although the evaluation of changes in ICP by measuring ONSD with USG is in parallel with the results obtained with invasive methods in many clinical studies, it has been reported that the measurement is 'applicant-dependent' as the technique's weakness.^{19,20} Since the accuracy of ONSD measurement with USG is related to the experience of the person measuring it, Tayal et al.²¹ reported that learning to measure ONSD with USG is more accessible than learning to measure ONSD with Doppler USG or assessing papilledema. Moretti et al.²² stated that it would be sufficient to observe ten average and three pathological optic nerve diameters to perform optic nerve USG. It can be used with repetitive measurements both in ICP evaluation and when monitoring of ICP is required. Thus, it can assist in clinical decisions and early therapeutic interventions in neurocritical care. ONSD value in terms of clinical decision;

- If <5 mm, ICP did not increase
- If >6 mm, clinically reflects a significant increase in ICP
- Clinical correlation/presence of papilledema should be examined in ONSD values between 5 and 6 mm.²³

ONSD should be measured 3 mm behind the optic disc, as this distance is where the optic nerve sheath is exposed to maximum diameter fluctuations due to ICP.²⁴ Studies have reported that the mean ONSD does not change with age, weight, or height but varies with gender.²⁵

Ideal ONSD measurement technique (Figure):

- The patient is placed in the supine position.
- If the patient is conscious, the eyes are asked to close their eyelids in a neutral position (facing forward).
- Gel or sterile water is applied to the eyelids.
- Linear probes in the 7.5-10 MHz range are used for imaging according to current protocols.
- The depth on the USG device is set as 4-5 cm. This adjustment provides optimum contrast between the optic nerve sheath and the periorbital adipose tissue when focusing on the retrobulbar area.
- The transducer is placed on the eyelids, taking care not to apply pressure.
- In the retro bulbar position, the sheath diameter is measured 3 mm posterior to the globe in the longitudinal axis.

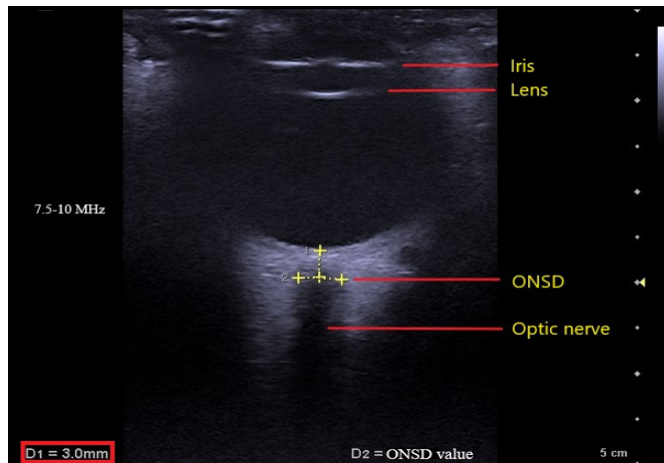


Figure. ONSD measurement technique

Two measurements should be made for each optic nerve. The first is the transverse plane in which the probe is placed horizontally; the second is the sagittal plane in which the probe is placed vertically. The result ONSD is the average of these measurements.

ONSD ultrasonography is a non-invasive, reproducible, and bedside method. This technique can be life-saving, especially when invasive ICP monitoring is contraindicated (e.g., due to coagulopathy) or when a specialist is unavailable for invasive monitor placement in an emergency.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Transcranial Doppler (TCD) ultrasound is a painless, non-invasive imaging method that can evaluate the brain's blood circulation using sound waves and detect medical problems that affect this circulation. With the widespread use of ultrasound in intensive care units (ICU), TCD has become an excellent alternative for patients requiring close follow-up. In particular, the fact that these patients require close monitoring, receive multiple treatments, often have unstable hemodynamics, and take critical drugs for this makes it difficult and sometimes even not permissible to transfer patients from ICU to computed tomography (CT) and magnetic resonance (MR). These problems cause time delays in the imaging of the patients, and as a result, serious issues can be experienced in diagnosis, treatment, and follow-up. TCD is an easy-to-use, reliable method that can be performed at the bedside without the need for patient transfer and does not interfere with the treatment and monitoring of patients.

TCD is mainly used in clinical practice for detecting and monitoring vasospasm in cerebral vessels in subarachnoid hemorrhage due to aneurysm rupture. In addition, ultrasound can detect stenoses and occlusions in the arterial system (Willis polygon and vertebrobasilar), evaluate the vessels in the intracranial circulation, detect cerebral microemboli, evaluate the reactivity of cerebral vasomotor activity, diagnose acute cerebrovascular diseases, evaluate arteriovenous malformations associated with encephalic sepsis, and treat encephalovenous malformations and associated brain dysfunction and encephalic sepsis-related brain dysfunction. Available. Ultrasound can be used as an auxiliary diagnostic method in confirming the clinical diagnosis of brain death.

Doppler takes its technical name from Christian Andreas

Doppler, who developed a device using double-bright colored lights in Prague in 1843. In the 1950s, Satomura and Kaneko used the first Doppler, the "rheograph".²⁶

Ultrasonography is applied with different methods. Information about the vessel wall, lumen width, and presence of atherosclerotic plaques can be obtained in B-mode ultrasonography and information about blood flow velocity with the Doppler technique. The principle of Doppler ultrasonography is that the radiating ultrasound waves emitted by the crystals detected by the Doppler probe applied on the vessel reflect the blood column in motion. If the reflected blood column is continuous, it is called a continuous wave; if it is in short bursts, it is called an intermittent wave. It is defined as "duplex ultrasonography," which is a combination of "real-time" imaging of the vessel (B-mode) and Doppler ultrasonography. Ultrasonography provides information about the vessel wall, while Doppler includes information about blood flow turbulence and the degree of stenosis if any.²⁷

Acoustic Windows

Bone windows are areas where ultrasonographic signals can be received at a certain depth during TCD application, and the bone thickness is thinner. There are three main bone windows:

- Orbital window:** The transorbital approach can examine the bilateral ophthalmic artery and internal carotid artery siphon.
- Temporal bone window:** Bilateral anterior, middle, and posterior cerebral arteries (ACA, MCA, and PCA, respectively) can be examined with the transtemporal approach.
- Foramen magnum window:** Intracranial vertebral arteries and basilar arteries are examined with a transforaminal or suboccipital approach.²⁸

Clinical Applications of Transcranial Doppler

1. Blood flow velocities:

a. Examination of extracranial vessels: Atherosclerotic lesions developing in the carotid artery bifurcation or carotid bulb may cause cerebrovascular events. The ischemic event may be due to an embolism ruptured from atherosclerotic plaque, or it may occur with hemodynamic failure. Small lesions do not affect the hemodynamic profile; however, lesions that cause narrowing of around 60% cause changes in blood flow velocities in the intracranial vessels. Minor atherosclerotic changes in the carotids result in distortions in waveforms in TCD. To summarize the findings to be obtained with TCD in carotid artery stenosis/occlusion, systolic and mean blood flow velocity and pulsatile index (PI) ($PI = \text{Systolic velocity} - \text{Diastolic velocity} / \text{Average velocity}$) decrease in ipsilateral MCAs; if the anterior communicating artery (ACoA) is open, mean and systolic blood flow velocities in the contralateral ACAs increase and flow in the ipsilateral ACA A1 segment reverses or disappears; if the posterior communicating artery (PCoA) is open, the mean and systolic blood flow velocities of the PCA, vertebral artery, basilar artery increase and the blood flow velocity in the ophthalmic artery is reversed.^{29,30}

b- Examination of intracranial vessels: Blood flow velocities in intracranial arteries can give essential findings. Generally, PI elevation is seen at low blood flow velocities. Diffuse blood flow velocity may indicate hemodynamic insufficiency; focal decreased blood flow velocity can be seen in focal arterial ectasia or proximal to the artery feeding the arteriovenous malformation. If there is stenosis in the artery, the blood flow velocity proximal to the stenosis is low, the PI is high, the blood

flow velocity is increased in the stenosis segment, and the blood flow velocity and PIs are low above the stenosis segment. Blood flow velocity changes can be detected with TCD only when the lumen narrowing exceeds 50-60%. In addition, it can be observed that while there is an occlusion in one artery due to the opening of the collaterals, the blood flow velocities in the other artery increase as a compensatory factor. For example, if ACoA is open in MCA occlusion, blood flow velocity increases in ACA and reverses blood flow velocity in the A1 segment. However, evaluating blood flow velocities at different depths and with contralateral arterial blood flow velocity is essential. For example, if the difference in blood flow velocity between the two MCAs is more significant than 30 cm/sec, there is unilateral stenosis or spasm. Focal stenosis should be considered if a blood flow velocity difference of more than 20 cm/sec is obtained in measurements made at different depths. To evaluate the difference between stenosis and vasospasm, if blood flow velocity is obtained from the same artery twice at a few days' intervals, it will be seen that the increase in blood flow velocities in stenosis remains the same. At the same time, there is a change in vasospasm.³¹ The blood flow velocities of the intracranial arteries and the depths at which they are detected are shown in Table.

Table. Normal cerebral blood flow velocity (mm/s) values measured by transcranial Doppler³²

	Systolic peak V	Diastolic end V	V mean
Middle cerebral artery	91±17	46±10	58±12
Anterior cerebral artery	86±20	41±8	53±10
Posterior cerebral artery	60±20	28±7.5	36±10
Vertebral artery/basilar artery	59±17	29±8	36±11
V: velocity			

2. Detection of the presence of embolism

Ideally, the bloodstream has no significant particulate suspensions, aggregates, or bubbles. In some cases, however, such particles may be present in the circulating bloodstream. Conditions such as carotid artery disease, prosthetic heart valve, atrial fibrillation, surgical interventions such as carotid endarterectomy, and cardiopulmonary bypass pose a potential risk for arterial-to-arterial embolism. The left ventricle, aorta, and carotid are the primary sources of embolism.³³ Doppler sonography, a non-invasive examination, can be a helpful method in detecting cerebral embolism and regulating and monitoring the treatment of cerebrovascular diseases. Embolism in cerebral arteries is sought, especially in MCAs and preferably bilaterally. For the detected high-intensity transients to be accepted as a "micro embolic sign," they must last less than 300 ms, be at least 3 dB greater than the ground activity, be unilateral, and have the characteristic "chirp" sound. It is difficult to distinguish between clinical and laboratory carotid and cardiac embolisms. Although not characteristic, it can be said that carotid embolisms are more superficial and cortical and are detected unilaterally by TCD.^{34,35}

3. Examination of vasospasm

Many studies have reported that vasospasm is a complication of subarachnoid hemorrhages. In mild and moderate vasospasm, blood flow velocity increases along the segment where the spasm develops due to arterial narrowing; however, cerebral perfusion does not appear to accompany it. In severe

vasospasm, irreversible changes occur with impaired cerebral perfusion, and infarcts may accompany the picture. TCD is the most essential tool in the diagnosis and follow-up of vasospasm. The presence and severity of vasospasm can be routinely monitored in many clinics using TCD.³⁶

4. Vasomotor reactivity and dynamic autoregulation tests

Static autoregulation tests are performed by evaluating arterial blood pressure responses to some pharmacological agents. In recent studies, dynamic autoregulation tests are taking the place of static tests. Fluctuations in arterial blood pressure were observed in dynamic tests, which were more reliable. In the most commonly used method, a cuff is attached to the calf of the patient in the supine position, and the vein is inflated with a pressure above 20 mmHg and waited for two minutes. Meanwhile, MCAs are detected at three depths, blood flow velocities are continuously displayed invasively or non-invasively, and cerebrovascular resistance (Cerebrovascular resistance=Arterial blood pressure/mean MCA blood flow velocity) is calculated. The cuff is suddenly loosened, and blood pressure, MCA velocity, and cerebrovascular resistance (CVR) are evaluated. This test gives valuable results in patients with symptoms of syncope and vertebrobasilar ischemia attack.³⁷

Vasomotor reactivity testing is performed by inhaling CO₂ or assessing blood flow velocity changes after acetolamide injection. The patient is inhaled 5% CO₂ for 2-3 minutes or is injected with acetazolamide, a carbonic anhydrase inhibitor. Ordinary individuals will have a 50% increase in MCA blood flow velocities; increases below 30% are considered pathological. With this test, the cerebral effects of hypo- or hypertension can be investigated, and objective information can be obtained about the need for surgery before carotid endarterectomy.^{38,39}

5- Intracranial pressure imaging

Cerebral circulation takes place in a closed environment surrounded by the skull. This environment includes brain tissue, blood volume, and cerebrospinal fluid. An increase in one of these three compartments due to edema due to infarcts, intracranial hematoma, tumors or head trauma may result in increased intracranial pressure. Cerebral perfusion pressure is the difference between arterial blood pressure and intracranial pressure. Therefore, increased intracranial pressure may result in impaired cerebral perfusion. Transcranial Doppler is a reliable tool for monitoring intracranial pressure. Changes in waveforms make it possible to follow changes in intracranial pressure. In cases where intracranial pressure increases, diastolic blood flow velocities in the cerebral arteries decrease and PIs increase.⁴⁰

6. Bubbles test

TCD can be used to diagnose "patent foramen ovale," a critical risk factor for stroke. In this test, salt or galactose particles are injected intravenously after MCAs are detected by TCD. Five seconds after the injection, the Valsalva maneuver is performed; if the patient has a right-left shunt, the passage of particles in the MCA bloodstream is observed during the Valsalva maneuver. Detection of the right-left shunt with the Bubbles test is more reliable than transesophageal echocardiography; its sensitivity and specificity are 90%.⁴¹

7. Brain death

TCD is a tool that can be used as an aid in the diagnosis of brain death. Although blood flows cannot be obtained with TCD in the case of brain death, it is possible to provide data such as loss or reversal of the diastolic blood flow wave or early and small systolic spikes.⁴²

CONCLUSION

USG-guided ONSD and TCD applications are used as easy, bedside and non-invasive techniques for neuromonitoring in intensive care units.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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Pulmonary candidiasis presenting as tumor-like shadow

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ABSTRACT

Lung fungal infections are rare and carry a high risk of death in critically ill patients. Further investigations including radiological imaging are needed for differential diagnosis. In this article, we present a patient with a tumor-like shadow on chest X-ray and a mildly necrotic soft tissue mass of 4 cm in the first computed tomography (CT) examination of the thorax, who was therefore pre-diagnosed with lung cancer. Due to the poor general condition of the patient, his family did not accept further examinations for cancer. Approximately 40 days later, the patient was taken to the intensive care unit with the complaint of respiratory distress. The bronchial sample was negative for malignant cells and *Candida tropicalis* was detected in cultures. The size of the mass decreased in CT controls after treatment with antifungal agents. We thought that the image on CT was due to *Candida tropicalis* infection and regressed with antifungal treatment. In conclusion, we can conclude that pulmonary candidiasis may present with atypical radiological findings. Fungal infections should be kept in mind in the differential diagnosis of lung cancer in cases with confusing mass-like images.

Keywords: Infection, candidiasis, diagnosis, pulmonary

INTRODUCTION

Candida types are among the opportunist fungi types, are the members of the normal flora, may be in the oral cavity and even in the respiratory tract, are among the most frequently observed fungi that are infection factors. They may lead to superficial infections or to invasive infections that threaten life.¹ Although the fungi infections, which may be clinically or radiologically confused with pulmonary cancer, are generally observed with *Aspergillus* fungi, it is also possible that -although rare- they are observed with candida-type fungi as well.² Our purpose in this paper is to present a case that was radiologically pre-diagnosed firstly as lung cancer however, later with the follow-ups, was diagnosed with pulmonary candidiasis.

CASE

The 76-year-old male patient applied to a medical center with the complaints of exhaustion for 6 months, cough, phlegm, general status disorder. The computerized thorax tomography (CTT) was received due to the detected bulk in the front-back lung graphics (Figure 1). After the CTT, the patient was pre-diagnosed with lung cancer since the general status of the patient was poor, the family of the patient did not accept further

examinations and tests. After about 40 days, the patient applied to a medical center with complaints of abdominal swelling, inability of defecate for a week, and respiratory problems. He was intubated in the medical center, and later was accepted in our intensive care unit for treatment and follow-up. In the history of the patient it was observed that he had Parkinson's disease for 15 years, atherosclerotic heart disease for 12 years, and 60 packages/year of cigarette smoking. It was determined in the physical examination that the patient was unconscious, the abdomen was in distension status, and the skin was dry and pale. Bilateral common rales were detected in the lungs. The general status was as follows; TA: 61/21 mmHg, pulse 128 pulse/min, Glasgow Coma Scale (GKS): 3, Acute Physiology and Chronic Health Evaluation II (APACHE II) score: 38. The medication was started with dopamine 5-20 mcg/kg/min, noradrenalin 0.1-1 mcg/kg/min infusion. In the laboratory examinations, the hemoglobin value was detected as 9 mg/dl, the number of thrombocytes was detected as $215 \times 10^3/\text{ul}$, and the number of leukocyte was detected as $18.9 \times 10^3/\text{uL}$, the urea was 184 mg/dl, serum creatinine 2.74 mg/dl, the erythrocyte sedimentation rate 77 mm/h, CRP 17.4 mg/L, procalsitonine 0.5 ng/ml, anti HIV negative. There were hematuria, leukocyturia, hipoproteinemia (6 g/dl), hipoalbuminemia (2.5 g/dl). The

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central venous pressure was 5 mm Hg. The 0.9% NaCl and 5% dextrose were given to the patient for hydration. After the hydration, the creatinine values became normal. The patient's hemodynamic values returned to the normal range and inotropic support was discontinued. In the CTT which was performed in the other medical center it was stated that "there were fusiform atelectasis in the size of 8 x 3.5 cm in the bulk inferior with the light necrotic soft tissue vision in 4 cm diameter with slight spicule contour in which ground glass densities were observed in the right-side pulmonary middle lobule and in the para-cardiac area" (Figure 2). In the CTT which was performed after the patient was accepted in our ICU, it was detected that the bulk had recessed to 24 x 20 mm, and showed cavitation.



Figure 1. Lung roentgenogram taken before admission to the intensive care unit



Figure 2. Thoracic CT image taken before admission to the intensive care unit

Fiberoptic bronchoscopy (FOB) was applied to the patient and the right side system subsegments were openly observed; and it was observed that the mucosa was natural. No findings were detected in favor of malignity.

On the 10th day of his hospitalization, a CTT was taken to check his situation and it was observed that the bulk was recessed to 16 x 17 mm. Upon the observation that the patient was not cachectic, and that the bulk had recessed in the pulmonary

graphics and tomography, we were doubtful about the previous lung CA diagnosis. No acid-resistant basil (ARB) was detected in the tracheal aspiration samples which were sent three times. *Candida Tropicalis* reproduced in the blood culture, urine, tracheal aspirate and rectal swab culture, and the patient was given Caspofungin Acetate (Cancidas®) on the 1st day with 1 x 70 mg dosage, and then with 1 x 50 mg dosage. It was observed in the CTT taken on the 24th day of his hospitalization that the cavity recessed to 14 x 15 mm; and on the 46th day it recessed to 8 x 10 mm. It was considered that the medical picture appeared due to candida tropicalis infection, and the recession occurred with the antifungal treatment (Figure 3, Figure 4).

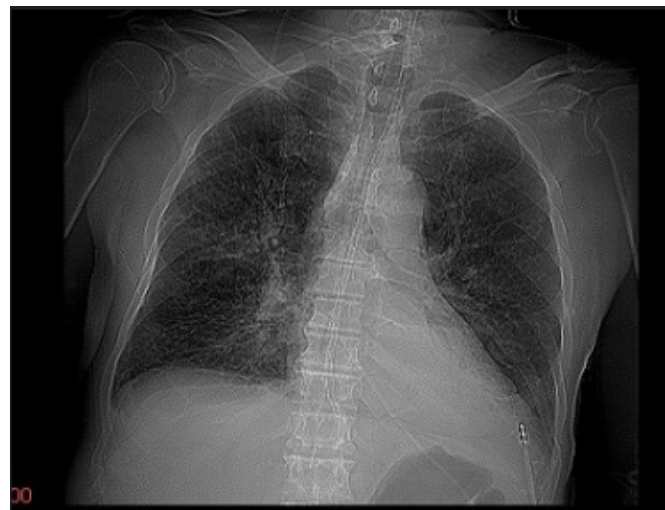


Figure 3. Chest roentgenogram of the patient after treatment



Figure 4. Thoracic CT image of the patient after treatment

In the follow-up of the patient it was observed that he had (a) fever; and in the blood and tracheal aspiration cultures, it was observed that there were only *Coly-Mycin®*-sensitive *baumanii* reproductions. However, the patient who had been receiving 3x150 mg *Coly-Mycin®* and sulbactam (and sulbactam) 2x1 (B-Laktam®) had acute kidney failure after 5 days. The highest value of the creatinine was 2.72 mg/dl (0.84-1.25 mg/dl) urea reached

150 mg/dl; but then the antibiotic dosage was adjusted according to the renal clearance and the kidney functions became normal. In the later blood and tracheal aspirate cultures it was observed that the *Acinetobacter baumannii* (*A. baumannii*) reproduction continued. According to the antibiogram results, the antibiotherapy was regulated again. In the following days, the general status of the patient was disrupted and hypothermia, hypotension and oliguria developed. Dopamine noradrenaline infusion was started. The patient was diagnosed with sepsis and septic shock due to *A. baumannii*. The patient whose cardiac and renal functions were disrupted progressively then had pancytopenia, lactic acidosis, and peripheral circulation disorder. The patient did not respond to intensive support treatment and antibiotherapy, and went exitus due to multiple organ failure.

DISCUSSION

Candida infections are the factors that are isolated with 4th frequency from ICU patients.³ The most frequent one among these is the *Candida albicans* (*C. albicans*) in the first row, and on the 2nd row, there is the *Candida tropicalis* (*C. tropicalis*). The gastrointestinal system is the most important way for the candidiasis to enter the body. It causes infection in the central nervous system, hepatosplenic candidiasis, abdominal and renal abscess, endocarditis, peritonitis and pneumonia.⁴

Together with hematologic malignancy, organ transplantation, multiple antibiotics use, burns, steroid treatment, long-term urethral catheter use, intravenous drug addiction and similar risk factors, the *Candida* reproduction in more than one body parts is accepted as being meaningful.^{1,3} In our case, the patient had *C. tropicalis* reproduction in the blood culture, urine, rectal and tracheal aspirate samples when he arrived at the ICU. Our patient did not have any diseases or characteristics like diabetes mellitus, AIDS, malignity, or chronic alcoholism that might cause immunosuppression. However, his being at a further age with the Parkinson's disease, and being bedridden were accepted as risk factors.

Focal/multifocal consolidation or diffuse infiltration may be observed in the radiological findings of the pulmonary candidiasis, but cavitation, adenopathy, bulk-like opacity or millier pattern are not expected.^{5,6} Cavitation or bulk-like vision is observed frequently in aspergillosis among fungal infections. Cases with *Candida* and *Pneumococcus* together with a bulk-like vision and with necrotic fungus ball formation are reported in the literature, but no cases with a bulk vision together with isolated candidiasis are reported.⁷

Cavity formation is rarely observed in candidiasis. Five different cases were reported in the literature. Two of these cases who were between the ages of 33 and 62 had diabetes mellitus, two of them had immune deficiency due to malignity, and one patient did not have any pathologies that would cause immune disorder.⁸⁻¹²

Our patient did not have any pathology that would suppress the immune system, which was reported by the other medical center he applied to before he came to us; and due to his being at a further age, lung cancer was considered the most probability, and we also considered that his pulmonary infections were ignored.

CONCLUSION

We may face pulmonary candidiasis with atypical radiological findings. Although rare, it forms the vision of a bulk and may be confused with lung cancer. By keeping this in mind, proper methods must be employed for discriminative diagnosis.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

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Concurrent diagnosis of Sjogren's syndrome and polycythemia vera: a rare co-existence

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ABSTRACT

This case report explores the unprecedented concurrent diagnosis of Sjogren's syndrome (pSS) and polycythemia vera (PV) in a 62-year-old woman presenting with erythrocytosis, classic pSS symptoms, and a positive JAK2-V617F mutation. While autoimmune diseases and hematological malignancies frequently coexist, the combination of PV and pSS has not been previously documented. Despite recurrent phlebotomies for PV, the patient experienced persistent symptoms and elevated inflammatory markers. The case underscores the complexity of managing rare coexisting conditions, emphasizing the importance of considering a broad spectrum of hematological malignancies in primary SS patients. The patient is currently receiving hydroxyurea and hydroxychloroquine with regular follow-ups, shedding light on the challenges associated with the treatment of such unique clinical scenarios. This report contributes to the medical literature by expanding our understanding of potential associations between autoimmune disorders and hematological malignancies beyond conventional patterns.

Keywords: Sjögren's syndrome, polycythemia vera, concurrent, diagnosis, co-existence

INTRODUCTION

Primary Sjogren's syndrome (pSS) is a chronic autoimmune disease and focal lymphocytic infiltration of the exocrine glands is the key pathological feature.¹ Polycythemia vera (PV) is a chronic myeloproliferative disorder characterized by JAK-2 mutations and increased red blood cell mass.^{2,3} Autoimmune diseases and hematological malignancies can often be observed together. Patients with SS are at a higher risk of developing lymphoproliferative diseases mainly low-grade B-cell lymphomas and predominantly marginal zone lymphoma. Moreover, PV can rarely be presented with paraneoplastic events including small vessel vasculitis.² However, PV and pSS co-existence has not been previously reported. We here want to present a case of concurrently diagnosed PV and pSS.

CASE

A 62-year-old woman was referred to our clinic with incidentally detected erythrocytosis. She had a medical history of hypertension and was under amlodipine 5 mg/day. Fatigue, arthralgias, dizziness were the main complaints of the patient. The patient exhibited classic symptoms of Sjogren's syndrome, including xerostomia, xerophthalmia, and arthralgias. The laboratory findings revealed: Hemoglobin 17.3 g/dl, hematocrit 49%, total leucocyte counts 11000/ μ l, platelet count 312000/L, erythrocyte sedimentation rate 45

mm/hour. Serum erythropoietin level was reported below the normal range. C-reactive protein was detected high: 61 mg/dl. Despite recurrent phlebotomies for PV, symptomatic relief was elusive, and inflammatory markers remained elevated. Other biochemical analysis was all in the normal ranges. Peripheral blood smear revealed no morphological abnormalities of erythrocytes. Splenomegaly was detected in physical examination, 2 cm under the left costal margin. There was no active focus of infection to explain the ESR and CRP elevation.

Serum erythropoietin level was low. The molecular analysis for JAK2-V617F was founded positive and BCR-ABL was negative. The JAK2 allele burden was calculated as 72%. Bone marrow biopsy was performed. Hypercellularity with prominent erythroid, granulocytic, and megakaryocytic proliferation was reported. According to the WHO 2016 criteria's, the patient was diagnosed polycythemia vera. Despite the decrease in hematocrit levels with recurrent phlebotomies, symptomatic relief was not observed in the patient and ESR and CRP levels were still high. Autoantibody profile including antinuclear antibody (ANA), rheumatoid factor, c-antineutrophil cytoplasmic antibody was performed. ANA profile revealed Anti- Ro/SS-A and Anti- La/SS-B positive. Minor salivary gland biopsy was performed, and pathological findings were

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consistent with pSS. The patient is receiving hydroxyurea 500 mg twice a day and hydroxychloroquine 200 mg a day and still on regular out-patient follow-up.

DISCUSSION

Concurrent association of hematologic malignancies and rheumatologic diseases is well known.³ Autoimmunity or paraneoplastic pathways are the main reasons to determine the relationship between each other.³ In a large cohort which was designed to estimate the risk of cancer in SS, 128 of 1300 patients developed cancers in a 9-year-follow up. However, chronic myeloproliferative disorders were not observed.⁴ This study revealed 11-fold higher risk of hematologic malignancy development in SS and the most cases were B-cell lymphomas. Patients with primary SS should be closely followed for the enhanced risk of hematological cancers but not only B-cell lymphomas.

CONCLUSION

The presented case of concurrent polycythemia vera (PV) and Sjogren's syndrome (pSS) stands as a rare and intriguing clinical entity. The coexistence of these two distinct conditions in the same patient challenges the conventional understanding of associations between autoimmune diseases and hematological malignancies. Despite the well-documented link between primary SS and an increased risk of hematologic cancers, particularly B-cell lymphomas, the manifestation of PV alongside pSS is a novel observation.

The patient's clinical course, marked by persistent symptoms and inflammatory marker elevation despite PV-directed interventions, underscores the intricacies of managing such complex cases. The utilization of hydroxyurea and hydroxychloroquine in the treatment regimen reflects the ongoing efforts to address the dual burden of autoimmune and myeloproliferative disorders.

This case contributes valuable insights to the medical community, prompting further exploration of potential connections between diverse autoimmune and hematological conditions. Additionally, it emphasizes the necessity of vigilant monitoring and comprehensive diagnostic assessments when encountering patients with overlapping clinical presentations, guiding clinicians toward more informed and tailored therapeutic strategies. Continued documentation and analysis of similar cases are crucial for advancing our understanding of the intricate interplay between autoimmune diseases and hematological malignancies.

ETHICAL DECLARATIONS

Informed Consent: The written consent of the patient was obtained for the article.

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