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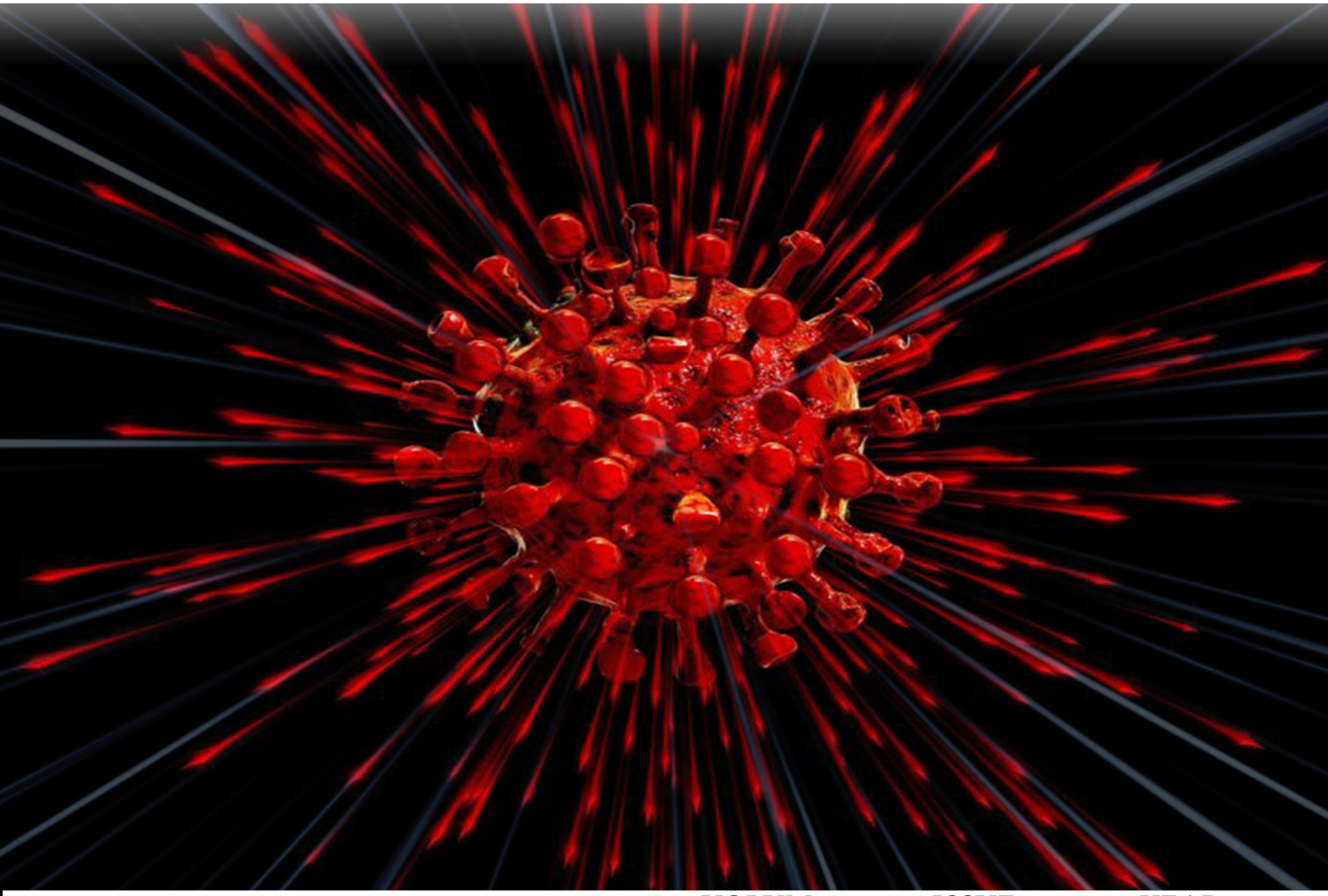

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Anesthesia management and challenges during interventional pulmonology procedures for central airway obstructions

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ABSTRACT

Aim: Central airway obstructions (CAO) are one of the main reasons for morbidity and mortality, often originate in the lungs, and are generally unresectable. Interventional airway procedure is a preferred method in these cases. This study aimed to analyze anesthesia management in patients undergoing interventional procedures for CAO. We aimed to highlight the problem and solutions that may be encountered in such cases.

Material and Method: The data of 49 patients who had interventional airway procedure were analyzed retrospectively. Patients' demographic data, type of interventional procedures, localization of the lesion, and duration of the procedure were analyzed. Vital parameters and arterial blood gases (ABG) levels had been recorded before anesthesia induction (T1), after rigid bronchoscope insertion (T2), 20th-minute of the procedure (T3), after extubation (T4), and in the postoperative care unit (T5).

Results: The mean age was 57.90±11.99 years. The mean duration of the procedure was 34.75±15.62 minutes. The majority of the patients had American Society of Anesthesiologists (ASA) III-IV physical status. CAOs were mostly found in the main bronchus. Tumors debulking, biopsy, mechanical dilatation, argon plasma coagulation, and mechanical tumor resection were the most performed procedures. Stent insertion was performed in 3 (6.1%) patients. Two patients (4.1%) had bleeding, 3 (6.1%) patients had desaturation, and 1 (2.1%) patient had atrial fibrillation.

Conclusion: Interventional airway procedures are frequently used for high risk patients with CAO and comorbidities. Detailed preoperative evaluation, periprocedural teamwork, and close hemodynamic and ABG follow-up are keys to success.

Keywords: Anesthesia, argon plasma coagulation, central airway obstruction, cryotherapy, interventional pulmonology, rigid bronchoscopy

INTRODUCTION

Central airway obstructions are one of the main causes of morbidity and mortality. Central airway obstructions (CAO) often originate in the lungs and are generally unresectable (1,2). The increase in lung cancer cases in recent years has also increased the incidence of CAO in the main airways (2). The major bleeding, atelectasis, pneumonia, and dyspnea are complications associated with CAO (2,3).

Advances in interventional pulmonology procedures are improving the treatment of patients with complex airway pathology caused by both benign and malignant diseases (1-3). Cryotherapy and argon plasma coagulation (APC) are among the techniques used for the treatment of CAO. During these techniques, a rigid bronchoscope is required for majority of the cases (1-3). General anesthesia is the preferred method for most of the procedures with rigid bronchoscopy (1-4). Perioperative management of patients with CAO is a very difficult process for anesthesiologists. Most of the patients have often American Society of Anesthesiologist (ASA) III/IV physical status, major comorbidities, and almost complete airway obstruction. During procedures for these patients, sharing airway with the pulmonologist make the process even more complicated for the anesthesiologist (5-8). For these reasons, meticulous perioperative management and collaboration between the anesthetists physicians and the interventional pulmonologists are crucial to reduce the mortality and morbidity rate.

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Our objective was to analyze challenging circumstances and solutions for anesthesia management in patients undergoing interventional procedures for CAO. We have retrospectively analyzed patients' perioperative data.

MATERIAL AND METHOD

The study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 25.05.2022, Decision No: 2012-KAEK-15/2518). Medical records of 49 patients undergoing interventional airway procedures due to CAO between July 2019 and July 2020 were analyzed. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The following information was available on the records: Patients' age, gender, body mass index (BMI), ASA physical status, type of the interventional procedure, localization of the lesion, the presence of comorbidities, duration of the procedure, and Modified Aldrete Score (MAS) to identify recovery time.

Anesthesia Protocol

The same total intravenous anesthetic procedure had been performed in all patients. Two large bore intravenous catheters had been inserted into the patients. 3 minutes after pre-oxygenation, 1 mg.kg−1 lidocaine, 1 mg.kg−1 methyl prednisolone, 2 mg.kg−1 propofol, 1 mg.kg−1rocuronium and 0.5 μg.kg−1 remifentanil had been administered for anesthesia induction. Fentanyl was not used to avoid coughing (9). After 90 seconds, patients had been intubated with a rigid bronchoscope, and ventilated manually. During rigid bronchoscopy, leak compensation had been achieved by a continuous flush with 100% oxygen. A radial artery catheter had been inserted to monitor the blood pressure and arterial blood gases (ABG) measurements. Adequate PaO_2 and $PaCO_2$ levels had been achieved with peripheral oxygen saturation (SpO_2) monitoring and intermittent ABG measurements. Maintenance of anesthesia had been performed by using propofol (50-75 μg.kg−1. min−1) and remifentanil (0.025-0.05 μg.kg−1.min−1) infusions adjusted to hemodynamic response. Additional rocuronium doses had been administered, and at the end of the procedure, the rocuronium effect had been reversed by administering 2-4 mg.kg−1 sugammadex intravenously. Ventilation was maintained with a standard semi-closed circuit. The ventilator was connected to the side port of the rigid bronchoscope with the circuit. Additionally, high flows (>12 L/min, up to 20 L/min) were used to compensate for leaks in the system (10). Throughout the procedures, ventilation was provided manually with instant follow-up and leak compensation. The patient's follow-up was coordinated between the anesthetists and the pulmonologists with close communication and observation.

All complications and adverse events were recorded during and after the procedure. After the intervention, patients had been followed in the postoperative care unit (PACU) until complete recovery. Recovery time was determined by using MAS records. The time to reach MAS 9-10 after discontinuation of anesthetic agents was accepted as the recovery time.

Throughout the procedure electrocardiography, SpO_2 measurements, and invasive arterial blood pressure monitorizations were performed. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), heart rate (HR), SpO_2, the pH, PaO_2, and $PaCO_2$ values recorded before anesthesia induction (T1), after rigid bronchoscope insertion (T2), after 20th-minute of procedure (T3), after extubation (T4), and in the PACU (T5) were analyzed. Additionally, the effects of BMI, age, and procedure time on recovery time were evaluated.

Interventional Procedures

All of the interventional procedures were performed by two interventional pulmonologists. According to the lesion location and size, after insertion of the rigid bronchoscope, suitable procedures of APC, mechanical tumor resection, cryobiopsy, cryotherapy, mechanical dilatation or stent placement procedures were used.

Statistical analysis

Statistical analysis of the study was made with SPSS for Windows 16.0 package program. Normality analyzes of variables were performed using the Shapiro Wilk test. Variables are expressed as mean-standard deviation in normally distributed parameters and median-interquartile range in non-normally distributed parameters. Comparison between the two dependent groups for the normally distributed parameter was performed by the Paired Samples T-test. Comparison between two dependent groups was performed using the Wilcoxon Test and the Repeated Measures ANOVA test, while the Friedman test was used for the analysis of non-normally distributed dependent multiple variables. Comparison between independent multiple groups for the normally distributed parameter was made with the one-way Anova-test, and the Kruskal-Wallis test for non-normally distributed parameters; Bonferroni correction was applied when analyzing the subgroups. Spearman correlation test was used for non-normally distributed boxed correlation and Pearson test was used for normal distribution boxed correlation. p-value<0.05 was accepted as statistically significant.

RESULTS

Data of 49 patients were analyzed. Demographic characteristics, ASA physical status, duration of the procedure, localization of the lesion, and recovery time are shown in **Table 1**. Patients had different comorbidities. 16 (32.6%) of the patients had hypertension, 11 (22.4%) had diabetes mellitus, 11 (22.4%) had cardiac diseases, 6 (12.2%) had chronic obstructive pulmonary disease, 6 (12.2%) had extrapulmonary malignancy, 2 (4.1%) had cerebrovascular diseases, and 5 (10.2%) had other coexisting diseases.

Table 1. Demographical and clinical characteristics of patients

	n: 49	Min-max
Age (year) (mean±sd)	57.90± 11.99	23-83
Gender (F/M) n-%	9-22.5 / 40-81.5	-
BMI (kg/m2) (mean±sd)	25.61±4.88	16.11-40.40
Duration of procedure (min) (mean±sd)	34.75 ± 15.62	9-82
Recovery time (sec)	195.61±118.62	60-600
ASA (2/3/4) n-%	2-4.1 / 36-73.4 / 11-22.5	-
Localization of airway lesion		
Trachea-carina (n-%)	12-24.4	-
Bronchus (n-%)	32-65.3	-
Tracheobronchial (n-%)	5-10.02	-

Data presented as mean±standard deviation, percentage, and minimum-maximum. ASA: American Society of Anesthesiologists; BMI: Body mass index, MAS: Modified Aldrete Score.

Tumor debulking was performed in the majority of the patients (**Figure 1a**, **Figure 1b**). Dilatation and cryotherapy were applied in 4 (8.2%) patients, while foreign body removal was performed in 2 (4.1%) patients. Stent insertion was performed in 3 (6.1%) patients (**Figure 2a, Figure 2b, Figure 2c, Table 2**).

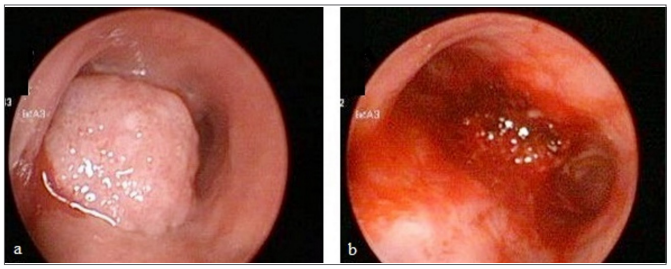

Figure 1. 1a. Tumor almost completely obstructing the left and right main bronchi in the carina of the trachea. **1b.** After debulking, view of the carina.

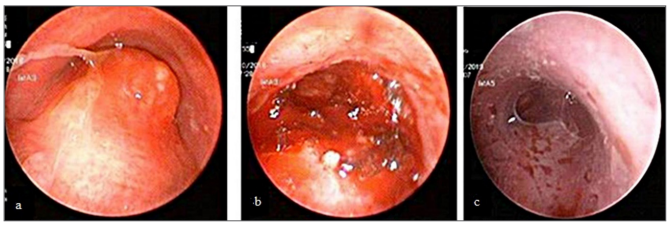

Figure 2. 2a. Endotracheal tumor obstructing the airway. **2b.** After debulking, the view of the trachea. **2c.** View of the trachea after silicone y-stent insertion.

Table 2. Distribution of interventional airway procedures

Procedures	n:49	%
Debulking		
APC	1	2.1
Cryoextraction	4	8.1
MTR	8	16.4
APC+MTR	2	4.0
Cryoextraction+APC+MTR	19	38.8
Cryobiopsy+APC	6	12.2
Dilatation+ Cryotherapy	4	8.2
Foreign Body Removal	2	4.1
Stent Insertion	3	6.1

Data presented as number and percentage. APC: Argon plasma coagulation, MTR: Mechanical tumor resection.

When the patients'complication were evaluated, 2 patients (4.1%) had bleeding, 3 (6.3%) patients had desaturation, and 1 (2.1%) patient had atrial fibrillation. None of the patients needed nitroglycerin or vasopressor due to hemodynamic changes during the procedure. We didn't encounter any complications during PACU follow-up.

The MAP values were significantly lower after insertion of the rigid bronchoscope according to basal values (T1) ($p<0.001$). When the HR was evaluated according to the basal values (T1), the decrease in the 20th-minute (T3) of the procedure was found to be statistically significant ($p<0.001$). The increase in SpO_2 compared to the pre-induction time (T1) was found to be statistically significant when the rigid bronchoscope was inserted (T2), at the 20th-minute of the procedure (T3), and after extubation (T4) ($p<0.001$). When ABG were evaluated, pH was found to be lower than basal values (T1) at all times. According to the basal value (T1), PaO_2 values were found to be statistically higher during rigid bronchoscope insertion (T2), at 20th-minute (T3) and after extubation (T4) ($p<0.001$). In PACU (T5), the PaO_2 values were found to be significantly lower, however, the values are clinically within normal limits. $PaCO_2$ values were found to be high at the time of rigid bronchoscope insertion (T2), at the 20th-minute of the procedure (T3) and after extubation (T4) when compared to the time before induction (T1) ($p<0.001$) (**Table 3**). There was no correlation between recovery time and BMI, age, and duration of procedure ($p>0.05$).

DISCUSSION

Our study showed that most of the patients had ASA III-IV physical status and comorbidity. Tumor debulking procedure with cryoextraction and mechanical tumor resection were performed on the majority of the patients. During the interventional procedure we observed stable hemodynamic trend and oxygenation, even if we found acceptable alterations particularly in pH and $PaCO_2$ levels. We also found limited and acceptable complications during the procedures.

Table 3. Vital parameters and arterial blood gas values of patients during procedure

Variables	T1	T2	T3	T4	T5	p
MAP* (mmHg)	95.0±19.6	75.6 ±20.1	93.8±22.2	101.5±19.7	97.3±15.9	<0.001
HR* (beat/min)	96.0±13.9	96.7±10.8	90.5±11	94.4±12.6	92.5±13.3	0.002
SpO_2** (%)	94 (92-97)	98 (98-98)	97 (91-98)	95 (93-96)	93 (91- 96)	<0.001
pH**	7.49 (7.43 -7.53)	7.42 (7.36 -7.45)	7.29 (7.26 -7.32)	7.32 (7.29-7.42)	7.43 (7.41-7.46)	<0.001
$PaCO_2$** (mmHg)	34.7 (31.1-42.1)	39.4 (36.3-43.9)	56.5 (49.6-62.8)	45.6 (43-57.9)	36.3 (33.1-38.1)	<0.001
PaO_2** (mmHg)	98.1 (71.2-174.3)	248.5 (220.6-320.3)	213.5 (99.9-345.8)	142.9 (118.6-160.7)	73.4 (60.1-80.8)	<0.001

*rmANOVA **Friedman. p < 0.005: According to T1. Data presented as mean and standard deviation and mean min-max.
HR: Hearth rate;MAP: Mean arterial pressure; $PaCO_2$: Partial arterial carbondioxide; PaO_2: Partial arterial oxygen; SpO_2:Peripheral oxygen saturation.

Anesthesia management for interventional pulmonology in patients with CAO poses a real challenge (5-8). These patients have severe dyspnea due to existing lung disease, severe comorbidities, and high ASA physical status (8). In addition, maintaining hemodynamic stability and providing adequate depth of anesthesia with anesthetic drugs is more difficult in elderly ages due to possible pharmacokinetic and pharmacodynamic changes (11-13). Therefore, for these patients, preoperative evaluation is very important. In the perioperative period, a detailed of evaluation of these problems and jointly decided procedure by the interventional pulmonology team is crucial for the successful management of anesthesia (7,14). The condition and the location causing the obstruction should be evaluated with a multidisciplinary approach. Since dyspnea is common in these patients, the position in which the patients are comfortable should be evaluated for dyspnea. If there occurs an airway collapse during the procedure, this evaluation can help to determine the position to be used during anesthesia induction (15). In this study, preoperative evaluation was done in collaboration with anesthesiologists and pulmonologists.

Anesthesia induction is another critical step in patients with CAO. Premedication before the procedure can be done if the general condition of the patients is suitable. However, it should be done carefully considering the serious problems that respiratory depression can cause in these patients who already have limited pulmonary reserves (15, 16). Premedication with atropine and glycopyrrolate, which were frequently used in the past, are no longer preferred (17). Additionally, for a possible airway collapse during anesthesia induction, the pulmonologist should be present and the rigid bronchoscope should be placed quickly (5, 16). In this study, premedication was not administered before induction of anesthesia, and none of the patients required emergency airway management due to airway collapse.

Anesthesia management during treatment is another critical step in patients with CAO. Patients with respiratory distress require O_2 support and cannot lie in the supine position. Muscle relaxants eliminate muscle tone that keeps the airway open (3, 5, 18, 19). Performing rigid bronchoscopy under deep sedation in which spontaneous breathing is preserved, can be an alternative to general anesthesia (20). However, in deep sedation, the possibility of hypoventilation, laryngospasm, insufficient relaxation of the laryngeal muscles, coughing, or involuntary movement of the patient make it difficult to insert the rigid bronchoscope into the trachea and the work of the team. It has been reported that intravenous induction of anesthesia in patients with CAO should be fast and smooth, and prevent airway irritation (20, 21). For these reasons, propofol and remifentanil, short-acting intravenous anesthetic agents, should be preffered for anesthesia induction and maintenance (21). Usage of muscle relaxant agents with rapid onset of action is also reasonable to enable fast insertion of rigid bronchoscope after induction with intravenous anesthetic agents. Succinylcholine is a depolarizing neuromuscular blocking agent with rapid onset and rapid recovery, which has been used since the 1950s (22). However, succinylcholine is less preferred due to the frequency of undesirable and serious side effects. Addtionally, as in this study, it may be more appropriate to use muscle relaxants with moderate duration such as rocuronium, since prolonged muscle relaxation may be needed in the procedures where complex interventional procedures are required (23). Rocuronium, usage at a dose of 1 mg.kg-1, provides rapid intubation around 60 seconds (24). One of the most important advantages of rocuronium is that it allows fast reverse after the procedure by using intravenous sugammadex. This important feature of rocuronium also allow rapid recovery in the case of possible intubation problems (25). In this study, we use the same anesthetic method with rocuronium to all patients and sugammadex was used to reverse the effects of rocuronium. We didn't encounter any intubation or extubation related complications. We believe that usage of rocuronium-sugammadex combination is an effective method to prevent problems during intubation and extubation period.

Ventilation is mostly performed through rigid bronchoscopy by conventional method or high frequency jet ventilation (21). In patients with severe airway obstruction, experienced personnel and appropriate adjustment of the jet ventilator are important for solving problems such as ventilation problems, carbon dioxide retention, and the risk of barotrauma (26,27). A ventilator is connected to the side port of the rigid bronchoscope with a standard semi-closed circuit. This is a conventional ventilation method for interventional bronchoscopy. High flows are (>12 L/min, up to 20 L/min) usually necessary to compensate for leaks in the system (10). In the study throughout the procedures, the conventional ventilation method was used. The ventilation was provided manually with instant follow-up and leak compensation. The patient's follow-up was coordinated between the anesthesiologist and the pulmonologist with close communication and observation. Barotrauma, severe carbon dioxide elevation and long recovery time were not observed in any of the patients during the procedures.

Bleeding, hypoxia, hypercarbia, and barotrauma are common complications during interventional bronchoscopy (26,27). In addition to the underlying comorbidities of the patients, the severity of the CAO also plays an essential role in the development of these complications (21,23). Comprehensive and multidisciplinary perioperative evaluation and preparation are crucial to prevent these complications. In the operating room, alternative airway equipments and devices; such as small-diameter intubation tube, double lumen intubation tube, high-frequency jet ventilator, and floroscopy should be available in case of acute life-threathening complications such as bleeding, pneumothorax, and unpredicted airway obstructions (5).

Monitoring of hemodynamic parameters and ABG measurements are frequently required follow-up methods in patients with CAO. Massive bleeding and sudden changes in hemodynamic parameters may occur in these patients, especially because of malign airway CAO. Additionally, sharing the airway with the pulmonologist and air leaks caused by the rigid bronchoscope may prevent effective ventilation. This insufficiency can often cause especially hypercarbia and hypoxia in patients (28, 29). In this study, invasive arterial pressure monitoring and intermittent ABG measurements were performed to ensure the safety of the interventional treatment and ventilation under general anesthesia. Stable hemodynamic parameters were achieved in these patients during the procedure, and moderate changes in pCO_2 and pH were observed in ABG measurements consistent with the literature. Furthermore, we did not encounter any serious problems that caused the process to be terminated.

There are different interventional treatment options to manage CAO through the rigid bronchoscope such as dilation of the tracheobronchial system, electrocautery, laser therapy, cryotherapy, brachytherapy, APC or insertion of airway stents (1,18). Argon gas is applied through a probe and is ionized into a plasma by contacting a high voltage electric current at the tip of the probe. Then It conducts a monopolar electric current to the proximal target lesion (30, 31). APC is a thermal modality and thus has similar airway fire risks as other thermal modalities. The risk of airway perforation is theoretically much lower than electrocautery and laser (32). Because of this feature, APC is a commonly used method especially for the treatment of complex vascular tumors or the lesions that tend to bleed. One of the most fearful complications due to APC is fire and airway burning because of the principle of the APC. Maintaining inspired concentration of oxygen at lower than 40% mostly is performed during APC application (33). In this study we disconnected the ventilator circuit during APC in coordination with the interventional bronchoscopy team. We didn't observe any fire and airway burning related to the APC procedure.

We have some limitations in this study. First, patients' data were collected retrospectively in a single center. Additionally, since mechanical ventilation with the conventional method is a routine method used in our center, no comparison could be made with jet ventilators and other methods. Prospective and comparative studies with a large number of patients are needed on anesthetic management in patients with CAO. Second, noninvasive methods such as transcutaneous carbon dioxide measurement and bispectral index monitorization could be also used. Due to the unavailability of these devices in our clinic at the time of these procedures, we could not use them. However, we thought that invasive arterial pressure monitoring and periodic ABG measurements could be sufficent in patients with CAO.

CONCLUSION

Patients with CAO have generally poor conditions. The mandatory simultaneous usage of the airway with the pulmonologist, performing the interventional procedure, makes the anesthesia management more difficult in such patients. Anesthesia management should conduct an appropriate preoperative assessment, maintain intraoperative convenient ventilation, use proper anesthesia agents and ensure perioperative close follow up. As a result, a multidisciplinary approach provided by skillled bronchoscopists and experienced anesthesiologists is essential in the interventional treatment of patients with CAO.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 25.05.2022, Decision No: 2012-KAEK-15/2518).

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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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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Original Article

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Comparison of the efficacy of transcutaneous electrical stimulation and interference current in patients with gonarthrosis

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ABSTRACT

Aim: In this study, it was aimed to evaluate the effects of transcutaneous electrical stimulation (TENS) and interference current (IFC) modalities on pain, function and quality of life in the treatment of patients with gonarthrosis.

Material and Method: The aim of this study is to evaluate the effects of TENS and IFC modalities on pain, function and quality of life in the treatment of patients with gonarthrosis and to compare them in terms of their superiority.

Results: 80 patients were included in the study. In the TENS and IFC groups, the degree of active-passive knee flexion and extension increased significantly on the 15th day of treatment (T15th day) and at the 3rd month after treatment (AT 3rd month), while it was at a similar level between the 15th day and the 3rd month of treatment. In the comparison of the 15th day of the treatment and the 3rd month after the treatment, the increase in the active-passive flexion and extension measurements in the IFC group was found to be statistically significant (flexion T15th day p=0.007 AT 3rd month p=0.000, extansion T15th day p=0.004 AT 3rd month p=0.031). The decrease in WOMAC total value at the 15th day of the treatment and at the 3rd month after the treatment was found to be significantly decreased in the IFC group (T15th day p=0.013, AT 3rd month p=0.000).

Conclusion: IFC both increased the range of motion of the knee joint in patients with gonarthrosis and contributed to the functional recovery in knee osteoarthritis.

Keywords: Gonarthrosis, TENS, interference current

INTRODUCTION

Osteoarthritis is the most common disease of joints in adults around the world (1). Felson et al. (2) reported that about one-third of all adults have radiological signs of osteoarthritis, although Andrianakos et al. (3), in an epidemiological study, found clinically significant osteoarthritis of the knee, hand, or hip in only 8.9% of the adult population. Gonarthrosis was the most common type (6% of all adults) . Treatment of gonarthrosis can be divided into non-surgical or surgical treatment. Non-surgical treatment comprises non-pharmacological and pharmacological treatment and non-pharmacological treatment comprises core first-line treatment for all patients with OA, including education, self-management, exercise and weight reduction. Other primary non-pharmacological treatments for gonarthrosis include walking canes and biomechanical interventions like braces and orthosis. Pharmacological therapy may include the use of paracetamol, topical or oral non-steroidal anti-inflammatory drugs (NSAIDs), or intra-articular corticosteroids. Surgical procedures are a last resort for end-stage gonarthrosis, the most effective type of which is total knee arthroplasty with rehabilitation (4). Commonly used treatment modalities are insoles, lasers, transcutaneous electrical nerve stimulation, ultrasound, electrotherapy, or acupuncture, but evidence is scarce, as is the effect size. However, applications of heat and ice are easy to use and quite effective (5). Electrical stimulation is a non-invasive treatment option that has been preferred since ancient times, in which the stimulus is applied superficially to the desired area with electrodes placed on the skin. Electrotherapy methods such as transcutaneous electrical stimulation (TENS), neuromuscular electrical stimulation (NMES), interference current (IFC), pulsed electrical stimulation (PES), non-invasive interactive neurostimulation (NIN) have previously been preferred

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and reported to be effective in the treatment of knee OA. However, there is not enough evidence about the superiority of these treatment methods over each other in the treatment of knee OA (6-8). There is very little evidence comparing the effects of modalities such as IFC or TENS in the treatment of knee OA, indicating which method should be preferred. Therfore, in our study, we aimed to evaluate the effect of TENS and IFC modalities on pain, function and quality of life in the treatment of gonarthrosis patients.

MATERIAL AND METHOD

The study was carried out with the permission of Hitit University Medical Faculty Clinical Researches Ethics Committee (Date: 11.05.2022, Decision No: 423). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted on 80 patients with bilateral gonarthrosis who applied to the Physical Medicine and Rehabilitation outpatient clinic of our hospital. Inclusion criteria included being between the ages of 40-75, being diagnosed with gonarthrosis according to the diagnostic criteria of the American College of Rheumatology and having bilateral stage 2-3 gonarthrosis according to the Kellgren Lawrence classification. Pregnancy, malignancy, pacemaker, cardiac arrhythmia, autoinflammatory disease, active infection and neuromuscular disease history were determined as exclusion criteria. Patients were randomized into two groups using the sealed envelope method. Forty patients in the first group were given 20 minutes (min) of hotpack, 20 minutes of conventional TENS (stimulation frequency 80 Hz, phase duration 200 ms, current density between 10-50 mA), 8 minutes of shortwave diathermy and 15 minutes of home program isometric quadriceps strengthening exercise. Forty patients in the second group were given 20 minutes of hotpack, 20 minutes of IFC (carrier frequency 4.0 kHz, pulse frequency 100 Hz), 8 minutes of shortwave diathermy and 15 minutes of home program isometric quadriceps strengthening exercise therapy.

Functional Assessment

Western OntarioMacMaster (WOMAC): WOMAC is a 24-item scale used to evaluate pain and function especially in hip and knee osteoarthritis. Each question is evaluated on a 5-point Likert scale. It has three subscales: pain, physical function and stiffness. The pain subscale is evaluated with five items. Therefore, it is scored between 0-20. The function subscale has 17 items, scored from 0 to 68. The hardness subscale has two items and is scored from 0 to 8. High scores indicate poor function, pain or stiffness (9).

Measurement of knee joint range of motion: All measurements in the treatment groups were evaluated by the FTR specialist before the treatment, on the 15th day of the treatment and at the 3rd month after the treatment. Knee flexion and extension of the patients were measured both actively and passively by goniometry.

Evaluation of Quality of Life

Short form-36 (SF-36): The quality of life was assessed using the validated Turkish version of the 36-item Short-Form Health Survey (SF-36). The SF-36 is a multidimensional tool measuring eight domains: physical functioning, physical role limitation, body pain, general health, vitality, social functioning, emotional role limitation and mental health. Domain scores range from 0 to 100 and higher scores indicate a better quality of life (10).

Statistical Analysis

Statistical analyzes were performed using SPSS version 20 package software. Descriptive statistics are summarized as numbers, percentages, mean and standard deviation. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov – Smirnov, Shapiro-Wilk tests). The numerical variables determined according to the normal distribution were compared between the two groups using the t test in independent and dependent groups. Numerical variables that did not show normal distribution were compared between the two groups using Mann Whitney U test and Wilcoxon test. Values with a p value of <0.05 were considered as statistically significant results.

RESULTS

Of the 40 patients with gonarthrosis in the first group, 57.5% were female (23), 42.5% were male (17). Of the 40 patients in the second group, 52.5% were female (21), 47.5% were male (19). There was no statistical difference between the groups in terms of gender distribution (p=0.623). While the mean age of the patients was 57.8±5.2 years in the TENS group, it was 55.8±7.5 years in the IFC group and there was no statistical difference between the two groups (p=0.265). The mean body mass index (BMI) was 31.9±6.2 kg/m^2 in the TENS group and 33±7.1 kg/m^2 in the IFC group. There was no statistically significant difference between the two groups (p=0.173). The mean pain duration of the patients was found to be 21 months in the TENS group and 25 months in the IFC group and no significant difference was found between the groups (p=0.453) (**Table 1**). In the TENS and IFC groups, the degree of active-passive knee flexion and

extension increased significantly on the 15th day of treatment and at the 3rd month after treatment , while it was at a similar level between the 15th day and the 3rd month of treatment (**Table 2**). There was no significant difference in knee range of motion measurements of TENS and IFC groups before treatment. In the comparison of the 15th day of the treatment and the 3rd month after the treatment, the increase in the active-passive flexion and extension measurements in the IFC group was found to be statistically significant (**Table 3**). There was no significant difference between the TENS and IFC groups in terms of WOMAC pain, stiffness and function sub-scores before treatment, on the 15th day of treatment and at the 3rd month after treatment. The decrease in WOMAC total value at the 15th day of the treatment and at the 3rd month after the treatment was found to be significantly decreased in the IFC group (TS p=0.013, TS 3rd month p=0.000) (**Table 4**). In the evaluations of the patients before the treatment, on the 15th day and at the 3rd month of the treatment, the quality of life parameters measured by the SF-36 questionnaire were compared between the two groups. There was no significant difference between the two groups in terms of physical function, social function, physical role difficulty, emotional role difficulty, mental health, energy/vitality, body pain and general health scores (**Table 5**).

Table 1. Demographic and clinical characteristics of the treatment groups

	TENS(n=40)	IFC(n=40)	p value
Age (Mean±SD)	57.8±5.2	55.8±7.5	0.265*
Female M/K	17/23	19/21	0.623**
BMI (Mean±SD)	31.9±6.2	33.±7.1	0.173*
Knee pain duration (months)	21 m	25 m	0.256***
K/L scale n(%)	Grade 2: 16 (40) Grade 3: 24 (60)	Grade 2:14 (35) Grade 3:26 (65)	0.453**

*T test in independent groups **Chi-square test ***Mann Whitney U test K/L: Kellgren Lawrence, SD standard deviation

Table 2. Comparison of active-passive flexion and extension values of TENS and IFC groups in three stages

	Before treatment (BT)	15th day of treatment (T15th day)	3rd month after treatment (AT 3rd month)	p (BT-T15th day)	p (T15th day -AT 3rd month)	p (AT 3rd month-BT)
TENS						
Active flexion	109±10.9	116±11.4	117±11	0.043	0.641	0.013
Passive flexion	119±9.9	121±7.6	122±8.4	0.036	0.763	0.021
Active extension*	-2.1±2.8	-1.9±2.6	-1.8±2.5	0.035	0.368	0.041
Passive extension*	-1.9±2.3	-1.4±2.1	-1.3±2.4	0.023	0.296	0.001
IFC						
Active flexion	111±9.9	121±8.9	122±9.7	0.017	0.051	0.021
Passive flexion	121±7.4	126±8.1	127±8.3	0.041	0.078	0.034
Active extension*	-2.4±2.9	-1.7±2.7	-1.6±2.5	0.029	0.596	0.012
Passive extension*	-1.7±2.3	-1.3±2.1	-1.3±2	0.013	0.631	0.024

*Wilcoxon test

Table 3. Comparison of the active-passive flexion and extension values of the patients before the treatment, at the 15th day of the treatment and at the 3rd month of the treatment.

	TENS Mean±SD	IFC Mean±SD	p value
Active flexion			
Before treatment	109±10.9	111±9.9	0.262
15th day of treatment	116±11.4	121±8.9	0.007
3rd month after treatment	117±11	122±9.7	0.000
Passive flexion			
Before treatment	119±9.9	121±7.4	0.065
15th day of treatment	121±7.6	126±8.1	0.011
3rd month after treatment	122±8.4	127±8.3	0.001
Active extension			
Before treatment	-2.1±2.8	-2.4±2.9	0.247
15th day of treatment	-1.9±2.6	-1.7±2.7	0.004
3rd month after treatment	-1.8±2.5	-1.6±2.5	0.031
Passive extension			
Before treatment	-1.9±2.3	-1.7±2.3	0.146
15th day of treatment	-1.4±2.1	-1.3±2.1	0.008
3rd month after treatment	-1.3±2.4	-1.3±2	0.041

Table 4. Comparison of WOMAC scores between groups

	TENS	IFC	p value
WOMAC-total			
Before treatment	50.2±19.2	51.7±21.3	0.071
15th day of treatment	36.4±18.7	32.4±20.9	0.013
3rd month after treatment	37.5±19.4	31.9±21.1	0.000
WOMAC-pain			
Before treatment	9.8±3.8	10.2±4.8	0.892
15th day of treatment	8.2±3.5	7.9±4.2	0.774
3rd month after treatment	7.2±3.6	7.6±4.3	0.813
WOMAC- stiffness			
Before treatment	3.4±2.1	3.7±2.2	0.059
15th day of treatment	3.1±2.3	3.4±2.1	0.771
3rd month after treatment	3.2±2.4	3.6±2.1	0.823
WOMAC-function			
Before treatment	34.6±14.9	36.1±15.2	0.278
15th day of treatment	29.4±14.4	30.1±15.3	0.417
3rd month after treatment	27.6±14.6	31.6±15.7	0.315

Table 5. Comparison of the patients' quality of life (SF-36) scores before the treatment, at the 15th day and at the 3rd month of the treatment between the groups

	Before treatment			15th day of treatment			3rd month after treatment		
	TENS Mean±SD	IFC Mean±SD	p value	TENS Mean±SD	IFC Mean±SD	p value	TENS Mean±SD	IFC Mean±SD	p value
PF	47.47±17.28	48.76±19.33	0.908	48.49±18.24	49.71±20.31	0.901	64.12±25.08	62.57±19.50	0.781
RP	11.50±20.53	18.55±25.99	0.336	12.55±21.51	18.50±26.50	0.335	46.31±42.50	50.98±36.35	0.763
BP	36.37±16.21	37.44±17.82	0.390	36.25±16.42	39.44±19.82	0.394	56.85±23.30	60.71±21.15	0.625
GH	48.83±24.01	44.55±18.57	0.568	48.81±23.84	45.54±19.00	0.567	51.56±19.30	48.79±20.32	0.883
V	50.10±21.03	50.09±22.37	0.971	51.20±20.39	51.24±22.35	0.871	57.70±21.19	55.56±24.40	0.696
SF	54.55±19.22	61.00±16.00	0.055	54.55±19.22	62.90±15.30	0.061	68.38±20.80	65.73±19.10	0.549
RE	38.76±38.86	37.52±38.01	0.590	39.01±29.23	33.44±37.51	0.573	55.53±38.11	45.60±37.12	0.335
MH	57.34±19.04	53.46±19.40	0.653	57.44±18.50	54.45±19.40	0.645	63.71±19.80	60.70±20.73	0.461

PF: physical functioning, RP:role limitations due to physical problems, BP: bodily pain, GH: general health perceptions, V:Vitalite, SF: social functioning, RE: role limitations due to emotional problems, MH: Mental health

DISCUSSION

Osteoarthritis (OA) is one of the most prevalent degenerative musculoskeletal diseases. This disease is affecting almost 5% of the global population (11). The knee is the most common joint affected by OA, which is characterized by irreversible degeneration of the articular cartilage at the ends of the bones such as femoral, tibial and patella cartilages. Knee osteoarthritis (knee OA) is a progressive disease that affects the entire knee joint. Knee OA is a condition driven by mechanical wear and tear as well as biochemical changes. Known risk factors for OA include aging, obesity and previous knee injuries (12). In our study in patients diagnosed with gonarthrosis with an increased number of women, BMI and mean age, it was observed that knee flexion, extension and WOMAC scores improved with both TENS and IFC treatments. Most of these improvements were sustained up to the third month after treatment. Our findings were primarily that both treatments were effective in patients with gonarthrosis. However, when TENS and IFC were compared, there were differences in knee flexion, extension and total WOMAC scores in the IFC group at the 15th day and 3rd month of the treatment. Our study, which indicates the efficacy of IFC in the treatment of gonarthrosis, provided evidence-based data on IFC. In the literature, there are studies that present similar and opposite views about IFC. Gundog et al. study showed that IFC treatments were effective interventions for the management of knee OA, with some advantages in pain and disability outcomes over the sham IFC. However, they could not find that different frequencies of the amplitude-modulated wave of IFC influenced the results, supporting various IFC frequencies that can be used for pain relief (7). Buenavente et al. (13) performed a meta-analysis to evaluate the effectiveness of IFC on knee osteoarthritis. Four studies were included for meta-analysis. It was concluded that IFC therapy in conjunction with therapeutic exercise is effective in decreasing pain and paracetamol intake in subjects with knee osteoarthritis. Zeng et al. (8) compared the efficacy of different electrical stimulation therapies with a control group in the pain relief of subjects with knee osteoarthritis. Twenty-seven studies were included and IFC was the only effective pain therapy when compared to controls. Thus, IFC therapy seems to be the best electrical stimulation option for pain relief in subjects with knee osteoarthritis. Adedoyin et al. evaluated the effectiveness of IFC and TENS in 46 patients with gonarthrosis, using pain and WOMAC scores. There was no significant difference in pain and WOMAC scores in the treatment groups within four weeks of treatment (14). In a study by Efterharsadat et al. (15), they compared action potential stimulation and IFC in 70 patients with gonarthrosis.The patients were evaluated with WOMAC, visual analog scales (VAS) and "Timed up and go (TUG)" and no significant difference was observed between the two groups in all parameters. In a review of non-pharmacological and non-surgical treatment methods in knee OA in 2019, it was emphasized that there are uncertainties regarding the efficacy of physical therapy modalities. Electroacupuncture, IFC, pulsed electromagnetic field, ultrasound and focal muscle vibration have been found to be effective in the treatment of patients with knee OA. It was stated that the efficacy of TENS, NMES, insoles, low-dose laser treatment could not be proven and homogeneous results could not be achieved. The modality with the most significant improvement in pain compared to the control group was found to be IFC (16). In the study of Burch et al. (17), investigated the benefits of the combination of interferential and patterned muscle stimulation in the treatment of osteoarthritis of the knee. A multi-center, randomized, single-blind, controlled study randomized 116 patients with OA of the knee to a test or control group. The test group received 15 min of IFC stimulation followed by 20 min of patterned muscle stimulation. The control group received 35 min of low-current transcutaneous electrical nerve stimulation (TENS). Both groups were treated for 8 weeks. Subjects completed questionnaires at baseline and after 2, 4 and 8 weeks. Primary outcomes included the pain and physical function subscales of the WOMAC OA Index and VAS for pain and quality

of life. Compared to the control group, the test group showed reduced pain and increased function. The test group showed a greater decrease in the WOMAC pain subscale, function subscale and stiffness subscale. More than 70% of the test group, compared to less than 50% of the control group, had at least a 20% reduction in the WOMAC pain subscale. When analyzing only patients who completed the study, the test group had a nominally significant greater decrease in overall pain VAS. Atamaz et al. (18) study aimed to compare the effectiveness of transcutaneous electrical nerve stimulation (TENS), interferential currents (IFCs) and shortwave diathermy (SWD) against each other and sham intervention with exercise training and education as a multimodal package. The study was a double-blind, randomized, controlled, multicenter trial 203 patients was inclueded. The patients were randomized by the principal center into the following 6 treatment groups: TENS sham, TENS, IFC sham, IFC, shortwave diathermy sham and shortwave diathermy. All interventions were applied 5 times a week for 3 weeks. In addition, exercises and an education program were given. They found a significant decrease in all assessment parameters, without a significant difference among the groups except WOMAC stiffness score and range of motion. However, the intake of paracetamol was significantly lower in each treatment group when compared with the sham groups at 3 months. Also, the patients in the IFC group used a lower amount of paracetamol at 6 months in comparison with the IFC sham group.

Our study had some limitations. First, the patient follow-up period in our study was limited to three months. Therefore, our findings did not include the long-term efficacy of TENS and IFC treatments. Second, patients who underwent sham IFC and IFC at different frequencies were not included in our study. By including the sham IFC group and the different IFC frequencies in the analysis, more comprehensive conclusions could be drawn about the effectiveness and frequency of IFC. Another limitation of ours is that the exercise program is performed by the patients at home and we cannot observe it by ourselves. However, exercise is an effective treatment method in increasing the range of motion and pain control in the long term.

CONCLUSION

In patients with gonarthrosis, TENS has been widely used for a long time and is among the well-known treatment options. However, there is little data on the use of IFC. In our study, we concluded that IFC both increased the range of motion of the knee joint in patients with gonarthrosis and contributed to the functional recovery in knee osteoarthritis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Medical Faculty Clinical Researches Ethics Committee (Date: 11.05.2022, Decision No: 423).

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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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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Original Article

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Poor quality of life and functioning in euthymic mood disorders

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ABSTRACT

Aim: This study's aim is to examine the relationship between clinical/demographic characteristics the quality of life (QOL) and functionality in patients with mood disorders.

Material and Method: Total of 280 participants, including participants with bipolar disorder I (BD I), bipolar disorder II (BD II) major depressive disorder (MDD) in remission, and healty control subjects (HC), were included. Beck Depression Inventory (BDI), World Health Organization Quality of Life Instrument Short Form Scale (WHOQOL-BREF), Beck Anxiety Inventory (BAI), Young Mania Rating Scale (YMRS), and General Functioning Assessment Scale (GAF) were used. The data were evaluated with the SPSS 25.0 statistical program.

Results: Compared with HC, patients with MDD had the lowest scores in the QOL total and subdomain scores (p=.001). There was a significant negative correlation between the QOL scores and the BDI scores, but there was a positive correlation between the educational level and the total QOL and social, enviromental domain scores. There was a significant negative correlation between the total QOL and physical domain and the number of depressive episodes. There was a significant negative correlation between the social domain and the number of hospitalizations, but there was a significant positive correlation between the physical, enviromental domain scores and the age of first episode.

Conclusion: QOL between MDD is lower than that of BD. Educational level, number of depressive episodes and hospitalizations, suicide attemps, age of first episode, and BDI scores correlated with QOL. Additionally, it was determined that the main factor affecting the QOL was residual depressive symptoms rather than type of mood disorder.

Keywords: Bipolar disorder I, bipolar disorder II, major depressive disorder, quality of life, functionality

INTRODUCTION

Mood disorders which include bipolar and associated disorders and depression disorders have a rate of prevalence of 2.6-7.8 % and 5-17 %, respectively (1,2). Depression is a syndrome that includes worthlessness, guilt, inadequacy, unwillingness and retarded thinking, loss of attention and concentration, and fatigue accompanied by a sad and overwhelmed mood (3). Depression is one of the common psychiatric disorders which cause loss of ability by affecting 15.7 million adults aged 18 and over in the USA (4). Bipolar disorder (BD) is a severe psychiatric disorder characterized by fluctuations in mood, energy, and behavior (5) that affects about 45 million people around the world (6). Quality of life (QOL) is defined as the individual's perception of their status in life in terms of the cultural structure and system of values they live in, their purposes, expectations, standards, and concerns (7). In a study, that evaluate the QOL of patients diagnosed with BD, it was reported that the disorder had negative impacts in many aspects, mainly education, work, economic status, functionality, social support, and relationships with relatives (8).

Moreover, it is reported that a significant portion of bipolar patients experiences residual symptoms, negative life events, impairment in psychosocial functionality, and life quality in the remission period (9). Similarly, it was observed that patients with depression tend to perceive their existent QOL at a lower level due to impairments in both mental and physical functionalities. Therefore, these persons withdraw from daily life and experience problems in their professional life (10). Even after depression entered remission following efficient treatment, it was reported that QOL only improved in certain patients (11). A longitudinal

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research compared patients diagnosed with BD I and II with patients diagnosed with depression in terms of QOL demonstrated that BD I's psychosocial functionality and QOL were worse than those with BB II and depression (12). In another study, it was reported that there was no difference in terms of psychosocial functionality between depression and BD in an existent depressive period (13). The main study hypothesis is that QOL may be impaired in patients with mood disorders, who are in remission. The manifestations of this impairment may be affected by demographic and clinical characteristics. The aim of this study is to evaluate in comparison QOL and functionality in euthymic patients with BDs, major depressive disorder (MDD) and healthy controls. Secondly, the relationship between QOL and clinical/demographic variables in disease groups will be examined.

MATERIAL AND METHOD

Data Collection and Ethical Considerations

The study was carried out with the permission of Tokat Gaziosmanpaşa University Clinical Researches Ethics Committee (Date: 06.03.2019, Decision No: 83116987-178). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This research is a descriptive and cross-sectional study. The study groups are consisted of 70 patients from each group of patients diagnosed with BD I, BD II, MDD and 70 healthy controls (HC) who did not have any mental disorder. Bipolar and depressive patients were randomly selected among the patients who had regular follow-up in psychiatry clinic. The inclusion criteria were as follows: i) diagnosis of BD I, or BD II, or MDD, according to DSM-5 criteria; ii) age between 18 to 65 years; iii) euthymia for at least 3 months before entering the study; iv) scored 17 points and under in the Beck Depression Inventory and 5 points and under in the Young Mania Rating Scale (for bipolar patients) which was applied during the interview . Exclusion criteria were as follows: i) intellectual disability and/or pervasive developmental disorder; ii) diagnosis of substance and/or alcohol related disorder, or any physical disorder. The healthy controls were included if they had no history of psychiatric, neurological and chronic medical diseases. Each stage of the research was carried out in accordance with the Helsinki Declaration's rules. Study data was collected between 10.03.2019-10.03.2020.

Measurements

Sociodemographic and data form: This form was prepared by the researchers. The participants' sociodemographic (Age, sex, marital status, level of education, living space, employment status, income level, physical illness), and clinical characteristics (Age at first episode, total number of depressive episodes, total number of hospitalizations, etc) were recorded.

Beck Depression Inventory (BDI): The ınventory developed by Beck et al., Turkish validity and reliability were completed (14). The cutoff score was calculated to be 17 points for the Turkish form of the scale, and higher points indicate the more severe depressive symptoms.

Beck Anxiety Inventory (BAI): This is a self-assessment ınventory comprised of 21 items used to evaluate the level and intensity of anxiety symptoms. Each item is rated on a four-point Likert scale ranging from 0=not at all to 3=severe. The total score ranged from 0 to 63. Score of 0-7 are categorized as normal/minimal anxiety, 8-15 as mild anxiety, 16-25 as moderate anxiety, and 26-63 as severe anxiety. The scale's validity and reliability for Turkish adaptation were completed (15).

Young Mania Rating Scale (YMRS): The scale was developed to measure the severity and alteration of the clinical symptoms in individuals who experience a manic episode. For the scale developed by Young et al., Turkish validity and reliability were completed. The scale is filled according to the interview made based on the patient's condition in the last 48 hours. The cut-off score was calculated as 5 point. (16).

Global Assessment of Functionality (GAF): In its form identified in the five-axis diagnosis system of the DSM, it is used to evaluate the individuals' functionality. It is commonly used in studies on the efficiency of treatment. The scale is scored between 1-100 points and comprises 10 different assessment steps in 10 point intervals. Higher scores on the scale mean better functionality.

World Health Organization Quality of Life Instrument (WHOQOL-BREF): The scale was developed to measure the quality of life associated with general health. The scale has 4 different domain, physical, psychological, social relationships, and environment, and the total score in these domains means the value for the quality of life. For the scale adopted by the World Health Organization, the Turkish validity and reliability study was completed (17).

Stastical Analysis

SPPS 25.0 statistical pack was used for data assessment. Descriptive statistics were provided for categorical and continuous variables in the study. The associations between categorical variables were analyzed using Chi-squared test. Moreover, among the prerequisites for parametric tests, the homogeneity of variances was controlled by the "Levene" test. The normality assumption was checked with the " Kolmogorov-Smirnov" test. To evaluate the differences between two groups, the "Student's t-test" was used when the parametric test prerequisite was fulfilled, and the "Mann Whitney-U test" was used when it was not fulfilled; for comparison of three or more groups, the ANOVA and among the multiple comparison tests, the

Tukey HSD test were used, and when it was not fulfilled, the Kruskal Wallis and among the multiple comparison tests, the Bonferroni-Dunn test were used. Stepwise multiple linear regression model was established to evaluate the sociodemographic and clinical characteristics that affect the participants' QOL. According to the model, the total QOL and subdomain scores was taken as the dependent variable, and sociodemographic (Age, sex, level of education, living space, employment status, physical illness), clinical variables (Age at first episode, total number of depressive episodes, number of manic episodes, number of hypomanic episodes, number of depressive episodes, BAI, BDI, number of hospitalization, attempted suicide), and group (BD I, BD II, and MDD) were taken as the independent variables, and the analysis was performed using the Backward method. A p-value less than .05 was considered to be statistically significant.

RESULTS

Total of 280 participants were included in the study; mean age was 43.55 (±11.75) years for the BD I group, 43.30 (± 12.78) years for the BD II group, 47.14(±9,13) years for the MDD group, and 41.83 (± 10.78) years for the HC. There was a significant difference among BD group (BD I, II) and the MDD group in terms of mean age (p<.005). The number of female participants in the BD II and MDD group was higher, and there was a significant difference compared to the other groups (p<.005). Demographic information of the participants is explained in **Table 1**.

When the patients were evaluated according to their clinical features, for the BD I group, hospitalization rates were statistically significantly higher than the BD II and, MDD group (p=.001). Age at first episode (years) were significantly higher in the MDD group, and there was a significant difference among bipolar groups (p=.001). The number of depressive episodes were higher in the MDD group but, there was not a significant difference among groups (p=.053). BDI and BAI scores were higher than the two BD groups in the MDD group, there was a significant difference between the groups (p=.001, p=.001, respectively). Considering the participants' QOL, it was found out that the total and subscale scores in the QOL scale were higher in healthy controls than patient groups (p=.001). The MDD group had lower scores for WHOQOL BREF subdomain (physical, psychological,

Table 1: Sociodemographic and clinical characteristics of the participants

Variables	Groups				$\chi 2/F$	P
	BD I (n=70)	BD II (n=70)	MDD (n=70)	Control (n=70)		
Age (years)	43.55(11.75)	43.30 (12.78)	47.14±9.13	41.83(10.78)	3.781	0.011
Sex Female	33 (47.1)	52 (74.3)	56 (%80)	37 (52.9)	23.256	<0.001
Marital status						0. 004
Single	15 (21.4)	21 (30)	5 (%7,1)	9 (12.9)	30.911	
Married	46 (65.7)	34 (48.6)	58 (%82,9)	56 (80)		
Divorced	7 (10)	6 (8.6)	4 (%5,7)	4 (5.7)		
other	2 (2.9)	9 (12.9)	3 (%4,3)	1(1.4)		
Level of education						0. 023
Primary school	34 (49.0)	27 (38.6)	40 (%57,1)	22 (31.4)	27.761	
Secondary school	9 (12.9)	10 (14.3)	4 (%5,7)	3 (4.3)		
High school	14 (20)	13 (18.6)	15 (%21,4)	26 (37.1)		
University	12 (17.1)	20 (28.6)	11 (%15,7)	18 (25.7)		
Living space						< 0.001
Village	11(15.7)	10(13.3)	3(43.3)	3(4.3)	39.000	
District	33(47.1)	22(31.4)	16(22.9)	10(14.3)		
City	26(37.1)	38(54.3)	51(72.9)	57(81.4)		
Employmentstatus						< 0.001
Unemployed	9(% 12.8)	6 (%8,6)	3 (%4,3)	1(%1.4)	30.212	
Housewife	24(34.3)	28(%40)	46(%65.7)	10(%14.3)		
Employee	12(%17.1)	10 (%14.9)	4(%5.7)	25(%35.7)		
Officer	8(%11.4)	12 (%17.1)	6 (%8.6)	20 (%28.6)		
Retired	17 (%24.4)	14 (%20)	11 (%15.8)	14 (% 20)		
Income level						0.007
<2800	65(%92)	61(%87)	26(%	26(%	70.019	
2800-3800TL	2(%3.5)	5(%7.1)	23(%	20(%		
>3800	3(%4.5)	4(%5.9)	23(%	24(%		
Physical illness						<0.001
Yes	22 (%31,4)	13 (%18,6)	41 (%58,6)	15 (%21,4)	31.827	

Results are presented as mean (standard deviation), or frequency (percentage). Results are from ANOVA or chi-squared test. BD I=bipolar disorder I; BD II=bipolar disorder II; MDD= major depressive disorder; TL=Turkish Lira.

social, and enviromental) than the BD I and BD II group (p=.006, p=.001, p=.001, p=.037, respectively). Considering the general functionality assessment, the MDD group had highest for GAF scores than the BD I and BD II group, while the highest mean score again belonged to the healthy control group (p=.001). The clinical characteristics of the groups were compared with ANOVA, data were presented in **Table 2**.

Multiple linear regression model was established to evaluate the sociodemographic and clinical characteristics that affect the participants' QOL. There was a significant negative correlation between the total QOL and, subdomains and the BDI scores (p<.001), but there was a positive correlation between the educational level and the total QOL and social, enviromental subdomain (p=.015, p=.004, p<.001, respectively). Additionally, there was a positive relationship between have a job and total QOL (p=.020). There was a significant negative relationship between the total QOL and physical subdomain and the number of depressive episodes (p=.049, p=.002, respectively). There was a significant negative relationship between the social subdomain and the number of hospitalizations (p=.045), but there was a significant positive relationship between the physical, enviromental subdomain and the age of first episode (p=.008, p=.022, respectively). There was a significant negative correlation between the history of suicide attemps and the enviromental subdomain (p=.047). There was a significant negative correlation between the group (BD I, BD II or MDD) and the total QOL and its psychological, social subdomain (p=.011, p=.014, p=.001, respectively). The data are shown in **Table 3**.

Multiple linear regression model was established to measure the sociodemographic and clinical characteristics that affect the patient group's QOL. In the BD I group, there was a negative correlation between the QOL subdomains (except enviromental), and the BDS scores (p=.003, p=.014, p=.029, respectively), but there was a positive relationship between the QOL physical subdomain and the number of manic episodes (p=0.024). In the BD II group, there was a significant negative correlation between the total QOL and, subdomains (except social) and the BDI scores (p<.001, p=.002, p<.001, p<.001, respectively), but there was a positive correlation between the enviromental subdomain and the educational level (p=.014). In the MDD group, there was a negative relationship between the total QOL and, subdomains and the BDI scores (p<.001), while there was a negative relationship between the physical subdomain and the number of depressive episodes, suicidal behavior (p=.015, p=.043, respectively), data were presented in **Table 4** and **Table 5**.

Table 2. Evaluation of scales and clinical features in groups

Scale	Groups	Mean±SD		F	p
GAF			HC>MDD>BD I. BD II	252.610	0.001[1**]
	BD I	56.93±7.288			
	BD II	56.29±7.357			
	HC	82.57±6.356			
	MDD	71.86±5.528			
WHOQOL-BREF total			HC>BD I. BD II. MDD	15.180	0.001[1**]
	BD I	66.42±9.313			
	BD II	64.61±7.940			
	HC	72.41±9.175			
	MDD	62.84±9.234			
Physical health			HC>BD I. BD II>MDD	4.253	0.006[1**]
	BD I	14.38±2.292			
	BD II	14.29±2.208			
	HC	14.70±2.444			
	MDD	13.36±2.377			
Psychological health			HC>BD I. BD II>MDD	11.167	0.001[1**]
	BD I	13.55±2.357			
	BD II	13.38±2.454			
	HC	14.80±2.150			
	MDD	12.61±2.105			
Social health			HC>BB I. BB II>MDD	5.605	0.001[1**]
	BD I	13.27±9.953			
	BD II	12.00±2.814			
	HC	14.26±2.710			
	MDD	10.65±2.832			
Enviromental health			HC>BD I. BD II. MDD	2.862	0.037[1*]
	BD I	13.26±2.043			
	BD II	13.06±1.827			
	HC	13.97±2.401			
	MDD	13.03±1.923			
Beck anxiety inventory			HC< BD II. BD I< MDD	19.277	0.001[2**]
	BD I	9.03±5.505			
	BD II	8.60±6.796			
	HC	4.34±4.656			
	MDD	14.97±4.575			
Beck depression inventory			HC< BD I .BD II<MDD	58.004	0.001[1**]
	BD I	7.67±3.331			
	BD II	7.61±3.553			
	HC	4.40±3.076			
	MDD	9.61±2.989			
Age at first episode (years)			BD I<BD II<MDB	241.148	<0.001[2**]
	BD I	24.38±9.81			
	BD II	29.24±10.46			
	HC	N/A			
	MDB	34.21±9.31			
Total number of depressive episodes			HC<MDD. BD I. BD II	87.623	0.033[2*]
	BD I	4.34±2.48			
	BD II	4.94±2.67			
	HC	N/A			
	MDB	5.44±2.63			
Total number of hospitalizations			BD I > MDD. BD II	69.445	0.001[2*]
	BD I	2.77±1.98			
	BD II	0.49±0.79			
	HC	N/A			
	MDB	0.6±1.26			

*p<0,05, **p<0,01, Abbreviations: SD: standard deviation; 1ANOVA (F), 2 Kruskal Wallis Test (H), GAF: Global Assessment of Functionality, WHOQOL-BREF: World Health Organization Quality of Life Instrument, HC: Healthy Control, BD I: Bipolar disorder I, BD II: Bipolar disorder II, MDD: Major depressive disorder

Table 3. Evaluation of quality of life subscales with sociodemographic and clinical characteristics

	WHOQOL-BREF total					Physical Health					Psychological Health					Social Health					Enviromental Health				
	B	SE B	β	t	95% CI	B	SE B	β	t	95% CI	B	SE B	β	t	95% CI	B	SE B	β	t	95% CI	B	SE B	β	t	95% CI
Gender	-1.657	.874	-.089	-1.896	(-3.378 -.064)	.294	.275	.062	1.069	(-.248-.836)	-.261	.264	-.056	-.986	(-.781-.260)	-.185	.356	-.030	-.520	(-.885-.516)	.324	.239	.079	1.356	(-.147-.795)
Education	.827	.337	.119	2.452/*	(.163-1.491)	.155	.106	.088	1.463	(-.054-.365)	.191	.102	.109	1.874	(-.01-.392)	.400	.137	.172	2.915/*	(.130-.670)	.548	.092	.361	5.945/**	(.367-.730)
Working status	.419	.179	.110	2.332/*	(.065-.772)	.023	.057	.024	.406	(-.088-.134)	.107	.054	.112	1.973	(.00-.214)	.091	.073	.071	1.243	(-.053-.235)	.059	.049	.071	1.205	(-.038-.156)
Age at onset	.027	.031	.048	.889	(-.033-.087)	.026	.010	.177	2.662/*	(.007-.045)	.000	.009	-.003	-.044	(-.019-.018)	-.023	.012	-.121	-1.857	(-.048-.201)	.019	.008	.154	2.304/*	(.003-.036)
Number of depressive episodes	-.344	.174	-.121	-1.981/*	(-.686-.002)	-.171	.055	-.237	-3.135/*	(-.279-.064)	-.090	.052	-.126	-1.720	(-.194-.013)	-.076	.071	-.079	-1.070	(-.215-.064)	-.036	.047	-.057	.751	(-.129-.058)
Number of hypomanic episodes	.324	.257	.068	1.263	(-.181-.829)	.275	.081	.227	3.401	(.116-.434)	.132	.078	.110	1.70	(-.021-.285)	-.071	.104	.045	.682	(-.134-.277)	.082	.070	.078	1.163	(-.057-.220)
Number of manic episodes	.577	.397	.094	1.453	(-.205-1.35)	.212	.125	.136	1.695	(-.034-.458)	.057	.120	.037	.475	(-.179-.294)	-.097	.162	-.047	-.603	(-.415-.221)	.100	.109	.075	.925	(-.113-.314)
BAI	-.023	.072	-.017	-.322	(-.165-.119)	-.043	.023	-.122	-1.872	(-.087-.002)	-.027	.022	-.078	-1.228	(-.070-.016)	-.029	.029	-.063	-.982	(-.087-.029)	-.003	.020	-.010	-.154	(-.042-.036)
BDI	-1.646	.129	-.658	-12.719/**	(-1.90--1.39)	-.258	.041	-.406	-6.330/**	(-.338--.178)	-.300	.039	-.478	-7.659/**	(-.377--.223)	-.305	.053	-.364	-5.784/**	(-.408--.201)	-.166	.035	-.304	-4.692/**	(-.236–-.096)
Attempted suicide	-1.098	1.292	-.036	-.850	(-3.64-1.44)	.669	.407	.087	1.645	(-.132-1.471)	-.590	.391	-.077	-1.510	(-1.360-.179)	.205	.526	.020	.390	(-.830-1.241)	-.704	.353	-.106	-1.992/*	(-1.40--.008)
Group	-1.476	.579	-.182	-2.550/*	(-2.61--.336)	-.276	.182	-.134	-1.512	(-.635-.083)	-.434	.175	-.214	-2.481/*	(-.779--.090)	-.785	.236	-.290	-3.333/*	(-1.249-.321)	-.089	.158	-.050	-.560	(-.401-.223)
Physical illness	-.173	.860	-.009	-.201	(-1.86-1.52)	-.481	.271	-.100	-1.777	(-1.014 -.052)	.557	.260	.117	2.143	(.045-1.069)	.157	.350	.025	.447	(-.533-.846)	-.014	.235	-.003	-.058	(-.477-.450)

Note. Results are from linear regression analysis. Group=BD I(bipolar disorder I); BD II(bipolar disorder II), MDD(major depressive disorder); WHOQOL-BREF=World Health Organization Quality of Life Instrument; BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; *P < 0.05; **P ≤ 0.001.

Table 4. Evaluation of quality of life subscales in patient groups with sociodemographic and clinical feature

		Physical Health					Psychological Health					Social Health					Enviromental Health				
		B	SE B	β	t	95% CI	B	SE B	β	t	95% CI	B	SE B	B	t	95% CI	B	SE B	β	t	95% CI
BD I	Gender	.858	.621	.208	1.382	(-.389-2.104)	-.126	.619	-.029	-.203	(-1.36-1.11)	-1.154	.824	-.206	-1.401	(-2.809-.500)	-.171	.579	-.043	-.296	(-1.334-.991)
	Education	-.005	.258	-.003	-.020	(-.523-.513)	.226	.257	.129	.881	(-.290-.742)	.296	.342	.129	.864	(-.392-.983)	.641	.240	.396	2.666/*	(.158-1.123)
	Working status	.024	.120	.030	.202	(-.217-.266)	-.022	.120	-.026	-.182	(-.263-.219)	.076	.160	.069	.477	(-.245-.397)	.082	.112	.106	.733	(-.143-.307)
	Age at onset	.013	.033	.056	.390	(-.054-.080)	.057	.033	.238	1.727	(-.009-.124)	-.012	.044	-.039	-.277	(-.101-.077)	.000	.031	-.001	-.010	(-.063-.062)
	Number of depressive episodes	-.106	.110	-.132	-.968	(-.326-.114)	-.119	.109	-.143	-1.091	(-.338-.100)	.110	.145	.101	.756	(-.182-.402)	-.022	.102	-.029	-.219	(-.227-.183)
	Number of hypomanic episodes	.186	.180	.135	1.031	(-.176-.548)	.062	.180	.044	.347	(-.298-.423)	.301	.239	.161	1.260	(-.179-.782)	.175	.168	.133	1.044	(-.162-.513)
	Number of manic episodes	.358	.172	.282	2.082/*	(.013-.703)	.339	.171	.258	1.979	(-.005-.683)	.027	.228	.016	.118	(-.431-.485)	.004	.160	.003	.026	(-.318-.326)
	Number of hospitalization	-.699	.921	-.099	-.759	(-2.54-1.151)	-.863	.918	-.118	-.940	(-2.707-.981)	-1.742	1.223	-.182	-1.424	(-4.198-.714)	-.148	.859	-.022	-.172	(-1.873-1.57)
	BAI	.046	.043	.166	1.069	(-.040-.132)	-.029	.043	-.101	-.675	(-.115-.057)	-.084	.057	-.224	-1.471	(-.198-.031)	-.038	.040	-.145	-.958	(-.119-.042)
	BDI	-.106	.110	-.132	-.968/*	(-.479– -.101)	-.240	.094	-.359	-2.554/*	(-.428– -.051)	-.280	.125	-.320	-2.243/*	(-.531- -.029)	-.119	.088	-.193	-1.355	(-.295- .057)
	Attempted suicide	.458	.828	.070	.554	(-1.205-2.12)	-.936	.825	-.137	-1.135	(-2.593-.721)	.300	1.099	.034	.273	(-1.90-2.50)	-.811	.772	-.129	-1.051	(-2.361-.739)

Note. Results are from linear regression analysis. BD I=Bipolar Disorder I; BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; *P < 0.05; **P ≤ 0.001.

Table 5. Evaluation of quality of life subscales in patient groups with sociodemographic and clinical features

		Physical Health				Psychological Health				Social Health				Enviromental Health			
		B	SE B	β	t	95% CI	B	SE B	β	t	95% CI	B	SE B	B	t	95% CI	B	SE B	β	t	95% CI
BD II	Education	.212	.232	.133	.914	(-.253-.677)	-.149	.293	-.084	-.508	(-.735-.438)	.474	.379	.233	1.252	(-.284-1.23)	.646	.215	.489	3.007/*	(.216-1.075)
	Working status	-.089	.109	-.100	-.811	(-.308-.130)	.071	.138	.072	.515	(-.205-.347)	.085	.178	.075	.477	(-.272-.442)	-.114	.101	-.155	-1.125	(-.316-.089)
	Age at onset	.009	.026	.041	.337	(-.043-.060)	-.047	.033	-.199	-1.435	(-.112-.018)	.004	.042	.016	.102	(-.080-.089)	.011	.024	.061	.445	(-.037-.058)
	Number of hypomanic episodes	.149	.123	.148	1.214	(-.097-.395)	-.049	.155	.043	-.314	(-.359-.261)	-.005	.200	-.004	-.027	(-.406-.395)	.000	.113	.001	.004	(-.227-.228)
	Number of depressive episodes	-.155	.098	-.187	-1.583	(-.350-.041)	-.003	.123	-.003	-.024	(-.250-.244)	-.123	.159	-.117	-.773	(-.442-.169)	.009	.090	.013	.100	(-.172-.190)
	Number of hospitalization	.476	.472	.102	1.007	(-.470-1.421)	.176	.596	.034	.295	(-1.01-1.36)	-.520	.770	-.087	-.676	(-2.06-1.02)	-.772	.437	-.200	-1.769	(-1.646-.102)
	BDI	-.230	.071	-.369	-3.227/*	(-.372- -.087)	-.373	.090	-.540	-4.159/**	(-.553- -.193)	-.195	.116	-.246	-1.681	(-.427-.037)	-.137	.066	-.266	-2.081/*	(-.269- -.005)
	BAI	-.116	.041	-.358	-2.831/*	(-.199- -.034)	-.029	.043	-.101	-.675	(-.140-.067)	-.402	.067	-.101	-.626	(-.176-.092)	.040	.038	.150	1.064	(-.036-.117)
	Attempted suicide	-.115	.608	-.019	-.189	(-1.333-1.10)	-.895	.767	-.134	-1.166	(-2.43-.642)	.072	.992	.009	.072	(-1.91-2.05)	-.942	.562	-.189	-1.675	(-2.068-.184)
MDD	Education	-.159	.203	-.083	-.784	(-.567-.248)	.293	.168	.191	1.738	(-.045-.630)	.632	.238	.280	2.651/*	(.154-1.110)	.344	.176	.232	1.953	(-.009-.697)
	Working status	-.086	.143	-.077	-.605	(-.372-.200)	.178	.118	.198	1.503	(-.059-.414)	.189	.167	.143	1.132	(-.146-.525)	.023	.124	.026	.183	(-.225-.270)
	Age at onset	.019	.029	.077	.666	(-.039-.077)	.012	.024	.062	.515	(-.036-.060)	-.014	.034	-.046	-.403	(-.082-.054)	.040	.025	.209	1.610	(-.010-.091)
	Number of depressive episodes	-.288	.115	-.326	-2.514/*	(-.518- -.059)	-.028	.095	-.039	-.290	(-.218-.163)	.077	.134	.074	.576	(-.192-.347)	-.019	.099	-.027	-.190	(-.218-.180)
	BAI	-.070	.051	-.137	-1.377	(-.173-.032)	.013	.042	.033	.317	(-.071-.098)	.096	.060	.159	1.610	(-.024-.216)	.041	.044	.102	-.887	(-.048-.129)
	BDI	-.416	.089	-.526	-4.679/**	(-.518- -.059)	-.392	.073	-.619	-5.347/**	(-.539- -.245)	-.622	.104	-.666	-5.997/**	(-.830- -.414)	-.280	.077	-.457	-3.658/*	(-.434- -.127)
	Number of hospitalization	-.025	.529	-.005	-.048	(-1.085-1.03)	.020	.438	.005	.045	(-.858-.897)	-.933	.620	-.154	-1.504	(-2.176-.309)	.107	.458	.027	.234	(-.811-1.025)
	Attempted suicide	2.150	.791	.297	2.719/*	(.566-3.734)	-.954	.655	-.164	-1.457	(-2.26-.358)	-.539	.927	-.063	-.582	(-2.39-1.31)	-.625	.685	-.111	-.913	(-1.996-.747)

Note. Results are from linear regression analysis. BD II=Bipolar Disorder II; MDD=Major Depressive Disorder; BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; *P < 0.05; **P ≤ 0.001.

DISCUSSION

The results showed that the QOL of patients with mood disorders such as BD I, BD II and MDD was impaired even during remission periods, and that the QOL in MDD was lower than in BD I and BD II. Education level, number of depressive episodes, number of hospitalizations, age at first attack, and BDI scores were correlated with QOL.

Life quality means the individual's perception of their physical, emotional, and social status, and it is primarily a subjective experience as it depends on how the individual perceives their satisfaction level in these different areas (18). The results of the this study, the MDD group had lower scores for QOL subdomain (physical, psychological and social) than the BD I and BD II group. A study comparing patients with BD and MDD in remission with HCs in terms of QOL, demonstrated that the QOL psychological domain score was lower in the MDD group. There was no difference between the MDD and BD groups regarding QOL total score and its subdomain scores (physical, environmental, social) (19). A possible reason for low QOL scores in MDD may be that functional recovery lags behind syndrome recovery, and QOL improvement lags behind clinical response (11,13). For this reason, some depression treatment experts recommend symptom improvement as the primary treatment aim. (20). In this research, patients with MDD were in remission, but the BDI and BAI scores of these patients remained higher than those of HCs, with negative effects in terms of QOL. This is consistent with previous studies that found that deterioration in QOL is associated with anxiety symptoms in patients with MDD (21). Global functionality assessment, the patient group with BD I and BD II had lower mean scores than the MDD group, while the highest score belonged to the HC. A follow-up study that compared BD patients with MDD patients in terms of psychosocial functionality reported that the MDD group had the highest functionality at work and the BD I group was unable to work for a more extended period than other groups (12). On the other hand, a cross-sectional by Van der Vort et al. reported no difference between MDD and BD in terms of functionality during a depressive attack (13).

Multiple linear regression model was established to measure the sociodemographic and clinical characteristics that affect the participants' QOL. According to the model, there was a negative relationship between the total QOL and, subdomains and the BDI scores. In a study evaluating the effect of depressive episodes on the QOL in bipolar patients, it was reported that the patients had lower scores in various areas of the QOL, and that QOL scores were

negatively correlated with the Hamilton Depression Rating scale scores (22). In another study, it was reported that sub-threshold depressive symptoms were predictive of lower QOL in bipolar patients (23). A similar situation is valid for patients with MDD, and it has been reported that MDD patients in remission have impairment in various domain of QOL (for example, mental, physical, social) (19). In this research, there was a positive relationship between the educational level and total QOL and, social, environmental domain, and a positive relationship was found between having a job and total QOL. In the literature, it is reported that generally, those with high education levels have better income and a better quality of work, better social capabilities, and thus, higher QOL (24). In a follow-up study evaluating the factors affecting depression, it was reported that low income, low education level and unemployment were associated with low quality of life, and higher education level is also associated with better QOL in bipolar patients (25,26). Additionally, studies in this field associated unemployment with poor QOL, and regularly working bipolar patients exhibited more social functionality (autonomy, professional functionality and interpersonal relations) compared to unemployed patients (27). There was a negative relationship between the total QOL and physical domain and the number of depressive episodes. That results suggest that previous depressive episodes, may have a greater impact on patients' perceived QOL, even if they are euthymic. In a follow-up study, in which bipolar patients were evaluated in terms of QOL, it was reported that one of the most effective factors on QOL was the number of depressive episodes (28). A study made in our country to evaluate the QOL of depressive patients demonstrated that patients who had a relapsing type depressive disorder had lower QOL in terms of physical functionality and general health perception than patients who had depression in a single period (29). This can be explained by the fact that patients with more depressive episodes experience more role and physical limitations due to emotional problems, with negative effects in terms of QOL (30). There was a positive relationship between the physical, enviromental domain and the age of first episode, but there was a negative correlation between the social domain and the number of hospitalizations. In a study evaluating QOL and functionality in patients with depression, it was reported that earlier age of onset was associated with functional impairment and worse QOL (31). The lower social domain scores of those with a higher number of hospitalizations may be due to the difficulty of maintaining their social relationships due to the intensity of illness. There was a negative relationship between the history of suicide attemps and the enviromental domain. In a prospective research conductec by Koivumaa-Honkanen et al. that shows a prospective correlation between life satisfaction (it is related to QOL) and future suicide completion. Although neither of theses researches was conducted with psychiatric patients, it is important QOL might be associated with suicidal behavior regardless of psychiatric disease and that low QOL could be a risk factor for suicide attempts (32). Another study showed that individuals with BD with a history of suicide attempt have a worse quality of life than individuals who have never attempted suicide (33).

An other multiple linear regression model was established to evaluate the sociodemographic and clinical characteristics that affect the patient's QOL. In the BD I, BD II and MDD group, there was a significant negative relationship between the total QOL and, subdomains and the BDI scores, but there was a positive relationship between the QOL subdomains (social, enviromental) and the educational level. Additionally, in the MDD group, there was negative relationship between the physical domain and, the number of depressive episodes and suicidal behavior. These results are in consistent with the literatüre (22,28,34). Although treatment goals are centered around the reduction of depressive symptoms in most clinical settings, remission does not denote normal QOL in depressed patients (11). In addition, bipolar disorder and MDD are chronic diseases, and subsyndromal symptoms may fluctuate during remission periods and, QOL scores may be affected differently (19).

The most important limitation is that cases were evaluated cross-sectional, not a longitudinal follow-up study. The lack of or the limited number of studies conducted with a similar population in our country and all cases being in the euthymic period reduce the generalizability of the outcomes. Moreover, the unknown time spent without treatment and medications can have a disturbing effect on functionality and QOL. Additionally, this study has its strengths. The fact that the study had a control group, evaluated bipolar subtypes, had more patients than similar studies, and acted elaborative in selecting the cases are the study's strengths.

CONCLUSION

We can conclude that most patients diagnosed with a mood disorder (BD I, BD II, MDD) experience lower QOL and loss of functionality even their clinical symptoms are suitable taken under control, suggesting

that keeping the pulse of improvements in QOL enhancement will likely be important for clinicians treating BD I, BD II and MDD. During remission period, worst QOL was observed in the patients diagnosed with MDD, which was correlated with depressive and anxiety symptoms, suggesting that QOL improvement lags behind clinical response. Furthermore, our study evaluated the impact of sociodemographic and clinical characteristics on QOL. Educational level, number of depressive episodes and hospitalizations, suicide attemps, age of first episode, and BDI scores correlated with QOL. Additionally, it was determined that the main factor affecting the QOL was residual depressive symptoms rather than the type of mood disorder. Therefore, future work should aim to develop new approaches to psychotherapy that focus on improving QOL and functionality. In addition, longitudinal studies with large samples and long follow-up periods are needed to better understand how the quality of life improves during mood disorders.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tokat Gaziosmanpaşa University Clinical Researches Ethics Committee (Date: 06.03.2019, Decision No: 83116987-178).

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.

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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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Original Article

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Giant cell tumor of the bone: an evaluation of prognostic factors associated with local recurrence and a comparison with the current literature

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ABSTRACT

Aim: Results of the surgical and medical treatments of giant cell tumor of the bone (GCT) in terms of local recurrence and prognostic factors associated with local recurrence are evaluated in this study.

Material and Method: Patients treated with either surgical or medical methods for GCT between 2011 and 2021 were retrospectively evaluated. Gender and age of the patients, localization of tumors, the existence of pathological fractures, grade of the tumor, soft tissue expansion, and resection types were evaluated. Postoperative local recurrence and metastasis were analyzed, and the risk factors associated with local recurrence were determined.

Results: The mean age of the 117 patients (51 female and 66 male) was 36.1±9.3 years. The mean follow-up was 71.2±48.3 months. Forty patients were Grade I, 56 were Grade II, and 21 were Grade 3, according to the Campanacci Grading System. Soft tissue expansion was present in 21 (17.9%) patients. 59.8% of the patients were undergone intralesional curettage, 32.4% of the patients were treated with marginal or wide local excision combined with adjuvant therapy with liquid nitrogen and poly-methyl methacrylate (PMMA) application, and 5.9% of the patients have treated with en bloc wide resection and reconstruction or arthrodesis. Two patients suffering from sacral involvement were treated with radiotherapy. There was local recurrence after surgery in 19 (16.2%) of the patients.

Conclusion: Local recurrence is an important cause of morbidity in the treatment of GCT, which is a benign but aggressive tumor of the bone. In this study, in which we investigated the causes of local recurrence, Campanacci Grade and soft tissue expansion were found to be associated with the development of local recurrence.

Keywords: Giant cell tumor, osteoclastoma, neoplasm, prognosis, recurrence

INTRODUCTION

Giant cell tumor of the bone (GCT) is a local aggressive primary bone tumor and accounts for 6% of the primary bone tumors (1). GCT is characterized by mononuclear stromal cells, primarily macrophages, and osteoclast-like giant cells in the histopathological examination. GCT is commonly seen in the 4th and 5th decades, and the most common symptom is pain (2). GCT is typically a solitary bone tumor, and 85% of them are seen in the metaphysio-epiphyseal regions of long bones (3). 10% of them are seen in the axial skeleton, and rarely (5%) of the GCTs are seen in the short bones of the hand and the foot (3).

GCTs are typically benign but rarely malignant de novo or due to the malignant transformation of the primary tumor. The main diagnostic challenge is that osteoclast-like giant cells may be seen in several pathological situations of the bone, such as aneurismal bone cysts, non-ossifying fibroma, chondroblastoma, and histiocytic fibroma. Henceforth, a thorough histopathological evaluation is crucial for the differential diagnosis of GCT.

There is no consensus on the treatment of the GCT, and several surgical and adjuvant techniques were defined in the literature. The main treatment modality for the primary local disease is surgery. Common

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adjuvant treatment options are liquid nitrogen, phenol, argon, and monoclonal antibodies. Generally applied treatment protocol for the treatment of GCT is adjuvant application after intralesional curettage and replacement of the defect with bone cement. On the other hand, reconstruction with endoprostheses or arthrodesis is another option for patients with broad soft tissue involvement or pathological fractures. The decision for the surgical treatment option generally depends on the feasibility of the curettage and local adjuvants against resection and partially the possibility of the local recurrence. Protection of the functionality of the limb while diminishing the risk for recurrence is aimed with local adjuvant treatments (4).

The main problem after the treatment of GCT is the local recurrence after surgery. Local recurrence is reported in 10% to 65% of the patients (5-8). Treatment options adjuvant to the surgery are reported as the main factor for the control of local recurrence (5-8). On the other hand, localization of the tumor, size of the tumor, grade, and several other factors may affect the local recurrence. This study aims to determine the recurrence rate after resection of GCTs and the factors associated with recurrence.

MATERIAL AND METHOD

After obtaining approval from Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 06.03.2019, Decision No: 2022/151), medical records of 117 patients operated on between 2011 and 2021 in a single center with the diagnosis of primary GCT were evaluated retrospectively. All the study procedures complied with the principles of the Declaration of Helsinki.

Gender, age, tumor localization, the existence of pathological fractures, Campanacci Grading System, Enneking Classification, soft tissue expansion, and the chosen therapeutical modality, i.e., intralesional curettage, curettage combined with resection, or en bloc resection were evaluated. Exclusion criteria were unconfirmed diagnosis of GCT despite the preoperative suspicion, admission with local recurrence and primary treatment made in an-other institution, missing medical records, unable to follow-up, and local recurrence of GCT treated with nonsurgical methods. All patients were discussed at the institutional musculoskeletal tumor council, and all these patients underwent surgery after biopsy.

The surgical technique of intralesional resection was performed from a cortical window, and curettage was done with a high-speed burr until no macroscopic tumor tissue was seen. After that, cryoablation was done with liquified nitrogen, and the bony defect was filled with polymethyl methacrylate (PMMA). Marginal or wide resection was performed on the patients if the tumor was big enough to lead to a pathological fracture or a pathological fracture existed, a broad soft tissue component existed, the joint was involved, or the defect was too wide for reconstruction. Two patients with iliac bone involvement were treated with segmental resection only. A patient with metatarsal involvement was treated with total excision of the metatarsal bone and reconstruction with an autologous nonvascularized fibular graft. Other patients were treated with endoprosthetic reconstruction or arthrodesis. Two patients with sacral involvement were treated with radiotherapy since their tumors were unsuitable for surgical resection.

All the patients were called for a follow-up examination in the 1st, 3rd, and 6th months after surgery. Local recurrence was screened with physical examination, radiograms, and CT scans. A yearly chest X-ray scan was performed for screening a possible pulmonary metastasis. A restaging was done for the treatment of local recurrences.

The data were analyzed with SPSS 22 statistical software (Chicago, IL, ABD). Univariate survival analysis was done with Kaplan-Meier survival estimation, and multivariate analysis of significant risk factors for local recurrence was done with the Cox regression analysis model.

RESULTS

The mean age of 117 patients (51 female, 66 male) was 36.1±9.3 years. The mean follow-up was 71.2±48.3 months. Ten patients (8.5%) had pathological fractures on admission. Forty-seven (40.2%) had tumors in the distal femur (**Figure 1** and **2**), 40 (34.2%) in the tibia, 12 (10.2%) in the distal radius, 6 (5.1%) in the proximal fibula, 5 (4.3%) in the pelvis (two in the sacrum, one in the acetabulum, two in the ilium), 5 (4.3%) in metatarsals, and 2 (1.7%) in phalanges of the hand. Forty (34.2%) of them were Campanacci Grade I, 56 (47.9%) were Grade II, and 21 (17.9%) were Grade III. Twenty-one (17.9%) patients had soft tissue expansion.

59.8% of the patients were treated with intralesional curettage (**Figure 1**) and 32.4% with marginal or wide resection. 5.9% of the patients were treated with en bloc wide resection, and two (1.7%) patients, who had sacral involvement, were treated with radiotherapy. Local recurrence after surgery was found in 19 (16.2%) of the patients, and six patients (5.1%) had pulmonary metastases.

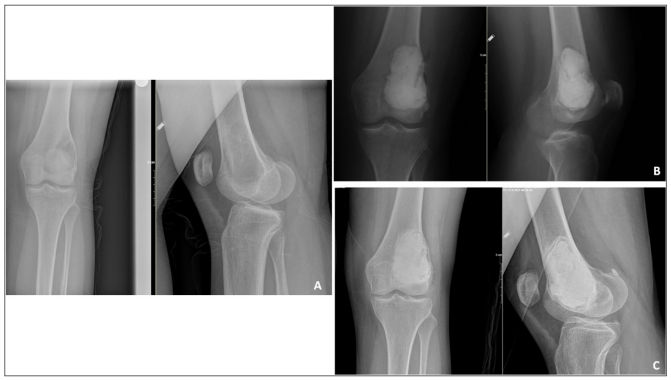

Figure 1. A) Conventional radiography of the left knee AP/Lateral projection, showing lytic lesion, septal, soap bubble appearance, narrow transition region, geographic destruction, cortical thinning, medullary, eccentrically located, hypodense lesion, no matrix calcification, no periosteal reaction, no soft tissue involvement. B) Postop radiography; intralesional curettage and augmentation with PMMA. C) Postop 3rd year radiography.

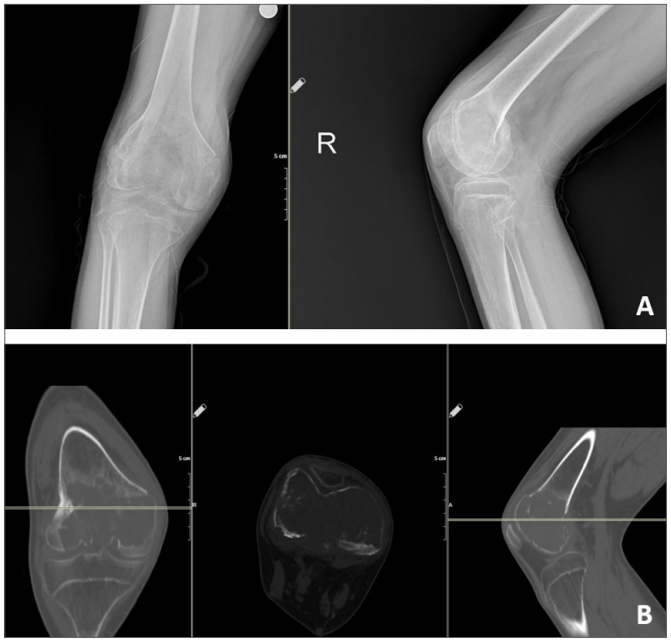

Figure 2. A) Conventional radiography of the right knee AP/Lateral projection, showing lytic lesion, septal, soap bubble appearance, narrow transition region, cortical destruction, medullary located, hypodense lesion, with pathological fracture. B) Coronal, axial and sagittal computed tomography images.

Three patients with femoral involvement were treated with endoprosthetic reconstruction after en bloc resection, and the local recurrence rate was 33.3%. Forty-four other patients were treated with curettage or marginal/wide resection, and only five had a recurrence. Two patients with proximal tibial involvement were treated with en bloc resection, and one of them had a recurrence. In contrast, only four patients treated with intralesional curettage had a recurrence. Two patients with iliac involvement were treated with segmental resection without reconstruction. Two patients with sacral involvement were treated with radiotherapy and one had recurrence. One patient with acetabular involvement was treated with intralesional curettage, and no recurrence was seen. Patients with distal radial involvement were treated with curettage or marginal/wide resection, and four of the 12 patients had a recurrence. All the recurrence patients were Campanacci Grade II. Five patients with fibular involvement were treated with intralesional curettage, and two of them had a recurrence, while one patient treated with wide resection had a local recurrence. One patient with metatarsal involvement was treated with total metatarsal excision and reconstruction with fibular autograft, while the other five were treated with curettage and reconstruction with PMMA. One of the patients with phalangeal involvement was treated with intralesional curettage, and the other was treated with wide resection and arthrodesis. None of these patients had a recurrence.

Demographic characteristics of cases and the specificities of tumors were summarized in **Table 1**. The median time for the first recurrence was 18.4 (6-38) months. Survival rates of the patients in the 1st, 2nd, and 5th years were 95.7%, 98.6%, and 84.3%, respectively. In the 1st, 2nd, and 5th years, survival rates without recurrence were 95.7%, 87.9%, and 84.4%, respectively. Potential risk factors for local recurrence are summarized in **Table 2**.

Table 1. Demographic characteristics of cases and the specificities of tumors

Parameters	Subgroups	N	%
Age			
	< 40		60.4
	≥40		39.6
Gender			
	Male	66	56.5
	Female	51	43.5
Localization			
	Distal Femur	47	40.2
	Proximal Tibia	40	34.2
	Distal Radius	12	10.3
	Proximal Fibula	6	5.1
	Pelvis	5	4.3
	Metatarsals	5	4.3
	Phalanges	2	1.7
Pathological fractures			
	Existent	10	8.5
	Absent	107	91.4
Soft tissue expansion			
	T1	96	80.1
	T2	21	17.9
Campanacci Grade			
	Grade I	40	34.2
	Grade II	56	47.9
	Grade III	21	17.9
Type of Resection			
	Intralesional Curettage	67	57.3
	Marginal /Wide local resection	41	35
	En bloc resection	7	6
	No resection	2	1.7
Local recurrence			
	Existent	19	16.2
	Absent	98	83.8

Table 2. Potential risk factors for local recurrence

Parameters	Subgroup	2-year Recurrence-Free Survival	5-year Recurrence-Free Survival	p
Age				0.235
	< 40	94.5	56.3	
	≥40	96.2	59.2	
Gender				0.309
	Male	86.8	75.3	
	Female	94.6	86.2	
Localization				0.142
	Distal femur	89.4	87.2	
	Proximal tibia	92.3	89.3	
	Distal radius	83.3	60.9	
	Proximal fibula	83.3	66.7	
	Pelvis	80.0	50.0	
	Metatarsals	100	100	
	Phalanges	100	100	
Pathological fractures				0.534
	Existent	90.0	80.0	
	Absent	91.7	82.8	
Soft tissue expansion				0.028
	T1	91.6	86.6	
	T2	71.4	65.9	
Campanacci grade				0.047
	Grade I	97.5	87.8	
	Grade II	92.6	84.8	
	Grade III	69.6	64.6	
Type of resection				0.169
	Intralesional curettage	93.7	87.3	
	Marginal /wide local resection	82.7	76.8	
	En bloc resection	71.4	71.4	
	No resection	50.0	50.0	

Gender and age were irrelevant to recurrence-free survival (p>0.05). Campanacci grade of the patients was related to five-year recurrence-free survival (p=0.047), and the rates for Campanacci grades I, II, and III were 87.8%,84.8%, and 64.6%, respectively. The 1st- and 5th-year recurrence-free survival rates were 90.0% and 80.0% in the patients with pathological fractures, while 97.2% and 82.8% in other patients, respectively. The existence of pathological fracture was not associated with recurrence-free survival (p=0.534). 60% of the pathological fractures were around the knee joint, and these patients were treated with marginal resection combined with augmentation with PMMA or en bloc resection combined with endoprosthetic reconstruction. The least recurrence-free survival rates according to the localization of the tumor were the distal radius and fibula, with 66.7% 5-year recurrence-free survival rates. Localization of the tumor was not associated with local recurrence (p=0.181). The 2- and 5-year recurrence-free survival rates in the T1 soft tissue expansion were 91.6% and 86.6%, respectively, while 71.4% and 65.9% were in the T2 group. The grade of soft tissue expansion was associated with local recurrence (p=0.028).

One- and 5-year recurrence-free survival rates were 97% and 87.9% in the intralesional curettage group, 92.7% and 76.8% in the marginal/wide resection group, and 85.7% and 71.4% in the en bloc resection group, respectively. The type of resection was not associated with local recurrence (p>0.05).

Nineteen patients with local recurrence were treated with a second intralesional curettage or wide resection, and none of them had re-recurrence. Six patients had pulmonary metastases. One of them had a pathological fracture after the treatment. Four of them had unifocal metastases and took denosumab adjuvant to the surgery. Two patients with multifocal metastases were treated with re-curettage only. None of the metastatic patients had secondary metastases or local recurrence.

Campanacci Grade of the tumor and soft tissue expansion were found to be risk factors for local recurrence. Age, gender, localization of the tumor, pathological fractures, and type of resection were not associated with local recurrence.

DISCUSSION

The pathogenesis of GCT is controversial and reported local recurrence rates were between 12% and 49% (2,8). Age, distal radius localization, proximal femur localization, intralesional curettage, soft tissue expansion, proximal fibula localization, pathological fractures, grade, marginal resection are previously reported risk factors for local recurrence (4,5,7-14). While age and gender were not found to be associated with local recurrence in this study, some studies claim that younger age is a risk factor for local recurrence (5,11). This may result from more conservative surgical choices for younger patients since broader resection decreases local recurrence in exchange for more morbidity, and surgeons may prefer intralesional curettage instead of wide resection for younger patients.

Some authors reported that localization of the tumor is associated with local recurrence (4,7,15). We found that the highest prevalence of local recurrence was seen in distal radial, with an odds ratio of 1.1 and a 66% 5-year recurrence-free survival rate, and proximal fibular involvement, but this difference was not statistically significant. Errani et al. (4) also reported that distal radial and proximal femoral involvement is associated with the risk of local recurrence. Other studies reported local recurrence rates between 20% and 88.9% for

tumors in the distal radius (4,9,15). The highest reported recurrence rate in the literature was 88.9% (7), and in this study, Balke et al. (7) reported that most of those patients had soft tissue expansion. Also, they did not use PMMA for bony defects. This may increase the local recurrence rate. We performed intralesional curettage for local lesions (Campanacci Grade I and II) and marginal or wide resection for Grade III lesions. We combined cryotherapy with surgery and applied PMMA to the defect. We found similar local recurrence rates after both treatment modalities. Three patients with GCT in the proximal fibula were treated with intralesional curettage, cryotherapy and PMMA; one had local recurrence; the other two had peroneal nerve damage. Local recurrence was treated with segmental resection. The proximity of neurovascular structures to the distal radius and the proximal fibula may challenge local control. Contrary to this, some reports claim that localization does not affect local recurrence (10,13).

Surgical treatment of GCT aims to ensure local control with minimum surgical morbidity and protect the limb's function. Intralesional curettage is associated with higher local recurrence rates but lesser morbidity than en bloc resection (6,7,16). Because of this, intralesional curettage is the main pillar of surgical treatment for most patients with Campanacci Grade I or II tumors, while the choice of wide resection is spared for more aggressive tumors with extraosseous invasion and unresectable tumors. On the other hand, curettage alone has the worst recurrence rate (21%-65%), and because of that usually combined with local adjuvants (5,7,11,17). Local adjuvant applications like phenol, hydrogen peroxide, cryotherapy with liquified nitrogen, augmentation with PMMA, and combinations of these decrease local recurrence rates (7,13,18-20).

We found lowest but insignificant ($p>0.05$) recurrence rate, 10.4%, after intralesional curettage. Recurrence rates after marginal/wide local resection and en bloc resection were 21.9% and 28.5%, respectively. The recurrence rate after intralesional curettage is reported between 12% and 65%, and approximately 20% after en bloc resection (7,11,17,21-23). Kivioja et al. (11) reported the lowest recurrence rate after wide resection as 12%, compared to intralesional curettage as 27%. Klenke et al. (5) reported that the type of surgical resection is not associated with recurrence-free survival.

Contrary to the current literature, we reported higher local recurrence rates after wide or en bloc resection than intralesional curettage. Two reasons may explain this. First, patients treated with wide or en bloc resection had soft tissue expansion or higher grades. We preferred marginal resection to wide resection to avoid higher complication rates and worse functional outcomes.

We applied cryoablation and PMMA augmentation to all patients after curettage or marginal/wide resection. After the combination of curettage and cryoablation, local recurrence rates were between 8% and 42%, while the combination of cryoablation and PMMA yielded better local recurrence rates (0%-20%) (4, 6, 24). Our previous report of 40 patients treated with curettage, cryotherapy, and PMMA found a recurrence rate of 7.5% (14). In this study, we reported a 14.4% recurrence rate, which is in accordance with previous reports. While we did not have another method for comparison in this study, it is evident that the combination of cryotherapy and PMMA is an effective adjuvant method.

On the other hand, usage of local adjuvants has reported complication rates between 12% and 50%(25, 26). Indeed, we observed temporary nerve paralysis in two patients with proximal fibular involvement and iatrogenic fractures in four patients with tumors around the knee. While nerve palsy of two patients recovered with observation, removing the cement, repeat augmentation with PMMA, and osteosynthesis with plates and screws were needed to treat the iatrogenic fractures. So, adjacent neurovascular structures and soft tissue should be well-preserved.

The effect of Campanacci grade on local recurrence is also controversial (6,9,12,15,27). We report that in Grade III patients, the risk of recurrence increased one-fold to the Grade I and two-fold to the Grade II ($p<0.05$). Parallel to our results, some authors reported that Grade III disease is associated with a higher risk of local recurrence(6,9,27). Still, Campanacci et al. (15) reported that the grade of the lesion is not associated with the risk of recurrence. Some studies performed in Eastern Asian countries reported lower recurrence rates in Grade III patient (8,12). This may be a result of the change in the type of surgical resection. Niu et al. (12) reported that they performed resection on 67.8% of Grade III tumors, and Pan Hu et al. (8) reported a resection rate of 47.5%. We performed wide local or en bloc resection on 76.1% of Grade III tumors, which is obviously more common than the aforementioned reports (8,12). We report a higher recurrence rate than these studies, despite the choice of a more aggressive surgical technique. This raises concerns about some other parameters affecting the local recurrence risk other than the grade and the type of resection.

There are conflicting reports about the association between the existence of a pathological fracture and the risk of local recurrence (9,12,28). O'Donnell et al. (9) reported that the existence of a pathological fracture is associated with a higher risk of local recurrence, but Niu et al. (12) reported that there is no relationship between pathological fractures and local recurrence risk. We performed intralesional curettage on the patients with pathological fractures and marginal or wide resection to others and found that

pathological fractures are not associated with recurrence rates (p>0.05). Among the patients with pathological fractures, we observed one local recurrence in a patient treated with intralesional curettage and one treated with marginal resection. We did not observe any recurrence in the patients treated with en bloc resection. Heijden et al. (3) reported a higher recurrence rate for curettage than resection. Our findings support that report. On the other hand, since we observed soft tissue expansion in the patients with pathological fractures, and the number of patients with pathological fractures is relatively low, our findings are inconclusive.

Soft tissue expansion is associated with a higher risk of recurrence (7,10,13). Becker et al. (10) reported 2.7 folds more, Balke et al. (7) reported 4 folds more, and Heijden et al. (13) reported 5 folds more risk of local recurrence with soft tissue expansion. We report 1.6 folds more risk of local recurrence in patients with soft tissue expansion (p<0.05). We performed intralesional curettage on 64.5% of T1 patients, and 23.8% of T2 patients. Technical difficulties for total excision of the tumor during curettage, possible incompetence of local adjuvants, and the need for better surgical margin for the patients with pathological fractures are reasons for the choice of resection as the treatment modality. The choice of surgical modality may lead to a bias.

Neoadjuvant denosumab is highly effective for advanced GCT, and a short-course is advised to facilitate surgery, whereas increased recurrence rates remain of concern. Randomized controlled trials are conducted on bisphosphonate-loaded bone cement and on optimal dose and duration of neoadjuvant denosumab (29). There are studies that say that denosumab and zoledronic acid have similar tumor responses and clinical benefits. Denosumab is a safe but costly alternative to zoledronic acid for treatment of surgically unsalvageable GCT (30). These treatments are used in cases of GCT. We used denosumab as adjuvant therapy in our four cases.

This study has several limitations. First, there may be some bias because of the retrospective nature of the study. Our relatively low sample size hardens our capacity to make a statistically significant conclusion for every parameter analyzed and every treatment group. Lastly, since we used same adjuvant modalities for every patient, we could not compare different options.

CONCLUSION

We observed that Campanacci grade and soft tissue expansion are associated with local recurrence after the treatment of GCT. We also observed a higher, but statistically insignificant risk of recurrence in the patients with distal radial or proximal fibular involvement. Because of this and the higher rate of surgical morbidity observed after curettage in the proximal fibular region, segmental resection is a preferable surgical. Soft tissue expansion in the scenario of a pathological fracture can increase the risk of recurrence.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 06.03.2019, Decision No: 2022/151).

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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Original Article

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Factors on development and severity of acute radiodermatitis: prospective single-center study

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ABSTRACT

Aim: Although prior literature has examined the treatment and patient-associated factors affecting the development and severity of acute radiodermatitis, there are relatively few prospective studies evaluating both. This study was prospectively designed to evaluate factors affecting the development and extent of radiation-induced acute skin toxicity called radiodermatitis (RD).

Material and Method: A total of 63 patients who underwent radiotherapy (RT) in Ankara Atatürk Research and Education Hospital between July 2017 and October 2018 were evaluated. Patients' demographic status, disease/treatment details, hemoglobin, ferritin, folic acid, Vit B12, and hemoglobin A1c values were recorded. The development and grade of RD were evaluated weekly by the same radiation oncologist using the Radiation Therapy Oncology Group (RTOG) radiation toxicity guideline.

Results: There was no significant relationship between the development of any degree of RD and gender, concomitant chemotherapy (CT), pre-RT CT, comorbid disease, RT technique and blood parameters (Hb, Hba1c, ferritin, folic acid and B12). The development of grade 2-3 RD was significantly affected by the number of operations (p=0.032) and total dose of RT (p=0.008). In patients with grade 2/3 RD, the RT dose at which RD first appeared was 20 Gy (range, 14-36); in patients with grade 1 RD, this value was 32 Gy (range, 16-56) (p=0.018).

Conclusion: There is no significant relationship between the development of acute radiodermatitis and Hba1c, hemoglobin, ferritin, B12 and folic acid levels. There was a significant correlation between grade of RD and repeated surgery, increase in total RT dose and early onset of RD.

Keywords: Radiotherapy, acute radiodermatitis, prospective

INTRODUCTION

Radiotherapy remains an essential component of cancer treatment, with nearly ½ of all cancer patients receiving RT during their illness (1). Radiodermatitis (RD) is skin toxicity of ionizing radiation, and approximately 95% of cancer patients receiving RT experience some form of RD, including erythema, dry and moist desquamation. These skin reactions often cause itching, and pain. However, RD is mostly moderate, with only 15-25% of it being severe (2,3). RD is often observed in patients receiving breast, head and neck, vulva, and sarcoma RT (2-4). The underlying causes are examined under two main headings: Treatment and patient-related factors (**Table 1**). As a result of RD, it causes a significant decrease in the quality of life of patients. In addition, the treatment of patients can be interrupted. This may lead to undesirable results in terms of oncological outcomes (5). Different parameters and indexes are being developed for the evaluation of RT (6,7). Also many treatment methods are being tried for the treatment of RD and there is no standard treatment. In the treatment of RD; hyperbaric oxygen therapy (HBOT), local antibiotics, herbal agents (aloe vera, calendula, etc), topical vitamins (ascorbic acid (ASC), pantothenic acid, etc), endogenous agents (hyaluronic acid (HA), epidermal growth factor (EGF) etc), pharmaceuticals (corticosteroids, statins etc) can be used (8). Oncological Nurse Forum (ONS) published a guideline in 2020 for the standardization of heterogeneous practices. This review does not recommend the use of aloe vera and curcumin which is frequently used according to this guideline, except in clinical studies. In addition, washing and skin care are recommended instead of topical nonsteroids. Topical steroids have been recommended in addition to skin washing in patients with itching and pain. However, even in most of the recommendations there is no

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consensus and the strength of the recommendation is weak (9). Finkelstein's published in 2022; Multinational Association for Supportive Care in Cancer (MASCC), British Columbia Cancer Agency (BCCA), Cancer Care Manitoba (CCMB), Oncology Nursing Society (ONS), Society and College of Radiographers (SCoR), and International Society of Nurses in Cancer Care (ISNCC) guidelines have been reviewed.All of these guidelines encourage the use of topical corticosteroids and recommended washing with soap and water. There is no consensus, especially regarding silver sulfadiazine, which is frequently prescribed by dermatologists.In this review, the necessity of further studies for RD was emphasized. If evaluated in the light of current literature, there is no single agent that is effective in RD (10).

Table 1. Factors affecting RD

Treatment-related parameters	Patient-related parameters
• Total dose	• Obesity
• Field Size	• Diabetes mellitus
• Fraction dose	• Malnutrition
• Energy	• Ethnic origin
• Use of bolus	• Age
• Number of beams	• Sex
• Type of chemotherapy	• Smoking
• Overall treatment time	• Genetic factors
	• Stage

RD: Radiodermatitis

The most basic approach is the evaluation and close follow-up of the patient in terms of prevention of RD. Pre-evaluation of risky groups is especially important in this respect. The presence of hematological parameters predicting RD is not clear. In previous studies, the relationship between these factors and RD has been investigated for different types of cancer (4,11). It is emphasized that some anemia parameters such as Ferritin, B12, and Folic acid should be evaluated about RD (4). In current study, the relationship between hematological parameters and the development of RD was investigated prospectively in a single center. There is limited literature data on the subject, and analysis will be made about whether there are hematological parameters predicting RD.

MATERIAL AND METHOD

All procedures performed in studies involving human participants were by the institutional and/or national research committee's ethical standards; and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional Review Board approval was obtained for this study. The study was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University Training and Research Hospital in July 2017 (Date: 12.07.2017, Decision No: 153).

Between July 2017-October 2018, 63 adult patients with stages 1-4, according to American Joint Committee on Cancer (AJCC) ver 8, treated with curative RT for head and neck, breast, vulva, sarcoma, and skin cancer in a tertiary radiation oncology clinic in Ankara were evaluated prospectively. Patient files and hospital electronic system data were used for data collection. The patients' demographic status, tumor size, disease stage, adjuvant treatment, weekly acute side effect assessment, and various treatments were noted.

Patients Selection

Patients who were in contact with the skin of the RT target area were included in the study. Patients with a pathological diagnosis and complete patient file data were prospectively evaluated in the study. Patients under the age of 18 without a pathological diagnosis were excluded. Patients with bone marrow involvement and chronic hematological disease were also excluded from the study.

Patients Simulation, Contouring and Planning

The planning CT of the patients was taken with the Aquilion LB Toshiba device at 3 mm cross-section and without contrast. Current contouring guides were used for contouring (12,13). Patients were treated with Helical Tomotherapy and Elekta Synergy Platform devices. The maximum dose in PTV was not exceeded by 110% in all plans.

Evaluated blood parameters

One week before the start of RT, complete blood count, ferritin, folic acid, B12, and hemoglobin A1c were requested from all patients.

Primary Endpoint

The primary endpoint is the evaluation of the formation and degree of acute RD. Skin changes in the RT field were examined by the same physician every week according to the Radiation Therapy Oncology Group (RTOG) manual to prevent inter-observer differences (**Table 2**) (14). The degree of RD is divided into 2 groups: grade 0-1 RD and grade 2-3 RD. Patients who were not followed up for acute side effects regularly were excluded from the study.

Table 2. RTOG acute radiation morbidity scoring criteria in skin (6)

Grade	Change
0	No change over baseline
1	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating
2	Tender or bright erythema, patchy moist desquamation/ moderate edema
3	Confluent, moist desquamation other than skin folds, pitting edema
4	Ulceration, hemorrhage, necrosis

RTOG: Radiation Therapy Oncology Group

Statistical Analysis

IBM SPSS Statistics v.20 (Armonk, NY: IBM Corp.) was used for statistical analysis. Non-parametric tests were used because the variables were distributed normally with visual and analytic methods. Mann-Whitney U test was used for the independent 2 groups. In the categorical two variables analysis, Chi-Square and Fisher -s Exact tests were used. The level of statistical significance was accepted at $p < 0.05$.

RESULTS

The patients' demographics are summarized in **Table 3**. The results of the anemia and diabetic profile values of the patients are presented in **Table 4**. RT technique (p=0.67), gender (p=0.27), concomitant chemotherapy (CT) (p=0.58), preRT CT (p=0.57), age (p=0.60), the presence of diabetes mellitus (DM) (p=0.50), Hb, HbA1c, ferritin, B12 and folic acid values were not significantly affecting the formation of RD.

Table 3. Patient demographics

Gender	
Male	25 (38.1%)
Female	38 (60.3%)
RT Technique	
IMRT	39 (61.9%)
3D RT	24 (38.1%)
Primer	
Head and Neck	22 (34%)
Breast	28 (44%)
Skin	6 (9.5%)
Sarcoma	4 (6.3%)
Vulva	3 (4.8%)
Stage	
1	7 (11%)
2	22 (34.9%)
3	25 (39.7%)
4	8 (12.7%)
DCIS	1 (1,6%)
Operation	
No	16 (25.4%)
Yes	47 (74,6%)
Concurrent CT	
Yes	35 (55,6%)
No	28 (44.4%)
CT before RT	
Yes	36 (57.1%)
No	27 (42.9%)
Comorbid Disease	
Yes	36 (57.1%)
No	27 (42.9%)
DM	
Yes	13 (20.6%)
No	50 (79.4%)
Smoking	
Smoker	50 (79.4%)
Non- smoker	27 (42.9%)
RD	
Yes	60 (95.4%)
No	3 (4.8%)
Grade of RD	
0	3 (4.8%)
1	34 (54%)
2	25 (39.7%)
3	1 (1.6%)

IMRT: Intensity Modulated Radiation Therapy, 3DRT: 3 Dimensional Radiotherapy, DCIS: Ductal Carcinoma In Situ, CT: Chemotherapy, RT: Radiotherapy, DM: Diabetes Mellitus, RD: Radiodermatitis

Table 4. Anemia and diabetic profile parameters

Parameters	Values (median)
Hemoglobin	12.4 (8.7-16.4)
Ferritin	104 (9.72-1269)
HbA1c (For DM +)	5.8 (5.46- 9.05)
B12	322 (159-1630)
Folic acid	7.2 (1.75-20)
Fasting blood glucose	83 (60-185)
Postprandial blood glucose	110 (105-276)

DM: Diabetes Mellitus

In the whole study population, 47 patients (74.6%) underwent surgery: 40 (85.1%) of them had 1, and 7 (14.9%) of them had 2 or more operations. Grade 2/3 RD was observed in 14 (35%) of the patients with 1 operation and 6 (85.7%) of the patients with more than 1 (p=0.032). A significantly higher rate of grade 2/3 RD was observed in patients with 2 or more operations (p=0.032).

No significant effect of RT fraction dose (1.8Gy vs. 2 Gy vs. 2.67 Gy) on RD was observed. A significant relationship was observed between RT total radiation dose and grade 2/3 RD (p=0.008) (**Figure 1**). The median total radiation dose was 50 Gy (range, 39-70) in patients with Grade 0/1 RD and 60 Gy in patients with grade 2/3 RD (range, 50-70 Gy) (p=0.008). The probability of grade 2/3 RD increased significantly with increasing total doses.

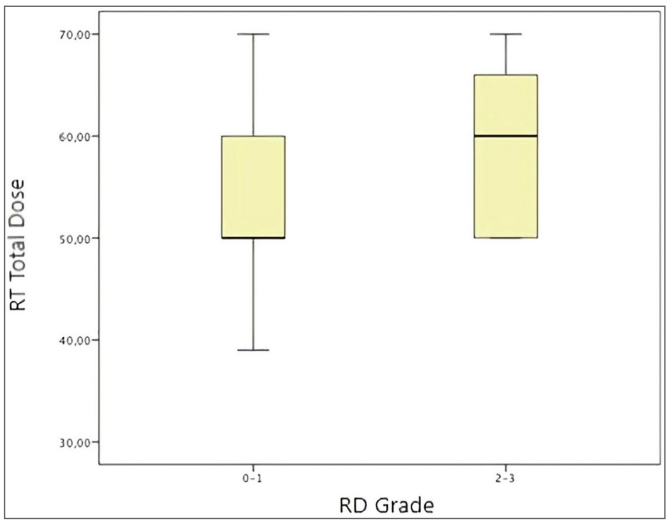

Figure 1. The risk of RD increases as the total dose of RT increases

In patients with grade 2/3 RD, the RT dose at which RD first appeared was 20 Gy (range, 14-36); in patients with grade 1 RD, this value was 32 Gy (range, 16-56) (p=0.018) (**Figure 2**). If grade 1 radiodermatitis started below 20 Gy, the risk of developing grade 2 and 3 RD increased. As the starting dose of grade 1 RD decreased, the risk of grade 2-3 RD increased throughout the treatment period.

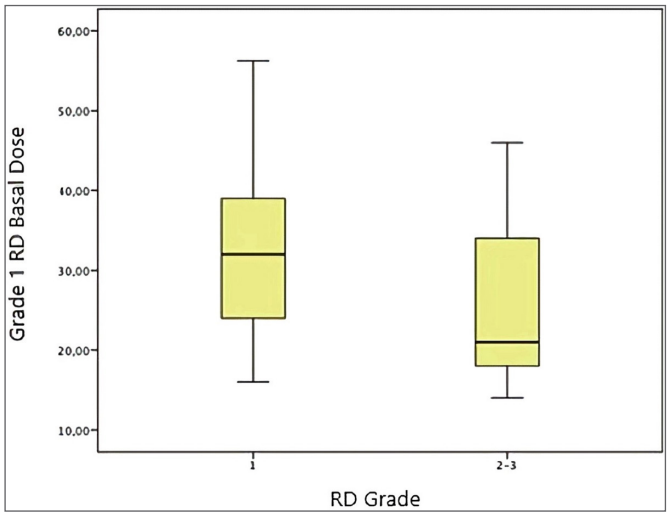

Figure 2. Relationship between the grade of RD and initial RT dose

DISCUSSION

In our study, no significant effect was found between RD development and blood levels of anemia and diabetic profile parameters. However, grade 2/3 RD is significantly affected by the number of operations performed by the patient before RT (p=0.032). A significantly higher rate of grade 2/3 RD was observed in patients with an operation number of 2 or more. A significant relationship was also observed between total radiation dose and grade 2/3 RD (p=0.008) (**Figure 1**). The median total dose was 50 Gy (range, 39-70) in patients with grade 0/1 RD; and 60 Gy (range, 50-70) in patients with grade 2/3 RD (p=0.008). In addition, patients with grade 2/3 RD had a median initial dose of 20 Gy (range, 14-36); In patients with grade 1 RD, the initial generation dose of RD was 32 Gy (range, 16-56) (p=0.018). The lower the threshold dose of RD, the higher the risk of grade 2/3 RD.

Radiation exposure to the skin causes cellular damage, aggravated by ROS formation and nucleic acid damage, and migration of inflammatory cells in the skin, and eventually, RD develops (15). Cellular damage is mainly observed in epidermal cells, basal epidermal cells, Langerhans cells, and endothelial and vascular cells (16). Increased cellular damage leads to an induced inflammatory cytokine and chemokine cascade. Chemokines and cytokines such as IL-1, IL-6, TNF-alpha, TGF-Beta, and histamine-like mediators increase in the micro-environment (17). In response to increased chemokines and cytokines, the endothelium is activated, and the expression of the adhesion molecules is accelerated and causes the migration of immune cells to the region, particularly leukocytes (17). Inflammation caused by the migration of immune cells increases the damage. In addition to these, stem cell loss due to RT negatively affects the skin's repair cycle (18). Histamine-like factors have shown increased capillary permeability and vasodilation. With increasing RT fractions, cellular damage increases, and if there is not enough time for repair, the damage becomes more evident towards the last stages of treatment (18,19). Dry desquamation develops due to erythrocytes' extravasation, and dry desquamation is usually the first clinical manifestation of RD. When RT damage is present in the basal cells and glandular tissue, epididymal necrosis with fibrinous exudate may occur. This is called moist desquamation. Finally, necrosis and ulceration of deeper tissues can be observed (17,20).

There was a relationship between total dose and RD by the literature. RT dose and fraction scheme play an important role in the development of RD (21). Consistent with the literature, a significant relationship was found between the total dose and RD in our study. In addition, a clinical RD initiation dose was noted in our study. Although dermal toxicity starts earlier in sensitive skin, it usually develops within 2-3 weeks (22,23). Dry desquamation starts in 3 weeks, nearly 30 Gy; moist desquamation starts in 4-5 weeks, nearly 45-50 Gy (4). Similar to our study, the time of first appearance of RD was also evaluated in Bontempo's prospective study, published in 2021 and including breast, head, neck and pelvic irradiation. According to this study, the first appearance of RD was approximately 11 days (24). In current study, in patients with grade 1 RD and not progressing to grade 2 or 3; the starting dose of grade 1 RD is 32 Gy (range, 16-56). In patients with grade 2-3 RD, the median dose at which RD occurs is 20 Gy (range, 14-36) (p=0.018). According to our study, it continued to be more severe in early-onset RD cases. Therefore, along with the RD grade, the dose at which grade 1 RD begins to occur should also be noted.

The low hemoglobin level can increase the radiosensitivity of the skin due to impaired tissue oxygenation. A limited number of studies evaluate the relationship between hemoglobin and RD (25,26). Gangopadhyay et al. (25) investigated the association between hemoglobin and mucocutaneous side effects in 227 patients with cervical cancer. In the patients receiving concurrent CT, patients with hemoglobin values of 12 or higher had a higher mucocutaneous side effect (p=0.001). On the other hand, in the study of Henke et al. (26), in 60 patients with head neck disease, lower hemoglobin levels were found to decrease the risk of RD, but the difference was not statistically significant (p=0.08). However, in our prospective study, no significant relationship was found between hemoglobin/ ferritin levels and RD.

The relationship between B12, folic acid levels and RT side effects is also a current research topic. These vitamins are important factors in DNA metabolism and wound healing (27). It is possible that there is a relationship between acute and chronic tissue damage due to radiation and vitamin values. In Debowska's research,

creams containing folacin were shown to improve skin conditions in patients receiving an RT (28). Our study did not demonstrate any relationship between blood folic acid and vitamin B12 levels and the timing and severity of RD. However, it would be more accurate to evaluate the difference in larger patient series with more homogeneous groups.

Smoking is known to impair wound healing by cutaneous vasoconstriction. Similarly, it may be thought that it adversely affects RD development with a similar mechanism (11,17). However, in the Kraus-Tiefenbacher study, no significant relationship was found between acute skin toxicities (erythema G0 versus G1 versus G2) and smoking during radiation therapy (p=0.064) in breast cancer (29). In the review published by Wong et al. in 2020, the effect of smoking on RT results and side effects in breast cancer patients was investigated (30). Skin changes were also analyzed in this review, and similar to our study, no article mentioned an increased risk in smokers. In this study, there was no significant relationship in terms of RD in smokers and nonsmokers patients.

RD development can be observed more frequently in elderly patients. because older age disrupts skin turnover (5,11,31,32). Advanced age is an unfavorable risk factor for many diseases (35). In general, although there is concern about an increase in side effects related to elderly patients, there is no significant increase in skin side effects (33). In the study of Wong et al. in 2021, it was observed that Older age was associated with increased risk of skin toxicities in 21 patients who underwent intraoperative radiotherapy (IORT) (34). However, unlike Wong's current study, many studies have not found a direct relationship between age and skin toxicity. Avoiding standard doses and fractions due to toxicity concerns in elderly patients has not been found to be correct in many recent publications (33,35). Similarly, no significant relation was found between RD development and RD grade and age in current study.

DM is a risk factor for RD when it causes adverse effects such as macrophage dysfunction, prolonged inflammatory phases, susceptibility to infection, and wound healing disorder (4,31). It was shown in the SBRT study of Kalman et al. that there was an increase in RT complications in patients with DM diagnosis (36). It is supported by studies that DM is a risk factor especially for radiation pneumonia (37). Similarly, in the study of Kuo et al., DM diagnosis was found to be significantly more risky in terms of infection and hematotoxicity, loss of body weight, and higher treatment-related mortality in head and neck patients (38). In our study, plasma blood glucose and Hba1c (for DM patients) values were evaluated, but no significant relationship could be detected.

Limitations of our study are small cohorts, not randomized and a single center study. RT areas and treatment doses are not homogeneous. However, the strength of the study is that it is prospective and all patients are evaluated by the same clinician. Randomized evaluation of patient groups with more similar treatments to detect factors predicting the development of RD will contribute more.

CONCLUSION

The severity of RD was associated with recurrent surgical intervention, RT total dose, and early onset of RD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Yıldırım Beyazıt University Medical Faculty Clinical Researches Ethics Committee (Date: 12.07.2017, Decision No: 153).

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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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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Original Article

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Can near infrared spectroscopy predict stroke in coronary artery by-pass graft?

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ABSTRACT

Aim: Central nervous system may be affected after coronary artery by-pass graft (CABG) and carotid artery stenosis is an important risk factor. Near infrared spectroscopy (NIRS) is used to measure the regional cerebral oxygen concentration ($rScO_2$). The aim of this study is to determine the relationship of $rScO_2$ in patients with carotid artery lesion and to determine the relation of stroke with $rScO_2$ changes.

Material and Method: The patients who had cardiac bypass surgery were involved in the study. Demographic characteristics and presence of carotid artery stenosis, were collected from the files. Bilateral rSO_2 measurements performed by 2 sensors. $RScO_2$ values are detected in 5 minutes of cross-clamp (XCL5), XCL30, XCL60, XCL90, XCL120 and after the by-pass.

Results: 57 patients were involved in the study (40 male and mean age 62.54±13.08). 17 (29%) patients had carotid stenosis. $rScO_2$ levels are statistically significantly decreased in the patients with stenosis after post-clamp 30 minutes. Three patients had stroke after surgery (5.2%). Two of the patients had carotid stenosis while one patient did not have.

Conclusion: $RScO_2$ decreased in carotid artery stenosis irrespective of the degree of the stenosis after 30 minutes of cross-clamp. Cerebral perfusion follow-up is important during the CPB and NIRS is a method that can be used for this purpose.

Keywords: Coronary artery by-pass graft, carotid artery stenosis, near infrared spectroscopy

INTRODUCTION

Today, coronary artery bypass graft (CABG) surgeries are widely applied with the use of cardiopulmonary bypass (CPB) in coronary artery disease. Although CPB provides great advantages in surgery, it has undesirable side effects on the cerebral system, respiratory system, circulatory system, renal system, and many organs due to non-physiological and perioperative procedures. These undesirable side effects contribute to postoperative morbidity and mortality (1). The mortality of coronary artery by-pass graft (CABG) surgery used in the treatment of coronary artery disease is less than 2%. However, central nervous system may be affected as an important morbidity (2). The resulting cerebral disorders can range from cognitive dysfunction to stroke. Cerebral hypo-perfusion, hemo-dilution, cerebral micro embolism and inflammatory response are blamed in the etiology. Therefore, it is very important to use methods to prevent the deterioration of brain perfusion during CABG (3,4).

Near infrared spectroscopy (NIRS) is a method used to measure the regional cerebral oxygen concentration ($rScO_2$). Although it has been in use for more than 20 years, there is no standardization (5-7).

In previous studies, it was stated that carotid artery lesions were the most important risk factor for stroke in CABG (8).

The aim of this study is to determine the relationship of $rScO_2$ detected by NIRS in patients with and without carotid artery lesion and to determine the relation of stroke with $rScO_2$ changes during the operation.

MATERIAL AND METHOD

The study protocol was approved by the İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Commitee (Date: 06.06.2022, Decision No: 188). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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This is a retrospective clinical study. This study was carried out at Cardiovascular Surgery Department of the Prof. Dr. Cemil Tascioğlu City Hospital. The patients who had cardiac bypass surgery between January 2018 and December 2021 were involved in the study. Written informed consent was obtained from each patient before the operation.

Patients who previously had a persistent cerebrovascular event were not included in the study. Demographic characteristics (age and gender), clinical findings, presence of carotid artery stenosis, history of cerebrovascular event (CVE) and presence of peripheral arterial disease were collected from the patient files. We defined carotid stenosis as mild (30-50%), moderate (50-69%) and severe (70-99%) or total-occlusion (100%) by North American Symptomatic Trial Collaborators (NASCET) criteria (9).

Continuous bilateral rSO_2 measurements were performed using a Masimo Cerebral Oximeter (Masimo Corp, CA, USA), by 2 sensors placed on the forehead. $rScO_2$ values from both hemispheres were recorded simultaneously at certain time points and were compared with each other to evaluate the changes at different stages of operation as follows: before anesthetic induction, in 5 minutes of cross-clamp (XCL5), 30 minutes of cross-clamp (XCL30), 60 of cross-clamp (XCL60), 90 minutes of cross-clamp (XCL90), 90 minutes of cross-clamp (XCL120) and after the by-pass.

Intra-arterial monitarization is made by measuring oxygen saturation (SO_2), mean arterial blood pressure (MBP), hematocrit (Htc) and body temperature.

CABG Surgical Procedure

Coronary bypass was performed using a standard cardiopulmonary pump. CABG surgeries were performed under general anesthesia after central venous catheter, arterial catheter, foley catheter, nasopharyngeal probes and rectal temperature probes were inserted. All surgeries were performed with a median sternotomy incision. In all patients, the left pleura was opened, the left internal mammillary artery was extracted as a graft, and the vena saphenous magna vein was prepared as a graft. In CABG surgeries, arterial cannulation from the ascending aorta and two-stage venous cannulation from the right atrium were performed, then CPB was started. The Terumo Advanced Perfusion System 1 heart-lung machine (Terumo Terumo® Advanced Perfusion System 1, Terumo ®, Ann Arbor, Michigan, USA) and the Inspire 8 membrane oxygenator (Inspire 8, LivaNova Sorin Group, Modena, Italy) were used for CPB. The cross-clamp, diastolic cardiac arrest was achieved by antegrade cold blood cardioplegia from the ascending aorta, mild-moderate hypothermic systemic cooling (28-32°C), and local cooling with cold icy saline. For myocard protection, maintenance was performed with cold blood cardioplegia at 20-minute intervals. After the distal anastomoses were completed, just before the cross-clamp was removed, the heart was started by giving warm blood cardioplegia and providing systemic warming. In CABG surgeries, proximal anastomoses were performed under partial clamping. A drain was placed in the mediastinum and thoracic cavity. All patients were taken to the cardiovascular surgery intensive care unit while intubated and connected to ventilators.

Statistical Analysis

Data were analyzed in SPSS software version 25.0. Continuous data were shown as arithmetic means ± standard deviation. Categorical data were expressed as number (%). The Student's t-test was used for continuous data analysis and the chi-square test was used for categorical data analysis. Fisher's exact test was used for some analyses, if necessary. Statistical significance was considered as $P \leq 0.05$.

RESULTS

57 patients were involved in the study. 40 (61%) were male and 17 (29%) were female. Mean age was 62.54±13.08. MBP, oxygen saturation, temperature, hematocrit, $rScO_2$ left and $rScO_2$ right values before induction, in five minutes of cross clamp and after coronary bypass can be seen on **Table 1**.

Table 1. General findings of the patients

Age (years)	62.54±13.08
Gender (male)	40 (70%)
Before anesthetic induction	
Mean blood pressure (mmHg)	87.54±15.37
Oxygen saturation (%)	96.2±0.69
Temperature (C)	36.45±0.5
Hematocrit	37.44±5.5
$rScO_2$-right	61.2±6.1
$rScO_2$-left	62.1±7.2
Cross Clemp (5th minutes)	
Mean blood pressure (mmHg)	70±10
Oxygen saturation (%)	93.5±0.77
Temperature (C)	31.84±3.52
Hematocrit	26.7±5.4
$rScO_2$-right	60.8±5.6
$rScO_2$-left	59±5.4
Coronary by pass	
Mean blood pressure (mmHg	62.77±9.93
Oxygen saturation (%)	99±1.3
Temperature (C)	33.9±2.84
Hematocrit	30±6.5
$rScO_2$-right	60.98±7
$rScO_2$-left	61.11±6.73

$RScO_2$: regional cerebral oxygen concentration

Oxygen saturation before induction was 96.2±3.69, increased to 99.33±1.08 in XCL5 and decreased to 98.89±1.51 after CBP. The difference between induction and XCL5 and after CBP were statistically significantly different (p<0.05) (**Figure 1**).

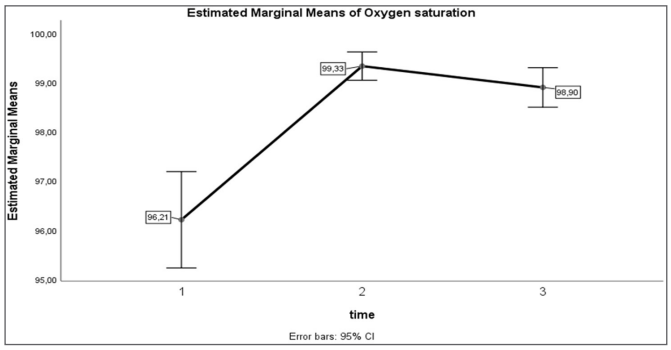

Figure 1. Oxygen saturation before induction, in XCL5 and after CABG

MBP before induction was 87.53±15.37, decreased to 68.28±11.25 in XCL5 and increased to 75.12±12.29 after CBP. The difference between all three groups were statistically significant (p<0.05) (**Figure 2**).

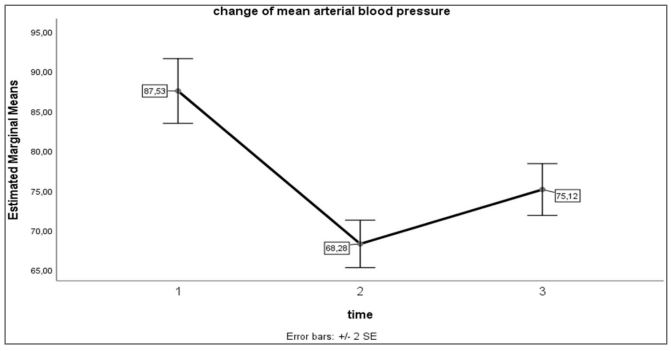

Figure 2. MAP before induction, in XCL5 and after CABG

Htc before induction was 37.44±5.32, decreased to 26.038±4.67 in XCL5 and increased to 27.12±2.72 after CBP. The difference between induction and XCL5 and after CBP were statistically significantly different (p<0.05) (**Figure 3**).

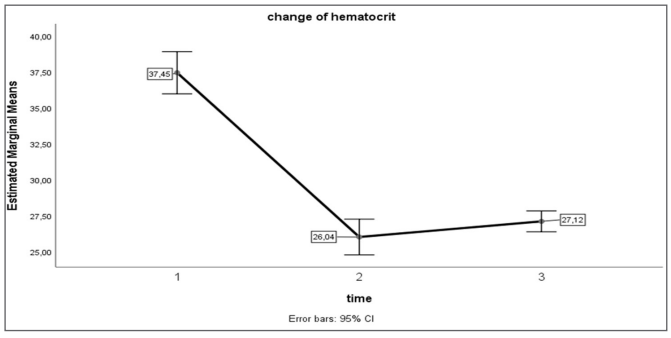

Figure 3. Htc before induction, in XCL5 and after CABG

$RScO_2$-right before induction was 61.39±8.91, decreased to 60.39±8.42 in XCL5 and increased to 63.84±6.9 after CBP. The difference between induction and after CBP were statistically significant (p<0.05) (**Figure 4**).

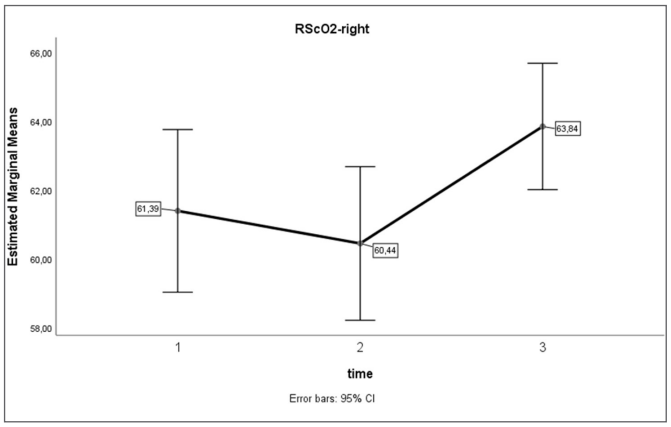

Figure 4. $RScO_2$-right before induction, in XCL5 and after CABG

$RScO_2$-left before induction was 61.84±9.04, decreased to 61.07±8.48 in XCL5 and increased to 63.7±6.1 after CBP. The difference between induction and after CBP were statistically significant (p<0.05) (**Figure 5**).

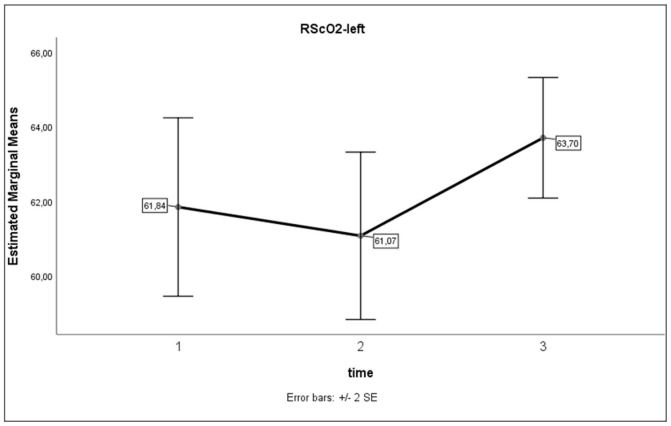

Figure 5. $RScO_2$-left before induction, in XCL5 and after CABG

Correlation analysis of $rScO_2$ right and left after XCL5 was made and they are found to be negatively correlated with age (R=-0.347, P=0.008 and R=-0.366, P=0.005, respectively) (**Table 2**).

Table 2. Correlation analysis of $rScO_2$ right and left after XCL5

	Age	
	R	P
$rScO_2$-right	-0.347	0.008
$rScO_2$-left	-0.366	0.005

$RScO_2$:regional cerebral oxygen concentration, XCL: Cross-clamp

Patients are grouped according to the presence of carotid stenosis. 27 (47.3%) patients had carotid stenosis while 30 (52.6%) did not have. When patients are grouped according to presence of carotid artery stenosis 4 of the patients (33.3%) had mild, 7 of the patients had moderate (58.1%) and one of the patient (8.3%) had severe stenosis in the right carotid artery. In left carotid artery 3 of the patients (20.6%) had mild, 9 of the patients had moderate (60.0%) and 3 of the patient (20.0%) had severe stenosis (**Table 3**).

Table 3. Presence of stenosis

	Right carotis stenosis	Left carotis stenosis	P
Total	12 (44.%)	15 (55.6%)	>0.05
Mild	4 (33.3%)	3 (20.6%)	>0.05
Moderate	7 (58.1%)	9 (60.0%)	>0.05
Severe	1 (8.3%)	3 (20.0%)	>0.05

$RScO_2$ right and left were analyzed during induction, XCL5, XCL30, XCL60, XCL90, and XCL120th minutes in patients with and without carotid artery stenosis. $RScO_2$ levels are statistically significantly decreased in the patients with stenosis after post-clamp 30 minutes (**Table 4**). In post clamp 30th minutes only $rScO_2$-left was statistically significantly decreased in the carotid artery stenosis group (56.88±7.37 vs. 62.08±8.81; p=0.038).

Table 4. Comparision of the groups in terms of carotid artery stenosis

	Carotid Stenosis				P
	(+)		(-)		
	Mean	SD	Mean	SD	
$rScO_2$-right-induction	63.06	9.14	60.65	8.8	0.239
$rScO_2$-left-induction	63.81	10.15	61.2	8.47	0.112
$rScO_2$-right-5	58.10	6.32	61.48	9.04	0.12
$rScO_2$-left-5	58.59	6.61	62.13	9.03	0.1
$rScO_2$-right-30	56.59	7.87	61.84	9.51	0.08
$rScO_2$-left-30	56.88	7.37	62.08	8.81	0.038
$rScO_2$-right-60	56.71	7.78	64.43	8.47	0.006
$rScO_2$-left -60	57.29	7.96	64.57	7.73	0.007
$rScO_2$-right-90	55.00	3.81	67.00	8.00	0.004
$rScO_2$-left -90	55.20	5.89	66.35	8.25	0.012
$rScO_2$-right-120	55.75	5.12	63.33	5.50	0.038
$rScO_2$-left -120	55.25	4.86	64.25	6.78	0.044

$RScO_2$:regional cerebral oxygen concentration, SD: Standard deviation

Three patients had stroke after surgery (5.2%). 2 of the patients had carotid stenosis while 1 patient did not have. The patients with carotid stenosis and stroke both had moderate unilateral stenosis (**Table 5**).

Table 5. Post-operative CVA

		Carotid Stenosis		P
		(+)	(-)	
		Count	Count	
Postoperative CVA	0	15	39	0.152
	1	2	1	

CVA: cerebrovascular accident

DISCUSSION

Major finding of this study is the decrease in $rScO_2$ levels in patients with carotid artery stenosis irrespective of the degree of the stenosis after 30 minutes of cross-clamp.

One of the main goals of anesthesia is to provide adequate tissue oxygenation. For this purpose, different monitoring techniques are used. This follow-up is even more important to minimize the effects of cardiopulmonary bypass during open heart surgery.

The brain is one of the most affected organs during CABG (10). In open heart surgery, cerebral protection was tried to be provided by methods such as increasing cardiac output, using inotropic agents, cooling the patient, using cerebral vasodilators and increasing hematocrit. Various methods have been used to monitor brain perfusion and evaluate metabolic activity. Cerebral ischemia markers such as mean arterial pressure, blood gas monitoring, jugular oxygen venous saturation, lactate, neuron-specific enolase (NSE) and S-100B were used (11-14). None of the traditional methods can show cerebral perfusion instantaneously and locally during CABG surgery. Near infrared spectroscopy (NIRS) noninvasively demonstrates real-time degradation of tissue oxygenation, allowing necessary interventions to be performed in a timely manner. $RScO_2$ measured by NIRS shows real-time changes in the supply-demand balance of area-specific tissue O_2 perfusion. Usually, perfusion disorder at the microvascular level can be detected before noticeable changes in systemic parameters. Clinical studies have shown that more than 20% reductions of $rScO_2$ from the patient's baseline are associated with neurological disorders. (15, 16).

Stenosis of 30-50% or more in the extracranial internal carotid arteries is defined as carotid artery stenosis (17). It is responsible for 10-15% of all strokes (18). Patients with a history of numbness, weakness, and transient ischemic attack in the face, arms, and legs in the previous six months are considered symptomatic (19).

Symptomatic patient, plaque structure, concomitant diseases and severity of stenosis are important in determining surgical indications (20). Surgical treatment is recommended for patients who are symptomatic and have stenosis greater than 50%, and patients who are asymptomatic but have stenosis greater than 70 % (21). In 2017, the European Society of Cardiovascular Surgery recommends routine CAS screening before CABG only for patients over 70 years of age, with a previous history of carotid stenosis and a previous central event (22). The reason for this may be the cost. However, since the coexistence of the two pathologies will increase mortality and morbidity, hence, many centers perform carotid artery screening before CABG (23). CAS was detected in a total of 17 (29%) patients with this screening, which was also performed in our clinic.

Since CABG surgery performed with CPB is carried out with lower arterial blood pressure and cardiac output, so cerebral perfusion decreases when CPB begins (24). In our study, a statistically significant difference was found between the MBP values measured preoperatively, XCL5 and after CPB. The significant decrease in MBP

detected in XCL5 is an indicator of cerebral-hyperfusion as expected during CPB.

Decrease in patient's Htc level is a natural process which occurs during the initiation of cardiopulmonary bypass and its primary cause is the volume of fluid that fills the perfusion pump (priming). However, if the Htc level is too low it may result in complications originating from poor tissue oxygenation such as impaired renal function, increased risk of myocardial damage, perioperative stroke (25). In our study, a statistically significant difference was found in the Htc values measured preoperatively, XCL5 and after CPB. The decrease in the hematocrit value detected in XCL5 is an indication of decreased cerebral perfusion as expected during CPB. A statistically significant difference was found between preoperative, XCL5 and postoperative CPB oxygen saturations. The elevation in XCL5 is due to perfusion from the heart-lung machine with 60% oxygen. During CPB, blood PO_2 pressure is targeted to be 100-180 mmHg. Higher values may cause air embolism. (26).

Measuring regional cerebral oxygen saturation via near infrared spectroscopy (NIRS) has become a widely used tool for intraoperative neuromonitoring during CPB in cardiac surgery. As the duration of CPB is prolonged, a decrease in cerebral perfusion and a number of complications ranging from neurocognitive impairment to cerebrovascular accident are observed (27). In our study, $rScO_2$ right and left were analyzed during induction, XCL5, XCL30, XCL60, XCL90, and XCL120th minutes in patients with and without carotid artery stenosis. $RScO_2$ levels are statistically significantly decreased in the patients with stenosis after XCL30, XCL60, XCL90, and XCL120th minutes. In the study, the $rScO_2$ value was found to be low in patients with only $rScO_2$-left in the XCL30. We think that this may be due to the higher number of patients with left carotid stenosis, although this is not statistically significant. In our study irrespective of the degree of stenosis cerebral oxygen saturations decreased in the stenosis group after post-clamp 30 minutes. In order to avoid this situation, it may be appropriate to keep the post-clamp time short or to increase the perfusion pressure or mean arterial pressure regardless of the level of carotid stenosis. In a study by Sungurtekin et al. (28), they found that MAP was the most effective factor in cerebral perfusion. In the study conducted by Tufo et al. (29), they found that neurological findings occur three times more in patients with a MAP value below 40 mmhg than in patients with a MAP value above 60 mmhg. In a study by Coskun et al. (30), they found that the follow-up of cerebral perfusion with a method like near-infrared spectroscopy (NIRS) will ensure that MAP is adjusted with interventions that will be made according to changes in NIRS.

In our study, postoperative stroke developed in 3 patients (5.4%). Naylor et al. (8) reported the postoperative stroke rate of 1% to 2% in all patient groups undergoing CABG. In another study involving patients with critically asymptomatic carotid stenosis, the postoperative stroke rate was 3%. The postoperative stroke rate reaches 5% in patients with bilateral carotid stenosis and 11% in patients with total stenosis (31In our study, 2 of the patients who had moderate stenosis had stroke. These findings may suggest that there is a risk of stroke in moderate stenosis.

Cerebral oxygen sat values were correlated with age in patients. This may be due to the increasing rate of atherosclerosis with age (32). This may be concordant with the 2017 European Society of Cardiovascular Surgery guidelines which recommends investigating CAS over 70 years of age. In our study, there was a negative correlation between age and $rScO_2$. The result is similar to the literature.

The limitations of this study are the retrospective nature of the study, the small number of patients, and the evaluation of only major cerebrovascular events such as stroke. Future large-scale, multicenter studies with a longer follow-up duration are required.

CONCLUSION

Cerebral hypo-perfusion is the most important causes of stroke, which is an important cause of mortality and morbidity in patients undergoing CABG. We think that perfusion follow-up is important in the early detection of cerebral hypo perfusion. NIRS is a non-invasive and easy method that can be used for this purpose. We think that taking measures to increase cerebral perfusion, such as increasing pump cardiac output and using inotropic agents, may reduce the risk of stroke in patients with CAS, in patients with CABG found to have decreased $rScO_2$ with NIRS during CPB. Thus, unnecessary increases in the perfusion flow rate and unnecessary use of medication can be avoided by $rScO_2$ monitoring.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Commitee (Date: 06.06.2022, Decision No: 188).

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.

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Original Article

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Increased QT dispersion and related factors in patients with systemic sclerosis

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ABSTRACT

Introduction: Cardiac arrhythmias and sudden death may occur as a result of ventricular myocardial fibrosis or ischemia in patients with systemic sclerosis (SSc). QT prolongation and QT dispersion, which facilitate the development of ventricular fibrillation, are important cardiac problems associated with increased mortality. In this study, we aimed to investigate the prevalence of corrected QT dispersion (cQTD) and related factors in our patients with systemic sclerosis compared to healthy controls.

Material and Method: The 12-lead electrocardiograms with a rate of 25 mm/s of patients with no previous history of cardiovascular disease and controls were analyzed. cQTD was defined as the difference between the maximum QT interval and the minimum QT interval. Nailfold capillaroscopy examination was performed. Disease activity was evaluated using revised European Scleroderma Study Group activity index.

Results: Forty-nine SSc patients (45 females, mean age 53.26±10.63 years, and disease duration 8.0 (1-25) years) and 41 controls (37 females, mean age 49.29±8.02 years) were included. While the frequency of smoking was significantly higher in controls ($p=0.025$), erythrocyte sedimentation rate was higher in patients ($p<0.001$). cQTD was significantly higher in the patient group compared to the control group (65.14±17.57 ms and 42.73±10.03 ms, respectively, $p<0.001$). A significant positive correlation was found between erythrocyte sedimentation rate and cQTD in the patient group. We found no association between cQTD and disease activity, medications, anti-SSA/Ro positivity, capillaroscopy paterns, presence of interstitial lung disease and pulmonary arterial hypertension.

Conclusion: In our study, cQTD, which indicates an increased risk for ventricular arrhythmia and cardiovascular mortality, was found to be significantly higher in the patients compared to the controls. Determining cardiac risks with an electrocardiogram, which is a non-invasive and easily available method, is important in the follow-up of SSc patients.

Keywords: Systemic sclerosis, cardiovascular mortality, QT dispersion

INTRODUCTION

Systemic sclerosis (SSc) is a chronic autoimmune disease characterised by extensive fibrosis of the skin and internal organs (1). It is thought to be developed as a result of interactions between factors affecting collagen synthesis, vascular changes, and immunological mechanisms. The fibrotic changes in diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc), which are the subgroups of SSc, are not limited to the skin but also in internal organs (2). While skin changes and contractures affect morbidity, internal organ involvement significantly affects both morbidity and mortality.

Cardiac involvement in SSc patients is mostly asymptomatic; therefore its exact prevalence is unknown. Myocardial fibrosis and pericardial disease, the main pathogenic features of cardiac involvement in SSc, are present in approximately 80% of the patients at autopsy reports (3). When clinical signs are present (10-35% of the patients with SSc), the prognosis is generally poor, with a 5-year mortality rate of approximately 70% (4). Heart blocks, atrial or ventricular arrhythmias can be seen in approximately 50% of the patients. Ventricular arrhythmia is the most common cause of death in patients with SSc after pulmonary fibrosis and pulmonary hypertension (5). The QT prolongation, an important cause of cardiac arrhythmias, can be detected in electrocardiography (ECG), which is an easy and non-invasive method. The QT prolongation is also seen

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in patients with SSc and can lead to life-threatening arrhythmias and even sudden cardiac death. Sudden cardiac death occurs in 5% of patients with SSc, and arrhythmias cause 6% of all-cause mortality in SSc (5). The prevalence of the QT prolongation in SSc has been shown to be 11-25% in previous studies (6, 7). Therefore, it is important to detect QT prolongation in SSc patients with high-risk. QT dispersion (QTd) is a marker of repolarization heterogeneity reported to be linked to an increased rate of arrhythmias (8). However, whether increased QTd is more common in SSc is still debated (9).

In this study, we aimed to investigate the prevalence of corrected QT dispersion (cQTD) and related factors in our patients with SSc compared to healthy controls.

MATERIAL AND METHOD

This study was carried out with the permission of Manisa Celal Bayar University Medical Faculty Clinical Researches Ethics Committee (Date: 30.03.2022, Decision No: 20.478.486/1283). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this cross-sectional study, 49 SSc patients who applied to our rheumatology outpatient clinics between March 2021 and March 2022 and 41 healthy controls with similar demographic characteristics as the patient group were included. According to the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2013 criteria, the patients with a score of 9 and above were classified as SSc (10). Patients with diabetes mellitus, hypertension, dyslipidemia, chronic renal failure, chronic liver disease, known coronary artery or structural heart disease, rhythm abnormalities were excluded. Patients using antiarrhythmic agents such as digitalis, and beta blockers were also not included. The SSc patients and healthy controls gave informed written consent.

Demographic information including age and sex of the study population, the clinical evaluation including a detailed medical history and physical evaluation of SSc patients were recorded. Disease duration was defined as the time from the onset of the first sign of disease to the baseline study visit, excluding raynaud's phenomenon. Body mass index (BMI), systolic and diastolic blood pressure were measured. The presence of SSc specific features such as raynaud's phenomenon, digital ulcer, gangrene, sclerodactyly, arthralgia, arthritis, tendon friction rubs, gastroesophageal reflux, diarrhea, cough, shortness of breath were also recorded. Skin involvement was assessed with the Modified Rodnan skin severity score (MR-SSS) involving the degree of skin thickening ranging from 0 (noinvolvement) to 3 (severe thickening) in 17 areas of the body (total score range: 0–51) (11). Patients were classified as limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the definition of Leroy et al (12). Tendon friction rubs, arthritis, myositis were determined as musculoskeletal system involvement. Nailfold capillaroscopy examination was performed to detect capillary changes indicating microvascular damage. The patients were classified as having early, active and late SSc patterns according to the capillaroscopy examination findings.

Complete blood count and biochemical markers (fasting blood glucose, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrolytes, total protein, albumin, lipids) erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) of whole study population were analyzed on the date ECG performed. In the SSc group, the most recent antibody test results were recorded from the hospital database.. Anti-nuclear antibodies (ANA) of the patients were examined by indirect fluorescent antibody (IFA) (hep-2 cells) and other antibodies including anti-centromere antibodies, anti-Scl-70, SSA/Ro, SSB/La, anti-Sm-RNP were measured by ELISA (enzyme linked immunosorbant assay) ELISA method. ANA titer above 1/160 was considered significant. ANA test was performed in healthy controls during the study and ANA positive controls were excluded.

In our rheumatology outpatient clinic, all SSc patients undergo routine follow-up tests such as echocardiogram, high-resolution computed tomography (HRCT), and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide (DLCO), at least once a six mounths. The latest findings of these tests were obtained from hospital records. Detection of at least one pathological pulmonary parenchymal finding including ground glass changes, honeycombing, subpleural opacity on HRCT was accepted as interstitial lung disease (ILD). Pulmonary artery pressure (PAP) ≥35 mmHg on echocardiography was accepted as pulmonary arterial hypertension (PAH). Disease activity was evaluated using revised the European Scleroderma Study Group (EScSG) activity index (13). The patients with a cut-off points ≥2.5 was accepted to have active disease (13).

Electrocardiogram and Measurement of Indices

A 12-lead ECG were recorded in the resting supine position using a commercial machine (GE Healthcare, MAC 2000) at a rate of 25 mm/s. ECG images were amplified 200%, and measurements were taken blindly in an electronic setting by the same person utilizing

manual ECG reading. The distance from the beginning of the QRS complex to the end of the T wave was measured as the QT interval. QTD was defined as the difference between the maximum QT interval and the minimum QT interval in any lead on a standard 12-lead ECG. cQTD was calculated with Bazett's formula (cQTD=QT interval / RR interval square root). Greater than or equal to 440 ms of cQTmax was accepted as prolonged QTc (14).

Statistical Analysis

Statistical analysis was performed using the Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA) 22.0 package program. Quantitative variables were expressed as mean±standard deviation (SD) or median (minimum and maximum), as appropriate. and qualitative variables were presented as numbers and percentages. In the statistical analysis of continuous data, normality of distribution was assessed using Kolmogorov-Smirnov test. The independent samples T-test or Mann-Whitney U test were used to compare numerical data between independent groups, while Pearson's chi-square or Fischer's exact test were used to compare categorical variables. When comparing continuous data between more than two subgroups, the ANOVA test was used for those with normal distribution, and the Kruskal-Wallis test for those without normal distribution. The correlation analysis between ECG variables and disease duration, laboratory values and disease activity parameters were evaluated with Pearson correlation analysis for variables showing normal distribution and Spearman correlation analysis for variables not showing normal distribution. At the level of $p \leq 0.05$, all results were considered statistically significant.

RESULTS

A total of 49 SSc patients and 41 healthy controls were included in the study. There was no statistical difference between the mean age of the SSc group (53.26±10.63) and the control group (49.29±8.02) (p>0.05). The frequency of smoking was significantly higher in controls (p=0.025). Erythrocyte sedimentation rate (ESR) was higher in SSc patients (p<0.001). Comparison of other demographic, clinical, and laboratory characteristics of the groups were summarized in **Table 1**.

Electrocardiographic parameters of the groups are also shown in **Table 1**. Maximum corrected QT (cQTmax) and cQTD intervals were significantly higher in the SSc group compared to the control group (cQTmax: 440.85±29.86 ms vs 411.92±33.06 ms and cQTD: 65.14±17.57 ms vs 42.73±10.03 ms). cQTmax was found to be higher than 440 ms in 41% of the patients have prolonged QTc

Table 1. Comparison of demographic, clinical, laboratory, and electrocardiographic variables between SSc patients and healthy controls

Variables	SSc (n=49)	Control (n=41)	p
Age (years)	53.26±10.63	49.29±8.02	0.052
Female (n, %)	45 (91.2%)	37 (90.2%)	0.791
Smoker (n, %)	7 (14.3%)	15 (36.6%)	0.025
BMI	25.81±4.97	26.00±3.06	0.824
Systolic BP (mm Hg)	118.73±13.45	115.25±15.20	0.254
Diastolic BP (mm Hg)	73.23±8.54	75.22±7.43	0.340
Haemoglobin (g/dL)	12.48±1.59	12.80±1.25	0.303
WBC (10^3/μL)	8.82±2.63	7.61±2.05	0.233
Creatinine (mg/dl)	0.62±0.25	0.64±0.14	0.654
ALT (U/L)	23.06±12.07	22.54±14.52	0.784
Glucose (mg/dl)	99.81±30.12	89.94±10.62	0.078
LDL-cholesterol (mg/dL)	110.05±20.65	108.00±18.81	0.299
HDL-cholesterol (mg/dL)	45.12±11.82	53.00±12.71	0.078
Triglyseride (mg/dL)	166.45±35.66	168.41±26.78	0.559
ESR (mm/hour)	34.18±25.12	15.95±8.96	<0.001
CRP (mg/dL)	1.82±3.10	0.98±0.91	0.107
Heart rate (beats/min)	78.15±13.73	76.34±9.19	0.487
cQTmax (ms)	440.85±29.86	411.92±33.06	0.001
cQTmin (ms)	373.79±30.23	373.12±29.08	0.916
cQTD (ms)	65.14±17.57	42.73±10.03	<0.001

SSc: Systemic sclerosis, BMI: Body mass index, Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, WBC: White blood cell, ALT: Alanine Aminotransferase, LDL-cholesterol: low-density lipoprotein- cholesterol, HDL-cholesterol: High-density lipoprotein-cholesterol, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, cQTmax: Corrected QT maximum, cQTmin: Corrected QT minimum, cQTD: Corrected QT dispersion

Twenty-one (42.8%) of the SSc patients were classified as lcSSc and 28 (57.2%) of them as dcSSc. The median diagnosis duration of the patients was calculated as 8 (1-25) years. The most common clinical finding in SSc patients was raynaud's phenomenon (92%). The clinical features of patients with lcSSc and dcSSc were given in a **Table 2**. The medications used in the SSc group were acetylsalicylic acid (67.3%), proton pump inhibitor (71.4%), calcium channel blocker (30.6%), bosentan (18.3%), corticosteroid (48.9%), hydroxychloroquine (26.5%), and immunosuppressive agents (azathiopurine, mycophenolate mofetil, methotrexate) (26.5%).

ANA was positive in 49 (100%) patients with SSc. The number of patients with positive anti-centromere antibody and anti-Scl-70 antibody were 9 (18.3%) and 28 (57.2%), respectively. Other antibodies found to be positive were anti-SSA (8.1%), anti-SSB (4.1%), and anti-Sm-RNP (8.1%). No ANA positivity was detected in the control group. According to the capillaroscopy patterns, SSc patients were classified as early (22.4%), active (44.8%) and late (32.4%).

In subgroup analyses, there were no significant differences in terms of ECG parameters between diffuse and limited SSc subgroups (p>0.05) (**Table 2**). There were no significant differences in QT intervals between early, active, and late SSc groups (p>0.05). The association of cQTD with smoking status, disease activity, medications,

anti-SSA/Ro positivity, capillaroscopy paterns, presence of ILD and PAH, involvement of musculoskeletal and gastrointestinal systems were summarized in **Table 3**.

Table 2. The clinical and electrocardiographic features of patients with lcSSc and dcSSc.

Variables	lcSSc (n=21)	dcSSc (n=28)	All patients (n=49)	p
Age (years)	52.9±9.8	53.5±10.2	53.2±10.5	0.861
Female (n,%)	21 (100)	24 (85.7)	45 (91.8)	0.071
Diagnosis duration (years)	10.0 (3-25)	6.5 (1-20)	8.0 (1-25)	0.060
ILD (n,%)	4 (19)	21 (75)	25 (51)	<0.001
PAH (n,%)	3 (14.3)	5 (17.9)	8 (16.3)	0.100
GIT involvement (n,%)	13 (61.9)	21 (75)	34 (69.3)	0.363
MSK involvement (n,%)	11 (52.4)	16 (57.1)	27 (55.1)	0.779
Digital ulcer (n,%)	2 (9.5)	4 (14.3)	6 (12.2)	0.688
MR-SSS	17.9±11.4	26.2±13.0	22.6±12.9	0.025
FVC (%)	81 (70-88)	71 (65-89)	75 (65-89)	0.002
DLCO (%)	71 (65-74)	68 (60-72)	70 (60-74)	<0.001
EScSG activity index	1.50 (0-6.25)	2.5 (0-6.25)	2.5 (0-625)	0.028
Heart rate (beats/min)	78.47±12.17	77.39±14.95	78.15±13.73	0.564
cQTmin (ms)	375.04±30.35	372.21±30.35	373.79±30.23	0.887
cQTmax (ms)	440.45±30.46	440.95±28.76	440.85±29.86	0.991
cQTD (ms)	64.71±16.45	66.85±18.41	65.14±17.57	0.675

lcSSc: limited cutaneous systemic sclerosis, dcSSc: diffuse cutaneous systemic sclerosis, ILD: Interstitial lung disease, PAH: Pulmonary arterial hypertension, GIT involvement: Gastrointestinal tract involvement, MSK involvement: Musculoskeletal involvement, MR-SSS: Modified Rodnan skin severity score, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, EScSG activity index: European Scleroderma Study Group activity index, cQTmax: Corrected QT maximum, cQTmin: Corrected QT minimum, cQTD: Corrected QT dispersion

Table 3. The association of cQTD with clinical and laboratory features of SSc

Variables		n	cQTD	p
Smoking	Yes	7	58.28±19.14	0.281
	No	41	66.24±17.15	
Active disease (EScSG index ≥2.5)	Yes	28	66.71±16.50	0.414
	No	21	62.57±18.79	
Hydroxychloroquine	Yes	13	64.77±11.81	0.968
	No	36	65.00±19.23	
Corticosteroid	Yes	24	65.30±15.06	0.981
	No	25	65.88±19.78	
Calcium channel blocker	Yes	15	63.66±13.06	0.739
	No	34	65.56±19.22	
anti-SSA/Ro	Positive	4	64.25±19.80	0.935
	Negative	45	65.15±17.47	
Interstitial lung disease	Yes	25	66.92±19.38	0.423
	No	24	62.97±15.32	
Pulmonary arterial hypertension	Yes	8	68.87±16.55	0.491
	No	41	64.17±17.71	
Capillaroscopy paterns	Early	11	62.00±23.43	0.053
	Active	22	63.45±13.97	
	Late	16	69.00±17.54	
Musculoskeletal involvement	Yes	27	67.62±19.30	0.236
	No	22	61.63±14.62	
Gastrointestinal involvement	Yes	34	66.82±18.07	0.259
	No	15	60.66±15.68	
Digital ulcer	Yes	6	63.60±17.59	0.154
	No	43	74.50±14.12	

cQTD: Corrected QT dispersion, SSc: Systemic sclerosis, EScSG activity index: European Scleroderma Study Group activity index.

When correlation analysis was performed, no correlation was found between disease duration, BMI, and cQTmax and cQTD (p>0.05). There was significant correlation between cQTmax and creatinine level (p=0.002, r =0.430) and between ESR and cQTD (p= 0.019, r =0.334) in the SSc group. The mean MR-SSS indicating severity of skin involvement was 22.67±12.92 in the SSc patients, and no correlation was found between MR-SSS and QT interval parameters. A significant correlation was found between cQTmin and antibody level in 4 patients with positive anti-SSA (P=0.017, r=0.340). There was no significant correlation between ECG parameters and PAB, left ventricle ejection fraction and EScSG activity index in the patient group (p>0.05). Correlation analysis between cQTD and variables of some clinical and laboratory features of SSc patients are shown in **Table 4**.

Table 4. Correlation analysis between cQTD and variables of some clinical and laboratory features of SSc patients.

Variables	r	p
Age (year)	0.182	0.087
Disease duration (year)	0.190	0.191
BMI (kg/m²)	-0.104	0.323
Systolic BP (mmHg)	0.201	0.195
Diastolic BP (mmHg)	0.127	0.354
ESR (mm/h)	0.334	0.019
CRP (mg/L)	-0.138	0.193
Albumin (g/dL)	-0.156	0.142
LDL-cholesterol (mg/dL)	0.109	0.554
HDL-cholesterol (mg/dL)	-0.169	0.238
Triglyseride (mg/dL)	0.226	0.121
MR-SSS	0.103	0.482
FVC (%)	-0.215	0.138
DLCO (%)	-0.165	0.257
PAP (mm Hg)	0.074	0.615
LVEF (%)	-0.181	0.212
EScSG activity index	0.239	0.098

cQTD: Corrected QT dispersion, SSc: Systemic sclerosis, BMI: Body mass index, Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, LDL-cholesterol: low-density lipoprotein- cholesterol, HDL-cholesterol: High-density lipoprotein-cholesterol, MR-SSS: Modified Rodnan skin severity score, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, PAP: Pulmonary artery pressure, LVEF: Left Ventricular Ejection Fraction, EScSG activity index: European Scleroderma Study Group activity index.

DISCUSSION

In this study, cQTD, which is an important indicator of ventricular arrhythmia, was found to be significantly higher in patients with SSc than in healthy controls. In the patient group, no association was found between clinical findings, disease duration, BMI, smoking status, capillaroscopy findings, MR-SSS, medications, and electrocardiographic findings. However, a significant positive correlation was found between ESR and cQTD in the SSc group.

Cardiac involvement occurs late in the course of the disease in patients with SSc and is associated with a poor

prognosis. In these patients, the frequency of ventricular ectopic beats increases and ventricular tachycardia attacks may be seen. These findings are thought to be the result of fibrosis or ischemia of the ventricular myocardium. Few studies investigating cardiac involvement in SSc patients have evaluated the prevalence and markers of ventricular arrhythmias (15). The presence of cardiac involvement of SSc patients can be detected by ECG, which is an easy and inexpensive method. For this purpose, Çiftçi et al. (16) examined heart rate and QT intervals in dcSSc by using 24-hour ambulatory ECG recording and found that a significant proportion of these patients had QT prolongation.

In the standard 12-lead ECGs, cQT values above 440 ms are considered to be higher than normal. In our study, the mean cQTmax value was 440.85±29.86 ms in SSc patients, and it was found to be higher than 440 ms in 41% of the patients. Massie et al. reported a prolonged cQT interval (422.4±47.10 ms) in 25% of their cohort of 689 SSc patients (17). Although there is no consensus, the normal range of cQTD is reported from 31±11 ms to 54±27 ms. A 50ms increase in the QT interval is shown to be associated with an increase in mortality (18). In our study, the mean cQTD was measured as 65.14±17.57 in the SSc group and was found to be significantly higher than in the control group.

In a study evaluating SSc patients without cardiac symptoms, it was reported that 14.6% of the patients had prolonged QTc. In addition, it was found that patients with dcSSc subtype had longer QT interval and patients with longer QT interval had higher MR-SSS (19). Similarly, in another study, a significant correlation was found between electrocardiographic ventricular repolarization indices and MR-SSS values in patients with SSc (20). Therefore, they recommended that patients with higher scores had to be followed closely for cardiac arrhythmias. Rosato et al. (21) reported that the presence of active capillaroscopic changes and digital ulcers were associated with higher QTc. However, in our study, no association was found between the disease subtypes, skin scores, capillaroscopic findings, and ECG findings. When different connective tissue diseases were examined, it was reported that there was a relationship between QTD prolongation and the development of complex ventricular arrhythmias in patients with anti-SSA positivity (22). In our study, there was no significant association between cQTD and anti-SSA positivity. We found a significant correlation between ESR, which is an indicator of disease activation in connective tissue diseases, and QTD in patients with SSc. This suggests that many biomarkers of ongoing systemic inflammation may be useful in determining the risk of arrhythmia in these patients.

Our main limitation is that some data including pulmonary function tests, HRCT and echocardiography findings were obtained retrospectively from patient's records. The lack of extensive cardiological evaluation (an objective test to detect the presence of coronary artery disease or detailed echocardiographic examination) by the same cardiologist in patients is another limitation. Manual calculation of QT measurements can also be seen as a limitation. However, taking blindly measurements by the same clinician shows that the difference between the groups is valuable.

CONCLUSION

In conclusion, the evaluation of QT dispersion in the prediction of cardiac arrhythmia and therefore sudden cardiac death with ECG, which is a noninvasive and inexpensive method, will be useful in the follow-up of patients with SSc. However, more comprehensive prospective studies and long-term follow-up are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Manisa Celal Bayar University Medical Faculty Clinical Researches Ethics Committee (Date: 30.03.2022, Decision No: 20.478.486/1283).

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.

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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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Original Article

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The relationship between ulcerative colitis activity and vitamin D, mean platelet volume and platelet distribution width

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ABSTRACT

Aim: In our study, we aimed to show the relationship between ulcerative colitis activity and vitamin D, platelet distribution width, and mean platelet volume.

Material and Method: Our study was conducted at the Internal Medicine Clinic. We planned to cross-sectionally investigate the severity of ulcerative colitis activity, vitamin D level, mean platelet volume, platelet distribution width and other laboratory parameters of patients admitted to the hospital. The Truelove and Witts' severity index was used to determine ulcerative colitis activity. In accordance with the guidelines, serum 25-OH vitamin D levels of >30 ng/ml were considered as sufficient vitamin D, 20-30 ng/ml as vitamin D insufficiency, <20 ng/ml as vitamin D deficiency, and <10 ng/ml as severe vitamin D deficiency.

Results: The study included 77 ulcerative colitis patients. Of the patients with severe ulcerative colitis activity, 10% had vitamin D deficiency and 90% had severe vitamin D deficiency ($p<0.001$). The patients with mild ulcerative colitis activity had the highest mean platelet volume (9.5±0.44), while the patients with severe ulcerative colitis activity had the lowest mean mean platelet volume (7.1±1.52) ($p<0.001$). Likewise, the patients with mild ulcerative colitis activity had the highest mean platelet distribution width (17.9±1.04), while the patients with severe ulcerative colitis activity had the lowest mean platelet distribution width (14.8±2.04) ($p<0.001$).

Conclusion: This study with a high level of evidence supports that 25-OH vitamin D has an anti-inflammatory effect in inflammatory diseases and that 25-OH vitamin D levels decrease as the disease activity increases. Moreover, the negative correlation between ulcerative colitis activity and mean platelet volume, platelet distribution width is demonstrated.

Keywords: Ulcerative colitis, vitamin D, mean platelet volume, platelet distribution width

INTRODUCTION

Ulcerative colitis (UC) is an inflammatory, edematous and ulcerative disease of the superficial parts of the colon mucosa and submucosa. Although various immune system mechanisms play a role in inflammatory bowel disease (IBD), especially cellular immunity is involved in the pathogenesis of IBD (1,2). In general, the first finding is bloody or non-bloody diarrhea; however, patients may also present with other complaints such as abdominal pain, nausea, and malaise. Despite frequent bowel movements, the fecal volume is low in UC. This is the result of rectal inflammation. Abdominal pain in all quadrants of the abdomen, especially in the lower quadrant, elevated fever, weight loss, the involvement of all segments of the colon, as well as local involvements occur (3). Vitamin D (VitD) precursors are found in our body and when the skin is exposed to certain wavelengths of the sun's ultraviolet rays, VitD is synthesized from these precursors to the body (4). Lack of VitD often leads to many factors such as lack of physical activity, malabsorption, low sunlight exposure, VitD deficiency due to diet, smoking and drinking alcohol (5). Serum VitD is measured using the most stable form of 25-hydroxyvitamin D (25-OH vitamin D). The level of serum 25-OH VitD reflects the level of VitD, sun exposure, dietary intake, supplementation and storage (6). When VitD forms, it is first converted into 25-OH VitD in the liver and then into 1,25-hydroxyvitamin D (1,25-OH vitamin D), an active VitD, in the kidney (7). Vitamin D deficiency causes osteoporosis and

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osteomalacia in adults and rickets in children and also plays a role in many autoimmune diseases such as multiple sclerosis and rheumatoid arthritis (8). One of the most important indicators of platelet reactivity is the mean platelet volume (MPV). The platelet distribution width (PDW) showing the heterogeneity of the platelet volume is a sign of platelet activation. PDW levels have been shown to be associated with an increase in carotid artery stenosis and vascular dementia in patients with diabetes mellitus (DM) (9). Platelet indices such as platelet count, PDW and MPV are associated with cardiovascular diseases developing due to arterial thrombosis (10). There is uncertainty about the most accurate method for measuring MPV; however, the cheapest and simplest method is the hemogram test. Large platelets which are more active metabolically and enzymatically have more prothrombotic potential. Patients with DM, primer hypertension, hypercholesterolemia, and active smokers and obese patients exhibit higher MPV values (11). Vitamin D deficiency in patients with IBD is higher than the general population. The incidence of VitD deficiency in IBD patients varies between 16% and 95% (12). Some studies have shown that there may be a correlation between the level of VitD and the severity of UC activity (13). This study was conducted to determine the correlation between the severity of UC activity and serum VitD level, MPV and PDW.

MATERIAL AND METHOD

This study was approved by the Balıkesir University Medical Faculty Clinical Studies Ethics Board (Date: 26/07/2017, Decision No: 2017/65). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from each individual who participated in the study.

Our study was conducted at the Internal Medicine Clinic of Our University, Faculty of Medicine. We planned to cross-sectionally investigate the severity of UC activity, vitamin D level, MPV, PDW and other laboratory parameters of patients admitted to the hospital. The diagnosis of UC was made using the guideline of the European Crohn's and Colitis Organization. The Truelove and Witts' severity index was used to determine UC activity (14). Serum 25-OH VitD level was measured with the spectrophotometric method using a Beckman Coulter AU 680 (California, USA) device. In accordance with the guidelines, serum 25-OH VitD levels of >30 ng/ml were considered as sufficient VitD, 20-30 ng/ml as VitD insufficiency, <20 ng/ml as VitD deficiency, and <10 ng/ml as severe VitD deficiency (15). Patients with any other comorbidities and on calcium and VitD supplements due to other conditions such as osteoporosis were excluded from the study.

Statistical Analysis

The statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences) Version 23.0 software. Normality of variables was tested with histogram charts and the Kolmogorov-Smirnov test. They were compared using Fisher's Exact test in 2x2 tables. One-Way analysis of variance (ANOVA) test was used in the comparison of normally distributed (parametric) PDW data while evaluated between UC activity severities. The Kruskal Wallis Test was used in the comparison of non-normally distributed parameters (non-parametric) while evaluated between MPV, 25-OH VitD, and UC activity severities. P <0.05 values were considered to be statistically significant.

RESULTS

The study included 77 UC patients. Of the patients, 44 (57%) were male and 33 (43%) were female. The mean duration of disease was 2.8±2 years (0.3-10 years). The mean age of the patients was 39±5 years; the mean age of female patients was 37±4 and the mean age of male patients was 41±5. It was found that the rate of VitD deficiency (<20 ng/mL) was as 70.1% and the rate of severe VitD deficiency (<10 ng/ml) was 25.9% (p=0.001).

The VitD groups were compared according to UC activity of the patients with UC. 94.12% of the patients with mild UC activity and 90.91% of the patients with moderate UC activity had VitD deficiency. Of the patients with severe UC activity, 10% had VitD deficiency and 90% had severe VitD deficiency (p<0.001). In post-hoc analysis, it was determined that UC activation was significantly higher in patients with severe VitD deficiency than in patients with moderate VitD deficiency and normal VitD levels (p<0.001). However, no significant difference was found between the other groups. As the severity of UC activity increased, the levels of VitD decreased (**Figure 1**). The MPV, PDW, and VitD values of the patients with UC were compared according to their UC activity severity. As UC activity increased, the values of MPV and PDW decreased (**Figure 2**).

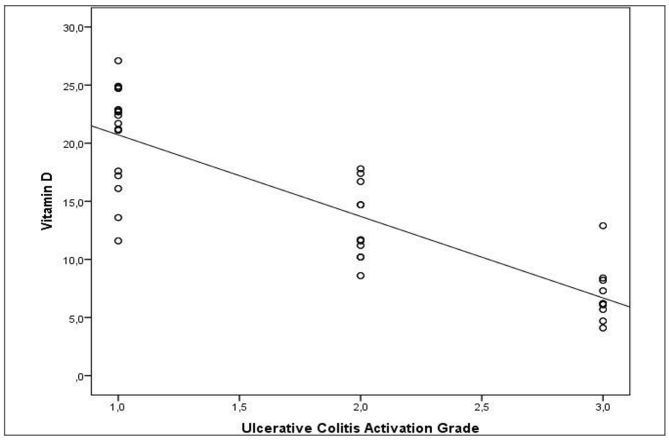

Figure 1. Correlation between severity of ulcerative colitis activity and vitamin D

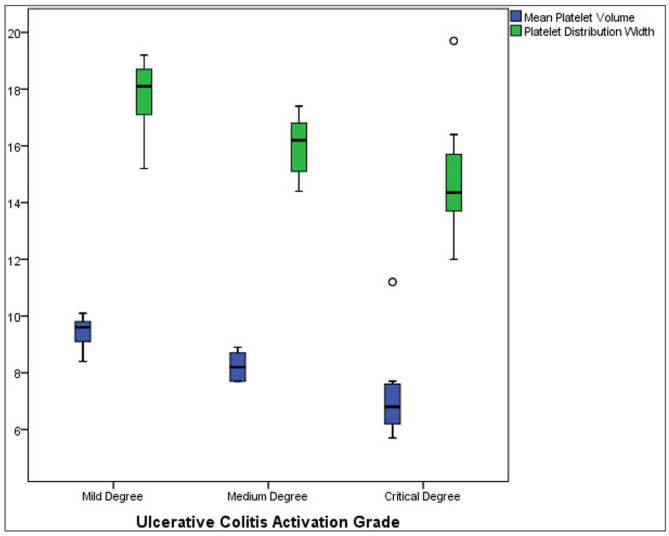

Figure 2. Boxer graph showing the correlation between mean platelet volume and platelet distribution width and ulcerative colitis activity

The patients with mild UC activity had the highest mean MPV (9.5±0.44), while the patients with severe UC activity had the lowest mean MPV (7.1±1,52) (p<0,001) (**Table 1**). Likewise, the patients with mild UC activity had the highest mean PDW (17.9±1.04), while the patients with severe UC activity had the lowest mean PDW (14.8±2.04) (p<0.001). Considering the mean values of 25-OH VitD, the patients with mild UC activity had the highest value (20.9±4.18), while the patients with mild UC activity had the lowest value (7.0±2.42) (p<0.001) (**Table 1**).

The MPV levels of the UC patients were compared according to the severity of UC activity (**Figure 3**). While MPV value was within normal limits in all patients with mild UC activity, this rate decreased to 72.23% in patients with moderate UC activity and to 10% in patients with severe UC activity (p<0.001). The PDW levels of the UC patients were compared according to the severity of UC activity (**Figure 4**). While PDW was high in all patients with mild and moderate UC activity, it was 50% higher in patients with severe UC activity (p<0.001) (**Table 2**). Considering the levels of VitD, 94,12% of the patients with mild UC activity and 90,91% of the patients with moderate UC activity had VitD deficiency, while this rate was 10% in the patients with severe UC activity and 90% of them had severe VitD deficiency (p<0.001) (**Table 2**).

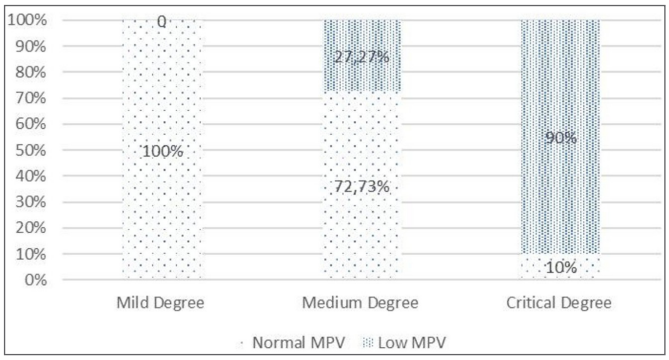

Figure 3. Distribution of mean platelet volume groups according to the severity of ulcerative colitis activity

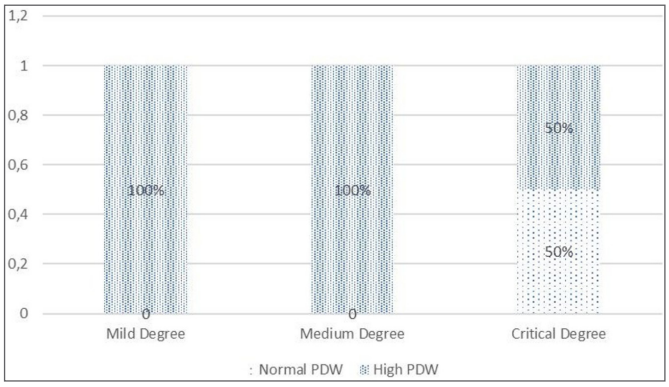

Figure 4. Distribution of platelet distribution width groups according to the severity of ulcerative colitis activity

Table 2. Comparison of severity of ulcerative colitis activity and MPV, PDW and vitamin D groups

	Severity of ulcerative colitis activity						p
	Mild		Moderate		Severe		
	n	%	n	%	n	%	
MPV							<0.001
Normal	34	(100)	16	(72.73)	2	(10)	
Low	0	(0)	6	(27.27)	18	(90)	
PDW							<0.001
Normal	0	(0)	0	(0)	10	(50)	
High	34	(100)	22	(100)	10	(50)	
Vitamin D							<0.001
Severe deficiency	0	(0)	2	(9.09)	18	(90)	
Moderate deficiency	32	(94.12)	20	(90.91)	2	(10)	
Normal	2	(5.88)	0	(0)	0	(0)	

MPV= mean platelet volume; PDW= platelet distribution width

Table 1. Comparison of MPV, PDW, vitamin D values with severity of ulcerative colitis activity

	Severity of ulcerative colitis activity						p
	Mild		Moderate		Severe		
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	
MPV	9.5±0.44	9.6	8.3±0.47	8.2	7.1±1.52	6.8	<0.001
PDW	17.9±1.04	18.1	16.0±0.96	16.2	14.8±2.04	14.4	<0.001
25 OH-D	20.9±4.18	22.4	13.2±3.14	11.7	7.0±2.42	6.2	<0.001

MPV= mean platelet volume; PDW= platelet distribution width; SD= standard deviation; OH-D= hydroxy D vitamin

DISCUSSION

This study demonstrated the negative correlation between the severity of disease activity and VitD, PDW, and MPV levels of the patients with UC. One of the important parameters of platelet function and activation parameters is PDW. The importance of PDW has been discovered recently. In retrospective studies on PDW, it was found that PDW could be used as a predictor for thrombolysis failure and ST-segment elevation myocardial infarction (16). High MPV levels have been associated with diseases such as myocardial infarction, acute ischemic stroke, and DM (17). In a study conducted in Poland, it was shown to be a practical predictive parameter for left ventricular failure developing in patients with the acute coronary syndrome (18). It is also supported by the study that it is also a predictive parameter in terms of preeclampsia and acute appendicitis for those with similar results (19,20). In clinical hematology, MPV can be used as a marker of platelet function and activation. It can also be used as a marker of inflammation (21). There is a negative correlation between MPV and rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis (22). In two studies with a limited number of patients on the correlation between decreased MPV value and severity of UC activity, Kapsoritakis et al. (23) proposed to use MPV as an effective marker of activity in IBD, but did not analyze the sensitivity and specificity. In a study conducted by Jaremo et al. (24), a negative correlation was found with MPV in 18 UC patients.

It was thought that VitD could be a part of the immune-regulatory system due to the determination of VitD receptor in the immune response-related cells and demonstration of VitD synthesis from the activated dendritic cells. Exposure of CD4 T lymphocytes to 1.25 (OH)2 VitD3 (1.25-Dihydroxyvitamin D3) inhibits Th1 lymphocyte proliferation and cytokine production by decreasing IL-2 and IFN-D secretion of CD4 lymphocytes. IL-6 expression, which is an important component of the autoimmune reaction, is inhibited by 1.25 (OH)2 VitD3 (25). The cause of low MPV in IBD is unclear. Some authors have suggested that decreased MPV may result from the depletion or sequestration of activated platelets in the intestinal vessels (26). Another reason for the decreased MPV may be the existence of a defect in the regulation of thrombopoiesis in IBD (27). In individuals with autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and IBD, T lymphocytes steer the immune system to induce the inflammatory response in the internal organs and peripheral tissues of individuals. When women were divided into 5 groups according to their VitD intake in the "Nurses Health Study I and II", a large society study, it was found that multiple sclerosis developed 40% less among women in the highest group (28). Experimentally, it has been shown that VitD deficiency exacerbates IBD and multiple sclerosis, and VitD suppresses multiple sclerosis and IBD in rats. Interestingly, the administration of VitD even if VitD is sufficient has been shown to inhibit autoimmunity in animals. In the US, the incidence of systemic lupus erythematosus (SLE) has increased threefold in African Americans and is seen in earlier ages, and the morbidity and mortality rates are higher than that of whites. On the other hand, the fact that the prevalence of the disease is not high among blacks who live in western Africa cannot explain that the prevalence of high SLE is only due to genetic reasons in black people in the USA (29). This difference may be related to low VitD concentrations resulted from reduced exposure to sunlight compared to black race living in western countries due to the penetration of ultraviolet rays through the skin with excess pigment. This hypothesis is also supported by other studies with the discovery of significantly lower levels of 25 OH VitD3 in patients newly diagnosed with SLE compared to controls. There is a correlation between low VitD levels and the severity of the disease, and therefore the treatment of VitD deficiency in SLE patients gains importance (29).

It was found that rheumatoid arthritis severity and VitD serum concentration were related. In the study by Caraba et al. (30), VitD level, insulin resistance, IL-2 and endothelial dysfunction were analyzed in patients with cardiovascular complications due to rheumatoid arthritis, and healthy group was assigned as the control group; as a result of the analyses, it was found that the patient group had a decrease in VitD level and an increase in IL-2 level, impaired endothelial dysfunction, and increased insulin resistance despite the normal values in the healthy group (30). It was stated that VitD levels were negatively correlated with the presence of inflammation. The study by Carvallo et al. (31) included 32 dialysis patients with VitD levels of ≤20 ng/mL. These patients received a replacement with cholecalciferol 100.000 UI/week/3 months and 16 volunteers were included in the control group. This study showed that cholecalciferol replacement has an anti-inflammatory effect (31).

In our study, we attempted to use a similar correlation on UC patients. According to the Truelove-Witts's classification, there was an inverse correlation between the severity of UC and serum levels of 25-OH VitD, and it was found that patients with mild and moderate UC had lower levels of VitD compared to the society while patients with severe UC exhibited significantly lower levels of 25-OH VitD.

The study by Hassan et al. (32) found no significant correlation between UC activity and concentration of 25-OH VitD. However, 25-OH VitD levels were studied

in patients undergone colon resection due to UC and no correlation was found. We are of the opinion that this result is caused by the analysis methods and errors related to the patient selection method because the studies have found that 25-OH VitD is affected by many factors such as the location of the patients, the region where the patient live, climate, ethnicity, and the drugs used. The study by Limketkai et al. (33) found an increase in hospitalization and number of operations due to IBD in people with low exposure to ultraviolet light, and lower levels of 25-OH VitD in these patients (33). Thus, it was stated that there was a significant correlation between 25-OH VitD levels and inflammatory diseases. The study by Dolatshahi et al. (34) found an inverse correlation between UC activity and 25-OH VitD levels. As the severity of UC increased, 25-OH VitD levels decreased. The negative correlation between UC and VitD revealed in this study supports our study.

The limitations of our study are single-center design, the inclusion of only patients with UC, not studying inflammatory parameters such as cytokines and acute phase reactants, studying only 25-OH VitD level and not studying an active form of VitD. The superiority of our study is that our sample size was larger than other studies.

CONCLUSION

This study with a high level of evidence supports that 25-OH VitD has an anti-inflammatory effect in inflammatory diseases and that 25-OH VitD levels decrease as the disease activity increases. Moreover, the negative correlation between UC activity and MPV, PDW is demonstrated. There are few studies in this respect and our study supports this theory. If the correlation between the disease severity and the levels of 25-OH VitD, MPV and PDW are supported by further studies and the other processes that may affect these parameters can be revealed more clearly, the parameters of 25-OH VitD, MPV and PDW might be predictive of the severity of disease activity. Moreover, 25-OH VitD replacement can be given according to the severity of disease activity, and 25-OH VitD can be considered in the treatment of patients with UC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Medical Faculty Clinical Studies Ethics Board (Date: 26/07/2017, Decision No: 2017/65).

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.

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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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Original Article

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The effect of polycystic ovary syndrome on intracytoplasmic sperm injection results in patients with endometriosis

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ABSTRACT

Aim: In this study, the fertility rate of women with polycystic ovary syndrome (PCOS) and endometriosis was compared with the control group, which included women with normoresponder (NR) endometriosis.

Material and Method: This is a retrospective study with control in infertile women aged 25-40, suffering from PCOS and endometriosis, referred to the infertility clinic of Medistate Hospital between September 2018- December 2020. The pregnancy outcomes of age-matched participants were compared.

Results: Results did not show a statistically significant association between case and control regarding age and body mass index (BMI) ($p>0.05$). There was a statistically significant difference between groups regarding anti-mullerian hormone (AMH) ($p<0.05$). Also, results did not find a statistically significant association between case and NR endometriosis regarding positive pregnancy outcomes ($p>0.05$).

Conclusion: Women with PCOS and endometriosis did not show a significant difference in terms of pregnancy outcome compared to women with NR women with endometriosis.

Keywords: Polycystic ovary syndrome, intracytoplasmic sperm injection, endometriosis

INTRODUCTION

In endometriosis, the endometrial tissue of the uterus extends out to the pelvic space,peritoneum and on to the organs like ovaries, intestines and the bladder. The disease spectrum is vast and ranges from large endometrioma cysts to small lesions on the pelvic organs, creating significant adhesions in the uterus, bladder and intestine and disrupting the anatomy of the pelvis (1-3). The disease treatment is still associated with many problems. Next to clinical examination and medical technologies such as imaging techniques and biomarkers, laparoscopy was the standard diagnostic method. The disease has different severities and the probability of the disease returning after drug treatments and surgery is high (4).

Some studies showed that the pregnancy rate is reduced in endometriosis patients because of abnormal folliculogenesis, decreased ovarian follicular reserve and reduced oocyte fertilization ability (5). Also, other studies showed that the in vitro fertilization (IVF) success rate in endometriosis patients is lower than in other patients (6). Also, the oocyte numbers, good-quality embryos, fertilized oocytes, and fertility success rate in endometriosis patients are low (7). In addition, an inverse relationship between the severity and degree of this disease and the monthly fecundity rate (MFR) has been reported (8). Some studies show a decrease in MFR and pregnancy and a decrease in embryo implantation after IVF in women with endometriosis (9). Endometriosis surgery and treatment have potential risks, benefits, and long-term effects on the quality of life that patients undergoing surgery should be informed about it (10).

On the other hand, polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder that affects 5-10% of women of reproductive age (5). The complex pathophysiology of PCOS involves chronic anovulation, high androgen levels, insufficient secretion of gonadotropins, and abnormal ovaries morphology (7). The clinical disorders of PCOS are infertility, hirsutism, irregular menstrual cycles or amenorrhea, acne, and hair loss (7). In PCOS patients, insulin resistance and obesity

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are the pathophysiology principles. As a result, the insulin increase in these patients stimulates the ovarian androgen production (11).

There are controversial opinions regarding the cause and treatment of infertile women who suffer from PCOS. Retrospective and prospective studies reported PCOS as a risk factor for increased pregnancy complications (5). Various studies reported an increased risk of premature birth, preeclampsia, gestational diabetes and hypertension, an increased risk of admission to the intensive care unit, and a mortality rate for newborns in pregnant patients (8,12). Some reports show an increase in the spontaneous abortion rate in PCOS patients (6). Complications of the first trimester of pregnancy in PCOS patients include congenital abnormalities of the fetus and miscarriage (8).

Due to the prevalence of PCOS and insufficient information on the pregnancy outcome of mothers with a history of PCOS, this study compared pregnancy outcomes of normoresponder endometriosis and PCOS/endometriosis patients underwent intracytoplasmic sperm injection (ICSI) to investigate the effect of PCOS in patients with endometriosis.

MATERIAL AND METHOD

This study was carried out with the permission of Beykoz University Ethics Committee (Date: 18.02.2021, Decision No: 1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a retrospective study with control in infertile women aged 25-40, suffering from PCOS and endometriosis, referred to the infertility clinic of Medistate Hospital between September 2018- December 2020. In this study, the total number of participants was 105 in two groups (54 with PCOS and endometriosis in the study group and 51 with normoresponder (NR) endometriosis in the control group). The pregnancy outcomes of age-matched participants were compared retrospectively.

Diagnosis of endometriosis was made by ultrasound and laparoscopic. Cases with male factors, chronic disease, and recurrent implantation failure were excluded from the study. Patients aged 25-40, with the first trial of ICSI with no other additional infertility factor are included.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to check the normality. Mean and standard deviations (SD) were measured to check each continuous variable, including age, body mass index (BMI), age of menarche, anti-mullerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), free testosterone, dehydroepiandrosterone sulfate (DHEA-SO4), fasting blood sugar (FBS), Hemoglobin A1C (HBA1C), prolactin (PRL), metaphase 2 (MII), number of embryos transferred (TEENS), number of embryos total oocyte, number of cryopreserved embryos, implantation rate and gestational sac. In all variables except free testosterone, the Mann-Whitney U test was performed to examine the difference between the two groups. in free testosterone, due to its normality, Independent t-test was used. SPSS v22was used for statistical analyses. A value of $p < 0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, two groups' total mean was measured based on the Mann-Whitney test with the power of 95%, effect size of 50%, and 0.05 type 1 error for at least 92 patients (13).

RESULTS

This study included one hundred five age-matched (31.42±3.37) and BMI-matched (25.45±1.44) women. **Table 1** shows descriptive statistics of study parameters.

Table 1. Descriptive statistics of study parameters in the infertile group of women

Study parameters	median (range)	mean ± SD
Age	32 (25-39)	31.42±3.37
BMI	25 (23-29)	25.45±1.44
Age of menarche	11 (10-14)	11.31±0.94
AMH	4 (1.1-12)	3.97±2.38
FSH	8 (6-9)	7.76±0.64
LH	8 (4-16)	8.88±2.36
E2	45 (31-54)	44.08±4.91
Free testosterone	0.96 (0.2-1.62)	0.95±0.33
DHEA-SO4	286 (159-412)	283.26±60.47
FBS	88 (73-98)	88.03±6.86
HBA1C	5.29 (4-5.9)	5.19±0.51
PRL	18 (5-29.3)	18.83±5.39
Total oocyte	9 (3-32)	11.69±6.11
MII	8 (3-27)	9.92±5.25
PN	7 (2-20)	8.35±4.49
TEES	1 (1-2)	1.48±0.502
Cryopreserved embryo(n)	2 (0-8)	2.2±1.50

SD, standard deviation.

Table 2 shows the comparison of case and control groups on the study parameters. As stated in **Table 2**, a Mann-Whitney test did not find a statistically significant association between case and control regarding age and BMI ($p>0.05$). There was a statistically significant difference between groups regarding AMH ($p<0.05$). There was not a statistically significant difference between case group and controls in regard to age of menarche ($p=0.731$), FSH ($p=0.744$), E2 ($p=0.990$), and TEENS ($p=0.929$). There was a statistically significant difference between the case group and controls regarding

LH, free testosterone, DHEA-SO4, FBS, HBA1C and PRL ($p<0.05$). There was a statistically significant difference between the case group and controls regarding cryopreserved embryo ($p<0.05$).

Table 2. Comparison of case and control groups

Study parameters	Case (PCOS and endometriosis) (n=54) M±SD	Control (Normoresponder endometriosis) (n=51) M±SD	p value
Age	31.33±3.2	31.53±3.57	0.958*
BMI	25.43±1.57	25.49±1.3	0.618*
Age of menarche	11.33±0.93	11.29±0.97	0.731*
AMH	5.98±1.61	1.84±0.3	<0.001*
FSH	7.74±0.68	7.78±0.61	0.744*
LH	10.74±1.51	6.92±1.25	<0.001*
E2	44.07±6.05	44.1±3.37	0.990*
Free testosterone	1.06±0.3	0.85±0.34	<0.001**
DHEA-SO4	295.46±62.03	270.35±56.56	0.033*
FBS	91.06±5.19	84.84±7.01	<0.001*
HBA1C	5.4±0.35	4.99±0.57	<0.001*
PRL	20.08±4.92	17.5±5.6	0.028*
Total oocyte	15.44±6.4	7.73±1.74	<0.001*
MII	13.04±5.6	6.63±1.59	<0.001*
PN	11.11±4.76	5.43±1.01	<0.001*
TEES	1.48±0.5	1.49±0.5	0.929*
Cryopreserved embryo	2.54±1.68	1.84±1.22	0.013*

M, Mean; N, number of subjects; BMI, body mass index; AMH, Anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, Estradiol; DHEA-SO4, dehydroepiandrosterone sulfate; FBS, Fasting Blood Sugar; HBA1C, Hemoglobin A1C; PRL, Prolactin; MII, Metaphase 2 Cell; TEENS, Number of embryos transferred; PN, Pronucleus Cell. *A Mann-Whitney test ** Independent t-test.

As stated in **Table 3**, a Chi-square test did not find a statistically significant association between case and NRr endometriosis regarding positive pregnancy outcome ($p>0.05$).

Table 3. The significant relationship between case and control groups and pregnancy results

Variable		pregnancy (-) (n=53) n (%)	pregnancy (+) (n=52) n (%)	p-value
PCOS	Yes	24 (45.3)	30 (57.7)	0.203*
	No	29 (54.7)	22 (42.3)	

*A Chi-square test. (+), positive; (-), negative

As stated in **Table 4**, the women with PCOS had a 26.66% abortion and 40.74% live births. The women with NR had an 18.8% abortion and 35.2% live births

Table 4. Abortion and live birth statistics in two groups

Pregnancy outcome variables	Patients with NR endometriosis (n=51) n(%)	Patients with PCOS and endometriosis (n=54) n(%)
Positive HCG	22 (43.15)	30 (55.55)
Abortion	4 (7.85)	8 (14.81)
Live Birth	18 (35.3)	22 (40.74)

Figure shows that the case group had higher abortion and live birth rates than the controls.

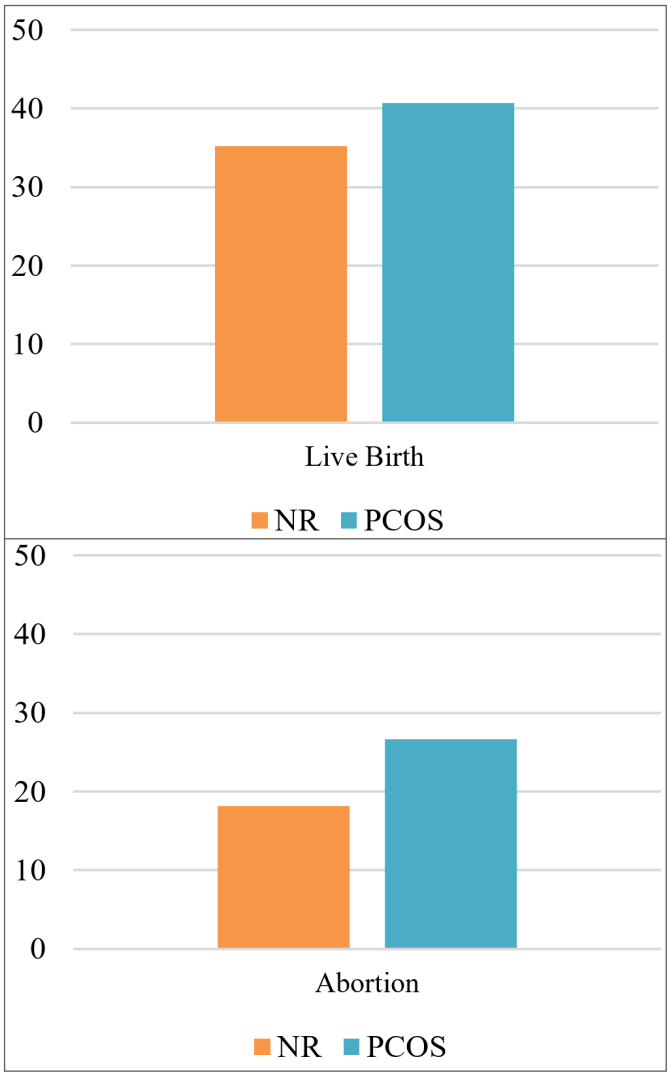

Figure. The effect of PCOS on the abortion and live birth rate

DISCUSSION

In this study, the fertility rate of women with PCOS and endometriosis was compared with the control group, which included women with NR endometriosis. For both groups, the ICSI-assisted treatment method was used for treatment. According to the results, women with PCOS and endometriosis did not show a significant difference in fertility compared to women with NR endometriosis group which is consistent with previous studies (14-16). In a similar study, Piltonen (17) showed that the embryo quality in endometriosis patients is not different from other referrals for ICSI. Examination of embryo quality in the present study also confirmed this finding. Therefore, it is suggested to control the inflammation caused by the disease before treating infertility by ICSI in endometriosis patients with medical or surgical treatments to increase the result of ICSI and its success rate (18,19).

Examination of fertility factors showed that although endometriosis caused the number of mature oocyte

obtained from these women to decrease after the treatment of the disease compared to the PCOS group, the pregnancy success rate from different aspects of pregnancy rate and live birth in the NR group of patients is not significantly different from the PCOS group. Some studies found that preterm delivery was more common in pregnant women with PCOS than in the control group (20,21). However, in others, which compared the results of pregnancy in women with PCOS based on age and weight with the control group, there was no statistically significant relationship between the two groups regarding the prevalence of premature birth (22).

In this study, the two PCOS and NR groups differ in the livebirth rate and abortion. In the study of Crespi (3), an increase in spontaneous abortion was reported in women with PCOS. Contrary to the above studies, the study by Alebić (1) showed that the rate of abortion in PCOS syndrome is probably not different from the control group. The difference could be because pregnant women with PCOS in previous studies were older than the control group, as age also plays a destructive role in increasing pregnancy complications (6). In the present study, only eight intrauterine deaths were reported in the PCOS group, which was not statistically significantly different from the NR group. In Zhai et al. (23), the rate of intrauterine death in both PCOS and NR groups was not statistically significant, which was consistent with the present study.

In the present study, the total oocyte number was higher in women with PCOS than in the NR group, which was statistically significant. In the study of Jiang et al. (9), which was conducted on pregnant women with PCOS, the total oocyte in the PCOS group was higher than in other disease groups, including NR, which was consistent with the present study. One of the limitations of this study was the low number of samples and lack of examination of the health factors of babies born from both groups. It is suggested, future studies should be conducted with a larger number of samples, in multiple medical centers, and with more variables related to the baby to draw more accurate conclusions.

CONCLUSION

The fertility rate of women with PCOS and endometriosis was compared with the control group, which included women with NR endometriosis. In conclusion, women with PCOS and endometriosis did not show a significant difference in fertility rate compared to women with NR.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Beykoz University Ethics Committee (Date: 18.02.2021, Decision No: 1)

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.

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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Original Article

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Hypothermia: what are the trends in recent studies? – a bibliometric analysis with global productivity

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ABSTRACT

Aim: Although the number of global studies on hypothermia, which plays an important role in morbidity and mortality in adults and newborns, has increased, there is still no bibliometric research on this subject in the literature. This study, it was aimed to determine trend topics and global productivity by using various statistical analyzes of scientific articles published on hypothermia.

Material and Method: Articles on hypothermia published between 1980 and 2021 were downloaded from the Web of Science (WoS) database and analyzed using various statistical and bibliometric methods. Spearman's correlation coefficient was used for correlation studies. Network visualization maps were used to identify effective studies, global collaborations, and trend topics with citation analyses.

Results: Out of a total of 14410 publications, 8157 articles were analyzed. The top 5 contributors to the literature are USA (n=2938, 36%), Japan (737, 9%), UK (641, 7.8%), Germany (576, 7%), and China (544, 6%). was. The first 3 journals that published the most articles were Resuscitation (n=296), Critical Care Medicine (146), Therapeutic Hypothermia, and Temperature Management (135). The top 3 most active institutions were League of European Research Universities (n=448), University of California System (274), and Pennsylvania Commonwealth System of Higher Education (221). The most active author was Marianne Thoresen (n=69).

Conclusion: The most studied trend topics in recent years are determined as hypoxic-ischemic encephalopathy, neonatal encephalopathy, out-of-hospital cardiac arrest, neonates, targeted management, therapeutic hypothermia, extracorporeal membrane oxygenation, perioperative hypothermia, emergency medicine, outcome, mortality, and perinatal asphyxia. This study will guide the authors who want to study in this area.

Keywords: Bibliometric analysis, hypothermia, therapeutic, neuroprotection, trends

INTRODUCTION

Hypothermia, an important issue in the history of medicine, is a decrease in core body temperature below 35°C (Mild hypothermia: 32°C to 35°C (90°F to 95°F), moderate hypothermia: 28°C to 32°C (82°F to 90°F), severe hypothermia: below 28°C (82°F)) and develops when the body's heat loss exceeds heat production (1,2). The temperature regulation center, which makes it possible to keep the core body temperature constant under changing environmental conditions, is located in the hypothalamus. If the body is exposed to cold, various mechanisms come into play to prevent heat loss and increase heat production. Death in hypothermia occurs by the mechanism of heart failure with asystole or ventricular fibrillation, which are factors that contribute to increased catecholamine levels, electrolyte disturbances, and cardiac oxygen depletion (2-4).

Although hypothermia is an emergency requiring immediate treatment, the therapeutic use of hypothermia is an important neuroprotection method. Therapeutic hypothermia is a promising neuroprotective intervention that has been shown to improve outcomes of nerve damage in humans. Until now, it has been proven that many neurological diseases such as stroke, traumatic brain injury, increased intracranial pressure, subarachnoid hemorrhage, spinal cord injury, hepatic encephalopathy, and neonatal peripartum encephalopathy are suppressed by therapeutic hypothermia (5). The neuroprotective role of hypothermia has been well established in cardiac arrest, hypoxic-ischemic encephalopathy, traumatic brain injury, and some other diseases (5-9).

Another special issue of hypothermia is neonatal hypothermia seen in newborns. According to the World

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Health Organization (WHO), neonatal hypothermia is defined as a core body temperature of < 36.5°C or a skin temperature of <36°C (10).

Bibliometrics examines articles using various statistical methods (11-13). As a result of the analysis of the information obtained from thousands of articles in the literature with various statistical and bibliometric approaches, important information about a subject such as the most active countries, institutions, journals, authors, international collaborations, and past and future trends can be determined (14-16).

Although the number of global studies on hypothermia, which plays an important role in morbidity and mortality in adults and newborns, has increased, there is still no bibliometric research on this subject in the literature. This study, it was aimed to identify trend topics and reveal global productivity by holistically analyzing scientific articles on hypothermia published between 1980 and 2021 using various statistical methods and bibliometric approaches.

MATERIAL AND METHOD

Since our research article is a bibliometric study, there is no need for an ethics committee approval.

Search Strategy

Web of Science Core Collection (WoS by Clarivate Analytics) database was used for the literature review. The search process was determined as 1980 - 2021. All publications with the phrase hypothermia in the title were accessed. So that researchers can access similar documents reproducibility codes: Title "hypothermia", Timespan: 1980-2021 (search findings may vary depending on different access dates, access date: 1 May 2022). VOSviewer (Version 1.6.16, Leiden University's Center for Science and Technology Studies, Netherlands) package program was used to create bibliometric network visualizations as a result of clustering analyses, citation analyses, and trend topic determination analyses (17).

Statistical Analysis

The website 'https://app.datawrapper.de' was used to create the world map showing the distribution of articles by country. The Exponential Smoothing estimator using seasonal smoothing was used in Microsoft Office Excel to estimate the number of articles that could be published in the next 5 years based on past publication trends. Statistical analyzes were performed with SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normal distribution test of the data was analyzed with the Shapiro-Wilks test. Correlation analyzes were performed to determine whether some economic development indicators (Gross Domestic Product (GDP), Gross Domestic Product per capita (GDP per capita), Human Development Index (HDI)) of countries affected hypothermia (data were obtained from the world bank (18)). Correlation analyzes were analyzed using the Spearman correlation coefficient as the data were not normally distributed. $p<0.05$ was accepted for a statistically significant relationship.

RESULTS

As a result of the literature review, there were a total of 14410 publications on hypothermia published in all research areas in the WoS database during the 1980-2021 period. Of these publications, 56.6% (n=8157) were Articles, 22.7% (n=3275) Meeting Abstracts, 6.9% (n=1000) Letters, 4.3% (n=615) Proceedings Papers, 4.2% (n=602) were in Review Articles, and the remainder in other publication types (Notes, Corrections, Book Chapters, Early Access, News Items, Book Reviews, Discussions, Poetry, Biographical-Items, Data Papers). Bibliometric analyzes were carried out with 8157 articles published in the Article category out of a total of 14410 publications. 94.2% (n=7686) of these articles were in English and the remainder in other languages (German (156), French (90), Russian (84), Spanish (60), Japanese (23), Turkish (12), Portuguese (9), Czech (8), Polish (7), Italian (6), Korean (3), Serbian (3), Bulgarian (2), Ukrainian (2), Croatian (1), Hungarian (1), Norwegian (1), Serbo Croatian (1), Slovenian (1), Welsh (1)) (**Table 1**). The h-index of 8157 articles was 158, the average citations per article 25.8, and the sum of times cited 210.431 (without self-citations: 158,258) (**Table 1**). Most of the articles were scanned in SCI-Expanded (n=7671, 94%) and Emerging Sources Citation Index (ESCI) (n=424, 5.2%).

Table 1. Language distribution and citations

Language	Number of articles			
English	7686	Total 8157 articles	h- index	158
German	156			
French	90			
Russian	84		Average citations per article	25.8
Spanish	60			
Japanese	23			
Turkish	12			
Portuguese	9		Sum of times cited	210431
Czech	8			
Polish	7			
Italian	6			
Korean/Serbian	3		Without self-citations	158258
Bulgarian/Ukrainian	2			
Croatian/Hungarian/ Norwegian/ Serbo Croatian/Slovenian/Welsh	1			

Development of publications over the years

The distribution of the number of articles published on hypothermia by years is shown in **Figure 1**. The values

related to the results of the Exponential Smoothing estimation model, which takes into account the seasonal correction used to estimate the number of articles that can be published in the next 5 years, are shown in **Figure 1**. According to the estimation model results, it was predicted that 366 (Confidence Interval 95%: 320-412) articles will be published in 2022 and 394 (CI 95%: 300-489) articles will be published in 2026 (**Figure 1**).

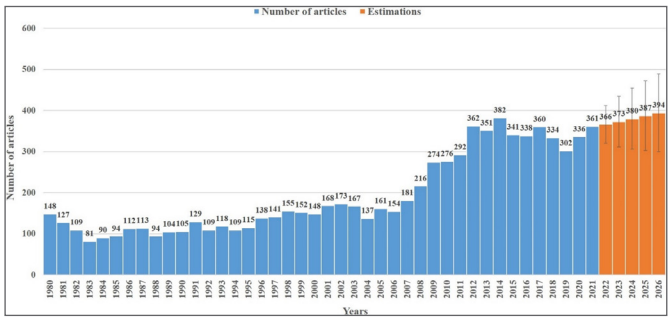

Figure 1. A bar chart illustrating the distribution of hypothermia articles published by year, as well as predictions for the number of articles to be published in the next five years.

Research Areas

The first 15 research areas with the most research on hypothermia are respectively; Neurosciences (1076, 13.2%), Critical Care Medicine (1073, 13.1%), Surgery (1034, 12.6%), Clinical Neurology (777, 9.5%), Pediatrics (755, 9.2%), Cardiac Cardiovascular Systems (726, 8.9 %), Anesthesiology (618, 7.5%), Emergency Medicine (610, 7.4%), Pharmacology Pharmacy (550, 6.7%), Medicine General Internal (494, 6%), Physiology (408, 5%), Peripheral Vascular Disease (339, 4.1%), Respiratory System (328, 4%), Medicine Research Experimental (283, 3.4%), Biochemistry Molecular Biology (206, 2.5%).

Active Countries

The distribution of the number of articles by country is shown in **Figure 2**. The first 21 countries that contributed the most to the literature by publishing more than 100 articles are respectively; USA (number of articles, n=2938, 36%), Japan (737, 9%), UK (641, 7.8%), Germany (576, 7%), China (544, 6%), Canada (482, 5.9%), France (304, 3.7%), Sweden (247, 3%), Netherlands (218, 2.6%), South Korea (208, 2.5%), Australia (194, 2.3%), Norway (182, 2.2) %), Italy (181, 2.2%), Austria (174, 2.1%), Spain (152, 1.8%), Turkey (147, 1.8%), Switzerland (144, 1.7%), Brazil (124, 1.5%) , Russia (115, 1.4%), India (103, 1.2%), and Poland (100, 1.2%) (**Figure 2**). Cluster analysis was performed among 60 countries that have published at least 5 articles from 110 countries that have published articles on hypothermia and whose authors have international cooperation, and it is shown in **Figure 3**a. According to the results of the clustering analysis, 10 different clusters related to international cooperation were formed (Colors for Cluster 1: red, Cluster 2: green, Cluster 3: blue, Cluster 4: yellow, Cluster 5: purple, Cluster 6: turquoise, Cluster 7: orange, Cluster 8: brown, Cluster 9: pink, Cluster 10: orange). In addition, the total link strength (international cooperation score) scores showing the cooperation power of 60 countries were calculated and the International cooperation density map created according to these scores was shown in **Figure 3**b (Highest scoring countries: USA (805), England in the UK (423), Germany (345), France (233), Austria (232), Italy (223), Sweden (215), Canada (214), Netherlands (207), Norway (201), Switzerland (201)).

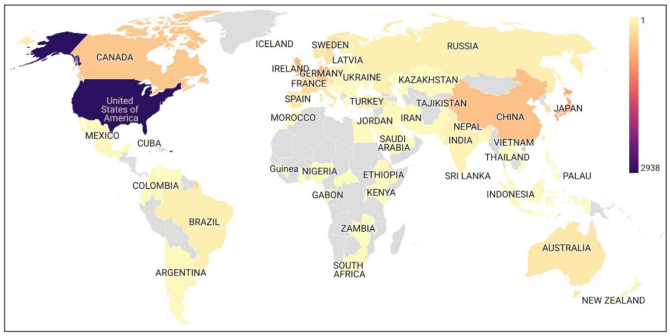

Figure 2. Global productivity world map showing the distribution of published articles on hypothermia by country

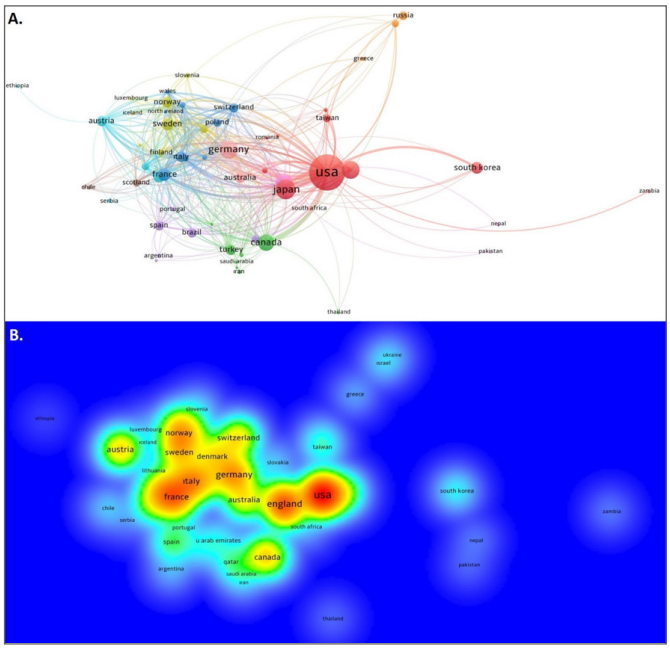

Figure 3. a. Network visualization map of results of cluster analysis showing international cooperation between countries on hypothermia Footnote: Each color denotes a distinct Cluster. The size of the circles representing the countries grows in proportion to the number of articles published by the countries. The lines indicate which countries they collaborate with. b. Density map showing the intensity of international cooperation of countries on hypothermia. Footnote: From blue to red (blue-green-yellow-red), the strength of international cooperation score increases.

Correlation Analysis

A positive moderate statistically significant correlation was found between the number of articles produced by countries on hypothermia and GDP, GDP per capita, and HDI values (respectively, r=0.709, p<0.001; r=0.702, p<0.001, r=0.666, p< 0.001).

Active Authors

The top 10 most active authors on hypothermia are respectively; Thoresen M. (69), Dietrich WD. (45), Kochanek PM. (43), Sterz F. (40), Schwab S. (38), Sessler DI. (37), Shankaran S. (34), Safar P. (32), Yenari MA. (32), Gunn AJ. (31).

Active Institutions

The 15 most active institutions on hypothermia are respectively; League of European Research Universities (448), University of California System (274), Pennsylvania Commonwealth System of Higher Education (221), University of Pittsburgh (178), University of London (142), University of Texas System (139), University of California San Francisco (128), Harvard University (126), Johns Hopkins University (121), Stanford University (111), University College London (109), US Department of Veterans Affairs (106), USA Veterans Health Administration (106), Imperial College London (104), University of Pennsylvania (98).

Active Journals

8157 articles published on hypothermia were published in 1794 different journals. The first 56 journals that contributed the most to the literature by publishing 25 or more articles from these journals, the total number of citations received by the journals and the average number of citations per article are presented in **Table 2**.

Citation Analysis

Among the 8157 articles reviewed, the first 20 articles with the highest number of citations according to the total number of citations are presented in **Table 3**. In the last column of **Table 3**, the average number of citations the articles received per year is given.

Table 2. The 56 most active journals that have published 25 or more articles on hypothermia

Journals	RC	C	AC	Journals	RC	C	AC
Resuscitation	296	12056	40.7	Journal of Applied Physiology	41	1055	25.7
Critical Care Medicine	146	8457	57.9	Journal of Maternal-Fetal & Neonatal Medicine	37	306	8.3
Therapeutic Hypothermia and Temperature Management	135	760	5.6	Life Sciences	37	774	20.9
Brain Research	117	4202	35.9	Acta Paediatrica	36	599	16.6
Annals of Thoracic Surgery	97	2432	25.1	Critical Care	36	1578	43.8
Plos One	92	1444	15.7	Neurological Research	36	702	19.5
Journal of Thoracic and Cardiovascular Surgery	91	3306	36.3	Shock	36	811	22.5
Journal of Neurotrauma	87	3958	45.5	Journal of Neurosurgical Anesthesiology	35	854	24.4
Anesthesia and Analgesia	86	2669	31.0	Journal of Thermal Biology	35	195	5.6
Stroke	85	8541	100.5	American Journal of Physiology-Regulatory Integrative and Comparative Physiology	34	924	27.2
Anesthesiology	81	5673	70.0	Anaesthesia	34	834	24.5
Journal of Cerebral Blood Flow and Metabolism	79	5901	74.7	Archives of Disease in Childhood-Fetal and Neonatal Edition	34	934	27.5
Acta Anaesthesiologica Scandinavica	76	2393	31.5	Neurosurgery	34	2080	61.2
American Journal of Emergency Medicine	75	785	10.5	American Journal of Perinatology	33	290	8.8
Journal of Trauma-Injury Infection and Critical Care	69	4465	64.7	Circulation	33	2621	79.4
Pediatric Research	68	2600	38.2	Anaesthesist	32	194	6.1
Cryobiology	63	979	15.5	Pediatric Critical Care Medicine	30	685	22.8
Pharmacology Biochemistry and Behavior	62	1034	16.7	Scandinavian Journal of Trauma Resuscitation & Emergency Medicine	30	561	18.7
European Journal of Pharmacology	54	1439	26.6	British Journal of Anaesthesia	29	839	28.9
Neuroscience Letters	49	1218	24.9	Experimental Neurology	29	1116	38.5
Journal of Perinatology	48	853	17.8	Intensive Care Medicine	29	1409	48.6
Journal of Surgical Research	47	786	16.7	Neonatology	28	489	17.5
Journal of Pediatrics	46	1920	41.7	Neuroscience	28	928	33.1
Bulletin of Experimental Biology and Medicine	45	26	0.6	Pediatrics	28	2746	98.1
Journal of Neurosurgery	44	3818	86.8	Annals of Emergency Medicine	27	1134	42.0
Neurocritical Care	42	1243	29.6	Neuropharmacology	26	555	21.3
Scientific Reports	42	555	13.2	Psychopharmacology	26	780	30.0
European Journal of Cardio-Thoracic Surgery	41	1072	26.1	Pediatric Neurology	25	965	38.6

C: Record count, C: Number of citation, AC: Average citation per document

Table 3. The top 20 most cited articles on hypothermia

No	Article	Author	Journal	PY	TC	AC
1	Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia	Bernard SA. et al.	New England Journal of Medicine	2002	3687	175.5
2	Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest	Holzer M. et al.	New England Journal of Medicine	2002	3426	163.1
3	Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy	Shankaran S. et al.	New England Journal of Medicine	2005	1787	99.2
4	Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial	Gluckman PD. et al.	Lancet	2005	1531	85
5	Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy.	Azzopardi DV. et al.	New England Journal of Medicine	2009	1117	79.7
6	Defense strategies against hypoxia and hypothermia	Hochachka PW.	Science	1986	968	26.1
7	Treatment of traumatic brain injury with moderate hypothermia	Marion DW. et al.	New England Journal of Medicine	1997	934	35.9
8	Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty-acids in rat-brain	Busto R. et al.	Stroke	1989	925	27.2
9	Lack of effect of induction of hypothermia after acute brain injury.	Clifton GL. et al.	New England Journal of Medicine	2001	904	41
10	Mild hypothermia increases blood loss and transfusion requirements during total hip arthroplasty	Schmied H. et al.	Lancet	1996	613	22.7
11	Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data	Edwards AD. et al.	BMJ-British Medical Journal	2010	601	46.2
12	Hypothermia but not the n-methyl-d-aspartate antagonist, mk-801, attenuates neuronal damage in gerbils subjected to transient global-ischemia	Buchan A. and pulsinelli WA.	Journal of Neuroscience	1990	547	16.5
13	Deep hypothermia with circulatory arrest - determinants of stroke and early mortality in 656 patients	Svensson LG. et al.	Journal of Thoracic and Cardiovascular Surgery	1993	477	15.9
14	Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction	Schwab S. et al.	Stroke	1998	473	18.9
15	Glutamate release and free-radical production following brain injury - effects of posttraumatic hypothermia	Globus MYT. et al.	Journal of Neurochemistry	1995	453	16.1
16	Prognostication after cardiac arrest and hypothermia a prospective Study	Rossetti AO. et al.	Annals of Neurology	2010	444	34.1
17	Hypothermia in trauma victims - an ominous predictor of survival	Jurkovich GJ. et al.	Journal of Trauma-Injury Infection and Critical Care	1987	444	12.3
18	Effect of hypothermia on the coagulation cascade	Rohrer MJ. and natalie AM.	Critical Care Medicine	1992	438	14.1
19	Childhood Outcomes after Hypothermia for Neonatal Encephalopathy	Shankaran S. et al.	New England Journal of Medicine	2012	436	39.6
20	The effects of mild perioperative hypothermia on blood loss and transfusion requirement	Rajagopal.an S. et al.	Anesthesiology	2008	431	28.7

PY: Publication year, TC: Total citation, AC: Average citations per year

Co-citation Analysis

There were a total of 116544 studies cited in the references section of all 8157 articles published on hypothermia. Among these studies, the 7 most influential studies with more than 350 citations and the most co-citations are respectively; Bernard et al. (2002) (Number of co-citations: NC=1079), Holzer et al. (2002) (NC=979), Shankaran et al. (2005) (NC=625), Gluckman et al. (2005) (NC=501), Azzopardi et al. (2009) (NC=388), Busto et al. (1989) (NC=386), and Busto et al. (1987) (NC=383) (19-25).

Keyword Analysis and Trend Topics

In all of the 8157 articles published on hypothermia, 9330 different keywords were used. Among these keywords, 105 different keywords used in at least 20 different articles are shown in **Table 4**. The cluster network visualization map showing the results of the clustering analysis performed between these keywords is shown in **Figure 4**. As a result of the cluster analysis, it was seen that hypothermia subjects were divided into 7 different clusters (Colors for Cluster 1: red, Cluster 2: green, Cluster 3: blue, Cluster 4: yellow, Cluster 5: purple, Cluster 6: turquoise, Cluster 7: orange). The trend network visualization map performed to identify trend topics is shown in **Figure 5**, and the citation network visualization map performed to reveal the most cited topics is shown in **Figure 6**.

Table 4. The 105 most frequently used keywords in articles on hypothermia

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
hypothermia	2747	cooling	56	core temperature	29
therapeutic hypothermia	564	oxidative stress	54	hemorrhagic shock	29
cardiac arrest	524	cerebral blood flow	50	hibernation	29
neuroprotection	242	hyperthermia	48	shivering	29
hypoxic-ischemic (or ischaemic) encephalopathy	225	intracranial pressure	47	subarachnoid hemorrhage	29
rat (s)	215	magnetic resonance imaging	46	metabolism	28
temperature	181	nitric oxide	46	coma	27
cardiopulmonary resuscitation	173	glutamate	45	electroencephalography	27
mild hypothermia	172	hippocampus	45	microglia	27
resuscitation	162	out-of-hospital cardiac arrest	45	critical care	26
body temperature	148	brain injury	44	microdialysis	26
ischemia	143	encephalopathy	44	induced	25
traumatic brain injury	143	moderate hypothermia	44	lactate	25
outcome (s)	140	reperfusion	44	mitochondria	25
cerebral ischemia	135	sepsis	42	coagulopathy	24
stroke	123	survival	42	ethanol	24
newborn	117	targeted temperature management	42	head injury	24
neonate (s)	114	brain edema	41	reactive oxygen species	24
rewarming	110	cytokines	41	infant	23
apoptosis	109	hypoxia-ischemia	40	liver	23
inflammation	97	myocardial infarction	39	perioperative hypothermia	23
thermoregulation	94	anesthesia	38	circulatory arrest	22
accidental hypothermia	92	extracorporeal circulation	35	emergency medicine	22
induced hypothermia	90	neurological outcome	33	hypothalamus	22
asphyxia	88	shock	33	lipopolysaccharide	22
heart arrest	88	children	32	blood-brain barrier	21
cardiopulmonary bypass	80	mild therapeutic hypothermia	32	brain temperature	21
trauma	77	pharmacokinetics	32	mri	21
perinatal asphyxia	74	fever	31	pediatric	21
brain	71	hemorrhage	31	brain ischemia	20
mortality	71	reperfusion injury	31	dopamine	20
ventricular fibrillation	67	spinal cord injury	31	heart	20
prognosis	65	extracorporeal membrane oxygenation	30	kidney	20
neonatal encephalopathy	64	surgery	30	microcirculation	20
hypoxia	59	birth asphyxia	29	normothermia	20

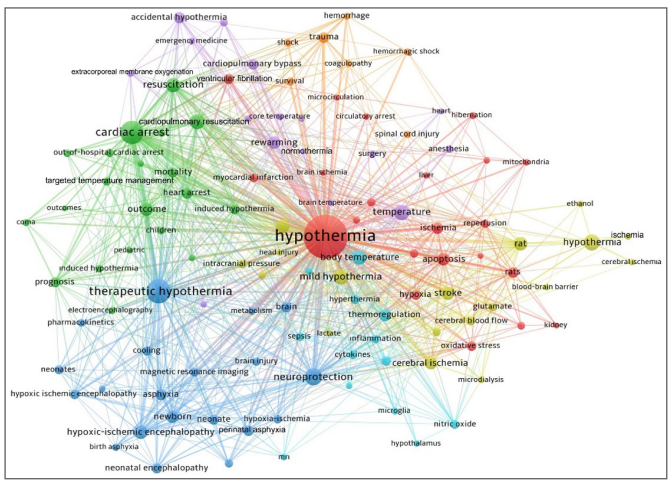

Figure 4. Network visualization map for cluster analysis based on keyword analysis performed to identify clustering of hypothermia. Footnote: Each color denotes a distinct cluster. The color of keywords in the same cluster is the same. The circle represents the number of times the keyword is used in articles. The larger the circle represents the number of times the keyword is used in articles.

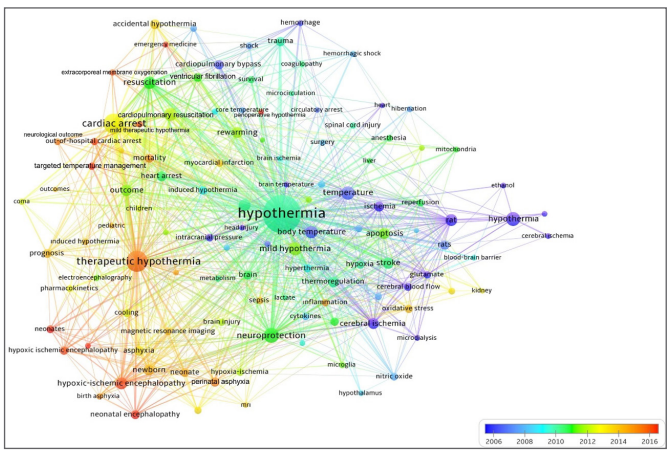

Figure 5. Network visualization map based on keyword analysis to identify past and current trends on hypothermia. Footnote: The article's topicality increases from blue to red as indicated by the indicator in the lower right corner of the figure (blue-green-yellow-red). The circle represents the number of times the keyword is used in articles. The larger the circle represents the number of times the keyword is used in articles.

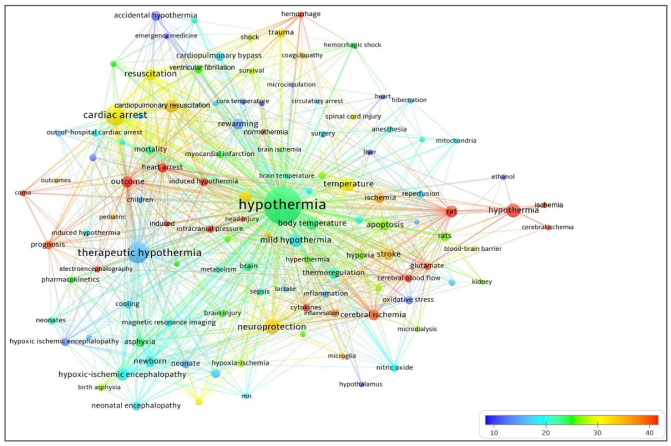

Figure 6. Network visualization map based on keyword analysis performed to identify the most cited topics on hypothermia. Footnote: The number of citations received by the subject increases from blue to red in the indicator in the lower right corner of the figure (blue-green-yellow-red). The circle represents the number of times the keyword is used in articles. The larger the circle represents the number of times the keyword is used in articles.

DISCUSSION

This study, in which the subject of hypothermia was evaluated, showed that the studies on hypothermia mainly focused on the neuroprotective effect of therapeutic hypothermia. This shows that therapeutic hypothermia is an important research topic. In addition, the increase in the annual average number of publications, especially in the 2008-2021 period, is higher than in previous periods. This may be related to both the development of technologies on hypothermia and the fact that therapeutic hypothermia applications are an important treatment method that keeps up to date.

Heart disease is still one of the main universal reasons for death. Acute myocardial infarction is one of the most common diseases in the world. (26,27). For this reason, millions of people lose their lives every year (28). This situation continues to be a global health problem despite all the precautions and developments in treatment strategies. Management of ischemic brain injury, especially due to late intervention after myocardial infarction, is a very difficult health problem. There are promising results regarding therapeutic hypothermia, which has been increasingly used in recent years in order to eliminate the morbidity and mortality that may occur after this situation (19,29,30). In this bibliometric analysis, although most of the studies involving therapeutic hypothermia applications are associated with ischemic encephalopathy, it is observed that this condition is predominantly associated with a prolonged cardiac arrest that develops after myocardial infarction. Another interesting result is that the broadcasts peaked especially with the COVID-19 pandemic. This situation can be evaluated as a result of the reflection of the therapeutic hypothermia applied to patients due to the increased frequency of severe hypoxia due to COVID-19 pneumonia and subsequent hypoxic encephalopathy in the publications.

When the articles were examined and the number of studies of the countries was evaluated, it was seen that particularly developed countries were at the forefront. This situation does not come as a surprise when we evaluate the economic power of an application that requires advanced technology such as therapeutic hypothermia and the pioneers in the production of these devices. In addition, the cooperation scores of the countries in the studies on these issues were again at the forefront in the developed countries.

When the co-authorship cooperation of countries on hypothermia is evaluated, although some international global collaborations have been observed, it is thought that regional international collaborations based on the geographical neighborhood are common in article production. When the journals that publish the most articles on hypothermia are evaluated, it is seen that therapeutic hypothermia comes to the fore. In addition, it was observed that the studies focused on neurology, anesthesia, and emergency journals. We can recommend that authors who want to publish on hypothermia consider these journals first.

When the analyzed articles were evaluated according to the total number of citations they received and the average number of citations received per year, it was observed that the studies on hypothermia were predominantly post-cardiopulmonary arrest, followed by neonatal encephalopathy. Studies have been published showing that hypothermia treatment applied after post-cardiopulmonary arrest and neonatal encephalopathy has positive clinical results. (19,20,23) These results suggest that therapeutic hypothermia applications will intensify in an increasing trend, especially in these subjects. In addition, it is not surprising that similar results are obtained when citation analysis is performed.

Neonatal hypothermia is one of the most important issues in hypothermia. According to the World Health Organization (WHO), neonatal hypothermia is defined as a core body temperature of < 36.5 °C or a skin temperature of < 36 °C (10). Neonatal hypothermia is a global health problem and is still an important risk factor for neonatal morbidity and mortality, especially in low- and middle-income countries (31). In a meta-analysis study conducted for East Africa with 20911 participants (a total of 12 potential studies), the prevalence of neonatal hypothermia was found to be 57.2% (95%CI; 39.5–75.0) (32). Awareness of neonatal hypothermia is still low in some African populations. Risk factors for neonatal hypothermia in the region include poverty, preterm

birth, night birth, home birth, low birth weight, early bathing of newborns, late initiation of breastfeeding, and inadequate knowledge among health workers (31,32). Ironically, neonatal hypothermia, which is frequently encountered in underdeveloped regions such as African countries, is reflected in the publications as a condition that needs to be treated, while in developed countries, it gains weight in publications where hypothermia is used for therapeutic purposes (33). In addition, the limited number of studies on neonatal hypothermia may be associated with less sensitivity in underdeveloped populations and ignorance of the diagnosis of neonatal hypothermia.

As a result of our literature review, we did not find any bibliometric study on hypothermia. It can be said as the advantage of our study is that our research is the first bibliometric study on this subject. In addition, the use of many statistical approaches such as international cooperation analysis, citation analysis, trend keyword analysis, and correlation analysis can be said to be the other superior aspects of our study. A limitation of the study is that we used only the WoS database in the literature review. However, citation analyzes cannot be performed in the PubMed database. In addition, the WoS database indexes the articles published in more effective journals (SCI-expanded, ESCI, and SSCI-indexed journals) compared to the Scopus database (34).

CONCLUSION

In this comprehensive bibliometric research, conducted on hypothermia, it was shared the statistical analysis information of 8157 articles published from the past to the present. The most researched trend topics in recent years were determined as hypoxic-ischemic encephalopathy, neonatal encephalopathy, neonates, targeted management, therapeutic hypothermia, out-of-hospital cardiac arrest, extracorporeal membrane oxygenation, perioperative hypothermia, emergency medicine, outcome, mortality, perinatal asphyxia. Developed countries with large economies had a say in global productivity and international cooperation. This study will guide the authors who want to study in this area.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since our research article is a bibliometric study, there is no need for an ethics committee approval.

Informed Consent: For this type of study, formal consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

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

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Original Article

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Comparision of the scoring systems to predict clinical outcomes in older adults with biliary pancreatitis: a cross-sectional study

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ABSTRACT

Aim: The issue of which scoring system is appropriate in older adults patients with acute biliary pancreatitis is an ongoing debate. We aimed to compare the efficiency of four existing scoring systems in predicting clinical outcomes in the elderly with acute biliary pancreatitis.

Material and Method: The study included patients aged 60 years and older with a diagnosis of acute biliary pancreatitis. Clinical findings, routine laboratory examinations, and imaging findings were retrospectively accessed through the hospital information system and reviewed. Then, the efficacy of Ranson, Bedside Index of Severity in Acute Pancreatitis (BISAP), Glasgow-Imrie, and Acute Physiology and Chronic Health Evaluation (APACHE) II scoring systems in predicting mortality, severity, organ failure, complications, intensive care unit (ICU) admission, and prolonged hospital stay (PHS) were compared.

Results: The Ranson score was compared with three other existing scoring systems in primary and secondary outcomes in 364 eligible patients. The area under the curve (AUC) values of the Ranson, BISAP, Glasgow, and APACHE II scores were 0.787 (95% CI: 0.649-0.925), 0.856 (95% CI: 0.784-0.929), 0.908 (95% CI: 0.854-0.961), and 0.836 (95% CI: 0.702-0.971) for mortality. Although the AUC of the Ranson score for mortality was lower than that of the other scores, no significant difference was found in pairwise comparisons with the other three scores ($p>0.05$ for all).

Conclusion: The Ranson scoring system was the weakest among the assessed scoring systems in predicting clinical outcomes in older adults with biliary pancreatitis.

Keywords: Acute pancreatitis, elderly, scoring methods, Apache II, roc curve

INTRODUCTION

Acute pancreatitis (AP) is an emergency of the gastrointestinal system that involves the acute inflammation of the pancreas (1-3). With the growing older adults population due to increasing life expectancy and advanced medical treatments, acute and chronic diseases of the cardiovascular, respiratory, and renal systems have become more common as well as hospitalizations due to AP (4-6). Gallstones are the most common cause of AP, and the frequency of acute biliary pancreatitis increases with age (7).

AP can manifest itself in a wide spectrum ranging from a clinically asymptomatic presentation to multiorgan failure and mortality; it is classified as mild, moderately severe, and severe according to the revised Atlanta classification (7,8). AP is a progressive disease and patients hospitalized with AP may develop organ failure and severe AP during follow-up (9,10). Mortality is directly related to the severity of AP and older adults patients are at high risk of mortality due to comorbidities. (11-13). Therefore, in order to predict prognosis and progression to severe AP, clinical findings, routine laboratory tests, and radiology results should be carefully evaluated together with multifactorial scoring systems in the follow-up and treatment of AP (14). Different scoring systems used for the prediction of prognosis in the setting of AP include Ranson's criteria, the Glasgow-Imrie scoring system, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, and the Bedside Index of Severity in Acute Pancreatitis (BISAP) (15-18). However, there are few studies that investigate the validity of these scoring systems in older adults patients with AP (19,20).

Accordingly, in this study, we aimed to compare the efficacy of the Ranson, BISAP, Glasgow, and APACHE II scores in predicting mortality, severity, organ failure, and complications in older adults patients with biliary pancreatitis.

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MATERIAL AND METHOD

This study was conducted in the Ankara City Hospital in accordance with the Declaration of Helsinki and it received approval from Ankara City Hospital Ethics Committee No. 2 (Date: 14.07.2021, Decision No: E2-21-716). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

Patients aged 60 years and older who were diagnosed with biliary AP in Ankara City Hospital between January 2013 and April 2019 were included in the study. Patients under the age of 60 and those with non-biliary etiology, who refused to be hospitalized, who died within the first 24 hours, and who did not have sufficient data in their files were excluded from the study (**Figure 1**).

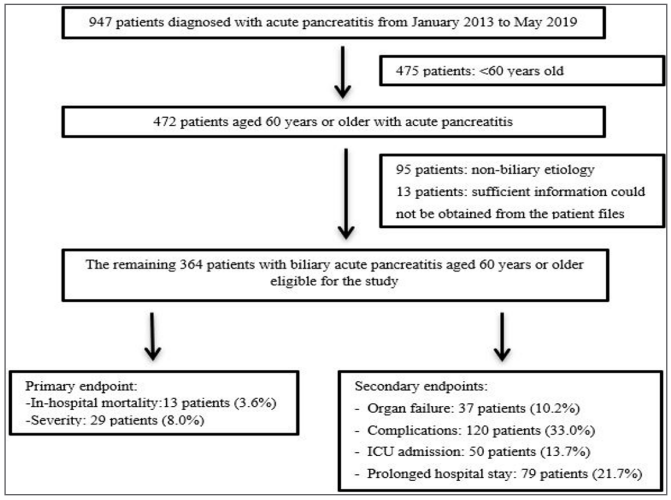

Figure 1. Flow chart showing the number of patients included and excluded and the primary and secondary endpoints observed.

The prognostic role of the Ranson score was evaluated in 364 eligible patients and the Ranson score was compared with 3 other existing scoring systems in terms of primary and secondary outcomes. Ranson and Glasgow scores in the first 48 hours of hospitalization and BISAP and APACHE II scores in the first 24 hours of hospitalization were calculated with laboratory and clinical parameters. Pairwise comparisons of Ranson with other scores were analyzed with area under the curve (AUC) values calculated with receiver operating characteristic (ROC) curve analysis.

Data Collection and Definitions

Many laboratory parameters were recorded in the first 48 hours of admission. Morphological subtype and local complications of AP were evaluated by radiological imaging. Age, gender, hospitalization day, presence of systemic complications, presence of intensive care unit (ICU) admission, disease severity, presence of organ failure, and mortality rate of the patients were clinically evaluated.

Patients with 2 of the following 3 criteria were diagnosed with AP: 1) sudden onset of abdominal pain radiating to the back, 2) serum amylase and/or lipase levels more than 3 times the upper limit of normal, and 3) pancreatic inflammation typical of AP detected on imaging.

Patients with stones, sludge, or microlithiasis in the gallbladder, biliary tract, or pancreatic duct identified with imaging methods and without any other obvious etiology were considered as having biliary AP. Patients with pancreatic or peripancreatic necrosis detected by advanced imaging methods (CT/MRI) were evaluated as having necrotizing AP. According to the revised Atlanta classification, the detection of acute peripancreatic fluid collection, pseudocyst, acute necrotic collection, walled-off necrosis, or splanchnic venous thrombosis with advanced imaging was considered as a local complication and exacerbation of an underlying comorbid condition was considered a systemic complication. Complications were defined as local and/or systemic. Severity was divided into three groups according to the revised Atlanta classification: 1) mild, without complications and organ failure; 2) moderately severe, with complications and/or organ failure lasting less than 48 hours; and 3) severe, with organ failure lasting longer than 48 hours. Organ failure was defined as patients scoring 2 or higher on the modified Marshall scoring scale. Cases were divided into two groups as severe and non-severe to compare severity dichotomously. Prolonged hospital stay was a stay of 10 days or more.

Study Outcomes

The primary endpoint of the study was to compare the Ranson score with other scores for mortality and severity. The secondary endpoint was a further comparison of the Ranson score with other scores in terms of organ failure, complications, intensive care hospitalization, and prolonged hospital stay.

Statistical Analysis

SPSS 26 (IBM) and MedCalc 20.0.8 (MedCalc) were used for statistical analysis. ROC curve analysis was performed to calculate the AUC values for the primary and secondary endpoints of the study. Pairwise comparison of ROC curve analyses was carried out to compare the AUC values of the scoring systems. In order to assess the predictive capabilities of the scoring systems, appropriate cut-off values for each system were determined using ROC curves with the Youden index method. Based on these cut-off values, the sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were found and risk analysis was carried out. In all analyses, a 2-sided value of $p < 0.05$ was considered statistically significant

RESULTS

Baseline Patient Characteristics

The mean age of the 364 patients included in the study was 74.4±8.9 years. Of the patients, 208 (57.1%) were female and 156 (42.9%) were male. Median length of stay was 6 days (min-max: 2-105). Necrotizing AP developed in 13 (3.6%) patients. While 66.8% of the patients had a mild course, 8% cases were severe. While no complications developed in 244 patients, local complications developed in 109 patients and systemic complications in 32 patients. While 85.2% of patients did not develop any serious clinical events, 13 (3.6%) patients died, 37 (10.1%) patients developed organ failure, and 50 (13.7%) patients required ICU admission. The baseline characteristics of the patients are summarized in **Table 1**.

Table 1. Baseline characteristics of patients.

Variable	N (%)
All patients	364 (100)
Age, years, mean±SD	74.4±8.9
Female	208 (57.1)
Comorbidities	
Hypertension	275 (75.5)
Diabetes mellitus	107 (29.4)
Coronary artery disease	157 (43.1)
Dysrhythmia	70 (19.2)
Chronic lung disease	93 (25.5)
Cerebrovascular disease	51 (14.0)
Chronic kidney disease	25 (6.9)
Chronic liver disease	6 (1.6)
Malignant diseases	16 (4.4)
Length of hospital stay, days, median (min-max)	6 (2-105)
Prolonged hospital stay, ≥10 days	79 (21.7)
Necrotizing pancreatitis	13 (3.6)
Severity	
Mild	243 (66.8)
Moderately severe	92 (25.3)
Severe	29 (8.0)
Complications	
None	244 (67.7)
Local complication	106 (29,1)
Systemic complications	32 (8.8)
Peripancreatic vascular complications	
Splanchnic venous thrombosis	3 (0.8)
Pseudoaneurysm	0 (0.0)
Serious clinical event	
None	310 (85.2)
Mortality	13 (3.6)
Organ failure	
None	327 (89.8)
Transient, <48 hours	8 (2.2)
Persistent, >48 hours	29 (8.0)
ICU admission	50 (13.7)
Mean score (min-max)	
Ranson score	3.2 (0-8)
BISAP score	1.7 (1-5)
Glasgow score	2.6 (1-7)
APACHE II score	7.3 (3-21)

APFC, acute peripancreatic fluid collection; ANC, acute necrotic collection; WON, walled-off necrosis; ICU, intensive care unit.

Comparison of Ranson Score with Other Scores

The AUC values of the Ranson, BISAP, Glasgow, and APACHE II scores were 0.787 (95% CI: 0.649-0.925), 0.856 (95% CI: 0.784-0.929), 0.908 (95% CI: 0.854-0.961), and 0.836 (95% CI: 0.702-0.971) for mortality and 0.775 (95% CI: 0.674-0.876), 0.918 (95% CI: 0.879-0.958), 0.885 (95% CI: 0.827-0.943), and 0.879 (95% CI: 0.804-0.954) for severity, respectively. Although the AUC of the Ranson score for mortality was lower than those of the other scores, no significant difference was found in pairwise comparisons with the other 3 scores ($p > 0.05$ for all) (**Figure 2**).

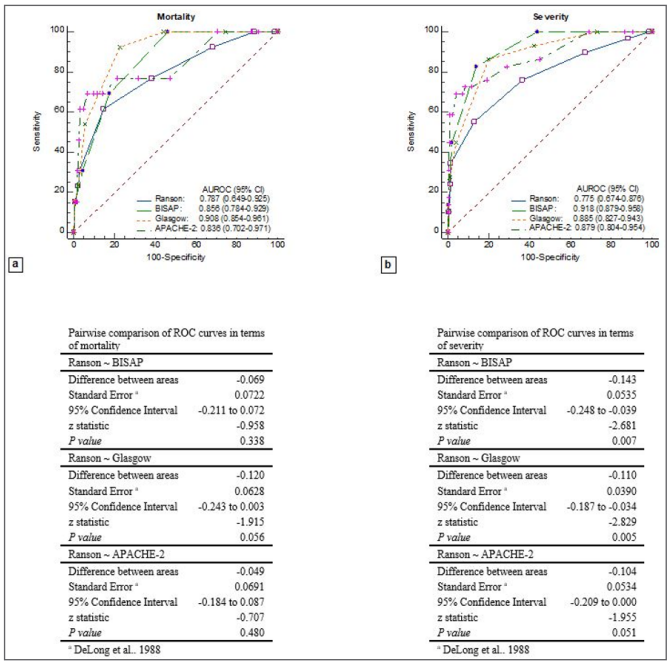

Figure 2. Comparison of the predictive value of Ranson score with other scores in terms of primary endpoints with ROC curve analysis. In terms of mortality, there was no significant difference between the AUROC values of Ranson and other scoring systems (a). For severity, the BISAP and Glasgow scores were significantly superior to the Ranson score (p=0.007 and p=0.005, respectively), while the APACHE II score was not significantly different from the Ranson score (p=0.051), but its AUROC value was higher (b). ROC, receiver operating characteristic; AUROC, area under the ROC curve; CI, confidence interval.

While the AUC values of the BISAP and Glasgow scores for severity were significantly higher than that of the Ranson score (p=0.007 and p=0.005, respectively), there was no significant difference between the Ranson and APACHE II scores (p=0.051) (**Figure 2**). When compared in terms of organ failure, complications, ICU admission, and prolonged hospital stay, which were determined as secondary endpoints, the AUC of the Ranson score was significantly lower than the AUC of the other 3 scores ($p < 0.05$ for all, except for the comparison with APACHE II for complications at p=0.228) (**Figure 3**).

When comparing the AUC values of the scores other than Ranson in terms of primary and secondary endpoints, no significant difference was found ($p > 0.05$ for all, except for the comparison of BISAP and APACHE II for complications at p=0.006). Pairwise comparisons of the AUC values of the scores are shown in **Table 2** and **Table 3**.

Predictive Values of the Scoring Systems

When the Ranson score was >4, sensitivity, specificity, PLR, and NLR were 61.5%, 85.5%, 4.23, and 0.45, respectively, for mortality and 55.2%, 87.2%, 4.29, and 0.51, respectively, for severity. The highest sensitivities for mortality and severity were obtained for the Glasgow score (93.2% and 86.2%, respectively), while the highest specificities were obtained for APACHE II (93.2% and 96.1%, respectively). The highest PLR values to accurately confirm mortality and severity were obtained for APACHE II (10.12 and 17.77, respectively), while the lowest NLR values to accurately exclude mortality and severity were obtained for the Glasgow score (0.09 and 0.17, respectively). Patients with Ranson scores of >4 had a 9.4-fold (OR: 9.4, 95% CI: 2.9-29.9) and 8.3-fold (OR: 8.3, 95% CI: 3.8-18.6) risk of mortality and severity, respectively, compared to those without. The highest risks for mortality and severity were 41.3-fold and 55-fold among those with Glasgow scores of >3 and APACHE II scores of >12, respectively (OR: 41.3, 95% CI: 5.3-322.6 and OR: 55.0, 95% CI: 21.0-144.1, respectively). The predictive values of the scores in terms of secondary endpoints are illustrated in **Table 4**.

Table 2. Predictive capabilities of scoring systems and comparison of predictive capability of Ranson score with other scores for 6 clinical outcomes

Outcome by scoring systems	AUROC (95% CI)	AUROC difference (95% CI)	z statistic	p value
Mortality				
Ranson (reference)	0.787 (0.649 to 0.925)	-	-	-
BISAP	0.856 (0.784 to 0.929)	-	-	-
Ranson vs. BISAP	-	-0.069 (-0.211 to 0.072)	-0.958	0.338
Glasgow	0.908 (0.854 to 0.961)			
Ranson vs. Glasgow	-	-0.120 (-0.243 to 0.003)	-1.915	0.056
APACHE II	0.836 (0.702 to 0.971)			
Ranson vs. APACHE II	-	-0.049 (-0.184 to 0.087)	-0.707	0.480
Severity				
Ranson (reference)	0.775 (0.674 to 0.876)	-	-	-
BISAP	0.918 (0.879 to 0.958)	-	-	-
Ranson vs. BISAP	-	-0.143 (-0.248 to -0.039)	-2.681	0.007
Glasgow	0.885 (0.827 to 0.943)			
Ranson vs. Glasgow	-	-0.110 (-0.187 to -0.034)	-2.829	0.005
APACHE II	0.879 (0.804 to 0.954)			
Ranson vs. APACHE II	-	-0.104 (-0.209 to 0.000)	-1.955	0.051
Organ failure				
Ranson (reference)	0.735 (0.635 to 0.834)	-	-	-
BISAP	0.904 (0.855 to 0.952)	-	-	-
Ranson vs. BISAP	-	-0.169 (-0.270 to -0.067)	-3.260	0.001
Glasgow	0.872 (0.821 to 0.923)			
Ranson vs. Glasgow	-	-0.137 (-0.212 to -0.063)	-3.614	<0.001
APACHE II	0.870 (0.799 to 0.940)			
Ranson vs. APACHE II	-	-0.135 (-0.235 to -0.035)	-2.651	0.008
Complications				
Ranson (reference)	0.563 (0.502 to 0.625)	-	-	-
BISAP	0.674 (0.616 to 0.732)	-	-	-
Ranson vs. BISAP	-	-0.111 (-0.180 to -0.041)	-3.124	0.002
Glasgow	0.624 (0.561 to 0.688)			
Ranson vs. Glasgow	-	-0.061 (-0.117 to -0.005)	-2.138	0.033
APACHE II	0.602 (0.538 to 0.666)			
Ranson vs. APACHE II	-	-0.039 (-0.102 to 0.024)	-1.206	0.228
ICU admission				
Ranson (reference)	0.739 (0.661 to 0.817)	-	-	-
BISAP	0.854 (0.797 to 0.911)	-	-	-
Ranson vs. BISAP	-	-0.115 (-0.206 to -0.024)	-2.474	0.013
Glasgow	0.824 (0.759 to 0.889)			
Ranson vs. Glasgow	-	-0.085 (-0.160 to -0.010)	-2.219	0.026
APACHE II	0.825 (0.759 to 0.892)			
Ranson vs. APACHE II	-	-0.086 (-0.169 to -0.003)	-2.038	0.042
Prolonged hospital stay (≥10 days)				
Ranson (reference)	0.513 (0.438 to 0.588)	-	-	-
BISAP	0.657 (0.589 to 0.725)	-	-	-
Ranson vs. BISAP	-	-0.144 (-0.226 to -0.062)	-3.446	0.001
Glasgow	0.595 (0.523 to 0.666)			
Ranson vs. Glasgow	-	-0.082 (-0.146 to -0.017)	-2.478	0.013
APACHE II	0.628 (0.556 to 0.700)			
Ranson vs. APACHE II	-	-0.115 (-0.190 to -0.040)	-3.003	0.003

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ICU, intensive care unit.

Table 3. Pairwise comparison of ROC curves* in terms of clinical outcomes of the 3 scoring systems other than Ranson

Outcome by scoring systems	BISAP	Glasgow	APACHE II
Mortality			
BISAP	-	0.253	0.665
Glasgow	0.253	-	0.278
APACHE II	0.665	0.278	-
Severity			
BISAP	-	0.339	0.139
Glasgow	0.339	-	0.894
APACHE II	0.139	0.894	-
Organ failure			
BISAP	-	0.334	0.153
Glasgow	0.334	-	0.960
APACHE II	0.153	0.960	-
Complication			
BISAP	-	0.134	0.006
Glasgow	0.134	-	0.483
APACHE II	0.006	0.483	-
ICU admission			
BISAP	-	0.394	0.336
Glasgow	0.394	-	0.972
APACHE II	0.336	0.972	-
Prolonged hospital stay			
BISAP	-	0.051	0.287
Glasgow	0.051	-	0.319
APACHE II	0.287	0.319	-

*The values in the table are the p values showing the significance of pairwise comparisons of the ROC curves of the scoring systems. ICU, intensive care unit.

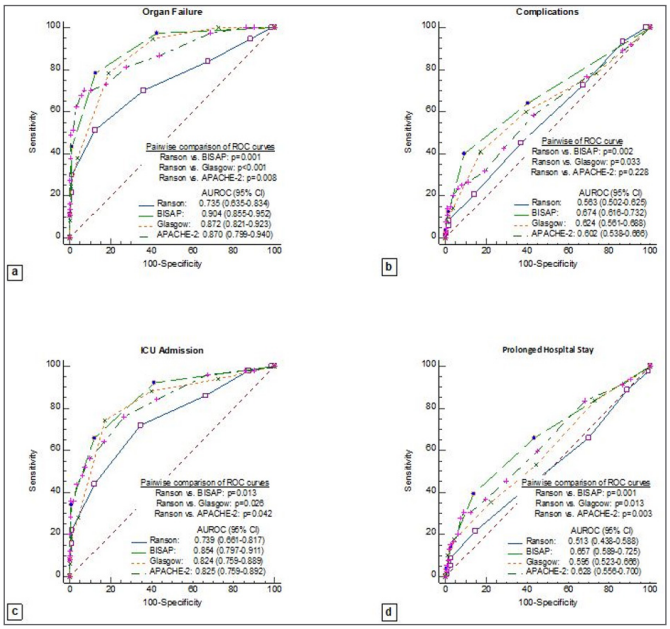

Figure 3. AUROC values of the 4 scoring systems for secondary endpoints and pairwise comparison of these values: (3a) for organ failure, (3b) for complications, (3c) for ICU admission, and (3d) for prolonged hospital stay (≥10 days). The predictive ability of the Ranson score for all 4 clinical outcomes (except when compared to APACHE II for complications) was significantly lower than those of the other scores. AUROC, area under the receiver operating characteristic curve; CI, confidence interval; ICU, intensive care unit.

Table 4. The predictive values of the scores in terms of secondary endpoints

Outcome by scoring systems	Cut-off points	No. (%) of patients over the cut-off	OR (95% CI)	Sensitivity (%)	Specificity (%)	PLR	NLR
Primary endpoints							
Mortality							
Ranson	>4	59 (16.2)	9.4 (2.9-29.9)	61.5	85.5	4.23	0.45
BISAP	>2	70 (19.2)	10.6 (3.2-35.9)	69.2	82.6	3.98	0.37
Glasgow	>3	91 (25.0)	41.3 (5.3-322.6)	92.3	77.5	4.10	0.09
APACHE II	>12	33 (9.0)	30.6 (8.8-106.8)	69.2	93.2	10.12	0.33
Severity							
Ranson	>4	59 (16.2)	8.3 (3.8-18.6)	55.2	87.2	4.29	0.51
BISAP	>2	70 (19.2)	30.1 (10.9-83.0)	82.8	86.3	6.02	0.19
Glasgow	>3	91 (25.0)	25.4 (8.5-75.7)	86.2	80.3	4.37	0.17
APACHE II	>12	33 (9.0)	55.0 (21.0-144.1)	69.0	96.1	17.77	0.32
Secondary endpoints							
Organ failure							
Ranson	>4	59 (16.2)	7.5 (3.6-15.6)	51.4	87.8	4.19	0.55
BISAP	>2	70 (19.2)	25.2 (10.8-59.0)	78.4	87.5	6.25	0.24
Glasgow	>3	91 (25.0)	15.5 (6.7-35.5)	78.4	81.0	4.13	0.26
APACHE II	>10	49 (13.4)	31.2 (13.7-71.1)	70.3	93.0	9.99	0.31
Complications							
Ranson	>3	144 (39.5)	1.4 (0.9-2.2)	45.0	63.1	1.22	0.87
BISAP	>2	70 (19.2)	6.7 (3.8-11.9)	40.0	91.0	4.43	0.65
Glasgow	>3	91 (25.0)	3.3 (2.0-5.4)	40.8	82.8	2.37	0.71
APACHE II	>10	49 (13.4)	3.9 (2.1-7.3)	25.0	92.2	3.21	0.81
ICU admission							
Ranson	>3	144 (39.5)	4.9 (2.5-9.4)	72.0	65.6	2.09	0.42
BISAP	>2	70 (19.2)	14.5 (7.3-28.6)	66.0	88.2	5.60	0.38
Glasgow	>3	91 (25.0)	13.7 (6.8-27.5)	74.0	82.8	4.30	0.31
APACHE II	>7	120 (32.9)	8.9 (4.4-17.9)	76.0	73.9	2.91	0.32
Prolonged hospital stay							
Ranson	>4	59 (16.2)	1.5 (0.8-2.9)	21.5	85.3	1.46	0.92
BISAP	>2	70 (19.2)	4.0 (2.3-7.1)	39.2	86.3	2.86	0.70
Glasgow	>4	26 (7.1)	4.9 (2.1-11.0)	17.7	95.8	4.20	0.85
APACHE II	>10	49 (13.4)	4.5 (2.4-8.5)	30.4	91.2	3.46	0.76

OR, odds ratio; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; ICU, intensive care unit.

DISCUSSION

The ROC curve analysis showed that the Ranson scoring system was inferior to the other considered scoring systems in predicting mortality in older adults AP patients. The BISAP and Glasgow scores were similar and superior to the Ranson score in predicting disease severity. The BISAP, Glasgow, and APACHE II scores were superior to the Ranson score in predicting organ failure, complications, ICU admission, and prolonged hospital stay.

With the increasing world population and increased life expectancy, AP has become more common in the older adults population (21). The few relevant studies available in the literature have shown that older adults patients with AP usually present with a more severe clinical picture with higher rates of permanent organ failure, pancreatic necrosis, and mortality (22-26). In a recent single-center study (27) and a study on the predictors of severity of AP in the older adults population (28), progression to severe disease was significantly more common in older adults patients. We also found similar results regarding progression to severe AP.

The Ranson score is the first scoring system used to evaluate biliary and non-biliary AP and it requires a timeframe of 48 hours for a complete score (15). Generally, a Ranson score of 3 or higher is required to diagnose severe AP. One study compared the Ranson, BISAP, APACHE II, and CTSI scores and found that the Ranson score's AUC values for predicting disease severity, pancreatic necrosis, and mortality were superior to those of the BISAP and APACHE II systems and that all patients who died had a Ranson score of ≥3 (29). Another study similarly compared Ranson, BISAP, Glasgow, and APACHE II scores and demonstrated that the Ranson score's AUC values for predicting disease severity and mortality were lower compared to BISAP and Glasgow scores in older adults patients. However, in younger patients, the Ranson score was superior to the other scoring systems in predicting disease severity and was superior to BISAP and APACHE II in predicting mortality (30). In the first of these studies, conducted by Ranson and Pasternack, biliary pancreatitis accounted for 36% of all cases of AP, whereas in the second study, biliary pancreatitis accounted for 75% of all cases among older adults patients and 51.5% of cases among younger patients with AP. Ranson and his colleagues reported the rate of biliary pancreatitis to be 14% in 1974 and 17% in 1977 (15,31). These findings suggest that the Ranson scoring system is less effective in older adults patients with biliary pancreatitis. We also found that the Ranson scoring system was less clinically useful in older adults patients with biliary pancreatitis.

The Glasgow scoring system employs parameters similar to those of the Ranson score as well as objective clinical evaluations and similarly requires 48 hours of follow-up (16). The APACHE II score was developed mainly for the assessment of ICU patients and has been used for the assessment of AP since 1989 (17,18). The BISAP is a more recent scoring system aimed at early detection of patients at risk for in-hospital mortality (11,18), and recent prospective clinical studies have shown it to be reliable in the evaluation of patients with AP (11). A recent study by Li et al. (30) revealed that the BISAP score is valid for predicting disease severity, pancreatic necrosis, and mortality in older adults patients, whereas the APACHE II score is more suitable for younger patients. In our study, we compared the BISAP, Glasgow, and APACHE II scores and found that BISAP and APACHE II were significantly different only in the prediction of complications, and the 3 scoring systems were not significantly superior to one another in terms of the remaining parameters. In reference to these results, besides etiology, we think that the relatively poor efficacy of the Ranson score in older adults patients may be attributed to the high prevalence of comorbidities in this population. The follow-up periods required by the scoring systems are a disadvantage in estimating severity and mortality in older adults patients with comorbidities, and parameters that are not related to AP interfere with the assessment of this disease.

The main limitation of our study is its retrospective design, which limits our access to the findings.

CONCLUSION

In conclusion, compared to the other scoring systems, the Ranson scoring system was less useful in predicting disease severity, organ failure, disease-related complications, admission to the ICU, and mortality in older adults patients with biliary pancreatitis. Further prospective studies with larger samples are needed to apply our results in clinical practice..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee No. 2 (Date: 14.07.2021, Decision No: E2-21-716).

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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Original Article

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The effect of body satisfaction on female sexual life after bariatric surgery: a follow-up study

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ABSTRACT

Aim: Discomfort with body shape is common among individuals with obesity and has effects on their sexual life. We aimed to investigate the effects of bariatric surgery on the body satisfaction and sexual life of women in this study.

Material and Method: The study consisted of 63 female patients who were aged between 20 and 55. Pre-operative psychiatric evaluations of the candidates were conducted and Hamilton Anxiety Scale , Hamilton Depression Scale, Arizona Sexual Experiences Questionnaire and Body Shape Questionnaire were used. Psychiatric evaluations of the patients were re-evaluated in the first year after surgery.

Results: The mean age was 35.4±8.6 years. While 87.3% of the participants had moderate-severe anxiety about the appearance of their bodies before the operation, 57.1% described problems in their sexual life. After the operation, 63.5% of the participants stated that they did not have any concerns about their body appearance, and 73% stated that they did not have any problems in their sexual life. The BSQ-34 scale score was found to be higher in those with an Arizona score of 11 and above before the operation ($p=0.045$; $p<0.05$). The results of the correlation analysis indicated that a positive ($r=0.257$) correlation was found between the pre-operative ASEX score and the BSQ34 scale score ($p<0.05$). The positive correlation between ASEX and BSQ34 scale score was also observed after the operation ($p<0.05$).

Conclusion: Our study showed that body dissatisfaction caused by obesity negatively affected sexual life and that increased satisfaction after bariatric surgery made positive contributions to sexual life.

Keywords: Sexual life, body satisfaction, bariatric surgery

INTRODUCTION

Obesity is an important public health problem that is increasing in prevalence all over the world and that reduces the quality of life. In addition to physical diseases, such as diabetes, hypertension, or respiratory system diseases, many psychiatric diseases such as depression, anxiety, sleep disorders, and sexual dysfunctions also impair the psychosocial functionality of individuals with obesity (1,2). From a sexual life point of view, which is an important area in people's lives, it is thought that conditions such as deterioration in body appearance, decrease in physical activity capacity, and decrease in the level of sex hormones in individuals with obesity may affect sexual life negatively (3,4). It has also been shown that obesity negatively affects sexual function by causing the person to feel ugly and dissatisfied with body image (5,6). Body image disorders accompanying obesity can contribute to the development of anxiety, depression, and low self-esteem and cause them to make negative evaluations about sexuality. In the literature, it has been reported that 56% of the women with obesity do not have a regular and satisfying sexual life and that more importantly, 23% avoid sex (7).

Although options to aid weight loss such as diet, pharmacotherapy, and exercise are recommended in the treatment of obesity, the results may not be satisfactory, especially in patients with morbid obesity. For this reason, bariatric surgery has been used as an effective method for weight loss in recent years (8). In addition to an average of 61.2% of body weight loss with this method, it has been shown that losing weight reduces all kinds of mortality and increases the quality of life in the long term (9). Many studies have shown that bariatric surgery also contributes to weight loss, sexual function, and quality of life. Changes in sex

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hormone levels and a decrease in depressive complaints are considered just two of the conditions that improve sexual life in both genders (10-13). On the contrary, there are studies indicating that rapid weight loss may have negative effects on sexuality and that the sexual life of people with excess skin after surgery is negatively affected (14).

Considering the literature, we can see that the effects of surgical techniques on sex hormones and sexual life are frequently studied. However, the scarcity of studies on body satisfaction, which is an important area, and its effect on sexuality, and the accompanying conflicting results draw attention. Considering the more frequency of female patients than male patients who presented to the surgery department, our study was planned to evaluate the contribution of bariatric surgery to sexuality in female patients through body image and satisfaction.

MATERIAL AND METHOD

The study was carried out with the permission of Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.04.2021, Decision No: 2021-105). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Sexually active female patients who were aged between 20 and 55 and presented to the general surgery outpatient clinic for bariatric surgery between 2020 and 2021 were included in the study. Women with a history of menstrual irregularity were not included in the study. Sixty-five female patients were selected among these patients by using the random sampling method. Psychiatric evaluations of the candidates were done before the surgery by a clinician and written consent was obtained from those who did not have psychopathology preventing the surgery. The participants were applied a socio-demographic data form, which was created by the researchers, the Hamilton Anxiety Scale (HAMA), the Hamilton Depression Scale (HAMD), the Arizona Sexual Experiences Questionnaire-Female Form, and the Body Shape Questionnaire (BSQ-34). Psychiatric evaluations of the patients were done for a second time in the first year after surgery. Two of the participants could not be reached, and therefore the scales were re-administered to 63 female patients.

The Socio-demographic Data Form

This form, which was prepared by the researcher, included questions about the participants' background and medical information, such as age, gender, marital status, height/weight, previous psychiatric illness, chronic illness, and the medications used.

The Hamilton Depression Scale (HAMD)

The Hamilton Depression Scale (HAM-D) was published by Max Hamilton in 1960 (15). It consists of 17 items that question the symptoms of depression in the past week. The highest score is 53. The scores are interpreted as follows: 0-7, no depression; 8-13, mild depression; 14-18, moderate depression; 19-22, severe depression; 23 and above severe depression. The Turkish validity and reliability study of the scale was carried out by Akdemir et al. (16)

The Hamilton Anxiety Scale (HAMA)

This scale (HAM-A) was developed by Hamilton in 1959 to determine the severity of anxiety (17). It consists of 14 items that evaluate the physical and psychic symptoms of anxiety. The evaluation is done between 0 and 4 points according to the severity of symptoms. The total score from the scale is interpreted as follows: 0-5, normal; 6-14, mild; 15 and above, severe anxiety. The Turkish reliability and validity study was carried out by Yazıcı et al. (18).

The Arizona Sexual Experiences Scale (ASEX)

The ASEX scale was developed in 2000 by McGahuey, Gelenberg, Laukes, Moreno, and Delgoda to evaluate disorders in sexual functions. It is a Likert-type evaluation scale consisting of five questions and separate forms for males and females. Each question is scored from 1 to 6 and a maximum of 30 points can be obtained. Low scores indicate a satisfying sexual response, while high scores indicate the presence of sexual dysfunction. In the validity and reliability study of the scale for Turkey, Cronbach's alpha values of internal consistency and reliability were found as 0.89 and 0.90, respectively, and its validity in distinguishing sexual dysfunction was proven (19) . In their study, the cut-off value was found as 11, and in our study, it was evaluated that those who got 11 and above from the scale had sexual problems.

The Body Shape Questionnaire (BSQ-34)

The BSQ-34 questionnaire was developed by Cooper and Taylor in 1987 to measure body shape concerns among women (20). The survey consists of 34 questions, each of which is scored between 1 and 6, and the highest score that can be obtained is 204. It shows that the higher the score obtained is, the higher the body dissatisfaction of the person is. The validity and reliability study of the Turkish version was carried out by Akdemir in 2012. The test-retest reliability result of the questionnaire that was adapted to our country was found to be r=0.81, Cronbach's alpha value for internal consistency was 0.96, and the reliability coefficient value was 0.88(21) . People under 80 points considered as not anxious about body shape, 80-110 slightly, 111-140 moderately and above 140 points thinks severely anxiety about body shape.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 25.0 software package was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation values (median and minimum-maximum where necessary). Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Mann-Whitney U test was used for the parameters that did not show a normal distribution. Wilcoxon signed ranks test was used to examine the differences between the pre-operative and post-operative values of the scale scores. Spearman's Rho test was used to analyze the correlations between the scales. In all tests, the statistical significance level was taken as 0.05.

RESULTS

A total of 63 female patients participated in the study, and the mean age was 35.4±8.6 years. While 90.5% of the participants were not diagnosed with any psychiatric diseases, 6 were using pharmacotherapy due to a diagnosis of anxiety disorder and were in remission under medication. The BMI value was determined as 44.3±3.6 before the operation. While 87.3% of the participants had moderate-to-severe concerns about the appearance of their bodies before the operation, 57.1% described problems in the sexual area. After the operation, 63.5% of the individuals stated that they did not have any concerns about their body appearance, and 73% stated that they did not have any problems in their sexual life (**Table 1**). While 2 of our patients had a mild level of anxiety about their body shape before the operation, it increased to a moderate level after the operation. At the same time, these 2 patients stated that although they did not have a sexual problem before the operation, they had problems in the sexual area after the operation.

Considering the mean scale scores of the patients, the post-operative BMI (p<0.001) values and the HAMA (p<0.001), HAMD (p<0.001), BSQ34 (p<0.001), and ASEX (p<0.001) scale scores were lower than the pre-operative values (p<0.05) (**Table 2**). When the groups were analyzed as two groups in terms of defining and not defining sexual problems, it was found that those with an Arizona score of 11 and above pre-operatively had a higher BSQ34 score (p=0.045; p<0.05). The HAMA scale scores were found to be higher in patients with an Arizona score of 11 and above post-operatively (p=0.014; p<0.05) (**Table 3**).

Table 1. Distribution of participants according to pre- and post-operative scale scores

	Frequency (n)	Percentage (%)
Pre-op BSQ34		
No worries at all	1	1.6
Slightly	7	11.1
Moderately	36	57.1
Severely	19	30.2
Pre-op ASEX		
<11	27	42.9
>11	36	57.1
Post-op BSQ34		
No worries	40	63.5
Slightly	21	33.3
Moderately	2	3.2
Severely	-	-
Post-op ASEX		
<11	46	73.0
>11	17	27.0

Table 2. Comparison of the pre-and post-operative scale scores

	Pre- operative	Post- operative	p
	Mean±sd	Mean±sd	
BMI	44.3±3.6	30.6±3.4	<0.001**
HAM-A	5.0±4.8	2.3±2.8	<0.001**
HAM-D	3.96±3.5	1.86±2.1	<0.001**
BSQ34	129.2±19.7	81.9±13.3	<0.001**
ASEX	12.5±5.3	8.3±4.1	<0.001**

* p<0,05, **p<0,001, Wilcoxon signed ranks test, BMI: Body mass index
HAM-A: Hamilton anxiety scale, HAM-D: Hamilton depression scale
BSQ34: Body shape questionnaire, ASEX: The Arizona sexual experiences scale

Table 3. Evaluation of the scale scores of the groups according to the ASEX score

	Pre-operative Arizona			Post- operative Arizona		
	<11	>11	p	<11	>11	p
BMI	45.4±4.6	43.4±2.3	0.214	30.9±3.7	29.9±2.2	0.525
HAMA	4.63±5.6	5.33±4.1	0.303	1.69±2.4	3.82±3.2	0.014*
HAMD	3.11±3.1	4.61±3.7	0.098	1.47±1.7	2.88±2.7	0.063
BSQ34	124.1±7.1	133.1±20.9	0.045*	79.6±10.8	88.2±17.3	0.107

* p<0,05, **p<0,001, Mann-Whitney U test, BMI: Body mass index, HAM-A: Hamilton anxiety scale, HAM-D: Hamilton depression scale, BSQ34: Body shape questionnaire

When the results of the correlation analysis were examined, a positive (r=0.257) correlation was found between the pre-operative ASEX score and the BSQ34 scale score (p<0.05). It was observed that the positive correlation between ASEX and BSQ34 scale score continued after the operation (p<0.05) (**Table 4**).

Table 4. Correlation between ASEX scores and BMI and other scales

	Pre-operative ASEX		Post- operative ASEX	
	r	p	r	p
BMI	-0.098	0.444	-0.166	0.194
HAMA	0.208	0.102	0.324**	0.009
HAMD	0.135	0.292	0.349**	0.005
BSQ34	0.257*	0.042	0.297*	0.018

* p<0,05, **p<0,001, Spearman's rho test, BMI: Body mass index, HAM-A: Hamilton anxiety scale, HAM-D: Hamilton depression scale, BSQ34: Body shape questionnaire

There was a moderate positive correlation between the pre-operative BSQ34 scale score and the HAMA (r=0.340) and HAMD (r=0.371) scale scores (p<0.05) (**Table 5**).

Table 5. Correlation between BSQ-34 and other scale scores

	Pre- operative BSQ34		Post-operative BSQ34	
	r	p	r	p
BMI	-0.091	0.480	-0.216	0.089
HAMA	0.340**	0.006	-0.194	0.128
HAMD	0.371**	0.003	-0.092	0.475
ASEX	0.257*	0.042	0.297*	0.018

* p<0,05, **p<0,001, Spearman's rho test, BMI: Body mass index, HAM-A: Hamilton anxiety scale, HAM-D: Hamilton depression scale, ASEX: The Arizona sexual experiences scale

DISCUSSION

In addition to weight loss, the main purpose of obesity treatment is to reduce obesity-related morbidity and mortality. Studies have shown that as dissatisfaction with body image increases, depressive symptoms also increase, and quality of life decreases, and it is also associated with a decrease in the individual's self-esteem (22). Considering studies on body image in individuals with obesity, it is seen that BMI has a significant effect on body dissatisfaction, and comparison of obese groups with non-obese groups causes more body dissatisfaction in these individuals (23). In addition, body dissatisfaction has been found to be higher in surgical candidates than in individuals with obesity treated with non-surgical methods (24). In a study, 73% of the surgical candidates stated that they were not satisfied with their bodies (25). Similarly, in our study, the rate of worrying about one's body was found to be moderate and severe at a rate of 87%, and the level of dissatisfaction was correlated with anxiety and depression scores. After surgery, approximately 63% of the patients stated that they were not worried about their bodies, and a significant decrease was found in their BSQ-34 scores. Two of our patients who had mild anxiety before the operation stated that their problems both in body shape and in the area of sexual life increased after the operation. Mento et al. (26) stated in their review that there was no change in the body image of people after surgery and that the discomfort felt from excess weight and negative body image before surgery was replaced by discomfort from excessive skin sagging after surgery. For this reason, it is thought that further studies are needed to evaluate other factors which include excess skin and cause individuals to maintain their negative perceptions.

It is also reported in studies that a significant part of the quality of life of individuals is related to sexual health and that there is a decrease in sexual satisfaction due to obesity. Women with obesity reported significant impairment in most areas of sexual function, including sexual desire, arousal, lubrication, orgasm, and satisfaction compared to healthy controls. Although the observed sexual dysfunction was associated with BMI, it was not completely attributed to the presence of anxiety or depression (27). This suggested that apart from physiological changes (especially the change in sex hormone levels), other psychological factors such as body image and body satisfaction that would affect sexual function were also important. In our study, this rate was 57%, and more than half of the patients complained about sexual dysfunction. When the participants were divided into two groups with and without sexual dysfunction, there was no significant difference in anxiety and depression scores. However, it was observed that body image concerns were significantly higher in the group that had sexual dysfunction compared to the group that did not. This finding was evaluated as supportive of the study by Çaynak et al. (28), which showed that body image had a significant effect on sexual life.

In a 1-year post-operative follow-up study examining the effect of bariatric surgery, significant reductions in depression and sexual pain levels and significant improvements in sexual desire, arousal, lubrication, and total sexual function scores were reported (12). In our study, 73% of the people stated after surgery that there was no problem in their sexual life. In their study, Mariano et al. (29) reported a decrease in physical and emotional difficulties, improvement in sexual functions, and an increase in the frequency of sexual practice after surgical treatment.

One of the important findings of our study was that the positive relationship we found between body satisfaction and sexual life in the pre-operative evaluation remained significant in the post-operative period, as well. In the literature, an increase in body shape satisfaction has been reported in those who have undergone weight loss surgery(30). In the review by Ivezaj and Grilo, research on body image, perception, and satisfaction after bariatric surgery was systematically reviewed, and findings from both cross-sectional and longitudinal studies showed overall improvements in body image following bariatric surgery. In addition, it has been reported that eating pathologies such as binge eating and night eating seem to be associated with greater post-operative body image dissatisfaction(31). Although studies on sexual life and body dissatisfaction are relatively few, it is also known that areas, such as sexual relationships, marital satisfaction, and social functionality, were positively affected by weight loss and improvement in body image(32). In this sense, our study supports that the body satisfaction of individuals is an important factor in terms of sexuality and sexual experiences.

However, although patients are generally more satisfied with their post-operative body shape, it is not clear how much their new body shape differs from what they idealize. Wee et al. (33) reported that 91% of morbidly obese participants who were candidates for bariatric surgery were willing to have the operation to reach their "dream weight" even if there was a risk of death. Munoz et al. (34), on the other hand, reported that unrealistic expectations of "idealized body shape" occur as a result of rapid weight loss in the early post-operative period. Gaudrat et al. (35) stated body satisfaction in the first year after the operation as the main factor predicting surgical satisfaction. Hult et al. (36), on the other hand, associated increased self-esteem after surgery with surgical satisfaction. However, in this study, the fact that body satisfaction and sexual dysfunctions were not explicitly questioned suggested that these two issues could be evaluated within weight loss, increased close relationship with the partner, and self-esteem among the participants.

Limitations of the Study

There are some limitations of our study. The inclusion of only female patients in our study prevents its generalization to the population; therefore, further studies including male patients are needed. In addition, the fact that the results of the study were obtained in a relatively short follow-up (12-month results) and that the subtitles of sexual experiences were not evaluated in detail were also considered as limitations.

CONCLUSION

Our study shows that there is a relationship between body satisfaction and sexual quality of life both pre-operatively and post-operatively and that bariatric surgery has a positive contribution to both areas. We need further studies to evaluate the possible mediator role of body satisfaction on sexual life.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee (Date: 14.04.2021, Decision No: 2021-105).

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.

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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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Original Article

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Correlation of the transcutaneous bilirubin and serum bilirubin levels measured before and after phototherapy in newborns: a prospective observational study

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ABSTRACT

Aim: The purpose of the present study was to show the reliability of the transcutaneous bilirubin (TcB) measurement as an alternative method to total serum bilirubin (TSB) when starting treatment with phototherapy (PT), which is one of the most important treatment methods of hyperbilirubinemia as a very common practice in the neonatal period and eliminates the disadvantages of blood collection.

Materyal and Method: Two measurements were made to evaluate whether there was a correlation between the total serum bilirubin and transcutaneous bilirubin level measurement for follow-up in newborns who were hospitalized and prospectively followed up in the Newborn Intensive Care Unit of Karabuk University Medical Faculty Training and Research Hospital between April 13 and June 30, 2022 (Level III Neonatal Center) who were scheduled for starting phototherapy. The primary result was the correlation between TcB and TSB at the first 24 hours and after, at the initiation of FT, termination of FT, and 12 hours after PT was discontinued.

Results: The TSB and TcB values of the newborns were measured at the beginning of PT, at the end of PT, and 12 hours after PT was ended. The first measurement values were 11.60±5.16 and 10.72±4.02, respectively; the second measurement values were 7.45±2.34 and 6.35±2.83, respectively; and the third measurement values were 8.03±2.45 and 7.35±2.63 mg/dL, respectively. A strong positive correlation was found among all measurement values. Also, when the newborns who received FT for the first 24 hours were evaluated by subgrouping, the high correlation between TcB and TSB levels continued.

Conclusion: The present study showed that there is a significant relationship between TcB taken from the covered skin and TSB at the start, end, and 12 hours after PT. Also, when the newborns who received PT for the first 24 hours were evaluated in a subgroup, it was found that TCB measurement predicted the TSB level at a high level before and after PT. Based on these findings, it was concluded that TcB measurement, including in the first 24 hours, is reliable in the follow-up of newborns receiving PT for the treatment of hyperbilirubinemia. However, we think that larger prospective controlled studies are required in this respect.

Keywords: Newborn, bilirubin, phototherapy

INTRODUCTION

Hyperbilirubinemia in newborns is very common (50-80%) in the first week of life (1). Although hyperbilirubinemia has a benign progression most of the time, it can result in serious neurological morbidities when it reaches high levels (2,3).

Phototherapy (PT) is considered a safe and effective treatment for the treatment of indirect hyperbilirubinemia in the neonatal period. The indication for starting treatment depends on the serum bilirubin levels, whether there are risk factors, pregnancy, and postnatal age.

Total serum bilirubin (TSB) measurement is considered the gold standard for monitoring bilirubin levels during and after PT. However, blood collection is painful, time-consuming, and increases the risk of infection (4). The transcutaneous bilirubinometry device works by directing light to the skin of the baby and measuring and analyzing the intensity of the returning wavelengths to predict TSB (5).

Transcutaneous bilirubin (TcB) measurement is recommended as a non-invasive test to predict bilirubin levels before the onset of PT in term and late-preterm newborns (6-8).

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Canadian Academy of Pediatrics recommends that the TcB and TSB and bilirubin levels of all newborns are measured at 24-72nd hours after birth (before the discharge from hospital) (9).

National Institute for Health and Care Excellence (NICE) Guidelines recommend TcB measurement in >35-week and >24-hour well-born newborns, or TSB measurement when this is not possible (10).

In some studies, although the use of TcB during and after PT was found to be beneficial in newborns, especially when measured on the covered skin, some studies report opposite results (11,12).

The present study was designed to examine the accuracy of TcB measured in the covered skin in estimating the TSB levels in newborns undergoing PT and starting PT within the first 24 hours, which are two controversial issues.

MATERIAL AND METHOD

The study was carried out with the permission of Karabük University Faculty of Medicine Noninvasive Clinical Researches Ethics Committee (Date: 13.04.2022, Decision No: 2022/859). The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Written informed consent was obtained from the parents.

The present study is a single-center, observational cohort study that was conducted on newborns who were prospectively hospitalized and followed up in the Neonatal Intensive Care Unit of Karabuk University Medical Faculty Training and Research Hospital (Level III Neonatal Center) between April 13, 2022, and June 30, 2022. All newborns who received PT treatment during the study and whose parents gave consent were enrolled in the study.

PT was initiated based on TSB levels according to the guidelines and by considering the gestational weeks, risk factors, and ages in hours of the infants.

In line with the recommendations of the Turkish Neonatology Association, the curves that included the gestational week (GW) and risk factors in newborns with a gestational age above 35 weeks and the tables that were prepared according to birth weights were used for newborns younger than 35 GW (13,14).

LED PT Units (Overhead PT light units capable of delivering 180 UW/cm2, Ertunç Özcan Medical Devices, Turkey) were used in the study. The eyes of the newborns who received PT were covered with PT glasses for protection. Disposable diapers were used to protect the genital area. When TSB fell below the relevant treatment threshold, PT was discontinued.

TcB was measured from the covered area right after the collection of the TSB samples (in 10 minutes). The measurements were made by an assistant physician who was trained and experienced in the use of MBJ20 (Beijing M&B Electronic Instrument Co. Ltd. [Beijing, China]). The TcB device was lightly touched to a covered area (forehead area covered by the eye patch) three times, and the average of the three values was taken. The instrument was calibrated regularly according to the manufacturer's instructions.

The Neonatology Specialist managed the frequency of TSB measurements. Total and direct bilirubin levels were measured and direct hyperbilirubinemia was discarded in addition to routine biochemistry parameters. For the next TSB measurement, blood was taken from the heel by puncturing with a needle. TSB levels were measured in the laboratory by using direct spectrophotometry (Abbott Architect C8000, Abbott, USA).

The primary result was the correlation between TcB and TSB in the first 24 hours and beyond, at the initiation of PT (1st measurement), at the termination of PT (2nd measurement), and 12 hours after PT was discontinued (3rd measurement).

Data Analysis

Statistical analyzes of the study results were performed by using the SPSS 20 (SPSS, Chicago, United States) program. Sociodemographic data were evaluated as mean and percentage. Since the kurtosis and skewness values of the data were at the +2;-2 limit, it showed a normal distribution (George, 2011). The difference between bilirubin values was analyzed with the Paired Sample T-test, bilirubin values in bivariate groups were analyzed with the Independent Sample T-test, and the relationship between bilirubin values was evaluated with the Pearson's correlation. The Bland-Altman graphs were used in the analysis of the bias against the mean to assess the presence of a proportional bias (15).

RESULTS

The mean delivery week of the 48 newborns that were included in the study was 36.10±2.47 weeks, the birth weight was 2855.21±618.194 grams, and the mean time to start phototherapy was 53.98±53.5 hours. The 1st-minute Apgar score of the newborns was calculated as a median of 8 points, and the 5th-minute Apgar score was calculated as 9 points. The TSB and TcB values of the newborns were evaluated in three rebound measurements at the beginning of PT, at the end of PT, and 12 hours after PT was ended. The first measurement values were 11.60±5.16; 10.72±4.02, respectively; the second measurement values were 7.45±2.34, 6.35±2.83 respectively; and the third measurement values were 8.03±2.45, 7.35±2.63 mg/dL, respectively (**Table 1**).

It was found that there was ABO incompatibility in 20.8% of newborns, Rh incompatibility in 10.4%, sepsis in 4.2%, perinatal asphyxia in 6.3%, cephalic hematoma in 2.1%, polycythemia 8.3%, and chorioamnionitis 4.2% (**Table 1**).

Table 1. Clinical characteristics of newborns

Characteristics	Mean±SD	Min-Max (Median)
Birth week	36.10±2.47	31-42 (36)
Birth weight	2855.21±618.194	1860-4510 (2830)
Phototherapy start time	53.98±53.5	3-222 (33.50)
Apgar score in the 1st minute		2-10 (8)
Apgar score in the 5th minute		4-10 (9)
Neonatal bilirubin 1	11.60±5.16	3.8-23.2 (11.3)
Transcutaneous bilirubin 1	10.72±4.02	3.10-19.80 (11.2)
Neonatal bilirubin 2	7.45±2.34	2.4-11.6 (7.4)
Transcutaneous bilirubin 2	6.35±2.83	1.3-13.6 (6.15)
Neonatal bilirubin 3	8.03±2.45	3-14 (7.9)
Transcutaneous bilirubin 3	7.35±2.63	3.4-24.5 (7.2)
	n	**%**
Presence of ABO incompatibility		
Yes	10	20.8
No	38	79.2
Presence of Rh incompatibility		
Yes	5	10.4
No	43	89.6
Presence of sepsis		
Yes	2	4.2
No	46	95.8
Presence of perinatal asphyxia		
Yes	3	6.3
No	45	93.8
Presence of cephalic hematoma		
Yes	1	2.1
No	47	97.9
Presence of polycythemia		
Yes	4	8.3
No	44	91.7
Presence of chorioamnionitis		
Yes	2	4.2
No	46	95.8
Total	48	100

The TSB and TcB values of the newborns at three different times are analyzed in **Table 2.** As a result of the analysis, significant differences were detected between TSB and TcB transcutaneous bilirubin values in each measurement ($p<0.001$). However, it was also found that there was a strong positive correlation among all measurement values.

To compare TSB and TcB values, firstly, the Bland-Altman method was applied to the related dataset by using the MedCalc program, and the graphs of the deviations of the observation values from the mean values were obtained as in **Figures 1-3.**

Table 2. Descriptive statistics of neonatal and transcutaneous bilirubin values of all newborns receiving PT

	TSB	TcB	Difference	p*	r**
1st measurement	11.60±5.16	10.72±4.02	0.88±2.14	0.000	0.921***
2nd measurement	7.45±2.34	6.35±2.83	1.1±1.98	0.000	0.724***
3rd measurement	8.03±2.45	7.35±2.63	0.67±1.51	0.000	0.837***

*Paired Samples T-test, **Pearson's correlation, ***Significant at 0.001.

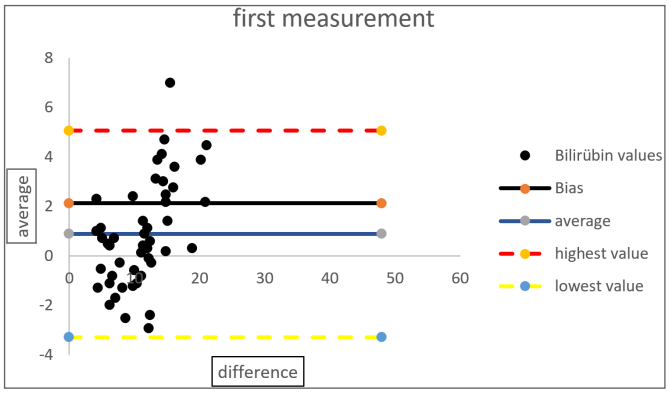

Figure 1. Paired graph of the difference between neonatal and transcutaneous bilirubin values in the first measurement (Bland-Altman plots graph).

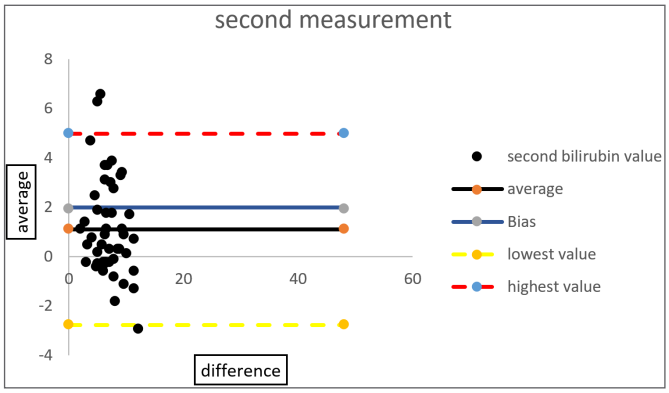

Figure 2. Paired graph of the difference between neonatal and transcutaneous bilirubin values in the second measurement (Bland-Altman plots graph).

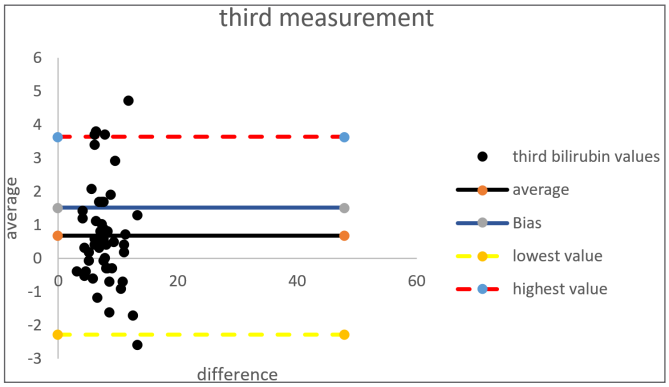

Figure 3. Paired graph of the difference between neonatal and transcutaneous bilirubin values in the third measurement (Bland-Altman plots graph).

When **Figures 1-3** are examined, it is seen that the averages of the differences in the measurement results obtained according to the two techniques show a normal distribution.

The values of the newborns receiving phototherapy before 24 hours

The TSB and TcB values of newborns who received phototherapy before 24 hours passed after birth are given in **Table 3**. The difference between TSB and TcB values was statistically insignificant (p=0.377).

Table 3. Descriptive statistics of neonatal and transcutaneous bilirubin values of newborns who received PT within the first 24 hours

	TSB	TcB	Difference	p*	r**
1st measurement	7.39±3.02	7.63±3.3	-0.24±1.12	0.377	0.941***
2nd measurement	6.64±2.35	5.99±2.42	0.64±1.3	0.050	0.853***
3rd measurement	7.32±1.98	6.78±2.42	0.54±1.61	0.175	0.749***

*Paired Samples T-test, **Pearson's correlation, *** Significant at 0.001.

DISCUSSION

The present study showed that there is a significant relationship between TcB taken from the covered skin and TSB at the beginning, during, and 12 hours after PT. TcB measurements taken from the uncovered skin were not evaluated. Also, when the newborns who received PT for the first 24 hours were evaluated in a subgroup in the study, it was found that TcB measurement predicted the TSB level at a high level before and after PT.

When the literature was reviewed, it was seen that there are parallel and opposite results to our results and there is no consensus.Contrary to the results of the present study, in their study comparing TcB and TSB by covering an area above the sternum in term and late preterm newborns who received PT between 34-41 GW, Murli et al.(16) found that there was a weak correlation between TcB and TSB measured at 0, 12, 24 hours after PT was discontinued, and concluded that the TcB measurement was not reliable in term and late preterm newborns who received PT.

Bhutani et al. (17) reported that up to 36-48 hours were required for bilirubin levels to rebalance after phototherapy to accurately evaluate TcB levels in uncoated skin areas. The findings of the present study showed that measuring TcB levels in the covered skin is safe at the beginning and immediately after PT, and that the disadvantages of waiting for 36-48 hours can be overcome in this way. This difference in results may be related to the device technology used in the study.

In a prospective study conducted in 2017 in the Haitian newborn population, in parallel with our findings, TcB and TSB levels were compared during phototherapy and 70 parallel TcB/TcB were measured in 35 term and preterm newborns, a good agreement was detected between TSB and TcB, and it was emphasized that TcB would show good compatibility with TSB in societies where serum bilirubin test is not widely available, and it could be used safely to guide the treatment of jaundice during phototherapy (18).

A study that was conducted in Iran partially supports the findings obtained in the present study. A total of 134 term and 36 preterm newborns who received FT were examined in this study and it was concluded that TcB measurement could be used safely in the evaluation of bilirubin levels in preterm and term newborns receiving FT, but it is slightly less reliable among preterm newborns (r: 0.921, P <0.001 in term newborns; r=0.887, P=0.001 in preterm newborns) (19).

In a meta-analysis that evaluated the reliability of TcB in premature newborns in 2019, it was concluded when 29 studies were evaluated that TcB values obtained from the forehead and sternum regions were well correlated with TSB and that it could be a reliable method to evaluate hyperbilirubinemia in premature newborns (20).

Again, in the study of Vasava et al. (21) conducted on 306 term and preterm newborns, it was concluded that the measurement of TcB strongly predicted the level of TSB at all gestational weeks and in different body regions.

In another study that had parallel results to the present study, Amneah et al. (22) conducted a study with 80 newborns who underwent PT by placing a patch on the skin and reported a strong correlation between TcB values from the patched skin and TSB levels.

In general, the significant correlation between TcB and TSB during PT is consistent with the findings of some previous studies conducted with preterm newborns.

Also, the results of the present showed the correlation between TcB and TSB after PT was discontinued.

The advantage of the present study was that it could show the high correlation between TcB and TSB in newborns who underwent PT in the first 24 hours when compared with previous studies.

Limitations of the present study; the sample size was small because of the single-center design and short study duration, the study included only the infant population in the neonatal intensive care unit, and the TcB-TSB correlation was evaluated only from the covered area.

CONCLUSION

TcB measurements were strongly correlated with TSB levels at 24 hours and beyond, at the start of PT, and after PT. However, we think that larger prospective studies are needed in this respect.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Karabük University Faculty of Medicine Noninvasive Clinical Researches Ethics Committee (Date: 13.04.2022, Decision No: 2022/859).

Informed Consent: Written informed consent was obtained from the parents. All parents signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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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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Original Article

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The effect of COVID-19 infection on anti mullerian hormone

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ABSTRACT

Aim: The possible impact of COVID-19 infection on female reproductive system is a controversial issue. The aim of this study was to investigate the effect of COVID-19 infection on anti mullerian hormone (AMH) as a predictor of ovarian response to ovarian stimulation.

Material and Method: This prospective study was conducted at a university-affiliated tertiary medical center between June 2021–February 2022. The study population included 79 reproductive-aged women (22-34 years) with COVID-19 infection. Blood samples were collected for AMH levels before COVID-19 infection and after three months of COVID-19 disease.

Results: The mean age of the study group was 28.11±3.49 years. Estradiol and Luteinizing Hormone (LH) was found to be lower after three months of COVID-19 disease ($p<0.05$). Follicle Stimulating Hormone (FSH) was significantly higher in post-COVID-19 group ($p<0.05$). Free T4 (FT4) and body mass index (BMI) were found to be higher after three months of COVID-19 disease but not significant ($p>0.05$). There was a statistically significant association between Pre-COVID-19 and Post-COVID-19 in terms of AMH ($p<0.05$). AMH values have decreased after COVID-19 infection in patients. There was a statistically significant association between menstrual volume and COVID-19 disease ($p<0.05$). According to the findings, menstrual cycle irregularity has increased after being infected with COVID-19.

Conclusion: In conclusion, the results showed that COVID-19 could adversely affect the AMH level and the female reproductive system.

Keywords: COVID-19, women's fertility, anti mullerian hormone, ovarian reserve

INTRODUCTION

In late 2019, a new virus (COVID-19) was first observed in China. On January 30, 2020, the World Health Organization (WHO) considered it an international threat to public health. COVID-19 became prevalent all over the world in a short time (1). At the global level, 591 million cases of COVID-19, including 6.5 million deaths have been confirmed since 16 August 2022, as reported by the WHO (2). Considering the power and spread of this virus, the WHO declared an emergency and recommended that the countries should reduce the personal transmission of this disease by reducing the contact rate and control its global spread (3). Several countries had to impose isolation in their cities. In the modern world, no virus had an extensive global impact as much as COVID-19. In addition, researchers have conducted several studies on the effects of this virus on people in the last three years (4).

The effects of the COVID-19 virus are evident in some dimensions and still unknown in some dimensions. Certainly, COVID-19 and its effects on various dimensions of human life have been studied by researchers for years. The effects of COVID-19 on the reproductive system, particularly on women, are highly important (5). Since it plays an important role in survival of the species, several researchers argue that one of the most important systems in the whole body is the reproductive system (6). It appears that COVID-19 leaves adverse effects on the female and male reproductive system. Particularly, the virus's potential pathogenicity on the granulosa cells and the ovarian and testicular tissues may impact ovarian and testicular function, oocyte quality, and spermatozoa with pregnancy outcomes (7). Consider the COVID-19 pandemic scale, there may be a potential decrease in fertility (8). For this reason, it is very important for women who plan to become pregnant in the future to carefully examine the effects of COVID-19.

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Anti mullerian hormone (AMH) is a glycoprotein dimer and a member of the transforming growth factor-beta family (9,10). This substance is secreted from the granulosa cells of primary, pre-antral, and small antral follicles (4-6 mm) of the ovary (11). AMH serum concentration depends on the number of small follicles and their ovarian reserves (12). AMH has always been considered as a marker to investigate ovarian function. AMH plays an important role in primary follicle growth (13).

Unlike other reproductive hormones, the state of the menstrual cycle does not affect the AMH levels. The serum AMH assay has recently played an increasingly important role in female fertility management (12).

Several studies have been conducted to evaluate the effect of the COVID-19 virus on women's fertility (14-16). In the present study, the effect of COVID-19 on AMH levels was assessed. The present study is significant for identifying the effects of COVID-19 on women's fertility and providing preventive treatments. Physicians can provide more effective treatments for pregnant women with a history of COVID-19 infection by determining the exact effects of COVID-19 infection in women. This study aims to investigate the effect of COVID-19 on AMH levels.

MATERIAL AND METHOD

This prospective study was carried out with the permission of Gümüşhane University Clinical Researches Ethics Committee (Date: 09.06.2021, Decision No: 2021/3). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Seventy nine women participated in this study during June 2021–February 2022.

The study population included 79 reproductive-aged women (22–34 years) with COVID-19 infection. The study excluded women during pregnancy, under fertility treatments, with ovarian failure, previous COVID-19 infection, or vaccinated women.

All respondents filled out an automatic questionnaire on gynecological, general medical and obstetrical background during recruitment and after three months. We took blood samples at AMH plasma levels during recruitment. The patients who applied to the clinic between the dates of the study and met the admission criteria were given detailed information about the purpose and scope of the study. Informed consent forms were signed by the patients who accepted to participate in the study, and a routine clinical procedure (history, physical examination, blood analysis, etc.) was performed. Serum samples were obtained by centrifuging the venous blood samples for 10 minutes at 4000 rpm for 10 minutes after the 30-minute coagulation period. Serum samples collected for biochemical and hormonal evaluation were examined in our hospital's biochemistry and hormone laboratory. Anti-mullerian hormone (AMH), prolactin, follicle stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and free T4 (FT4) values were recorded. The scale for measuring hormones was nanograms per milliliter (ng/ml).

A polymerase chain reaction (PCR) test for COVID-19 was employed to analyze individuals infected with SARS-CoV-2, the virus that causes COVID-19. The PCR test's positive result was considered a COVID-19 infection.

Statistical Analysis

The Kolmogorov-Smirnov test performed to check the normality, and based on the test results, A Wilcoxon signed-rank test and Paired t-test were used to check statistical significance. Median, range, mean and standard deviations (SD) measured to check each continuous variable, including age, BMI, AMH, FSH, E2, LH, prolactin, FT4, and TSH. Pearson's chi-squared test is used to determine whether there is a statistically significant difference between menstrual volume and COVID-19 infection. The Paired Samples Z-Test was used to determine the significance of menstrual volume after COVID-19 infection. SPSS v26 used for statistical analyses. A value of p-value < 0.05 was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, two groups' total mean was measured based on the Mann-Whitney test with the power of 85%, effect size of 31%, and 0.05 type 1 error for at least 77 patients (17).

RESULTS

This study included seventy nine age (28.11 ± 3.49) and BMI (25.32 ± 4.12) women. **Table 1** shows descriptive statistics of study parameters. **Table 2** shows the comparison of pre-COVID-19 and post-COVID-19 groups on the study parameters. As stated in Table 2, a Mann-Whitney test did not find a statistically significant association between pre-COVID-19 and post-COVID-19 in regard to BMI ($p> 0.05$). There was a statistically significant difference between groups in regard to FSH, estradiol and LH ($p<0.05$). There was not a statistically significant difference between pre-COVID-19 and post-COVID-19 in regard to PRL ($p=0.471$), FT4 ($p=0.053$) and TSH ($p=0.866$).

Table 1. Descriptive statistics of study parameters (n=79)

Study parameters	median (range)	mean ± SD
Age	28 (22-34)	28.11±3.49
BMI	25 (17.3-40.8)	24.84±4.12
AMH	1.6 (0.8-3.7)	1.75±0.7
FSH	5.85 (1.79-10.1)	5.74±1.85
Estradiol	41.5 (6.98-330.9)	59.68±54.76
LH	5.34 (1.68-22.8)	6.45±3.62
Prolactin	20.255 (4.42-143)	23.55±15.19
FT4	1.045 (0.52-8.03)	1.26±0.96
TSH	1.61 (0.47-4.96)	1.81±0.87

SD, standard deviation.

Table 2. Comparison of pre- COVID-19 and post- COVID-19 groups

Study parameters	Pre-COVID (n=79) M±SD	Post-COVID (n=79) M±SD	p value
BMI	24.71±1.96	24.94±4.01	0.074
AMH	2.01±0.7	1.49±0.61	<0.001*
FSH	5.42±1.71	6.06±1.94	0.034**
Estradiol	66.06±58.34	53.3±50.48	0.016*
LH	7.68±4.3	5.22±2.2	<0.001*
Prolactin	24.76±18.85	22.34±10.31	0.471*
FT4	1.22±0.94	1.3±0.97	0.053*
TSH	1.83±0.82	1.79±0.92	0.866*

M, Mean; N, number of subjects; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; FT4, Free Tiroksin; TSH, thyroid-stimulating hormone. *A Wilcoxon signed-rank test. ** Paired t-test

There was a statistically significant difference between pre-COVID-19 and post-COVID-19 in regard to AMH ($p<0.05$). The post-COVID-19 group had significantly lower value than the pre-COVID-19 (M=1.49; SD=0.61 vs. M=2.01; SD=0.7).

As stated in **Table 3**, a chi square test found that there was a statistically significant association between the menstrual volume and COVID-19 infection ($p<0.05$). The Pairwise Z-Tests found that the percentage of women with the fixed menstrual volume was significantly higher for the pre-COVID-19 period (43% from n=34) than three months after COVID-19 infection. The percentage of women with decreased menstrual volume was significantly higher for the post- COVID-19 period (78.5% from n=62) than before the COVID-19 illness.

Table 3. The relationship between menstrual volume and COVID-19 infection

Variable	Pre-COVID (n=79) n (%)	Post-COVID (n=79) n (%)	p value
Menstrual volume			<0.001†
It has fixed	34 (43) ††	12 (15.2)	
It has decreased	35 (44.3)	62 (78.5) ††	
It has increased	10 (12.7)	5 (6.3)	

†A Chi-square test. †† Pairwise Z-Tests

In this study, four groups were considered for the menstrual cycle (patients with a menstrual cycle shorter than 28 days, cycles between 28 and 35 days, cycles longer than 35 days, and prolonged menstrual cycles). According to research findings, 32/79 (42%) women have faced menstrual cycle irregularity after being infected with COVID-19.

Figure 1 shows that the women's AMH decreases after the COVID-19 infection. Values of E2 and LH have also reduced. However, BMI and FSH have increased in women in the time period.

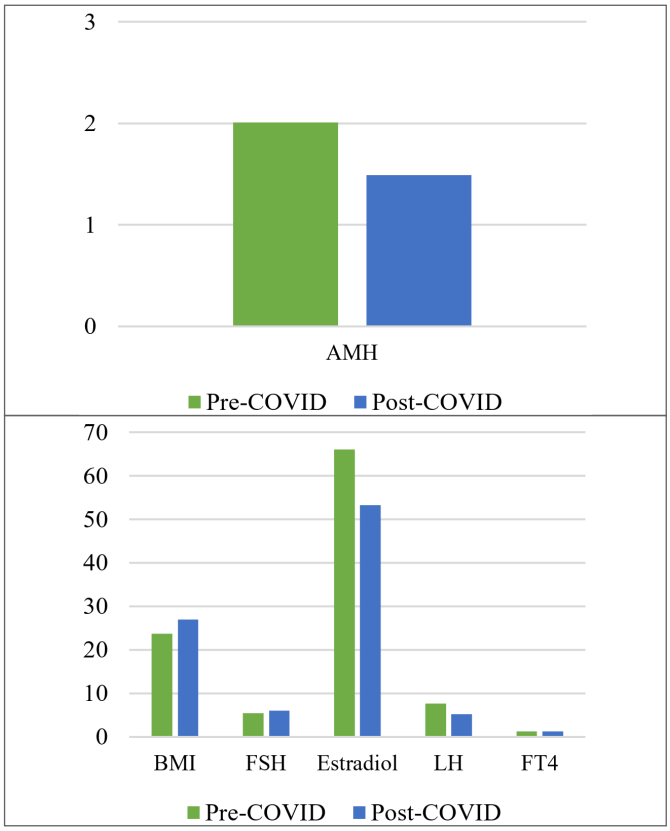

Figure 1. The effect of COVID-19 disease on study parameters

DISCUSSION

In our study, we investigated the impact of infection with COVID-19 on female reproductive system. AMH levels as a marker for predicting ovarian response were significantly lower in the post-COVID-19 group. AMH levels decreased 25% after COVID-19 infection in women. FSH and FT4 were significantly higher in the post-COVID-19 group. E2 and LH were significantly lower in the post-COVID-19 group. Menstrual volume decreased significantly in the post-COVID-19 group. In the post-COVID-19 group, 42% had changed menstrual cycle.

The COVID-19 pandemic caused the prevalence of depression, stress, and anxiety among women in general. Many studies reported shorter or longer menstrual cycles and irregular menstrual volume because of psychological pressure in pandemics (18-21) and COVID-19 vaccination (22,23). A few studies assessed the effects of COVID-19 infection on menstrual cycle and volume in women of

reproductive age. Khan et al. (24) demonstrated alterations in menstrual patterns and increased irregular periods because of infection by COVID-19 in women of reproductive age. Their study reported irregular periods (60%), increased cycle length (35%), and alterations of menstrual pattern (16%). Li et al. (25) reported menstrual abnormalities, altered menstrual flow (25%), and alterations in menstrual cycle pattern (28%) in COVID-19 positive women accepted in Wuhan hospital. Patients who were more severely ill encountered longer menstrual cycles. Vast of the majority of women returned to their regular cycle after months. Ding et al. (26) noted the effect of COVID-19 infection on two groups of mild and severe cases. The more severe patients encountered irregular menstruations, increased dysmenorrhea, more frequent amenorrhea and higher flow. Our study approves of these results. The current study showed that the menstrual volume and menstrual cycles of post-COVID-19 patients were adversely affected.

According to Li et al. (25), the reproductive aged women diagnosed with COVID-19 had AMH levels and sex hormone concentrations comparable to those of the controls. Kolanska et al. (14) reported no mid-term and long-term effects of COVID-19 infection on AMH levels. Their study demonstrated there was not association between mild COVID-19 infection and ovarian reserve as evaluated by AMH levels in women of reproductive age. Herrero et al. (27) demonstrated that number of retrieved oocytes and oocyte maturity rate in women undergoing assisted reproductive technology procedures for confirmed COVID-19 infection were decreased compared with controls. Our study disapproves of these results. In the present study, we indicated that AMH levels from post-COVID-19 patients decreased compared with before COVID-19 infection. In contrast Orvieto et al. (28) reported no statistically significant difference in fertilization rate and number of oocytes obtained in 9 women included to their study. However, their study showed the top-quality embryos rate were significantly lower after COVID-19 infection.

As a limitation of the present study, we analyzed the enrolled patients three months after infection with COVID-19. Consequently, further studies should be done to investigate if one can revert these ovarian alterations after a long time allowing physicians to design an optimized fertility protocol for those recovering from COVID- 19 and prevent the possible complications. More definite evidence can be given about the reproductive performance of female patients recovering from COVID-19 through studies with larger populations.

CONCLUSION

The results described this evidence that infection with COVID-19 could damage ovarian reserve, alter the AMH level and potentially affect reproductive outcomes. More researches are needed to estimate the effect of COVID-19 on women's reproductive system. These results can be used to straighten the public health policies and improve the clinical interventions. In the end, the present study gives a solid ground for more research to assess the possible effects of the COVID-19 on the women's fertility.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gümüşhane University Clinical Researches Ethics Committee (Date: 09.06.2021, Decision No: 2021/3).

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.

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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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Original Article

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Unemployment among cancer patients during COVID-19 pandemic

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ABSTRACT

Aim: The survival rate of cancer patients is increased which resulted in an increased number of cancer survivors in working life. Return to work of cancer patients resulted in improved health outcomes and quality of life. However, cancer survivors have a high risk of unemployment. The COVID-19 pandemic caused global economic distress and put a great burden on the healthcare system which affected the cancer survivors further. COVID-19 may be a concurrent risk along with cancer, as a barrier for return to work. We investigated the factors that are associated with unemployment among cancer survivors, during the COVID-19 pandemic. Thus, we aimed to detect risk factors for unemployment amongst cancer patients during the COVID-19 pandemic. Therefore, we aimed to maintain the employment status of cancer survivors and prevent undesired individual and global economic and health outcomes.

Material and Method: This is a cross-sectional, descriptive study. Control patients who applied to the Medical Oncology outpatient clinic were over 18 years old, diagnosed with cancer, completed adjuvant chemotherapy and/or radiotherapy treatment, the disease has not relapsed, and working before March 2020 were included in the study. The survey collection process for the study was carried out between July 2020 and November 2020.

Results: There were 146 participants (65 male (44,5%) and 81 female (%55,5)). 42 (28.8%) of the 146 participants stated that they quit their jobs during the pandemic. Being a government employee, having a good-high household income and a high degree of education was protective against losing their jobs.

Conclusion: It is very important to understand the causes of unemployment among cancer survivors and solve these issues in order to increase the well-being, quality of life, and survival of the patient, as well as improve the economic and social status of society.

Keywords: Unemployment, cancer, COVID-19, pandemic

INTRODUCTION

Thanks to the advances in cancer care, the survival rate of cancer patients is increased (1,2). This resulted with an increased number of cancer survivors in working life (2). Furthermore, return to work of cancer patients resulted with improved health outcomes and quality of life (3). Also, job insecurity is an important predictor for depression and poorer cognitive function in female breast cancer survivors (4). Despite this important situation cancer survivors have a high risk of unemployment (5). A meta-analysis showed that being a cancer survivor increased the unemployment 1.37 times when compared with a healthy control group. This meant a %39 increased unemployment in cancer survivors (6). In another meta-analysis, it is shown that %53 of the cancer survivors lost their jobs (7). Another meta-analysis of return to work of cancer patients showed that overall RTW rate was %57 (%50-60) and the rate of resuming in work was between 25-73% (8). The unemployment of a cancer survivor is not just an individual problem of the patient, but negatively effects the working life and the society (9).

COVID-19 pandemic caused a global economic distress and put a great burden on the healthcare system (10). This situation affected the cancer survivors further. Firstly, cancer survivors are particularly susceptible for having a more serious course of disease than the normal population (11). They are also more prone to financial problems than other chronic diseases (12) and unemployment (5). COVID-19 may be a concurrent risk along with cancer, as a barrier for return to work (13).

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It is important to investigate unemployment among cancer survivors during COVID-19 pandemic. However, until now, relatively few studies investigated this topic. One study investigated financial toxicity in young adult cancer survivors (14), another one searched the effect of COVID-19 on job security among female breast cancer survivors (4). But these studies investigated the effects of unemployment during the pandemic among other factors such as psychological distress, in populations with cancer. However, we investigated the factors that are associated with unemployment among cancer survivors, during COVID-19 pandemic. Thus, we would suggest correcting these risk factors in order to maintain employment status of cancer survivors and prevent the undesired individual and global economic and health outcomes.

MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki, and in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. We performed the study between July 2020 and November 2020 after the ethical approval was obtained from Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 22.07.2020, Decision No: 2020-07/721).

This is a cross-sectional, descriptive study. Control patients who applied to Ankara Oncology Training and Research Hospital Medical Oncology outpatient clinic, over 18 years old, diagnosed with cancer, completed adjuvant chemotherapy and / or radiotherapy treatment, the disease has not relapsed, and working before March 2020 were included to the study. The survey collection process for the study was carried out between July 2020 and November 2020. Questionnaires were offered to all eligible patients according to the format suitable for the patient (face-to-face, distribution and collection of questionnaires and telephone questionnaire methods), and they were made on a voluntary basis. In the questionnaire prepared by the researchers, general demographic information of the patients, information about their working life, information about cancer diseases and changes in employment status during COVID-19 pandemic were collected. Information about the cancer diseases, stage and treatment status of the employees was checked from the hospital electronic information management system. The frequency of changes in the employment status of the patients (leave, dismissal, leaving the job) in the patient group after the outbreak of the pandemic was examined.

Statistical Analyses

Statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY). There were no missing data on the variables in the study. The Shapiro–Wilk test was used to evaluate the distribution of the data. Descriptive data are presented as the median, with the interquartile range (IQR) for non-normally distributed numerical variables and as the frequency (n) and percentage (%) for categorical variables. A chi-square test was used to compare nominal variables between independent groups. Spearman's correlation analysis was used to evaluate the correlation between numerical and ordered categorical variables. The Mann–Whitney U test was employed to compare linear variables between independent groups. A value of $p < 0.05$ was considered statistically significant.

RESULTS

There were 146 participants (65 male (44,5%) and 81 female (%55,5)). The descriptive properties of the participants are given in **Table 1**.

Table 1. The descriptive properties of the participants

	N (%)	Years
Age		
Male	65 (44.5)	41.8±9.7
Female	81 (55.5)	43.8±6.2
Accommodation		
Province	39 (26.7)	
District	105 (71.9)	
Village	2 (1.4)	
Education		
Primary school	34 (23.3)	
High school	57 (39)	
University	55 (37.7)	
Marital status		
Married	111 (76)	
Single	24 (16.4)	
Divorced	11 (7.6)	
Income		
Low	21 (14.4)	
Average	58 (39.7)	
Good	58 (39.7)	
High	9 (6.2)	
Chronic disease (other than cancer)		
No	21 (14.4)	
Yes	125 (85.6)	
Total	146	

When the cancer diagnoses of the participants were examined, it was seen that there was a total of 18 diagnosis groups. When the groups with less than 10 cases are combined under "others" heading; 73 people

(50%) have breast cancer, 19 people (13%) testicular cancer, 13 people (8.9%) colon cancer and 41 people (28.1%) have other cancer diagnoses. When cancer stages are evaluated, 2 people (1.4%) Stage 0, 28 people (19.2%) Stage 1, 56 people (38%) Stage 2, 56 people (38%) Stage 3, and 4 people (2.7%) was identified as stage 4.

Forty of the participants (27.4% – 11 missing data) stated that they could not apply to the hospital for their chronic diseases. 33 of them stated that they could not go to the hospital because of the fear of contagion, and 4 of them stated that they could not go to the hospital because they could not get an appointment.

When data of the participants about working life is examined, it is seen that 10 people (6.9%) work without insurance, 62 people (42.5%) are contracted workers, 17 people (11.6%) are self-employed, and 57 people (39%) are working as a civil servant (government employee).

42 (28.8%) of the 146 participants stated that they quit their jobs during the pandemic. According to the employment status, it is seen that all 10 uninsured employees quit their jobs, 27 (43.5%) of 62 employees with contracted worker status (SGK), and 4 out of 17 self-employed (23.5%), and 1 (1.8%) of 57 people working as civil servants quit their jobs. In the cross-table statistics, it was determined that the frequency of leaving the job of those working as uninsured or contracted workers was statistically significantly different from those working as civil servants (Fisher's exact test, $p<0.001$). When employees were divided into 2 groups as civil servants and others, non-civil servants left their jobs 26.25 times (95% CI: 3.71-185.6) higher.

The status of quitting their jobs was analyzed according to the income status, gender, and age. While 76.2% of those who stated their income status as low quit their jobs, 91.4% of the participants who stated their income status as good did not quit their jobs. According to the chi-square analysis, the difference was statistically significant ($p<0.001$). When the income levels of the participants are combined in two groups as low-medium and good-high, those with low-medium income status left their jobs 9.41 times (95% CI: 3.04-29.15) higher. Statistical analyses showed no difference in the frequency of leaving work according to gender and age.

In our study, when the frequency of leaving the job is examined according to education level, 52.9% of primary school graduates quit their job, while 12.7% of university graduates quit. The difference was found to be statistically significant ($p<0.001$).

DISCUSSION

In our study, we found that approximately 30 percent of the participants left their jobs during COVID-19 pandemic. Being a government employee, having a good-high household income and high degree of education were protective against losing their jobs.

Thom et al. (14) conducted a cross-sectional survey about economic distress among adult cancer survivors during COVID-19 pandemic. They found that 19% of the participants lost their job and 15% reported decreased pay. Chapman et al. (4) investigated the effects of COVID-19 pandemic on job security amongst breast cancer survivors. As a result of the outbreak, 50 (21.41%) participants stated they were no longer working or had been furloughed by their employer. In a cross-sectional survey with 1510 patients, Matthews et al. (15) found that COVID-19 pandemic caused an acute employment loss, which increased from 4% to 14% in March 2020.

In their systematic review, Gordon et al. (16) showed that cancer survivors who have a low income at the beginning are expected to have more financial toxicity. Another study found that experiencing job loss or a furlough during the pandemic was associated with lower income ($\chi2=9.5$; $P=.002$) and lacking full-time employment ($\chi2=6.8$; $P=.009$) (14). Similarly in our study, we found that lower household income resulted with unemployment. Our study also showed that lower degree of education was associated with leaving job. Other studies also showed that cancer patients with lower education are more susceptible to losing their jobs (3,17).

In their review Mehnert et al. (7) proposed advanced tumor stage and having an additional chronic disease increased the unemployment among cancer survivors. However, in our study we did not find an association between tumor stage or having a chronic disease and leaving job.

In our study, the frequency of leaving job did not differ according to age or sex. Thom et al. (14) also found that job loss was not associated with age, race/ethnicity, time since treatment, or education. Similarly in a systematic review by Tavan et al., (8) the authors noted no articles analyzed gender as a factor for return to work, or resuming the employment. However, there are studies that show cancer survivors with old age are more prone to lose their jobs (3,17).

In the present study, approximately 30% of the participant stated that they could not perform their hospital visits, due to the fear of acquiring COVID-19 infection. In a study in Turkey, Guven et al. (18) found that more than 90% of the participants had some degree of COVID-19 fear and approximately 85 percent of patients expected an interruption in their patient care.

CONCLUSION

It is very important to understand the causes of unemployment among cancer survivors and solve these issues in order to increase the well-being, quality of life, and survival of the patient, as well as improve the economic and social status of the society.

The most striking finding in our study is cancer patients who are government employees or civil servants did not have to leave their jobs when compared to paid workers and self-employed persons. This is not investigated extensively in literature; however, we think that this is very important. The employment status itself should not be a risk factor for losing jobs. There should be legal protective measures to keep cancer patients in working life, in times like COVID-19 pandemic which causes economic crisis. There also should be professional rehabilitation and return to work (RTW) programs, which are designed for the specific needs of the cancer survivors. This would increase the return to work and being employed among this population.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 22.07.2020, Decision No: 2020-07/721).

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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Erythromycin resistance in *Group A Beta-hemolytic streptococci*

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ABSTRACT

Aim: *Streptococcus pyogenes* (*Group A Beta-hemolytic streptococci*, GABHS) is one of the important bacterial pathogens in clinical microbiology. It often causes upper respiratory tract infections such as tonsillitis, pharyngitis, and laryngitis. It also leads to complications such as acute rheumatic fever and post-streptococcal glomerulonephritis. Early diagnosis and treatment of these bacterial infections will prevent suppurative and non-suppurative complications, the transmission of infection to other people, and chronic carriage. Today, the treatment of streptococcal infections relies entirely on chemotherapy. *Beta hemolytic group A streptococci* and generally other *beta-hemolytic streptococci* in groups B (GBBHS), C, and G are generally sensitive to many chemotherapeutics, especially Penicillin and Erythromycin. In patients with penicillin allergy, erythromycin, amoxicillin-clavulanate, or oral cephalosporins are used instead of penicillin. However, it has recently been understood that there are strains resistant to Erythromycin in GABHS and are increasing. In this study, the situation in our region of Erythromycin resistance, which is used as an alternative for people allergic to Penicillin in the treatment of streptococcal infections, was investigated.

Material and Method: In our study, throat swab samples were taken from 150 pharyngitis patients and 94 GABHS were obtained by applying the Bacitracin-SXT test with the culture method, and antibiotic susceptibility tests were performed on these 94 GABHS by Kirby-Bauer agar disc diffusion method.

Result: GABHS was found susceptible to Bacitracin and resistant to SXT. GBBHS is resistant to Bacitracin and SXT. other *beta-hemolytic streptococci* were resistant to Bacitracin and susceptible to SXT.

Conclusion: In this study, Erythromycin's resistance was found to be 19.1%. it is observed that Erythromycin resistance has increased over the years when compared to previous studies. Erythromycin should not be used empirically in treatment. An antibiotic susceptibility test should be performed and the antibiotic should be selected according to the results of the antibiogram test.

Keywords: Penicillin, erythromycin, *Streptococcus pyogenes*, tonsillitis, pharyngitis, laryngitis

INTRODUCTION

Streptococci can be found in the normal flora of humans, but also can be important bacterial pathogens. Specifically, GABHS is the most important causative agent for acute pharyngitis. They cause both suppurative and non-suppurative complications. Streptococci are gram-positive bacteria, which are round or oval and form pairs or rings. They form longer rings in mediums containing blood and serum. They are non-motile and they do not form spores. Most of them have a capsule that contains hyaluronic acid. Streptococci which have capsules are resistant to phagocytosis. They are facultative anaerobes and are catalase and oxidase negative (1-4). They can grow in simple media, but the amount and the rate of growth increase when substances like blood, serum, and glucose are added to the media. Their growth is maximum in media containing horse or sheep erythrocytes. Selective media for streptococci are known as; Trypticase soy, heart infusion, Todd-Hewitt infusion media, Columbia agar, Colistin-Nallidixic acid agar (CNA), Phenyiethyi alcohol agar (PEA), and chocolate agar (5). Not only the nutrients but also fermentable carbohydrates that can affect the hemolysis of *beta-hemolytic streptococci* are useful. They grow better in anaerobic or with a CO_2 concentration of 10% conditions, at 37°C in a period between 18-24 hours (1,5-7). Streptococci have a colony morphology of white-grey color, with a diameter of 1-2 µm on blood agar. M-protein-forming strains have a dull appearance. Strains that do not form or form fewer M proteins have bright colonies (8). Generally, streptococci colonies formed on the blood agar show different features. According to hemolysis properties, they form

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either small or large complete hemolysis zones (beta hemolysis), due to partial lysis of erythrocytes, a green hemolysis zone (alpha hemolysis) is formed, or there is no hemolysis at all (gamma hemolysis) (4).

Group A Beta Hemolytic Streptococci can cause diseases such as erysipelas, scarlet fever, tonsillopharyngitis, infective endocarditis, post-streptococcal diseases, acute joint rheumatism, and acute glomerulonephritis (4,9-11). It is most commonly seen in the age group 5-15 years. The probability is lower in people who are under 3 or above 5 (7,12). GABHS' are isolated from the normal population in 5-25% proportions (1,13,14). The transmission is by direct contact or via droplets. Contaminated food such as milk, eggs, and ice cream can cause food poisoning or pharyngitis epidemics. Transmission to belongings or clothes does not carry a significant risk (1,7,15-17).

Today, the treatment of streptococcal infections is completely based on an antimicrobial basis. Generally, streptococci are susceptible to penicillin and erythromycin (18). For this reason, when streptococci are isolated, the treatment can be started without the need for antimicrobial resistance tests. However, nowadays, it is found that there are resistant origins of *Group A Beta-hemolytic streptococci*, and the resistance is on increase (19). The first choice of treatment is penicillin (20). GABHS' are susceptible to penicillin (14). Starting penicillin treatment within 9 days after the onset of symptoms prevents the formation of acute joint rheumatism (1,6,8,21). Erythromycin is preferred in patients with penicillin allergy. In addition, ampicillin, amoxicillin, cefaclor, and cefadroxil can also be used (18). However, it should be kept in mind that patients who have a penicillin allergy have a 10% probability of having a cephalosporin allergy too (22). It is found that there is a 6-38% probability of failure in oral or penicillin treatment of GABHS (23). Erythromycin used in this study is an antibiotic from the macrolide group. This group of antibiotics is called macrolides due to the presence of a macrocyclic lactone ring, with one or two deoxyribose radicals connected to it. They are also referred to as the name of the first member of the group (erythromycin group antibiotics). Erythromycin is the best and most commonly used alternative for penicillin as primary indications are limited. In this study, we aim to investigate the resistance of Group A Beta Hemolytic Streptococci to erythromycin.

MATERIAL AND METHOD

This article is a thesis work. It was made and completed with the approval of the institution before 2020. Ethical approval was not obtained because there was no ethics committee at that time. All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. In this study, 150 throat swab samples were examined. Sore throat, fever, headache, nausea, vomiting, and other symptoms and signs were investigated. Throat cultures of 150 patients with a diagnosis of acute tonsillopharyngitis were taken by using a sterile swab, in accordance with the technique. In our study, throat swab samples were taken from two tonsil surfaces with the help of a tongue depressor and cotton swabs. Swabs were dipped in sterile broth tubes to prevent the material from drying out and immediately inoculated on 5% defibred sheep blood agar and incubated for 24 hours in an oven at 37°C. At the end of incubation on sheep blood agar, colonies showing beta hemolysis were found to be streptococci by Gram stain and negative catalase reaction. Later, to obtain pure culture, its passages were made and incubated at 37°C for 24 hours. Bacitracin susceptibility test was performed to distinguish whether *beta-hemolytic streptococci* with single colony passage were from group A or not. For this purpose, Bacitracin discs (oxoid) each containing 0.04 units of Bacitracin were used. After overnight incubation at 35-37°C, it was analyzed by the Kirby-Bauer disk diffusion method. A few colonies of streptococci showing beta-hemolysis on Kirby-Baner Disc Diffusion Method 5% sheep bloody agar was taken and inoculated into 1-2 ml broth. It was incubated at 37°C for 2-5 hours. When turbidity was equal to the MC Farland 0.5 standard, with the help of a cotton-tipped eraser, before planting, sowing was done on 5% sheep blood agar surface, which was dried in an oven with the lids ajar and upside down, to spread all over in the form of zigzag lines intersecting each other. The plates were left to dry at room temperature for 5-16 minutes. While the discs (penicillin-G, erythromycin, SXT, bacitracin) were arranged on the plate oxoid firm discs were used. The diameters of the zones of inhibition were measured from the lower face of the plate. Zone sizes measured in millimeters were evaluated according to **Table 2** and the results were reported as sensitive, less sensitive, and resistant. The active substance amounts of Bacitracin, trimethoprim-sulfamethoxazole, Erythromycin, and Penicillin discs used in this test are shown in **Table 1**.

Table 1. Amount of substance per antibiotic disc

Antibiotic name	Amount of active matter on the drive
Bacitracin	0.04 units
Penicillin G	10 units
Erythromycin	15 micrograms
Trimetoprimt+ Sulfamethoxazole	1.25+23.75 micrograms

Table 2. Antibiotic resistance and susceptibility status according to disc diffusion diameter

Antibiotic Name	Diameter of growth prevention area (mm)		
	Resistant	Medium susceptible	Susceptible
Penicillin-G	≤11	12-21	≥22
Erythromycin	≤13	14-17	≥18
Trimetoprimt+ Sulfamethoxazole	≤10	11-15	≥16
Bacitracin	≤8	9-12	≥13

RESULTS

In our study, a total of 150 patients of different ages and genders who were isolated beta-hemolytic streptococcus from throat cultures were evaluated. Of the *beta-hemolytic streptococci*, 94 were identified as Group A (62.7%) and 56 (37.3%) as Non-*Group A Beta-hemolytic streptococci* by Bacitracin test (**Table 3**).

Table 3. Distinctive properties of streptococci

Streptococci	Hemolysis	Susceptibility		Results	
		Bacitracin	SXT	Number	%
Group A S. pvogenes	Beta	+	-	94	62.7
Group B S. agalactiae	Beta	-	-	7	4.7
Other Beta Hemolytic Streptococcus	Beta	-	+	49	32.6

SXT: Trimetoprim sulfometaksazol

According to the characteristics seen in **Table 3**, 94 (62.7%) of them were GABHS among a total of 150 *Beta-hemolytic streptococci* (BHS). GABHS was found susceptible to Bacitracin and resistant to SXT. Among all BHSs, 7 (4.7%) were Group B and resistant to Bacitracin and SXT. 49 (32.6%) of them were evaluated as other *beta-hemolytic streptococci*. They were resistant to Bacitracin and susceptible to SXT. Erythromycin and Penicillin susceptibility was detected by disk diffusion method from 94 BHS strains which were identified as Group A by the Bacitracin-SXT test. The results are shown in **Table 4**.

Table 4. Antibiogram results of 94 strains identified as GABHS

Antibiotic name	Diameter of growth prevention area (mm)		
	Susceptible	Medium susceptible	Resistant
Penicillin-G	94 (100%)	-	-
Erythromycin	67 (71.3%)	9 (9.6%)	18 (19.1%)
Trimethoprim+ Sulfamethoxazole	-	-	94 (100%)
Bacitracin	94 (100%)	-	-

As can be seen in **Table 4**, in the antibiotic susceptibility trial to 94 GABHS strains, 67 (71.3%) were susceptible, 9 (9.6%) were moderately susceptible, and 18 (19.1%) were resistant to Erythromycin. In the susceptibility experiment with Penicillin-G, 94 of them (100%) were found to be susceptible, and no moderately susceptible and resistant strains were found.

DISCUSSION

GABHSs are known to be one of the most common factors causing pharyngitis among all age groups. Causes of non-suppurative infections that have an adverse impact on personal and community health like acute rheumatism and post-streptococcal glomerulonephritis should be considered as occurring only after GABHS infections which makes it clear how important *beta-hemolytic streptococci* are in terms of diagnosis, treatment, and patient follow-up.

Today, in Group A streptococcal pharyngitis cases, Erythromycin is used in cases of allergy to Penicillin without doing antibiograms. However, it has recently been reported that there are refractory origins against Erythromycin in GABHS (11,24-30). In our study, throat swab samples were taken from 150 pharyngitis patients and 94 GABHS were obtained by applying the Bacitracin-SXT test with the culture method, and antibiotic susceptibility tests were performed on these 94 GABHS by Kirby-Bauer agar disc diffusion method. As mentioned in the findings section, 67 (71.3%) of the 94 strains were sensitive to Erythromycin, 9 (69.6%) were moderately sensitive, and 18 (19.1%) were found to be resistant. While all 94 strains (100%) were sensitive to Penicillin, no moderately sensitive and resistant strains were found. In various studies conducted in our country and published between 2000-2006, erythromycin resistance in *S. pyogenes* was generally reported to be below 10%, but between 0% and 23% (31,32,36). Again in 2021, in a study conducted in our country, Altun et al. (33) found that BHS isolates (23.5%) were resistant to erythromycin. In our study, if the moderately sensitive group is added, the resistance ratio was found to be towering at 28.7%.

Erythromycin was first used in Gram (+) coccal infections in 1952. Especially for patients who are sensitive to Penicillin, Erythromycin has been used as an alternative in the treatment of streptococcal infections. Penicillin-G is still valid in the treatment of *S. pyogenes* infections and Erythromycin is a safe and useful drug (34). Erythromycin resistance of *S. pyogenes* was first reported 30 years ago in Birmingham (Australia) hospital. Erythromycin-resistant strains of GABHS were reported in the UK, USA, and Canada in 1968. More than 50% of the *S. pyogenes* strains isolated in Japan in the late 1970s were resistant to Erythromycin. In the US, this resistance was reported as 5% (25). The prevalence of *S. pyogenes* infections in Western Australia has been investigated and resistance to Erythromycin has increased from 1% in 1985 to 9.1% in 1986 and 17.6% in 1987 (24). A 1988 study by Philips and his colleagues, showed that Erythromycin resistance increased with the number of months. Total resistance was reported as 22.8% in 413 cases (35). In a study conducted by Seppala et al. (26). in Finland, they stated that the sensitivity of GABHS to Erythromycin varies according to different regions and years. For instance, from January to December 1990, the resistant strain increased from 7% to 20%. In the same study, resistance differences were also found between

regions and they stated this was between 2% and 29%. The same researchers cannot explain the reason for the difference in resistance between time and regions

As can be seen from the studies conducted, Erythromycin resistance varies according to countries, years, months, and regions, and the reason for these differences in the resistance stays unknown. However, in-vitro studies suggest that resistance may be with plasmids or bacteriophages (25).

In this study, Erythromycin's resistance was found to be 19.1%. Among many studies conducted to date, Erythromycin resistance (0%-23%) has been found in GABHS and it is observed that Erythromycin resistance has increased over the years from all these studies.

CONCLUSION

Erythromycin should not be used empirically in treatment. To have a good response from the treatment we apply to the patient, first of all, an antibiotic susceptibility test should be performed and the antibiotic should be selected according to the results of the antibiogram test. The war between microorganisms and antibiotics continues, and resistance rates to antibiotics are increasing day by day. Studies should be continued at different times to assess erythromycin resistance over the years.

ETHICAL DECLARATIONS

Ethics Committee Approval: This article is a thesis work. It was made and completed with the approval of the institution before 2020. Ethical approval was not obtained because there was no ethics committee at that time.

Referee Evaluation Process: Externally peer-reviewed.

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

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Pain management in ST-segment elevation myocardial infarction: an observational analysis

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ABSTRACT

Aim: ST-segment elevation myocardial infarction (STEMI) is one of the most severe forms of pain. However, the guidelines give quite a few places for pain control in STEMI and, do not offer strong recommendations on this issue. This study aimed to reveal which medications are given to STEMI patients for pain control until they arrive at the catheter laboratory, in which situations they are used, and the frequency of use.

Material and Method: A total of 272 consecutive STEMI patients were prospectively collected. Medications were administered to the patients until they arrived at the angiography laboratory; vital signs, comorbidities, referral status, infarction types, the time between the onset of pain and the admission to the emergency department, and the door-balloon time were also noted. The patients' pain characteristics and intensity were evaluated.

Results: It was observed that 96.3% of the patients presented with chest pain. The pain of diabetic patients was severe according to the visual analog scale (VAS) score (p=0.023). It was witnessed that 9.92% of the patients were administered drugs for analgesic purposes. The most commonly administered medication was paracetamol. It was noticed that morphine was used frequently after paracetamol. Medication administration for analgesia was more common in referred patients (p=0.040).

Conclusion: Physicians behave timidly in their clinical practice in pain control of STEMI and move away from the guideline. In terms of comfort and hemodynamic stabilization of the patients, it will be beneficial for the applications in the field to give more place to the treatments for pain control in the guidelines.

Keywords: ST-segment elevation myocardial infarction, chest pain, pain relief, morphine, paracetamol

INTRODUCTION

Acute ST-segment elevation myocardial infarction (STEMI) is a condition with mortality risk and often presents to the emergency department with chest pain (1). Apart from chest pain, patients may experience pain in the lower jaw, back, left arm, left shoulder, and abdomen (2-4). In contrast to the incidence of typical chest pain decreasing with age in acute myocardial infarction (AMI), angina equivalent symptoms, dyspnea, anxiety, palpitations, heart failure, and neurological, and abdominal symptoms increase (3,5). Apart from elderly patients, the frequency of chest pain is less common among the complaints of acute myocardial infarction in diabetic patients, and silent myocardial infarcts can be observed (1,6).

Although chest pain is still the most common symptom of acute myocardial infarction, the guidelines did not focus on pain relief as much as antiaggregant and anticoagulant treatments and did not make clear recommendations. Nevertheless, pain control provides the patient comfort and reduces the burden on the heart by preventing vasoconstriction that occurs when pain triggers sympathetic activation (2).

It is noted in the 2017 European Society of Cardiology (ESC)'s Guidelines that opioids (e.g., morphine) can be used in pain control with a class 2a recommendation. However, it is indicated that morphine may delay the effect of oral antiplatelet treatments and therefore cause early failure in treatment (2). In addition, it may cause nausea, vomiting, hypotension, and bradycardia (1,7,8).

When we look at daily practice, we observe that the administration of drugs for pain control to AMI patients in the emergency department is low due to the clinical hemodynamic status of the patients and the fear of the side effects of the drugs given for analgesia. In this study, we aimed to examine the severity of pain in STEMI patients, whether the patients were administered for pain control, and, if so, which drugs were given.

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MATERIAL AND METHOD

This study was carried out with the permission of Gaziantep İslam Science and Technology University Coordinatorship of Local Ethics Committee for Non-Interventional Clinical Researches (Date: 26.04.2022, Decision No: 111.16.14). Informed consent was obtained from all patients in this study. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki.

Study Design

The study is an observational analysis study. Data were obtained prospectively through face-to-face interviews, emergency department and ambulance transfer documents, cardiology clinical files, and coronary angiography system.

The following data of the patients were recorded: age, gender, comorbidity, type of myocardial infarction, culprit lesion, presence of pain, the time between the onset of pain and admission to the emergency department, door-balloon time, referral status, antiaggregant, anticoagulant and drugs preferred for analgesia.

Selection of the Participants

Patients referred to our center, a state hospital where primary coronary angiography is performed 24/7, with the diagnosis of STEMI, were included in the study, either from our emergency department, the same district, the neighboring communities, or the surrounding provinces. After the ethics committee's approval, data were collected as of 27 April 2022. Data collection was performed by G.Power 3.1 (Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany), selecting type I error 0.05 and power of 90% (1- β =0.90). Based on previous studies, the required sample size was determined at least 272 consecutive STEMI patients.

The patient age group was chosen as 18-99 years. Patients presenting with cardiac arrest were not included in the study. Patients (n=3) who were unclear about which drugs were administered until they were admitted to the coronary angiography unit were excluded from the study.

Measurements and Outcomes

The definition of STEMI is based on the electrocardiogram (ECG) changes in the ESC fourth universal myocardial infarction guideline (9).

Although it is used in the chronic pain scoring system, the Visual Analogue Scale (VAS) scoring system, which is also reliable in acute pain, was used in grading pain (10). Patients were scores between 0-10. 0 was recorded as no pain, and ten as very severe pain. Less than three is classified as mild, 3-6 as moderate, and seven or more as severe pain. Since there was no patient with a score below 3 in our study, the evaluations were made 3-6, and 7 and above.

Statistical Analysis

Statistical Package for the Social Sciences version 25.0 software program (SPSS, IBM, Corp.; Armonk, NY, USA) was used for data analysis in this study. Descriptive data on the sociodemographic information of the patients are given as n (%) or Mean± SD tables. The Chi-Square test or Fisher's Exact test was used to compare the groups according to VAS score groups and diabetes mellitus, drugs used for analgesic, acetylsalicylic acid use, and referral status and analgesic drug use. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 272 consecutive patients with STEMI were included in the study. The mean age of the patients was 58.20±12.94 years, and 75.4% (n=205) were male.

When the patients were divided according to VAS, it was observed that there were no patients in the mild pain group with a score of 3 or less. While 12.9% (n=35) of the patients had moderate pain, 87.1% (n=237) reported severe pain. 96.3% (n=262) of the patients suffered chest pain at admission. Demographic information, VAS score, and admission symptoms of the patients are presented in **Table 1**.

Table 1. Demographic data, comorbidity, symptoms, and VAS score of STEMI patients

		N	%
Age, Mean ±SD		58.20±12.94	
Gender	Male	205	75.4
	Female	67	33.3
DM	No	192	70.6
	Yes	80	29.4
HT	No	177	65.1
	Yes	95	34.9
CAD	No	206	75.7
	Yes	66	24.3
CVD	No	268	98.5
	Yes	4	1.5
VAS	3-6	35	12.9
	7≤	237	87.1
Chest pain	No	10	3.7
	Yes	262	96.3
Back pain	No	240	88.2
	Yes	32	11.8
Abdominal pain	No	223	82.0
	Yes	49	18.0
Arm pain	No	216	79.4
	Yes	56	20.6
Referral status	No	88	32.4
	Yes	184	67.6

DM: Diabetes Mellitus; HT: Hypertension; CAD: Coronary Artery Disease; CVD: Cerebrovascular Disease; SD: standard deviation, VAS: visual analogue scale

It was observed that 67.6% (n=184) of the patients were referred from other hospitals (**Table 1**). The most

common type of myocardial infarction was 57.7% (n=157), the inferior myocardial infarction. It was determined that the mean time between the onset of pain and admission to the emergency department was 517.37±1611.34 minutes, and the mean door-balloon time was 71.41±94.96 minutes (**Table 2**).

Table 2. Clinical characteristics of the patients in the emergency department and the catheter laboratory

		N	%
MI type			
Anterior & anterolateral		98	36.0
Lateral		16	5.9
Inferior & inferolateral		157	57.7
Posterior & posterolateral		1	0.4
	Min	**Max**	**Mean±SD**
ER- SBP (mm Hg)	70.00	160.00	126.48±30.53
ER-DBP (mm Hg)	15.00	134.00	74.59±15.63
ER-HR (bpm)	35.00	140.00	77.16±18.27
CL-SBP (mm Hg)	52.00	180.00	121.70±22.48
CL-DBP (mm Hg)	40.00	110.00	71.65±13.98
CL-HR (bpm)	40.00	142.00	77.73±17.38
Onset of pain-ER (minute)	10.00	20160.00	517.37±1611.34
Door-Balloon (minute)	5.00	780.00	71.41±94.96

ED- SBP: Emergency department- systolic blood pressure, ED-DBP: Emergency department- diastolic blood pressure, ED-HR: Emergency department- heart rate, CL-SBP: Catheter laboratory- systolic blood pressure, CL-DBP: Catheter laboratory- diastolic blood pressure, CL-HR: Catheter laboratory- heart rate

It was observed that 7%(n=19) of the patients were not given acetylsalicylic acid until they arrived at the catheter laboratory. It was determined that 10.3%(n=28) of the patients were given clopidogrel loading as the second antiplatelet, and 8.5%(n=23) were given ticagrelor loading. It was found that 8.8%(n=24) of the patients were given Heparin iv, 50.7%(n=138) enoxaparin sc, and 0.4%(n=1) enoxaparin iv as anticoagulant treatment. It was also marked that 40.07%(n=109) of the patients were not given any anticoagulant treatment (**Table 3**).

Table 3. Data on antiaggregant and anticoagulant administered

Medications		**N**	**%**
Acetylsalicylic acid	No	19	7.0
	Yes	253	93.0
Clopidogrel	No	244	89.7
	Yes	28	10.3
Ticagrelor	No	249	91.5
	Yes	23	8.5
Prasugrel	No	272	100.0
	Yes	0	0.0
Heparin iv	No	248	91.2
	Yes	24	8.8
Heparin sc	No	272	100.0
	Yes	0	0.0
Enoxaparin sc	No	134	49.3
	Yes	138	50.7
Enoxaparin iv	No	271	99.6
	Yes	1	0.4

In terms of pain control, it was observed that 9.92%(n=27) of the patients were administered drugs for analgesia. The most commonly administered drug for this purpose was paracetamol (4.4%, n=12), followed by morphine (2.6%, n=7) as the second most frequently administered (**Table 4**).

Table 4. Data on analgesics administered to patients

Analgesics		**N**	**%**
Paracetamol	No	260	95.6
	Yes	12	4.4
Dextroprofen	No	270	99.3
	Yes	2	0.7
Metamizole	No	271	99.6
	Yes	1	0.4
Tenoxicam	No	270	99.3
	Yes	2	0.7
Tramadol	No	271	99.6
	Yes	1	0.4
Morphine	No	265	97.4
	Yes	7	2.6
Diclofenac	No	271	99.6
	Yes	1	0.4
Fentanyl	No	272	100.0
	Yes	0	0.0
Pethidine	No	271	99.6
	Yes	1	0.4

When the referral status of patients who received analgesic medication was examined, a statistically significant relationship was observed between medication administration and referral (p=0.040). It was found that 85.25%(n=23) of the patients who were administered analgesic drugs were referred to (**Table 5**).

Table 5. Comparison of the referral status and analgesic use

	Referral Status		**p**
	No N(%)	**Yes N(%)**	
Administration of analgesics			0.040
No	84 (34.3)	161 (65.7)	
Yes	4 (14.8)	23 (85.2)	

Chi-Square test, p<0.05 statistically significant.

In addition, our study revealed a statistically significant relationship between VAS score and diabetes mellitus. It was determined that 80%(n=64) of the patients with diabetes mellitus had a VAS score of ≥ 7, while 20%(n=16) had a VAS score between 3-6 (p=0.023). No statistically significant relationship was observed when the VAS score was compared with the patients treated with analgesic drugs, (p=0.222). Moreover, no statistically significant relationship was observed when the VAS score was compared with the patients given acetylsalicylic acid (p=0.752) (**Table 6**).

Table 6. Comparison of VAS score groups and diabetes mellitus, analgesic drugs, and acetylsalicylic acid use

	VAS Score		p
	3-6 N(%)	7≥ N(%)	
DM			0.023[a]
No	19 (9.9)	173 (90.1)	
Yes	16 (20.0)	64 (80.0)	
Administration of analgesics			0.222[b]
No	34 (13.9)	211 (86.1)	
Yes	1 (3.7)	26 (96.3)	
Acetylsalicylic acid			0.752[b]
No	2 (10.5)	17 (89.5)	
Yes	33 (13.0)	220 (87.0)	

DM: Diabetes Mellitus, VAS: visual analogue scale, a: Chi-Square test, b: Fisher's Exact test, p<0.05 statistically significant.

DISCUSSION

In our study, 96.3% of the patients presented with chest pain, and no patient was in the mild pain group according to the VAS score. We determined that the pain severity of diabetic patients was in the severe pain group according to their VAS scores. We witnessed that only 9.92% of the patients were given drugs for analgesia. We have seen that paracetamol is used most frequently in drug administrations for analgesia. It was determined that most patients administered drugs were transferred from another hospital for primary percutaneous intervention.

In the study, chest pain was the most common pain region in acute myocardial infarction, consistent with the literature (1). In addition, severe chest pain was observed more frequently, consistent with previous research (11). Diabetic patients may not have typical chest pain in acute coronary syndromes and acute myocardial infarction due to autonomic neuropathy (12,13). In the literature, it has been that diabetics patients are less likely to present with chest pain due to acute myocardial infarction (1,6). However, in our study, unlike in the literature, severe pain was observed in diabetic patients presenting with STEMI. This issue may be because the mean age of our patients was younger than in other studies, and the neuropathy associated with diabetes was less developed.

The opioid group, especially morphine, is recommended for pain control in patients with acute STEMI (2). It is known that morphine decreases gastric motility, increases nausea and vomiting, delays the effect of oral antiplatelets in absorption, and may cause respiratory depression, cause bradycardia, and hypotension at high doses (1,14,15). In addition, the TREAT trial, published recently, showed that morphine use was associated with early reinfarction and less bleeding in STEMI patients administered fibrinolytic therapy and dual antiplatelet therapy (16). Apart from morphine, another opioid that can be preferred in acute myocardial infarction is pethidine. Nielsen et al. (17) showed that pethidine has similar efficacy and safety as morphine in ischemic chest pain in acute myocardial infarction. Pethidine, like morphine, has side effects such as nausea, vomiting, and respiratory depression (14). Studies have revealed that fentanyl, another opioid, can be an alternative to morphine in ischemic chest pain (18). It has been demonstrated that fentanyl has fewer gastric side effects than morphine. Like morphine, fentanyl has been observed to delay the absorption of oral antiplatelets, but no study compares the two (14).

Apart from the opioid recommendation, another essential point we know is that nonsteroidal anti-inflammatory drugs are contraindicated because of increased major adverse cardiovascular events (MACE) in acute myocardial infarction (14). Physicians are encountering STEMI experience fear and confusion in choosing analgesic therapy due to limited data, the lack of hemodynamic stability of patients, and the side effects of drugs. In the study of Rahul et al. (19), it was stated that morphine should be chosen in acute myocardial infarction in evaluating the questionnaire made to medical practitioners and the administrations made in practice. However, it was observed that the most administered drug was pentazocine. We detected that only 9.92% of the patients were administered drugs for analgesic purposes. In our study, opioids recommended as the first choice were not the most commonly used drug. The most commonly used was paracetamol. The second most frequently used drug was morphine. This may be due to fear of possible side effects of morphine such as hemodynamic or reinfarction, or because it is a narcotic group drug, paperwork procedures are required during its use, and the patient loses time for primary percutaneous intervention during the supply of analgesic drugs. This is supported by the fact that administering analgesic drugs to referral patients is significantly higher than in non-referral patients.

One of the remarkable results of our study is the onset of pain, the time of arrival to the emergency department, and the time of the door-balloon. The prolonged time between the onset of pain and arrival to the emergency department may be why patients do not want to come to the hospital because of Coronavirus disease 2019 (COVID-19). Soylu et al. (20), in their study comparing STEMI patients during the pandemic and pre-pandemic period, showed that the prehospital period was longer during the pandemic period.

The door-balloon time of our patients is close to the median of the door-balloon time in the literature (21). However, it was observed that there were strikingly high times in our door-balloon times. When the patient files were examined, it was observed that ECG could not make the diagnosis of STEMI in the emergency department. However some patients were diagnosed with STEMI after being noticed after cardiac enzyme follow-up.

Our study showed that patients with acute STEMI were also deficient in antiplatelet and anticoagulant treatments. While acetylsalicylic acid was not given to 7% of the patients, 40.07% did not receive anticoagulants. In addition, it was observed that no patient with a door-balloon time longer than 120 minutes was given fibrinolytic therapy. This shows problems in diagnosing STEMI in the emergency department and administering treatment algorithms.

Our study has several limitations. It is unknown whether the emergency medicine specialist or the general practitioner evaluated the patient in the hospitals that referred them. For the diabetic patient group, it is unknown how many years the patients have had diabetes and whether their diabetes is under control. Another limitation is that it is unknown whether the glyceryl trinitrate administered to the patients was given for blood pressure control or analgesic purposes, so these patients could not be included in the study.

CONCLUSION

We concluded that using medications for analgesic purposes in STEMI patients is insufficient and ignored. Although opioid use is mentioned in the guidelines, we found that paracetamol, which is not more effective, is preferred in STEMI pain control. In addition to the delays in the diagnosis of STEMI, there is a problem of not completing oral antiplatelet and anticoagulant therapy before the catheterization laboratory. It would be beneficial for best medical practices in the field to include more about pain management in the guidelines for STEMI, which is among the severe pain types.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Gaziantep İslam Science and Technology University Coordinatorship of Local Ethics Committee for Non-Interventional Clinical Researches (Date: 26.04.2022, Decision No: 111.16.14).

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Evaluation of effect of nilotinib in an experimental corneal neovascularization model

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ABSTRACT

Aim: This study aims to investigate the neovascularization-inhibiting effect of topical nilotinib and to determine the effective dose of nilotinib.

Material and Method: In this study, 42 healthy Wistar albino rats were randomly divided into six groups. The left corneas of all rats except group 1 were cauterized with silver nitrate. Group 1 was the healthy control, with no corneal vascularization, which did not receive any treatment; Group 2 (sham) did not receive treatment, only topical DMSO; Groups 3, 4, and 5 received topical nilotinib at doses of 10, 20, and 40 µM three times a day, respectively; Group 6 received 5 mg/dL topical bevacizumab three times for a day for seven days. On the 8th day, photographs of the corneas were taken, and the percentage of corneal neovascularization area was calculated. Following all rats being killed via anesthesia, the corneas were removed to determine the levels of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) ELISA and corneal immune staining.

Results: Other than Group 3, the percentage of neovascular corneal area was lower in the treatment groups compared to Group 2 ($p<0.05$). The intensity of VEGF and PDGF immune staining was also lower in the treatment groups. The treatment groups showed no significant differences compared to Group 1, except Group 3. The VEGF ELISA levels were statistically significantly lower in the treatment groups compared to Group 2 ($p<0.05$), with the exception of Group 3. The PDGF ELISA levels were statistically significantly lower in the treatment groups compared to Group 2 ($p<0.05$), and the Group 4 PDGF levels were statistically the lowest among the treatment groups.

Conclusion: Nilotinib was as effective as bevacizumab in the regression of corneal neovascularization. We observed that nilotinib was effective at doses of 20 µM and more.

Keywords: Corneal neovascularization, nilotinib, bevacizumab, VEGF, PDGF

INTRODUCTION

The cornea is optically clear, which is necessary to maintain visual acuity; defects in any of its layers due to infection, chemical or traumatic injury, or autoimmune disease can impair corneal clarity and therefore reduce visual acuity. Corneal neovascularization (CNV) has been reported in different corneal pathologies, and vessels sometimes appear to play different roles in the pathology (1). The cornea maintains avascularity by maintaining homeostasis, in which proangiogenic stimuli are balanced by antiangiogenic factors. Vascular endothelial growth factor (VEGF) is a member of the platelet-derived growth factor (PDGF) supergene family. VEGF has five sub-members, namely VEGF-A, -B, -C, -D, and placental growth factor (PGF), which can bind to three separate tyrosine kinase cell surface VEGF receptors (2).

PDGFs are growth factors released by vascular endothelial cells (VECs) in sprouting vessels and, like VEGFs, act through binding to the tyrosine kinase receptor (3). Antiangiogenic efficacy can be significantly affected by the inhibition of both VEGFRs and PDGFRs by a tyrosine kinase inhibitor (TKI) (4).

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Bevacizumab is a monoclonal antibody that binds to VEGF, thereby inhibiting VEGF-mediated signaling pathways and blocking angiogenesis (5). Bevacizumab, originally approved for the treatment of metastatic colorectal cancer, has been used in ophthalmology (off-label) with promising results in the treatment of exudative age-related macular degeneration, proliferative diabetic retinopathy, retinal vein occlusion, and iris rubeosis (6-8). Recently, studies have reported topical and subconjunctival bevacizumab for the treatment of corneal neovascularization. Although corneal neovascularization was not completely eliminated in these studies, it was reported that bevacizumab had a significant effect (9-14).

Nilotinib is a new-generation TKI that inhibits PDGF and indirectly VEGF, it has been approved for the treatment of chronic myeloid leukemia (CML) and shown to reduce fibrosis (15-18). In this study, we evaluated the clinical safety and efficacy of topical nilotinib for the treatment of CNV and compared these effects with topical bevacizumab.

MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles. This study was carried out with the permission of The Fırat University Experimental Animal Studies Ethics Committee (Date: 02.09.2020, Decision No: 2020/05).

This study used 42 Wistar albino male rats aged 8–10 weeks and weighing 250–300 g. A power analysis was conducted to determine the number of animals to be used in the experiments, whether the animals were to be divided into groups (and if so, each group would have at least eight animals), and with 8% deviation, type 1 error (α)=0.05, and type 2 error (β) (power=0.80) In order for the rats to continue feeding, chemical burns were created only on the left cornea with the use of silver nitrate.

Bevacizumab (Altuzan, Roche, USA) and nilotinib (Tasigna, Novartis, Switzerland) were dissolved in dimethylsulfoxide (DMSO). Topical treatment started one hour after the corneal burn procedure and continued for seven days (19). These rats were randomly divided into six equal groups: Group 1 was the healthy group, where a chemical corneal burn was produced in all the other groups. Group 2 (sham group) did not receive treatment, only topical DMSO three times a day. Groups 3–5 received 10 μM, 20 μM, 40 μM (respectively) topical nilotinib and Group 6 received 5 mg/dL topical bevacizumab three times a day (20).

Rat corneas were photographed at X40 magnification using a Sony digital camera (CCD IRIS model DXC 107 AP) mounted on a slit lamp microscope. The percentage of neovascularization area in the photograph to the entire corneal area was calculated using MATLAB R2007b version 7.5 (MathWorks, Natick, Massachusetts, USA) software.

The enucleated eyes were fixed in 10% buffered formalin solution and cut in the dorsoventral position so that the cornea, iris, lens, and optic nerve were in the same plane. Tissue samples were then routinely processed and cut to a thickness of 5 μm and stained by Hematoxylin & Eosin (H&E). Selected samples were stained by periodic acid–Schiff and Masson's trichrome. The thickness of the central cornea and corneal epithelium was measured via software. The number of leucocytes and vessels was counted in per mm^2 in corneal stroma between the limbuses. The percentage of damaged corneal epithelium was determined by measuring damaged epithelium/total epithelium.

The avidin–biotin complex (ABC) method was used for immunohistochemistry. The sections were deparaffinized in xylene and dehydrated using a series of graded alcohols. An UltraVision™ ONE Detection System: HRP Polymer/AEC Chromogen (ThermoFisher Scientific, Rockford, IL, USA) was used according to the manufacturer's protocols. Briefly, antigen retrieval was accomplished by microwaving the sections for 15 min in citrate buffer at pH=6 and then allowed to cool for 20 min. The sections were washed in PBS, and primary antibodies were applied after a hydrogen peroxide block (5 min) and an Ultra-V block (5 min). The sections were incubated in primary antibodies, including VEGF (Bioss, 1/100, bc-0279R) and PDGF (PDYN, 1/100, A5830) Then, an incubation with primary antibodies against immunodetection was performed for 60 min at 37°C with biotinylated goat anti-polyvalent, followed by peroxidase-labeled streptavidin using a labeled streptavidin biotin kit with 3- amino-9-ethylcarbazol (AEC, ThermoFisher Scientific, Rockford, IL, USA) as the chromogen substrate. The sections were counterstained with Gill's hematoxylin for 30 sec, and coverslips were attached using aqueous mounting media.

The corneal tissue samples were studied immediately. The protein levels in the supernatants were determined by the Lowry method (21). The VEGF and PDGF levels in the supernatants were measured using the Enzyme-Linked Immuno Sorbent Assay (ELISA) method. All results were calculated in units of mg/protein.

The tissue VEGF levels in the supernatant were studied using the rat VEGF-ELISA kit (Sunred Biotechnology Company, reference no. 201-11-0660) in accordance with the kit procedure. Absorbances were read

spectrophotometrically at 450 nm in an EPOCH 2 (BioTek Instrument, Inc., USA) microplate reader. All results are expressed in units of ng/L. The measuring range of the kit was 11–3000 ng/L, and its sensitivity was 10.127 ng/L. The intra-assay CV was <9%, and the inter-assay CV was <11%.

The tissue PDGF levels in the supernatant were studied using the rat PDGF ELISA kit (Sunred Biotechnology Company, reference no. 201-11-0692) in accordance with the kit procedure. Absorbances were read spectrophotometrically at 450 nm in an EPOCH 2 (BioTek Instrument, Inc., USA) microplate reader. All results are expressed in units of ng/mL. The measuring range of the kit was 0,05–15 ng/mL, and its sensitivity was 0,05 ng/mL.

This study was conducted in accordance with the ARVO Ophthalmic and Vision Research Statement on Animal Use. The subjects were kept at room temperature (22–25°C) for 12 h of light (7:00 AM to 19:00 PM) and 12 h of darkness (19:00 PM to 7:00 AM) and fed ad libitum in specially built cages.

Statistical Analysis

Data obtained in the study were analysed statistically using the Statistical Package for the Social Sciences (SPSS) version 22.0 software (SPSS Inc., Chicago, IL, USA). The data obtained were stated as mean±standard deviation (SD). The One-Way ANOVA test was applied for multiple comparisons. In paired comparisons between groups, the post hoc Tukey test was applied. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Neovascular Area

The neovascularization area percentage was significantly smaller in Groups 4, 5, and 6 compared to Group 2 ($p<0.05$). Although the area of neovascularization was less in Group 3 compared to Group 2, no statistically significant difference was observed ($p>0.05$). Further, there was no statistically significant difference when Groups 4, 5, and 6 compared to each others ($p>0.05$) (**Figure 1**).

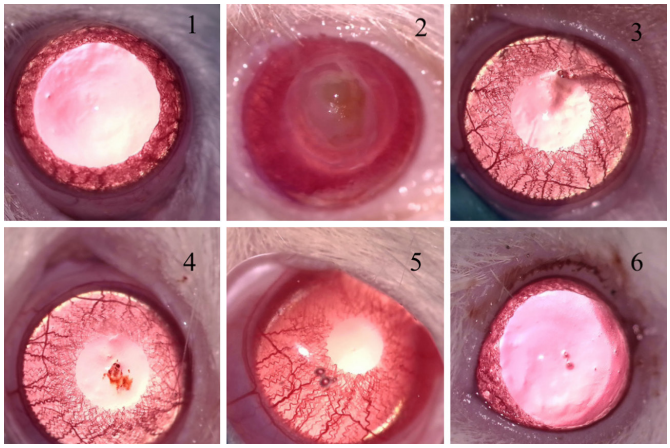

Figure 1. Comparison of corneas in control and treatment groups,.1: Normal cornea in Group 1. 2: Diffuse keratitis and severe neovascularization in Group 2. 3: Moderate neovascularization in Group-3. 4-6: Minimal epithelial keratinization and mild neovascularization in Group 4,5 and 6.

Histopathological Changes

In Group 1, corneas were well organized with the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. No inflammatory cell infiltration was present. However, all animals in Group 2 and some rats in Group 3 showed corneal neovascularization, multifocal moderate polymorphonuclear cell (PMNC) activity, macrophage infiltration, corneal hemorrhage, corneal rupture, and anterior uveitis (**Figure 2**). Uveitis lesions were characterized by neutrophilic infiltrations in the iris leaflet and processus ciliaris.

These changes were not noted in other treatment groups, including Groups 4, 5, and 6. However, these animal groups showed corneal stromal scar formation and thinning of the epithelial layer (**Figure 2**). The subepithelial scars consisted of either fibroblasts or collagen fibers.

The number of corneal vessels and inflammatory cells were higher in Group 2 than the treatment groups ($p<0.05$). In fact, almost no inflammatory cell infiltration or neovascularization was detected in Groups 4, 5, and 6 (**Table 1**). Groups 4, 5, and 6 prevented inflammatory infiltration and vascularization. Corneal thickness and central corneal epithelial thickness were altered in the treatment groups as compared to the control group. However, this increase was not statistically significant ($p>0.05$) (**Table 1**).

Table 1. Histological measurements in control and treatment groups

Groups	Number of vessels/ corneal stroma (mm²)	Number of PMN cells/ corneal stroma (mm²)	Central corneal thickness	Central corneal epithelial thickness	Epithelial damage (as % of corneal epithelium)
Group 1	0.00 ^{b*c*}	0.00 ^{b*c*}	106.32±21.94 ^{b*c*}	28.55±4.78	0.00 $^{b*c*\ d*e*f*}$
Group 2	4.42±3.06^{a*c*d*e*f*}	5.99±7.81^{a*c*d*e*f*}	229.24±106.87 ^{a*d*e*f*}	26.52±8.80	12.13±4.95 ^{a*d*e*f*}
Group 3	1.15±1.62^{a*b*d*e*f*}	1.90±2.44 ^{a*b*d*e*f}	205.34±49.73 ^{a*d*e*}	28.95±19.50	9.68±3.95 $^{a*d*\ e*}$
Group 4	0.00 ^{b*c*}	0.00 ^{b*c*}	150.34±17.19 ^{b*c*}	28.55±11.53	2.87±1.17 ^{a*b*c*f*}
Group 5	0.00 ^{b*c*}	0.00 ^{b*c*}	139.23±13.18 ^{b*c*}	34.45±10.94	1.20±1.57 $^{a*b*c*\ f*}$
Group 6	0.00 ^{b*c*}	0.00 ^{b*c*}	174.66±12.79 ^{a*b*}	26.73±12.01	7.79±1.88 $^{a*b*d*\ e*}$

a: According to the group 1, b: According to the group 2, c: According to the group 3, d: According to the group 4, e: According to the group 5, f: According to the group 6 shows significant difference (*=p<0.05)

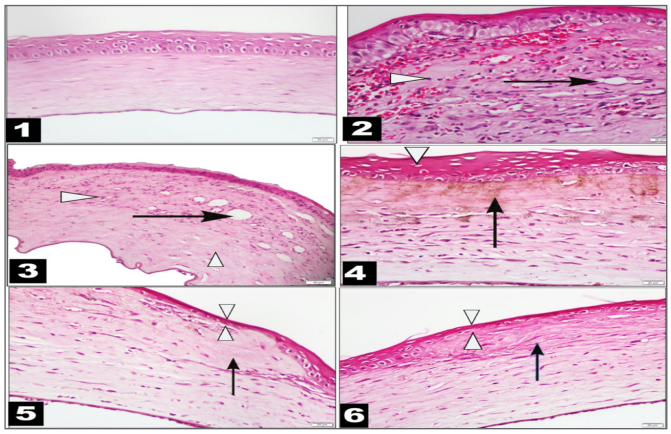

Figure 2. Comparison of histological analysis of the corneas in control and treatment groups, H&E, x40. 1: Normal corneal histology in Group 1. 2: Epithelial necrosis (arrow head), diffuse neutrophilic infiltration in corneal stroma and anterior chamber in Group 2. 3: Moderate neutrophilic infiltrate (arrow head) and neovascularization (arrow) in Group-3. 4: Epithelial keratinization and subepithelial fibrosis in Group-4. 5: Thinning in corneal epithelium and subepithelial fibrosis in Group-5. 6: Thinning in corneal epithelium (arrow heads) and subepithelial fibrosis in Group-6.

VEGF ELISA Levels

The mean VEGF levels in Groups 1, 2, 3, 4, 5, and 6 were 597.78±41.65, 1204.69±242.99, 863.57±72.17, 611.54±72.35, 643.48±124.30, and 674.69±96.61 pg/mg protein, respectively. A comparison of Groups 1 and 2 revealed that VEGF levels were significantly increased in the sham group ($p<0.05$). A comparison of Groups 2 and 6 revealed that VEGF levels were significantly decreased in the bevacizumab group ($p<0.05$). While group 3 and bevacizumab groups were compared, VEGF levels significantly decreased ($p<0.05$), it was statistically insignificant when compared with Groups 4 and 5 ($p=0.96$ and 1.00, respectively) (**Table 2**).

Table 2. VEGF and PDGF ELISA levels in control and treatment groups

Groups	VEGF (pg/mg protein)	PDGF (pg/mg protein)
Group 1	597.78±41.65^{b*c*}	4.79±1.06 ^{b*c*}
Group 2	1204.69±242.99^{a*d*e*f*}	10.62±2.02 ^{a*d*e*f*}
Group 3	863.57±72.17 ^{a*d*e*f*}	8.02±0.68^{a*d*}
Group 4	611.54±72.35 ^{b*c*}	5.13±0.68^{b*c*e*f*}
Group 5	643.48±124.30 ^{b*c*}	7.31±1.11^{b*d*}
Group 6	674.69±96.61 ^{b*c*}	7.83±1.55^{b*d*}

a: According to the group 1, b: According to the group 2, c: According to the group 3, d: According to the group 4, e: According to the group 5, f: According to the group 6 shows significant difference (*:$p<0.05$)

PDGF ELISA Levels

The mean PDGF levels in Groups 1, 2, 3, 4, 5, and 6 were 4.79±1.06, 10.62±2.02, 8.02±0.68, 5.13±0.68, 7.31±1.11, and 7.83±1.55 pg/mg protein, respectively. A comparison of Groups 1 and 2 revealed a significant increase in PDGF levels in the sham group ($p<0.05$). PDGF levels signigficantly decreased while bevacizumab group compared with Group 2 ($p<0.05$), it was statistically insignificant when compared with Groups 3 and 5 ($p=1.00$ and 0.97, respectively). Among the nilotinib groups, Group 4 PDGF levels significantly decreased when compared with Groups 3 and 5 ($p<0.05$) (**Table 2**).

Immunohistochemical Findings: The positive immunoreaction of VEGF was characterized by red granules in the cytoplasm of infiltrated PMNC, macrophages, neovascular endothelium, and limbal vasculature. Positive staining for VEGF was detected in Groups 2 and 3 in the corneal inflammatory infiltrate. In other treatment groups, no positive immunostaining was detected (**Figure 3**).

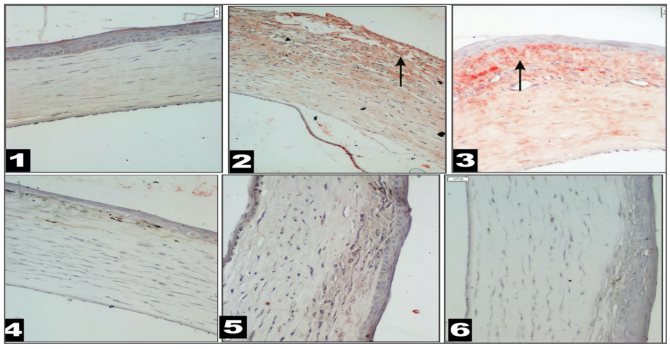

Figure 3. Comparison of immunohistochemical analysis of the VEGF in corneas in control and treatment groups, ABC Method, x40. 1: No positive immunoreactivity to VEGF in Group-1. 2: Diffuse immunoreaction in in neutrophiles (arrow), macrophages, and keratocytes in Group-2. 3: Diffuse staining in inflammatory infiltrate in neutrophiles (arrow), macrophages, and keratocytes in Group-3. 4-6: No immunostaining in other treatment groups, including Groups 4, 5, and 6.

The positive expression of PDGF was detected by red granules in the cytoplasm of fibroblasts, vascular endothelium, and keratocytes in subepithelial scar tissue. No positive expression of PDFG was seen in Group 1 (**Figure 4**).

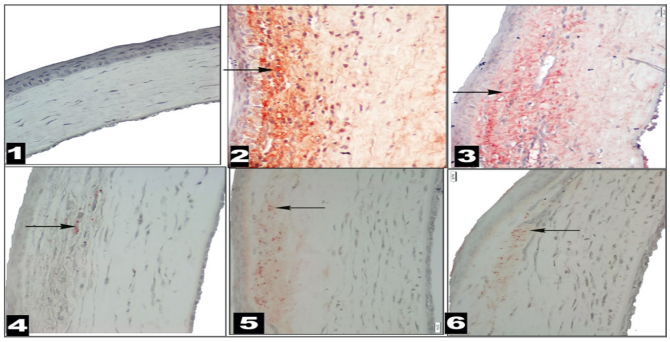

Figure 4. Comparison of immunohistochemical analysis of the PDGF in corneas in control and treatment groups, ABC Method, x40. 1: No positive immunoreactivity to PDGF in Group-1. 2: Diffuse immunoreaction in fibroblasts (arrow), vascular endothelial cells and keratocytes in Group-2. 3: Diffuse immunoreaction in fibroblasts (arrow), keratocytes, and vascular endothelial cells in Group-3. 4: Weak immunostaining in fibroblast in subepithelial scar tissue in Group-4. 5-6: Mild to moderate immunostaining in fibroblast in subepithelial scar tissue in Groups 5 and 6.

DISCUSSION

In our study, we investigated the effect of nilotinib on experimental corneal neovascularization, tried to determine the most effective dose, and compared these treatments with those of bevacizumab. We observed that the effect of 20 μM and 40 μM nilotinib doses on VEGF was similar to that of bevacizumab, but the 20 μM nilotinib dose was more effective on PDGF than bevacizumab and other nilotinib doses.

CNV can occur due to chemical burns, ischemia, infection, trauma, and inflammation, and it affects approximately 1.4 million people per year (22). The main causes of corneal neovascularization are infectious diseases, inappropriate contact lens use, and the vascular response to corneal transplantation (23). Neovascularization is created by many cellular factors (24).

VEGF expression is elevated in both animal models and human corneas with CNV and is secreted by multiple cell types, such as epithelial cells, vascular endothelial cells, macrophages, and fibroblasts (25,26). VEGF is a family of proteins with five members (VEGF-A, -B, -C, -D, and PGF) that bind to three distinct tyrosine kinase cell surface VEGF receptors and are key mediators in the development of neovessels (24-27). VEGF-A is the target of several drugs and mediates pathological neovascularization through VEGFR2 activation. VEGF-A receptors, VEGFR1 and VEGFR2, are secreted by VECs. VEGF-induced effects enhance the growth, migration, and survival of endothelial cells (26-28).

PDGF is an important growth factor released by VECs for neovascularization. Newly formed vessels will regress spontaneously unless they are surrounded by pericytes, an event promoted by PDGF-β. PDGF stimulates VEGF transcription via the tyrosine kinase PDGF receptors (a and β). Sprouting endothelial cells secrete PDGF, and pericytes express PDGFR-β. Therefore, inhibition of the PDGF signaling pathway impairs pericyte recruitment. PDGF plays a stabilizing role on newly formed blood vessels. In one study, inhibition of PDGFR-β not only had a longer efficacy but also resensitized CNV to VEGF blockade. PDGF is effective in the progression from VEGF-dependent nascent neovascular sprouts to stable, mature vessels (24,29,30).

Antiangiogenic therapy holds great promise for the treatment of corneal neovascularization. Bevacizumab, an anti-VEGF monoclonal antibody, has been applied in the treatment of a variety of systemic malignancies (31). The effects of topical bevacizumab on the inhibition of corneal neovascularization have been demonstrated in many studies (11,20,32-34). Although anti-VEGF agents are effective, VEGF is not the only molecule involved in angiogenesis. PDGF is a molecule that also affects angiogenesis, and inhibiting this pathway could be more effective. It was determined that simultaneously blocking both the PDGF and VEGF pathway was more effective than blocking each pathway alone (29). Yet another study found that combination therapy with sunitinib resulted in greater inhibition of neovascularization in animals treated with bevacizumab alone (35).

Nilotinib is a TKI that is very potent in the treatment of CML and targets several TKs (15-17); although it has been used in eye surgery before due to its antifibrotic effects (36), it also has anti-angiogenic properties by acting on VEC and inhibiting PDGF (15,37,38). In a study by van Steensel et al. (39), in which the effectiveness of imatinib and nilotinib on orbital fibroblasts was evaluated in vitro, it was shown that imatinib and nilotinib inhibited PDGF.

Liu et al. (18) reported that the suppressive effects of nilotinib on VEGF and VEGFR in liver fibrosis were effective at 20 μM in their animal experiment. In the in vitro study of Hadzijusufovic et al. (15), the growth-inhibitory effects of nilotinib were observed in the presence and absence of VEGF; they also reported that, unlike imatinib, nilotinib suppressed endothelial cell migration in VEGF-induced tube formation. In addition, the effects of 10–20 μM doses of nilotinib and imatinib on endothelium were compared, where 20 μM nilotinib was more effective than the other doses. Based on this study, we designed our topical dose by adding 40 μM to see whether it would be more effective.

To our knowledge, there is no study on the effect of nilotinib on corneal angiogenesis so far. In our study, we chose three treatment groups to receive nilotinib doses of 10 μM, 20 μM, and 40 μM three times a day. Among the treatment groups, the nilotinib 10 μM dose was less effective in reducing neovascularization areas than the other treatment groups. This indicated that the 10 μM dose of nilotinib may be ineffective compared to the higher doses.

Baek et al. (40) stated that imatinib, a TKI, reduces the recruitment of immune cells in the corneal epithelium, and its therapeutic efficacy is similar to or better than cyclosporine treatment. Onder et al. (41) found that regorafenib, a multiple-TKI, when compared with bevacizumab and dexamethasone, had inhibitory effects on alkali-induced CNV in rats. In a study comparing rats with corneal burns receiving a nintedanib thermo-sensitive hydrogel, nintedanib, and dexamethasone, it was reported that the CNV area of the subjects receiving the nintedanib thermo-sensitive hydrogel was lower than the other groups (42).

We included bevacizumab in our study, which has been shown to be effective in experimental CNV in most studies and has been compared with different TKIs, and compared it with nilotinib (43,44).

Our study had some limitations. First, the pharmacokinetic and pharmacodynamic effects of the drug were not evaluated. Second, only short-term effects were evaluated; long-term effects were not evaluated. Third, the effect of the drug on other neovascularization pathway markers and other administration methods were not considered. The final limitation of our study is the lack of in vitro studies such as human umbilical vein endothelial cells culture to demonstrate cellular toxicity.

CONCLUSION

Our study shows that nilotinib may be dose-dependently effective in preventing corneal neovascularization. In addition, auxiliary materials such as thermo-sensitive hydrogel can be used, which can increase the topical effect or prolong the duration of the drug effect. Further studies are needed to evaluate the effect of nilotinib on corneal neovascularization.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of The Fırat University Experimental Animal Studies Ethics Committee (Date: 02.09.2020, Decision No: 2020/05).

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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Original Article

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Prognostic factors between the proximal femoral nail and bipolar hemiarthroplasty in femoral intertrochanteric fractures

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ABSTRACT

Aim: In the treatment of intertrochanteric femur fractures, proximal femoral nail (PFN), and bipolar hemiarthroplasty (BPH) are widely used. This study aimed to compare these two types of implants depending on risk factors regarding patients.

Material and Method: PFN (Group 1) was applied to 40 of the 89 patients (44 female, 45 male) aged between 51-80 (mean 68.16±6.78) and BPH (Group 2) was applied to 49 of them. Age, gender, fracture side, fracture mechanism, additional disease, Body mass index (BMI), Albumin level, Hemoglobin (Hb) decrease level, T-score, American Society of Anesthesiologists (ASA) classification, type of anesthesia, surgery type, operation time, hospital stay and full weight-bearing time, Harris Hip Score (HHS) in preoperative and postoperative periods, classification of intertrochanter fracture according to the AO Foundation and Orthopedic Trauma Association (AO/OTA), postoperative complications were recorded.

Results: Group 1 was younger with a mean age of 64.55±6.23 years compared to Group 2 ($p < 0.05$). Most of the fractures were 3A2 type and the result of low energy ($p > 0.05$). In group 1, operation time was 46.78±5.29 minutes and hospital stay was 2.48±0.75 days, which was shorter, most surgery types were closed, T-score was -2.49±0.59 and better, the time of full weight-bearing was 3.48±0.78 months, Hb decrease was 1.17±0.37 g/dL and less, Albumin level was 3.11±0.4 g/dL and higher ($p<0.05$). In Group 2, the age was the highest (72.6±5.2) and the T score was the lowest (-2.9±0.4) in the 3A2 fracture type ($p<0.05$). HHS was better in the BPH group at the sixth month ($p<0.05$), and there was no difference between the two groups at the end of one year ($p>0.05$).

Conclusion: Prognostic markers for treatment outcomes in individuals with intertrochanteric fractures are still unknown. It is important to determine the factors that will contribute to the long-term functional results in these patients.

Keywords: Intertrochanteric femur fracture, proximal femoral nail, bipolar hemiarthroplasty, prognostic factors, functional outcomes

INTRODUCTION

With the aging population, the rise in additional diseases such as osteoporosis increases the incidence of hip fractures (1). Fractures of this region bring along functional disorders. Most of the patients can not return to premorbid mobility levels. Millions of people experience major problems due to these fractures, which put a heavy burden on the health system (2). Intertrochanteric femur fractures constitute 50% of hip fractures and the mortality rate within a year is 15-20%. This type of patient is accompanied by many morbidities such as diabetes, lung, heart, hypertension, and low general condition. Therefore, the surgery of these patients is important because of the complications and results (3). Biomechanical studies make intramedullary implants suitable for trochanteric fractures due to their load-bearing and high mechanical resistance properties (4). However, some patient-related features may prevent using these implants all the time. Bipolar hip prostheses are widely used in trochanteric region fractures, especially in unstable fractures (5). Functional results vary from the position of the implant in the femoral neck to the course of the fracture and patient data. Osteosynthesis in the correct position provided by the implant can procure a good union and minimize mechanical complications (6).

The aim of this study was to evaluate the prognostic markers that affect the functional outcomes of PFN or

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cementless BPH, which we performed in patients with an intertrochanteric femur fracture, by comparing the risk factors affecting these results.

MATERIAL AND METHOD

This study was designed as a retrospective cohort study. This study was approved by İstinye University Clinical Researches Ethics Committee (Date: 03.03.2022; Decision No: 3/2022.K-21). All procedures were performed by the ethical rules and principles of Declaration of the Helsinki.

Between the years 2017-January and 2019-November, 103 patients who had PFN or cementless BPH surgery were recorded and analyzed in our hospital with the diagnosis of intertrochanteric femur fracture. Those with pathological fractures, multiple fractures, who did not come to the controls and we could not reach were excluded from the study. 89 patients constituted the study group. Age, gender, fracture side, fracture mechanism (low-high energy), additional disease, BMI, Albumin level, Hb decrease level (Hb level difference before and after the operation without blood transfusion) of all patients, T-score for osteoporosis, also ASA classification, type of anesthesia, surgery type (open-closed), operation time, hospital stay and full weight-bearing time, HHS in preoperative and postoperative periods, classification of intertrochanter fracture according to AO/OTA, postoperative complications were recorded using the hospital archive and patient controls (**Table 1**).

The AO-OTA classification and the patient ages were divided into 3 groups as 3A1, 3A2, 3A3, and 50-60, 61-70, 71-80. Additional diseases of the patients were Diabetes mellitus (DM), cardiac–hypertension, pulmonary, and neurologic. Those with BMI ≥ 25 kg /m² were overweight, albumin level between 3,4-5,4 g/dl was normal, and those with T-score ≤ -2.5 were osteoporosis. Postoperative complications were recorded regarding wound infection, deep vein thrombosis (DVT), urinary-pulmonary infection, bedsore, and implant-related.

HHS (7); Components are pain, function, range of motion, and deformity. The function is separated into two categories: activities of daily living and gait. The meaning of scores: 90–100 excellent, 80–89 good, 70–79 fair, and <70 poor. It was evaluated preoperatively and at 6, 12 months postoperatively.

Statistical Analysis

SPSS 21.0 program was used in the analysis. The chi-square test was used to examine the association between categorical variables. The correlation test was used to examine the relationship among numerical variables. The difference between the numerical variables according to the categorical variables with two groups was analyzed with the t-test, and the difference between the categorical variables with three or more groups was analyzed with the ANOVA test. The statistical level of significance was established at p <0.05.

Table 1. The relationship between the implant types and the clinical features of patients

	PFN		BPH		p value
	N	%	N	%	
Age (Years)					.015*
50-60	13	32.5	5	10.2	
61-70	14	35.0	16	32.7	
71-80	13	32.5	28	57.1	
Mean±Sd	64.55±6.23		71.12±5.74		
Gender					.602
Female	21	52.5	23	46.9	
Male	19	47.5	26	53.1	
Side					.098
Right	25	62.5	22	44.9	
Left	15	37.5	27	55.1	
AO-OTA					.181
3A1	14	35	17	34.6	
3A2	20	50	30	61.2	
3A3	6	15	2	4.0	
Anesthesia					.806
Spinal	35	87.5	42	85.7	
General	5	12.5	7	14.3	
Fracture mechanism					.606
Low energy	30	75	39	79.6	
High energy	10	25.0	10	20.4	
Surgery type					.001*
Open	3	7.5	49	100	
Closed	37	92.5	-	-	
Additional illness					.652
Only one	8	30.8	12	36.4	
>1	18	69.2	21	63.6	
Postoperative complication					
Wound Site	4	30.8	1	20.0	.636
DVT	2	15.4	2	40.0	
Urinary-pulmonary infection	1	7.7	1	20.0	
Bedsore	4	30.8	1	20.0	
Implant related	2	15.4	-	-	
	Mean ±Sd		**Mean ±Sd**		
Operation time (minutes)	46.78 ±5.29		58.73±7.01		.001*
Hospital stay (day)	2.48±0.75		4.59±1.0		.001*
BMI	26.5±4.14		26.94±4.29		.627
ASA	2.63±0.63		2.84±0.59		.105
T-score	-2.49±0.59		-2.83±0.5		.004*
Full weight - bearing (month)	3.48±0.78		postoperative day		.001*
Hb decrease (g/dL)	1.17±0.37		2.05±0.45		.001*
Albumin (g/dL)	3.11±0.4		2.84±0.33		.001*

PFN: proximal femoral nail BPH: bipolar hemiarthroplasty AO-OTA: AO Foundation and Orthopedic Trauma Association BMI: body mass index ASA: American Society of Anesthesiologists classification Hb: hemoglobin Sd: Standard deviation, *Significance; p<0,05

RESULTS

The mean follow-up time of 89 patients (44 female, 45 male) aged between 51-80 (mean 68,16±6,78) was 28.6 (range 24-33) months. PFN (Group 1) was applied to 40 of the 89 patients and cementless BPH (Group 2) was applied to 49 of them. PFN patients were younger with an average age of 64.55±6.23 compared to those who underwent BPH (p <0.05), there was no difference between the two groups concerning gender (p> 0.05). Most of the fractures were 3A2 type according to AO-OTA and were the result of low energy, and there was no difference among the fracture sides (p>0.05). Spinal anesthesia was applied to most of the patients in the two groups, and most of the patients had more than one additional disease. although postoperative complications were higher in group 1, there was no significant difference between the two groups (p>0.05) (**Table 1**).

In group 1, operation time was 46.78±5.29 minutes and hospital stay was 2.48±0.75 days, which were shorter, most surgery types were closed, T-score was -2.49±0.59 and better, the time of full weight-bearing was 3.48±0.78 months, Hb decrease was 1.17±0.37 and less, Albumin level was 3.11±0.4 g/dL and higher (p<0.05). The mean BMI was >25 kg/ m^2 in both groups, and there was no difference between ASA scores (p>0.05) (**Table 1**).

When we examined the AO-OTA fracture type in two groups with various factors, in the BPH group, the age was the highest (72.6 ±5.2) and the T score was the lowest (-2.9±0.4) in the 3A2 fracture type. The age was the lowest (64.0±5.6) and T score was the best (-2.4±0.5) in patients with 3A3 fracture type who had BPH (p<0.05). We found no difference in these parameters in the PFN group (P>0.05). Most of the 3A1 and 3A2 fracture types in the PFN group were performed with low energy and the 3A3 type with high energy (p<0.05). We did not detect such a difference in the BPH group. There was no significant difference in AO-OTA fracture types in the two groups in terms of gender, operation time, BMI, and postoperative complications (p>0.05) (**Table 2**).

Table 2. Comparison of the fracture types according to AO/OTA with clinical features of patients.

	AO – PFN	AO - BPH
	P value	P value
Age	.097	.025*
Gender	.284	.490
Fracture mechanism	.001*	.153
Operation time	.935	.277
BMI	.280	.240
T-score	.118	.046*
Postoperative complication	.211	.405

*Significance; p<0,05

From a functional point of view, HHS was better in the BPH group compared to PFN at 6 months (p<0.05), but there was no difference between the two groups at the end of one year (p>0.05) (**Table 3**). Also, there was no difference between the two groups in terms of preoperative HHS (p>0.05). When we compare the scoring made in the postoperative periods with the preoperative period, although it was seen that there was a positive relationship in itself, the patient scores could not reach the preoperative levels (**Figure**) (**Table 4**).

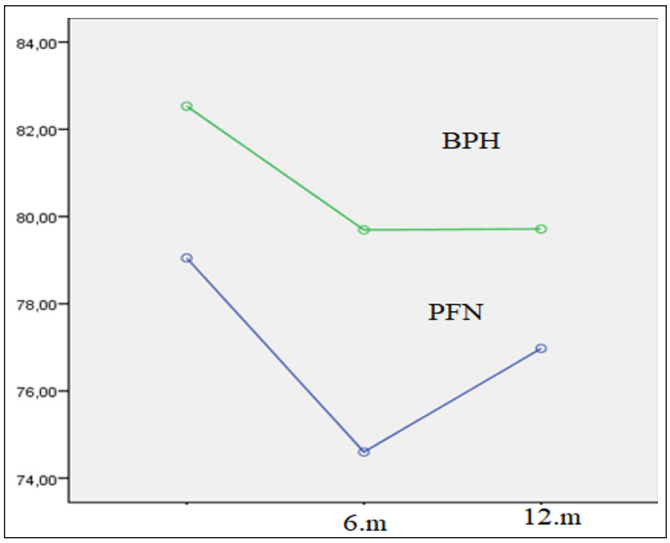

Figure. In two groups, preoperative and postoperative 6th-12th. month HHS comparison.

Table 3. Comparison of the implant types and HHS

Month	PFN	BPH	p value
	Mean±Sd	Mean±Sd	
Harris Hip Score			
6.	74.6±6.05	79.69±5.99	.001*
12.	76.98±6.22	79.71±7.18	.061
Preoperative Harris Hip Score	79.05±6.16	82.53±5.53	.188

*Significance; p<0,05

Table 4. The correlation of preoperative and postoperative HHS with implant types

Month		Preoperative Harris Hip Score	
		PFN	BPH
Harris Hip Score			
6.	r	.960*	.873*
	p	.001	.001
12.	r	.968*	.946*
	P	.001	.001

*Significance; p<0,05 r ; correlation

DISCUSSION

Femoral intertrochanteric fractures, which are frequently seen based on osteoporosis in the elderly, maintain their importance in terms of high mortality and morbidity. The majority of hip fractures are observed in adults over the age of 65, and half of these

fractures are in the intertrochanteric region, and they are more common in women. It usually develops as a result of high-energy events such as traffic accidents and falling from a height in the young age group, and as a result of low-energy injuries such as simple falls in the elderly (8). It was shown in a study that major traumas such as traffic accidents caused these fractures more than factors related to falling (9). In this research, the average age of all patients with intertrochanteric fracture was 68.16±6.78, whom we divided into two groups by applying PFN and BPH in the treatment, but the average age of the PFN group was younger than the BPH group, the fracture mechanism was mostly due to low energy, and our data are consistent with the literature. We attribute the almost equal distribution of gender in this type of fracture in our region, to the fact that men take a less active role in work activities but face more injury risks, and low functional mobility increases the susceptibility to hip fracture (10).

It was shown that advanced age and low socioeconomic level negatively affected mobility (11). Patients over 75 years of age generally have osteoporosis, slow fracture healing, bedridden complications, and high mortality rates (3). In this study, most of the patients had more than one additional disease and wound site, DVT, urinary-pulmonary infection, bedsore, and implant-related postoperative complications were observed. We attribute the lack of difference between the two groups in these respects to the unique characteristics of the fractures in this region.

Intertrochanteric fractures are classified to figure out the long-term clinical prognosis of implants, provide direction for various surgical procedures, and indicate fracture stability (12). Although the prevalence of AO/OTA 31-A3 fractures is limited, the rate of implant failures in these fractures is higher than in AO/OTA 31-A2 and A1 fractures (13). In this study, most fractures in the two groups were 3A2, and the fact that we did not see any difference between the surgical option and the fracture types showed us that our implant option was not the only one in all types of fractures in this region. The fact that most of the 3A1 and 3A2 fracture types in the PFN group were with low energy, and 3A3 with high energy, will guide the prevention of the severity of injuries in the 3A3 fracture type with high complications (13, 14). In addition, the fracture type we had BPH was 3A2 in those with the highest age and the lowest T score, whereas we did not detect any difference in these parameters in the PFN group, showing us that we can use PFN in most fracture types including these parameters.

The incidence of osteoporosis increases with the aging population (15). Some studies have shown that osteoporosis has negative consequences in intertrochanteric fractures (16). The important points in this type of fracture are early mobilization, full-weight bearing, and firm stabilization. However, the fact that most of the patients are advanced age and osteoporotic has a great impact on implant complications and morbidity (17, 18). Failure to attain early weight-bearing is well documented, especially in the case of this fracture kind, which affects old individuals (19, 20). It was stated that early administration of intravenous bisphosphonate treatment in individuals with an intertrochanteric fracture was a safe way for managing osteoporosis. In impoverished nations, osteoporosis care is frequently overlooked due to reasons such as insufficient awareness and financial constraints (21). In this study, while in the BPH group on the first postoperative day, full weight-bearing was achieved, it was at 3.48±0.78 months in the PFN group. Our BPH application in the group with a lower T-score and the complications related to implants and bedsores in the PFN group are consistent with the literature and show that we consider early mobilization.

It was found that high BMI was a protective agent against hip fractures, whereas limited functional mobility was a potential risk for hip fractures (10). Studies which found that higher BMI values were related to a decreased frequency of hip fractures supported the relevance of good nutrition (22). They reported that individuals having intracapsular fractures had lower BMI ratings than those with intertrochanteric fractures (23). At most, 20% of individuals with intertrochanteric fractures had BMIs below 18 kg/m2, compared to almost 50% of them with intracapsular fractures. In this study, the mean BMI >25 kg/m2 in both groups indicates that there may be other risk factors in fractures of this region within the scope of protection.

The Mini Nutritional Assessment (MNA) identifies poor nutritional status as a high-risk factor for fracture development in any area of the body (24). The advantages of good/healthy nutrition as functioning, comorbidity, and outcome, were also observed in other studies related to hip fractures (25). Good nutrition may be linked to a lower risk of fractures and a faster functional recovery from hip fractures. Albumin is a good marker as an indicator of malnutrition (26). It was found that albumin levels could not indicate improved functional results independently (27). In this study, albumin values were below the average in both groups, but we attribute the higher albumin in the PFN group compared to the BPH group to the lower mean age of the patients in this group.

In a study about PFN and hemiarthroplasty, they showed that in the elderly, the PFN group had a longer operation time (28). In contrast, They reported that the surgery time in PFN patients was less than in the hemiarthroplasty group in the elderly (8). This difference in the literature

may be due to reasons such as fracture reduction, implant differences, and surgical ability. In another study, they reported that the PFN group's surgery time and intraoperative blood loss were much less than those of the hemiarthroplasty group, with no significant difference related to average hospital stay between the two groups (5). It was reported that despite the reduced surgery duration, the quantity of postoperative and intraoperative early bleeding was greater in hemiarthroplasty patients (1). Controlling hemodynamics in patients with a high ASA score and a requirement for postoperative intensive care has been highlighted as a challenge. In this study, operation time, hospital stay, and Hb decrease levels were observed to be much lower in the PFN group than in the BPH group. Although there was no difference between the two groups on these results concerning ASA scores and anesthesia type, we think that the closed method of most of the surgeries in the PFN group was effective on the results.

They showed that the rates of DVT and pulmonary embolism were significantly higher in BHA according to PFN (1). In another study, they reported no significant differences between the two groups in postoperative complications such as bedsores, DVT, lung infection, and urinary tract infection (5). It was also found that no late postoperative infections in either the BHA or PFN individuals, however early postoperative wound infection rates were comparable (29). Although bedsore, wound site, and implant-related issues were more prevalent in the PFN group in this research, no difference in postoperative problems in general among the two groups has been detected. As a result, the surgeon's preference and expertise may be used to evaluate each case and choose the best treatment technique.

They showed that higher HHSs were observed in the hemiarthroplasty group for up to six months and higher levels at twelve months in the PFN group (8). At 18 months, both groups' values increased, but the PFN group's growth was greater. According to research, higher albumin of serum, younger age, and Activities of Daily Living (ADL) at discharge were all linked to greater hip function, as defined by HHS (30). They stated that the pre-injury function was favorably connected to treatment response. It was found that as people aged, their HHS decreased, as well (20). The hip function was linked to older age, which was a non-modifiable and independent risk factor (30). In this study, the mean age was higher in the BPH group. Although there was no difference between the preoperative HHS in the two groups, the HHS was better at 6 months in the BPH group than in the PFN group, but there was no difference between the two groups at the end of one year. There was a positive correlation between the preoperative and postoperative HHS. Since this scoring includes many parameters in itself, it provided better scores in the BPH group compared to the PFN group in the early period and showed that other factors should be considered in the evaluations.

The limitations of this study were that it was carried out in a single center, the small sample size, the retrospective nature of the research, and the inability to compare with other surgical methods used in the treatment of fractures in this region.

CONCLUSION

While most studies investigated risk factors for intertrochanteric fractures, they focused more on unstable fractures (12,30). This study will contribute to the literature as it covers all fracture types in the trochanteric region. Prognostic markers for treatment outcomes in individuals with intertrochanteric fractures are still unknown. It is important to determine the factors that will contribute to the long-term functional results in these patients. This research will add a different perspective to the literature in terms of comparing many parameters with patient function in intertrochanteric femur fractures.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of İstinye University Clinical Researches Ethics Committee (Date: 03/03/2022; Decision No: 3/2022.K-21).

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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Original Article

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Prenatal characteristics and management of pregnants with fetal cerebellar malformation: 4-year single center experience

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ABSTRACT

Introduction: Fetal cerebellar malformations (FCM) are known as very rare central nervous system malformations that occur as hypoplasia or agenesis of the cerebellum or vermis. In this study, the characteristics, diagnostic methods, risk factors and management of pregnant women diagnosed with FCM in the prenatal period were investigated.

Material and Method: The patients who diagnosed with prenatal FCM in the perinatology center between March 2017-February 2021 were included, retrospectively. The frequency of fetal magnetic resonance imaging (MRI), amniocentesis and/or karyotype analysis rates, and termination frequency were evaluated. In addition, the factors affecting the amniocentesis and the termination/follow-up decision were investigated.

Results: A total of 42 pregnant with FCM were included. The median gestational age was 24.0 years, and the mean gestational week was 25+2 (SD±5+1) weeks. Nearly half (40.5%) of patients were diagnosed before 24 weeks of gestation and 45.2% were primiparous. Cerebellar hypoplasia was observed in 47.6%, while vermis agenesis was observed in almost one third (31.0%); and also 19.0% had multiple FCM. The fetal USG was used in all pregnant women, fetal MRI was performed in only 4.8% for diagnosis of FCM. The rate of amniocentesis and karyotype analysis were 11.9% and 7.1%, retrospectively. No any complications were observed after the amniocentesis. The termination rate was 30.9%. The mean gestational week of those who had live birth was higher than those who were terminated (24+4 vs 20+5) (p=0.019).

Conclusion: The frequency of FCM diagnosis has increased with the development of modern medicine and technology. There is no relationship between demographic characteristics of pregnant women and FCM. Socio-economic levels and religious belief differences affect the termination and birth rates.

Keywords: Cerebellar malformation, cerebellar hypoplasia, vermis hypoplasia, pregnancy, termination

INTRODUCTION

Primary cerebellar malformations can be seen in isolation from other brain anomalies, or they can occur as part of a syndrome accompanied by anomalies of other organs. Generally, there is an underlying genetic etiology (1,2). There is no consensus on the terminology, definition and mechanism yet (3). There are many cerebellar malformations such as cerebellar hypoplasia/hyperplasia, isolated vermian hypoplasia, Dandy-Walker malformation, pontocerebellar hypoplasia and vermis hypoplasia, and they are usually a part of many genetic disorders and syndromes (1,2).

The fetal cerebellar malformations (FCM) were evaluated by fetal ultrasonography (USG) in 18-22 gestational weeks in the prenatal period. While the diagnosis of cerebellar malformations is usually made by prenatal USG, fetal magnetic resonance imaging (MRI) is also used in a few cases (4). Fetal MRI is mostly used in the second half of pregnancy, and it is used especially when cerebellar hemorrhage is suspected or when USG cannot be used adequately or sufficient images cannot be obtained with USG (5). Griffiths PD et al. (6) reported that in their multicenter prospective cohort study (MERIDIAN), fetal USG had an accuracy of 68% and fetal MRI was 93% accurate in the diagnosis of central

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nervous system anomalies. On the other hand, it has been shown that diagnostic accuracy rates in central nervous system anomalies are as good as fetal MRIs if fetal USGs are performed by specialist sonographers (7,8).

After diagnosing FCMs, amniocentesis and/or karyotype analysis are performed to detect congenital cardiac anomalies, other multiple anomalies and genetic etiology (9). Bahram et al. (10) reported that all of these fetuses had multiple anomalies, although the termination rate was reported as 26.0% in which pregnant women with fetal cerebellar anomaly (Blake's pouch cyst).

Our primary aim is to evaluate the characteristics, diagnostic methods (fetal USG/MRI), accompanying anomalies and risk factors of pregnant who are diagnosed with FCM in the prenatal period. The investigations of management, amniocentesis rates, genetic etiologies and termination rates were the second aim of the study.

MATERIAL AND METHOD

This study was carried out with the permission of University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (Date: 19/01/2022, Decision No: 2022-25). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients Selection

All pregnant women diagnosed with fetal cerebellar hypoplasia/aplasia and vermis hypogenesis/agenesis between March 2017 and February 2021 were included in the study, retrospectively. In case of anomaly accompanying FCM in pregnant women, the patient was excluded from the study. After giving written or verbal information about the study, written consent was obtained from the patients who agreed to participate in the study.

Data Collection and Assessment of Patients

Demographic data of pregnant women (gender, age, gestational week) were analyzed. Fetal USG/MRI usage rates, the frequency of amniocentesis and/or genetic analysis were investigated. The termination rates of the patients were recorded. In addition, the effects of demographic characteristics, gestational weeks and ages on the amniocentesis, genetic analysis and terminations were examined.

Statistical Analysis

Datas were analysed using the SPSS 25.0 (IBM, Armonk, NY: IBM Corp.) program Continuous variables were expressed as mean ± standard deviation, median (interquartile range, IQR), and categorical variables as numbers (n) and percentages (%). When the parametric test assumptions were met, t-test was used to compare differences between independent groups. When parametric test assumptions were not met, Mann-Whitney U test was used to compare differences between independent groups. The Chi-squared or Fisher's exact probability tests used to compare demographics. In all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

A total of 64 pregnant women were diagnosed with FCM during the study period. Due to a lack of medical records, 22 cases were excluded from the study (**Figure**). Overall 42 patients were included. The median pregnancy age was 24.0 years (minimum 18.0-maximum 38.0, IQR 23.0-29.0). The mean gestational week at the time of diagnosis was 25+2 weeks (SD ± 5+1 weeks) (**Table 1**). The rate of prenatal diagnoses before 24 weeks was 40.5% (n=17) and 45.2% (n=19) were primiparous. The numbers of gravida, parity, abortion and curettage at the time of diagnosis are shown in **Table 1**.

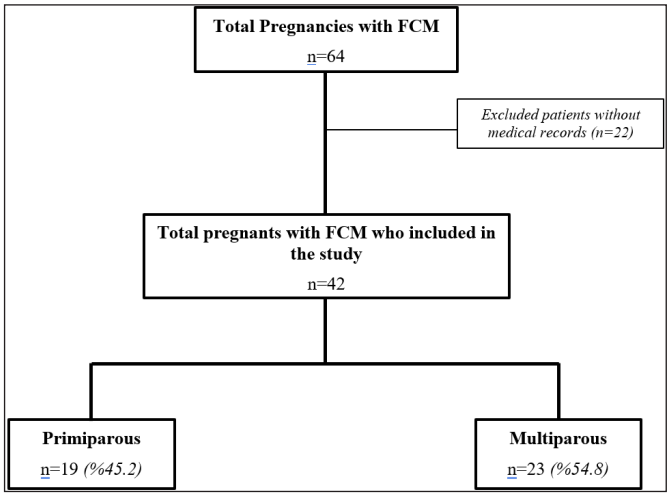

Figure. Distribution of patients enrolled in the study period.
*FCM: fetal cerebellar malformation

Table 1. Demographic characteristics of patients with FCM

Pregnancy age (year) [median (min-max, IQR)]	**24.0** (18-38, 23-29)
Gestational week (weeks) [mean (±SD)]	**25^{+2}** ($\pm5^{+1}$)
History (n) [median (min-max)]	
Gravida	2 (1-5)
Parity	1 (0-4)
Abortion	0 (0-2)
Curettage	0 (0-1)
The type of FCM [n (%)]	
Cerebellar hypoplasia	**20 (47.6)**
Cerebellar agenesis	**4 (9.5)**
Vermis hypoplasia	8 (19.1)
Vermis agenesis	13 (30.9)
Corpus callosum agenesis	6 (14.3)
Vermian cleft	2 (4.8)
Multipl FCM [n (%)]	8 (19.0)

FCM: fetal cerebellar malformation, IQR: interquartile range, min: minimum, max: maximum, SD: standart deviation

When fetal cerebellar malformations were examined in detail, cerebellar hypoplasia was observed in nearly half of the pregnant women (47.6%), and vermis agenesis was found in almost one-third (31.0%) (**Table 1**). In addition, it was observed that 19.0% (n=8) of the pregnant women had multiple FCM (**Table 1**). We found that there was no statistically significant relationship between pregnancy age, gestational week, number of abortions and/or curettage and FCM types.

While fetal USG was used in the diagnosis of all pregnants, fetal MRI was used in only 2 (4.8%) pregnant women. However, while amniocentesis was performed in 11.9% (n=5) of the pregnant women, karyotype analysis was performed in 7.1% (n=3) (**Table 2**). While no complications were observed in any of the pregnant women who underwent amniocentesis; No genetic anomaly was found in any of the fetuses whose karyotype analysis was performed. Termination occurred in 40.0% (n=2) of the pregnant women who underwent amniocentesis, and delivery in 60.0% (n=3). While 2 of the pregnant women who underwent amniocentesis and were terminated had multiple FCMs, only one had cerebellar agenesis.

Termination was performed in 30.9% (n=13) of the pregnant women diagnosed with FCM during the study period, while live birth was performed in all other pregnant women (**Table 2**). We observed the mean gestational week of the pregnant women with FCM who gave birth was statistically significantly higher than those who were terminated by Mann-Whitney U test (mean gestational week 24+4 vs 20+5) (p=0.019).

Table 2. The association of pregnancy age and gestational week with FCM types

	*Pregnancy Age (year) [median (min-max)]	§Gestational Week [median (min-max)]
Serebellar hipoplazi		
+	23 (19-34)	24^{+2} ($18-37^{+5}$)
-	26 (18-38)	26+5 (18-34)
Serebellar agenezi		
+	28 (23-37)	22^{+4} (20-28)
-	24 (18-38)	26 ($18-37^{+5}$)
Vermis hipoplazisi		
+	28 (18-38)	26^{+6} (18-34)
-	23 (19-37)	25^{+2} ($18-37^{+5}$)
Vermis agenezisi		
+	26 (21-31)	26^{+4} (18^{+3}-34)
-	23 (18-38)	27^{+2} (18 -37^{+5})
Korpus kallosum agenezisi		
+	23 (23-37)	24^{+6} (18-29)
-	24 (18-38)	25+2 (18 -37^{+5})

*No statistically significant relationship between pregnancy age and FCM types (p=0.493), *No statistically significant relationship between gestational week and FCM types (p=0.611)

Table 3. The diagnosis methods and interventions of pregnants with FCM

	n	%
Diagnosis with		
Fetal USG	42	100
Fetal MRG	2	4.8
Amniocentesis		
Yes	5	11.9
No	37	88.1
Karyotype analysis		
Yes	3	7.1
No	39	92.9
Results		
Live birth	29	69.1
Termination	13	30.9

FCM: fetal cerebellar malformation, MRI: Magnetic resonance imaging, USG: ultrasonography

DISCUSSION

Central nervous system malformations are the second most common congenital malformations after cardiac anomalies and constitute one-third of malformations diagnosed in the prenatal period (11, 12). Cerebellar malformations (hypoplasia, agenesis) is a term that generally defines the cerebellum as volume loss or embryological failure (13, 14). Although many factors play a role in its etiology, there is no consensus on the terminology, definition and mechanism yet. It may occur as a result of acquired or congenital genetic disorders with different neurodevelopmental outcomes (3, 13, 14). In this study, the characteristics, management and outcomes of pregnant women diagnosed with prenatal FCM are shown.

Although it is thought that central nervous system malformation is more common in primiparous women, this rate is controversial since curettage rates are not known clearly (15-18). Most of the migration and proliferation processes of neurons occur in the second trimester, and the majority of intrauterine central nervous system malformations are diagnosed at 18-20 weeks of gestation (19, 20). While nearly half of the pregnant women included in our study were primiparous, similar to the literature; the mean gestational week at the time of diagnosis was slightly higher than in the literature (mean 25+2 weeks). In our country, the inadequacy of regular follow-up rates of pregnant women and the low rate of reaching the perinatology center may explain the delayed diagnosis. In addition, it has been reported in the literature that the rate of fetal cerebellar hypoplasia is higher in multiparity pregnant women (21). In our study, the numbers of multiparous and primiparous pregnants were found to be similar.

Cerebellar hypoplasia is defined as a diffuse decrease in the cerebellar biometry in which the anatomy and echogenicity of the cerebellum are normal (3, 5). There may be hypoplasia of only the hemispheres or the vermis, or hypoplasia of both can be seen together (3, 5, 22). In recent years, with the development of technology and the use of fetal MRI, the detection rate of cerebellar hypoplasia has increased (23). Also, In the study of Howley MM et al. (24), it was shown that only 26.4% of cerebellar hypoplasia cases had isolated cerebellar hypoplasia and that other central nervous system malformations were accompanied in the majority of cases. In our study, it was observed that 19.0% of cerebellar hypoplasia/agenesia cases had accompanying multiple anomalies.

As part of normal follow-up during pregnancy, a fetal USG is recommended to determine fetal anatomy between 18 and 22 weeks of gestation. During these gestational weeks, major intracranial structures are embryologically formed and can be well visualized sonographically (25). However, fetal MRI can be used for diagnosis, since it cannot be determined whether vermian lobulation has been completed before the 24th gestational week (22, 25). In our study, while fetal USG was used in all pregnant women, fetal MRI was found to be less used. We thought that the high USG experience of the physicians in the perinatology center, the low rate of accompanying multiple anomalies and the low number of patients affected the use of fetal MRI.

Cerebellar malformations can also be seen together with aneuploidy (especially trisomy 21 and 18) and some congenital anomalies (3, 5). It is recommended to use advanced evaluation methods such as amniocentesis and/or karyotype analysis in cases where malformations are seen in fetal USG, accompanying genetic syndromes are detected, or there are uncertain findings in USG (26, 27). Although amniocentesis is a reliable diagnostic method, complications may develop after the procedure (28). In our study, the rate of amniocentesis was found to be 11.9%; karyotype analysis was performed at 7.1%. No genetic anomalies were detected.

In pregnant women with prenatal fetal central nervous system malformation, termination rates have been reported as 48-60% and live birth rates as 35-47% (29). Also, in the study performed by Tan Ag et al. (30), the termination rate was found to be 48.2% in pregnant women with fetal central nervous system anomaly; It was stated that 92.7% of these were done by medical induction, and only 7.3% of them were terminated by surgical method. In our study, the termination rate was lower than the literature, and the live birth rate was higher than the literature. It was thought that the low termination rates were explained by the lower socioeconomic levels of the pregnant women included in the study compared to European countries, and the difference in their religious beliefs.

Limitations of the study; (1) the single-center data of our study constitutes an important limitation in the generalization of our results; (2) Since it is retrospective, the follow-up of pregnant women and the postnatal life expectancy and development of fetuses with FCM are unknown.

CONCLUSION

We reported the results of a cohort study including the characteristics and management of pregnant women with FCM in our perinatology center. The frequency of diagnosis of FCM is increased with the development of modern medicine and technology. Socio-economic levels and religious belief differences of pregnant affect the termination and birth rates.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (Date: 19/01/2022, Decision No: 2022-25).

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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Original Article

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The evaluation of success and failure of methotrexate treatment in ectopic pregnancy

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ABSTRACT

Aim: Regardless of medical advancements, ectopic pregnancy (EP) is still an essential factor in the mortality rate of women of reproductive age. The main aim of this study was to determine predictive factors associated with the success of the response to treatment with single-dose and two-dose methotrexate (MTX) regimens in women with tubal EP.

Material and Method: This retrospective study examined the electronic records of 130 patients who underwent treatment due to EP were included in the study. The patients were divided into two groups: the successful MTX treatment group (n: 85) as the case group and the failure of MTX treatment group (n: 45) as the control group.

Results: Age-matched (30.62±4.36) and body mass index (BMI)-matched (24.37±2.29) patients diagnosed with EP were treated with MTX. The mean beta-human chorionic gonadotropin (β-hCG) value on the first day of treatment was 1639.84±524.96 mIU/mL in the successful and 5866.76±1875.51 mIU/mL in the unsuccessful group. 85 of 130 (65%) were successfully treated with MTX. Five of 45 (35%) failed medical treatment and required laparoscopic surgery. The longest ectopic mass diameter was significantly higher in the failure of MTX treatment group ($p<0.05$). There was a statistically significant difference between groups in regard to the β-hCG values on days 1, 4, 7, and 14. The β-hCG values on the first day were significantly higher in the failure of MTX treatment group($p <0.05$). There was no statistically significant difference between a single-dose regimen and multi-dose treatments.

Conclusion: We found that an initial β-hCG value was a predictive parameter for MTX's effective medical care of ectopic pregnancy. Vaginal bleeding was identified as a risk factor for the success of MTX treatment.

Keywords: Ectopic pregnancy, methotrexate, medical treatment

INTRODUCTION

Despite medical advances, ectopic pregnancy (EP) is still an important factor in the mortality rate of women of reproductive age (1-3). EP causes six percent of pregnant women's deaths in the first trimester of pregnancy, and only one-third of the women with EP with tubal rupture can give birth to a healthy child in the future (4-7). EP is referred to the implantation of fertilized oocytes in a place other than the endometrium. The most prevalent place is the fallopian tube (8). EP is a prevalent complication worldwide and its prevalence rate varies in different countries (9).

The EP prevalence in the west is about 2% among the general population, but it is as high as 20% among patients undergoing tubal surgery in a previous EP (10). No statistics have been published about the prevalence of EP among Turkish women. EP prevalence has been increasing in the last three decades (11).

EP is the main problem of women of reproductive age. It is usually manifested with symptoms of amenorrhea, lower abdominal pain, vaginal bleeding, mass in the uterine appendages, and some cases, rupture of the fallopian tube (12). EP occurs for different reasons, all of which prevent the successful migration of the fertilized oocytes to the endometrium (13). The most important risk factors for the occurrence of EP are tubal surgery even tubal ligation, history of the previous EP, fetal contact with diethylstilbestrol (DES) and history of pelvic inflammatory disease (PID) (14). Intrauterine devices (IUD) and infertility increase the chance of EP(15,16). It is challenging to diagnose EP due to extensive clinical manifestations (17). The known treatments for EP include surgery and pharmacotherapy using methotrexate (MTX) (18).

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Tanaka et al. (19) treated an interstitial pregnancy with MTX for the first time in 1982. MTX is a leucovorin antagonist that prevents DNA synthesis, cell repair and division by inhibiting the Dihydrofolate reductase enzyme, to which trophoblast tissue is highly sensitive. The common side effects of MTX include nausea, diarrhea, mouth ulcers, and liver disorders, and its rare side effects include neutropenia, fever, pneumonia, and alopecia. Hepatic complications are usually seen with high doses and are rarely seen after the dosage in EP (6). Single-dose and multiple-dose regimens are the two prevalent protocols for administering MTX (20).

This study investigated patients' success rates with single-dose and two-dose diets. Determining the predictive factors in the failure of this treatment is very important. This study aimed to identify factors predicting the success of the response to treatment using single and two-dose MTX regimens among the women who had tubal EP.

MATERIAL AND METHOD

This retrospective study was approved by the Bezmialem Foundation University Non-Interventional Clinical Researches Ethics Committee (Date: 06.09.2022, Decision No:2022/263) All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. One hundred nine women participated in this study form December 2019 -March 2022.

Women between the ages of 20 and 40 were included in this study. All women get pregnant spontaneously and with tubal. After performing the previously mentioned tests and measuring the body surface using weight and height, the patients were treated with MTX, 50mg/m2 intramuscularly, MTX injection day was considered as day one. Then, beta human chorionic gonadotropin (β-hCG) was measured again in the same center on days four, seven and fourteen. If this reduction was below 15% between days four and seven, the second dose of MTX started with the same initial dose of the injection and started again with a new day. In case of a heartbeat after injection doses, intra-abdominal bleeding, or severe pain along with the unstable hemodynamic status of the patient, laparotomy was performed.

In this study, successful treatment was considered as the complete return of β-hCG level to below 10 mIU/ml after the initial dose of MTX without any other internal or surgical intervention. Patients who needed more than one dose or underwent surgery had treatment failure. In the end, the patients of the successful group (n=85) were compared with those of the failure group (n=45) in terms of factors predicting this success rate.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to check the normality, and the nonparametric tests were performed given the non-normality of the groups before the statistical analyses. Mean and standard deviations (SD) were measured to check each continuous variable, including age, body mass index (BMI), hemoglobin (Hb), platelet (PLT), Aspartate Aminotransferase (AST), Alanine Aminotransferease (ALT), blood urea nitrogen (BUN), β-hCG. The Mann-Whitney U test was performed to study the difference between the two groups. SPSS v22 was used for statistical analyses. A value of $p < 0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, the two groups' total mean was measured based on the Mann-Whitney test with a power of 95%, effect size of 50%, and 0.05 type 1 error for at least 92 patients (21).

RESULTS

This study included one hundred thirty women age-matched (30.62±4.36) and BMI-matched (24.37±2.29). The descriptive statistics of study parameters were omitted for brevity.

As stated in **Table 1**, a Mann-Whitney test did not find a statistically significant association between case and control in regard to age and BMI ($p>0.05$). Kruskal–Wallis H did not find a statistically significant association between groups in regard to age, BMI, PLT, AST, ALT, and BUN ($p>0.05$). There was a significant difference between the three groups in terms of the β-hCG values on days 1, 4, 7, and 14 ($p<0.05$) (**Table 2**). The Hb was significantly lower in the unsuccessful group ($p<0.05$). The longest ectopic mass diameter was significantly higher in the unsuccessful group ($p<0.05$).

As stated in **Table 2**, Mann-Whitney U did not find a statistically significant association between successful MTX treatment and failed MTX treatment regarding age, BMI, PLT, AST, ALT, and BUN ($p>0.05$). The β-hCG values on the first day were significantly higher in the unsuccessful group compared successful group (1639–5866) ($p<0.05$). The β-hCG values on days 4, 7, and 14 were significantly lower in the unsuccessful group compared successful group (1639–5866, 1517–796, 1099–81, and 35–7) ($p<0.05$). The Hb was significantly lower in the unsuccessful group ($p<0.05$). The longest ectopic mass diameter was significantly higher in the unsuccessful group ($p<0.05$).

Table 1. Comparison of numeric parameters between three groups

Study parameters	Successful MTX after first doses M±SD (n=47)	Successful MTX after second doses M±SD (n=38)	Failure of MTX treatment M±SD (n=45)	p
Age	30.6±4.04	30.63±5.07	30.64±4.14	0.998*
BMI	24.06±1.8	24.66±2.76	24.45±2.33	0.216**
Hb	11.26±0.82	11.4±0.69	7.97±0.69	**<0.001****
PLT	253893.62±61685.82	247184.21±67119.44	271711.11±66705.13	0.202*
AST	15.74±9.31	13.32±3.73	14.53±3.15	0.088**
ALT	16.85±5.56	17.37±7.51	15.69±4.21	0.710**
BUN	17.85±5.13	17.68±5.24	17.98±4.46	0.893**
D-0 β-hCG	1362.43±231.64	1982.95±583.34	5866.76±1875.51	**<0.001****
D-4 β-hCG	1018.79±266.94	2133.37±664.51	796±343.68	**<0.001****
D-7 β-hCG	828.68±251.47	1433.68±457.62	81.69±41.63	**<0.001****
D-14 β-hCG	18.72±12.11	56.66±50.12	7.98±6.55	**<0.001****
Longest ectopic mass diameter (mm)	12.3±3.95	30.84±4.74	44.29±6.94	**<0.001***

M, Mean; N, number of subjects; SD, standard deviation; MTX, methotrexate; BMI, body mass index; Hb, hemoglobin; PLT, platelet; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferease; BUN, blood urea nitrogen; β-hCG, Beta human chorionic gonadotropin. *One way ANOVA; **Kruskal–Wallis H test

Table 2. Comparison of numeric parameters between two groups

Study parameters	Successful MTX treatment (first or second doses) M±SD (n=85)	Failure of MTX treatment M±SD (n=45)	p
Age	30.61±4.5	30.64±4.14	0.982
BMI	24.33±2.28	24.45±2.33	0.467
Hb	11.32±0.76	7.97±0.69	**<0.001**
PLT	250894.12±63870.04	271711.11±66705.13	0.176
AST	14.66±7.42	14.53±3.15	0.062
ALT	17.08±6.47	15.69±4.21	0.475
BUN	17.78±5.15	17.98±4.46	0.636
D-0 β-hCG	1639.84±524.96	5866.76±1875.51	**<0.001**
D-4 β-hCG	1517.07±737.75	796±343.68	**<0.001**
D-7 β-hCG	1099.15±467.36	81.69±41.63	**<0.001**
D-14 β-hCG	35.68±39.33	7.98±6.55	**<0.001**
Longest ectopic mass diameter (mm)	20.59±10.22	44.29±6.94	**<0.001**

M, Mean; N, number of subjects; All variables tested by a Mann-Whitney U test.

Table 3 shows the comparison of nominal parameters in three groups. As can be seen, the highest frequency of localization information in total was tubal (93.1%), ovarian (2.3%), cervical (2.3%), cesarean scar (2.3%), and abdominal (0%). There was not a statistically significant association between demographic features (smoking, gravida and abortus) and MTX treatment results (p> 0.05). There was not a statistically significant association between localization information and MTX treatment results (p> 0.05). There was a statistically significant association between parity and MTX treatment results (p> 0.05).

As stated in **Table 4**, there was not a statistically significant association between demographic features(localization, smoking, gravida, abortus, and parity) and MTX treatment results (p> 0.05).

Table 5 compares presenting symptoms and historical factors in three groups. As can be seen, there was not a statistically significant association between historical factors (abortion, infertility, insemination,in vitro fertilization, PID, endometriosis, pelvic surgery, and EP) and MTX treatment results (p> 0.05). There was a statistically significant association between vaginal bleeding as presenting symptoms and MTX treatment results (p-value < 0.05). The Pairwise Z-Tests found that the vaginal bleeding was significantly higher in the unsuccessful group.

There was a statistically significant association between pain as presenting symptoms and MTX treatment results (p< 0.05). The Pairwise Z-Tests found that the pain was significantly higher than in the successful group.

Table 3. Comparison of demographic features between three groups

Study parameters	Categories	Total	Successful MTX after first doses (n=47) n(%)	Successful MTX after second doses (n=38) n(%)	Failure of MTX treatment (n=45) n(%)	p
Localization						1*
	Tubal	121 (93.1)	44 (93.6)	35 (92.1)	42 (93.3)	
	Ovarian	3 (2.3)	1 (2.1)	1 (2.6)	1 (2.2)	
	Cervical	3 (2.3)	1 (2.1)	1 (2.6)	1 (2.2)	
	Cesarean Scar	3 (2.3)	1 (2.1)	1 (2.6)	1 (2.2)	
	Abdominal	0 (0)	0 (0)	0 (0)	0 (0)	
Smoking						0.247*
	No	59 (45.4)	23 (48.9)	20 (52.6)	16 (35.6)	
	Yes	71 (54.6)	24 (51.1)	18 (47.4)	29 (64.4)	
Gravida						0.115*
	1	67 (51.5)	27 (57.4)	18 (47.4)	22 (48.9)	
	2	54 (41.5)	17 (36.2)	20 (52.6)	17 (37.8)	
	3	9 (6.9)	3 (6.4)	0 (0.0)	6 (13.3)	
Abortus						0.541*
	0	105 (80.8)	35 (74.5)	32 (84.2)	38 (84.4)	
	1	24 (18.5)	11 (23.4)	6 (15.8)	7 (15.6)	
	2	1 (0.8)	1 (2.1)	0 (0.0)	0 (0.0)	
Parity						**0.010***
	No	83 (63.8)	38 (80.9)	21 (55.3)	24 (53.3)	
	Yes	47 (36.2)	9 (19.1)	17 (44.7)	21 (46.7)	

*Pearson Chi-Square Test † The Pairwise Z-Tests

Table 4. Comparison of demographic features between two groups

Study parameters	Categories	Total	Successful MTX treatment (n=85) n(%)	Failure of MTX treatment (n=45) n(%)	p
Localization					1*
	Tubal	121 (93.1)	79 (92.9)	42 (93.3)	
	Ovarian	3 (2.3)	2 (2.4)	1 (2.2)	
	Cervical	3 (2.3)	2 (2.4)	1 (2.2)	
	Cesarean Scar	3 (2.3)	2 (2.4)	1 (2.2)	
	Abdominal	0 (0)	0 (0)	0 (0)	
Smoking					0.101*
	Yes	59 (45.4)	43 (50.6)	16 (35.6)	
	No	71 (54.6)	42 (49.4)	29 (64.4)	
Gravida					0.110*
	1	67 (51.5)	45 (52.9)	22 (48.9)	
	2	54 (41.5)	37 (43.5)	17 (37.8)	
	3	9 (6.9)	3 (3.5)	6 (13.3)	
Abortus					0.619*
	0	105 (80.8)	67 (78.8)	38 (84.4)	
	1	24 (18.5)	17 (20.0)	7 (15.6)	
	2	1 (0.8)	1 (1.2)	0 (0.0)	
Parity					0.069*
	Yes	83 (63.8)	59 (69.4)	24 (53.3)	
	No	47 (36.2)	26 (30.6)	21 (46.7)	

*Pearson Chi-Square Test

Table 5. The presenting symptoms and historical factors of three groups

Presenting symptoms and historical factors of three groups	Total	Successful MTX treatment n (%)	Successful MTX 2 Doses treatment n (%)	Failure of MTX treatment n (%)	p
Vaginal Bleeding	97 (51)	27 (35)	30 (56.6)	40 (66.7)†	**0.002***
Pain	48 (25)	26 (34)†	15 (28.3)†	7 (11.7)	**<0.001***
Abortion Story	5 (3)	3 (4)	1 (1.9)	1 (1.7)	0.525*
Infertility History	10 (5)	5 (6)	2 (3.7)	3 (5)	0.620*
Insemination History	9 (5)	6 (8)	1 (1.9)	2 (3.3)	0.135*
In vitro fertilization	10 (5)	4 (5)	1 (1.9)	5 (8.3)	0.340*
Pelvic Inflammatory Disease History	3 (2)	1 (1)	1 (1.9)	1 (1.7)	0.987*
Endometriosis History	2 (1)	1 (1)	0 (0)	1 (1.7)	0.657*
Pelvic Surgery History	2 (1)	1 (1)	1 (1.9)	0 (0)	0.574*
Ectopic Pregnancy History	4 (2)	3 (4)	1 (1.9)	0 (0)	0.209*

*Pearson Chi-Square Test † The Pairwise Z-Tests

DISCUSSION

The most prominent finding of this research was the significant relationship between patients' symptoms and the success of MTX treatment. Women with symptoms of vaginal bleeding significantly responded negatively to MTX treatment and became candidates for surgery. Pain symptoms in patients who respond positively to MTX treatment are prevalent. This study reports that 34.6% of patients needed surgical excision. Existing literature shows surgical intervention is necessary in 5–25% of cases (22-25).

This study showed no statistically significant difference between a single-dose regimen and multi-dose treatments. According to previous studies, there is an association between a single-dose regimen and a higher failure rate than a multi-dose regimen (12% vs. 7%) (26). On the contrary, equal significance between the two protocols was reported in some studies (27). Since the single-dose method is associated with side effects and lower costs, it is more accepted. One of its disadvantages is that a percentage of patients do not respond sufficiently to the initial dose, increasing the need for more doses, or they may suffer from severe abdominal pain and rupture of the pregnancy site during the treatment, resulting in surgery and treatment failure. Knowing the predictive factors of treatment failure to prevent these cases is essential.

Although it has been known that high levels of pretreatment β-hCG are the most important predicting factor related to MTX treatment failure, it remains unclear which treatment modality is suitable for a specific range of pretreatment β-hCG values (22, 28). Lipscomb et al. (29) reported that the initial β-hCG value is the most important factor determining failure in single-dose regimen of MTX treatment. Mol et al. (18) compared the impact of β-hCG values on single-dose regimens ad multi-dose regimens of MTX treatment. When the β-hCG value is less than 1500mIU/ml, the single-dose regimen is recommended, and the multi-dose regimen should be used when it is less than 3000mIU/ml. Erdem et al. (20) demonstrated that the β-hCG value above 4000mIU/ml is the most important cause of MTX treatment failure. Menon et al. (30) patients with the β-hCG value above 5000mIU/ml are more likely to fail MTX treatment. Our study confirms these results. The β-hCG value is a determining factor in the success of the treatment. In our study, according to the mean level of the β-hCG value on the first day (5866mIU/ml), the β-hCG value above 5000mIU/ml is a significant risk factor in treatment failure.

The limitations of a study are the small sample size and single center. For this cause, more interventional and observational trials should be done based on a more complete multiple-center randomized. For future work, we will design a survey study on women with vaginal bleeding and pain symptoms regarding MTX treatment.

CONCLUSION

As a result, we demonstrated that initial β-hCG values were predictive parameters for the effective medical treatment of EP by MTX. An initial β-hCG value>5000 mIU/ml was predictive of its failure. Vaginal bleeding was identified as a predictive factor of MTX treatment failure. There were no significant differences between single-dose and multi-dose MTX protocols in terms of the successful treatment of EP

ETHICAL DECLARATIONS

Ethics Committee Approval: This retrospective study was approved by the Bezmialem Foundation University Non-Interventional Clinical Researches Ethics Committee (Date: 06.09.2022 Decision No:2022/263).

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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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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Original Article

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Our experience with percutaneous endoscopic gastrostomy and long-term follow-up results

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ABSTRACT

Aim: Percutaneous endoscopic gastrostomy (PEG) is the preferred method for long-term enteral feeding of patients who cannot be fed orally for various reasons and have a functioning gastrointestinal system. In this study, we aimed to present and discuss the demographic characteristics, indications, and early and late complications of patients implanted with the endoscopic PEG in our center.

Material and Method: In this study, we retrospectively evaluated age, gender, chronic diseases, indication for PEG, complications during the procedure, complications arising from PEG during patient follow-up, and survival times of 84 patients who underwent PEG between January 2016 and January 2020 from the electronic medical file system.

Results: Of the 84 patients enrolled in the study, 59.5% (n=50) were male and 40.5% (n=34) were female. The mean age of the patients was 61.35±19.52 years. The endoscopic PEG success rate was 97.6%. Of the requests for PEG, 58.6% (n=50) were for patients in intensive care units. The most common indications for PEG insertion were cerebrovascular accident (CVA), chronic nervous system disease, and hypoxic-ischemic encephalopathy. Complications related to PEG were observed in 11 patients. All complications were mild, and no severe complications were observed. While one of the complications developed in the early period (<30 days), the other complications occurred in the long term (> 30 days). No deaths from causes related to the PEG procedure have been observed.

Conclusion: In patients with inadequate oral intake, PEG is a safe and appropriate option for continuous enteral feeding because of its low complication and mortality rates.

Keywords: Percutaneous endoscopic gastrostomy, complication, enteral feeding

INTRODUCTION

Enteral or parenteral feeding is used to support nutrition in patients with inadequate oral intake. Enteral feeding is safer and less expensive because it provides enteral stimulation, strengthens the mucosal barrier, and reduces the risk of bacteremia (1–3).

Percutaneous endoscopic gastrostomy (PEG) is the preferred feeding method for long-term enteral feeding in patients who cannot be fed orally for various reasons and have a functioning gastrointestinal system. PEG Procedure, first used in children by Gauderer and Ponksy in 1980, can be performed surgically, radiologically, or endoscopically (4,5). Endoscopic PEG is the preferred method because most centers do not perform radiological PEG, it is less invasive than the surgical method, and the procedure duration is shorter.

In this study, we aim to present and discuss the demographic characteristics, indications, and early and late complications of patients who underwent endoscopic PEG implantation in our center.

MATERIAL AND METHOD

The study was designed and conducted according to the principles of the Declaration of Helsinki. This study was approved by the Karadeniz Technical University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.01.2022, Decision No: 2021/360). Since this was a retrospective study, no informed consent was obtained from the patients.

Our study included 84 patients who underwent PEG between January 2016 and January 2020. We retrospectively evaluated age, sex, chronic diseases, indication for PEG,

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complications during the procedure, complications resulting from PEG during patient follow-up, and survival using the electronic medical file system. We investigated whether the mortality of patients was due to the primary disease or the complication that may occur after the PEG procedure. Complications that occurred within 30 days of the procedure were considered early complications, whereas complications that occurred after 30 days were considered late complications. We evaluated the routine laboratory results of all patients before the procedure, stopped feeding patients with a nasogastric tube at least 8 hours before the procedure, and administered prophylactic antibiotics (1 gram of cefazolin 2 hours before the procedure) to all patients who were not receiving antibiotic treatment.

All procedures were performed in the endoscopy department by two gastroenterologists under the supervision of an anesthesiologist using sedoanalgesia (propofol, midazolam, or ketamine, depending on the physician's choice). The gastrointestinal canal was examined up to the second part of the duodenum with esophagogastroduodenoscopy. PEG was performed using the Pull technique recommended by Gauderer et al. (4) in patients with no pathology in the gastrointestinal tract. After the procedure, all patients underwent an endoscopic examination to check whether the PEG bumper was in place and whether there was any bleeding. Twenty-four hours after the procedure, the patients were given water first and gradually started to be fed through the PEG tube.

Statistical Analysis

The SPSS Windows version 23 program was used for statistical analysis. Continuous variables were evaluated for normal distribution by the histogram, Q-Q graph, and Shapiro-Wilk or Kolmogorov-Smirnov tests depending on the number of variables. Normally distributed continuous variables were presented as mean±standard deviation, and a t-test for independent variables was used to compare the two groups throughout the study. Other continuous variables are presented as median (IQR) and the nonparametric Mann-Whitney U test was used to compare groups. Categorical variables were presented as frequencies and percentages, and the Pearson chi-square test or Fischer exact probability test was used to compare the groups. We used Kaplan-Meier for survival analysis. A p-value below 0.05 at a 95 percent confidence interval is considered statistically significant.

RESULTS

Of the 84 patients enrolled in the study, 59.5% (n=50) were male and 40.5% (n=34) were female. The mean age of the patients was 61.35±19.52 years, and there was no statistical difference between the male and female gender in terms of age (p=0.063) (**Table 1**).

Table 1. Demographic data of the patients

Variable	
Male/Female, n (%)	50 (59.5) / 34 (40.5)
Age, mean±SD, year	61.35±19.52
Male	58.08±17.9
Female	66.15±21.05

Transillumination and indentation could not be achieved in 2 of 84 patients; therefore, endoscopic PEG could not be performed and they were referred to surgery. The endoscopic PEG success rate was 97.6%.

During the follow-up period, 73.8% (n=62) of patients had died, while 26.2% (n=22) were still alive. The median survival time from the time of the procedure was nine months. Survival was higher in men than in women (p=0.036).

Patients were most frequently consulted for PEG procedures from the anesthesiology intensive care unit (ICU), gastroenterology, and internal medicine ICU (**Table 2**). 58.6% (n=50) of PEG requests were from intensive care clinics.

Table 2. Clinical distribution of PEG requests

	n	%
Anesthesia ICU	31	36.9
Gastroenterology	19	22.6
Internal medicine ICU	9	10.7
Neurology ICU	5	6
Neurology	4	4.8
Chest Diseases ICU	4	4.8
ENT	3	3.6
Emergency	3	3.6
Medical Oncology	3	3.6
Others	3	3.6

*ENT: Ear-Nose-Throat, ICU: Intensive care unit

When patients' comorbidities were evaluated, the most common were hypertension in 45.2% of patients (n=38), diabetes mellitus in 15.5% (n=13), coronary artery disease in 13.1% (n=11), and 10%.7 (n=9) congestive heart failure (**Table 3**).

Table 3. Comorbidities of the patients

	n, (%)
Hypertension	38 (45.2)
Diabetes mellitus	13 (15.5)
Coronary artery disease	11 (13.1)
Congestive heart failure	9 (10.7)
Chronic kidney failure	7 (8.3)
Atrial fibrillation	6 (7.1)
Pulmonary emboli	4 (4.8)
Others	8 (9.6)

The most common indications for the use of PEG were cerebrovascular accidents (CVA), chronic nervous system diseases, and hypoxic-ischemic encephalopathy (**Table 4**).

Table 4. PEG indications of patients

Indications	n. (%)
Neurological Diseases	
CVA	38 (45.2)
Chronic nervous system diseases	21 (25)
HIE	12 (14.3)
Malignancy	11 (13.1)
ENT	9 (10.7)
GIT	2 (2.4)
Multiple trauma	2 (2.4)

*CVA: Cerebrovascular accidents, HIE: Hypoxic ischemic encephalopathy, ENT: Ear-Nose-Throat, GIT: Gastrointestinal tract

Complications related to PEG were observed in 11 patients. All complications were minor complications, and no major complications were observed. While one of the complications occurred in the early phase (< 30 days), the other complications occurred in the long term (> 30 days). No deaths from causes related to the PEG procedure have been observed. In Kaplan-Meier overall survival analysis, life expectancy was 94% at 1 month, 82.1% at 2 months, 70.2% at 3 months, 53.6% at 6 months, 45.2% at 1 year, and 35.3% at 3 years (**Figure**).

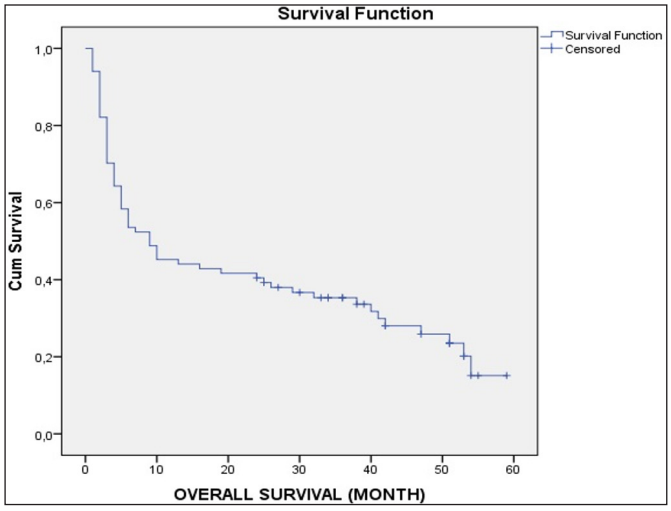

Figure. Overall survival expectancy according to Kaplan-Meier analysis

Table 5. Complications related to PEG and their duration

Early Complication (<30 days)	
Bleeding	2
Late Complication (>30 days)	
Buried bumper	4
Blockage	2
Infection	2
Leak	1

DISCUSSION

Nasogastric tube feeding is recommended for patients with a functioning gastrointestinal tract who cannot tolerate oral intake and require nutritional support for less than four weeks. Whereas the European Society for Gastrointestinal Endoscopy guideline recommends that enteral nutrition with percutaneous access should be considered on a case-by-case basis when nutritional support is required for more than four weeks (6). The 4-week period was set to avoid complications such as infection that may occur with percutaneous access as much as possible. Our patients were also unable to tolerate oral intake for at least 4 weeks.

In studies performed by different clinics, the success rate of endoscopic PEG varies between 94-99% (7). In this study, the endoscopic PEG success rate was 97.6%, which is consistent with the literature. In two patients, endoscopic PEG could not be performed because transillumination and indentation could not be achieved and they were referred to the general surgery clinic for surgical PEG.

Dysphagia due to neurological disorders is among the main reasons for the need for PEG (8,9). In our country, in a study conducted by Kartal et al. (10) in Erzurum, the need for PEG due to neurologic causes was found to be 76.4%, while Şit et al. (11) found this value to be 60% in Bolu region. In accordance with the literature, 84.5% of our patients needed PEG due to swallowing problems due to neurological causes.

The mortality rate that may occur as a result of the PEG procedure is low, less than 0.5% (12). In our study, no patient died as a result of the PEG procedure, and all deaths were related to the patients' diseases.

Major and minor complications may occur after the PEG procedure. Studies have reported complication rates ranging from 4% to 13.6% (13). In our study, complications occurred in 11 patients (13.1%), with no patients experiencing a major complication. Two of the complications occurred in the early phase, whereas the others occurred in the late phase.

Early complications occurred in the first 48 hours as bleeding around the PEG insertion site and were controlled with simple measures such as compresses. While long-term buried bumper syndrome developed in 4 patients, the patients' PEG tubing was removed and reinserted in another location after the wound site healed. In two patients, infection around the PEG tube was treated with antibiotic therapy. Since antibiotic prophylaxis was fully administered in all of our patients, we assume that wound infection was not observed in the early phase. The tube of the patient who had a leak on the side of the PEG tube was replaced with a wider tube. The tube of a patient with a blocked tube was opened with pressurized water, while the tube of another patient was replaced.

Patients requiring PEG have a high mortality rate in the early period because of their comorbidities and underlying diseases. In studies predicting a 30-day

mortality rate, the results were as follows: Peksöz et al. (14) 36%, Erdil et al. (15) 26.8%, Coşkun et al. (16) 8.6%, Aksoy et al. (17) 1.5%, and Duzenli et al. (18) %12.5. In our study, the 30-day mortality rate was 13.1%. The 3-month mortality rate varied from 15.7% to 42% in different studies (19,20). In our study, the 3-month mortality rate was 30.9%.

CONCLUSION

PEG is a reliable option to avoid complications that may arise from parenteral nutrition and to maintain enteral nutrition in patients with functioning GI tract and inadequate oral intake because it has low mortality and complication rates, is simple and inexpensive to use, and does not require general anesthesia.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Karadeniz Technical University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.01.2022, Decision No: 2021/360).

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.

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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Case Report

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Arias-Stella reaction and frightening cytological changes in endocervical polyp: a rare case report

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ABSTRACT

The Arias-Stella (AS) reaction is hormone-dependent atypical endometrial changes characterized by hyperplasia, hypertrophy, vacuolization, pronounced nuclear atypia, pronounced nuclear pleomorphism, and prominent nuclear hyperchromasia in glandular epithelial cells. It is very rare to see AS-related changes in extra uterine areas, especially in an endocervical polyp. Since this benign lesion is very similar to misdiagnoses such as adenocarcinoma, it is very critical to recognize AS reaction in extrauterine areas. The interpretation of pathological findings involves many difficulties, for example, due to the generally small size and fragmentation. Considering the clinical history and good interpretation of the nuclear details are extremely important for correct diagnosis. Here, we present the frightening cellular changes associated with AS observed in an endocervical polyp encountered after abortion in a middle-aged pregnant woman, together with the literature findings.

Keywords: Endocervical polyp, Arias-Stella reaction, frightening cytological changes

INTRODUCTION

The Arias-Stella (AS) reaction is a benign, proliferative change that usually occurs in the Mullerian epithelium in response to hyperprogestational states (1). In this change, marked hypertrophy and vacuolization in the glands of the epithelium and prominent nuclear pleomorphism, atypia, and hyperchromasia are observed in the nuclei. Although this occurs routinely during pregnancy (normal and external), it can also be observed following gestational trophoblastic diseases and the use of progestational agents (1,2). Although it is most commonly encountered in the glandular epithelium of the endometrium, changes related to the AS reaction have been reported in many extrauterine regions, including the endocervical gland, endocervical polyp, endometriosis, adenomyosis, and tubal epithelium (2,3). Recognition of AS-related changes in the extrauterine regions is very important, as it has the potential to be misinterpreted as serous or clear cell carcinoma or an endometrial intra-epithelial carcinoma (3,4). There are very few publications in the literature describing the AS reaction in endocervical polyp (5,6). Here, we present an endocervical polyp we observed in the abortion material of a middle-aged female patient and the frightening cytological changes due to the AS reaction we observed in this polyp.

CASE

A 41-year-old female patient has an uneventful first-trimester pregnancy. An incidental endocervical polyp was detected during routine prenatal examinations. Her pregnancy was terminated as abortion at the 10th week with abnormal uterine bleeding. In the histopathological examination, an endocervical polyp of 0.5 cm in size was detected between the decidualized fragments and choral elements showing changes related to AS. It was observed that the cells forming the endocervical glands in this polyp randomly had significant nuclear atypia. There were atypical cells, prominent nuclear enlargement, nuclear pleomorphism, nuclear hyperchromasia. Nuclear pseudo inclusions were also observed in these atypical cells. When the chromatin distribution of these cells was examined, it was noted that the chromatin was in the form of staining. Nuclear pseudo inclusions were also observed in these atypical cells (**Figure 1-4**). Glands containing the described changes were surrounded by decidualized stromal cells. There was no increase in mitotic activity in atypical cells, and the basement membrane between epithelial cells and stroma appeared quite smooth and there were no signs of desmoplastic response or invasion. In the applied immunohistochemical study, Napsin

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was positive in atypical cells, while Ki-67 and p53 were not positive. In the presence of current clinical and histopathological findings, the case was interpreted as changes in the endocervical polyp due to AS.

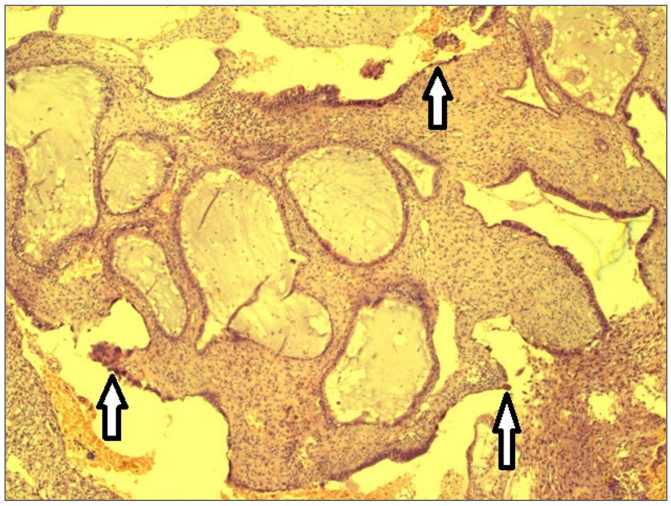

Figure 1. An endocervical polyp has atypical cells interspersed between normal glands in focal areas (arrows) (x4, H&E)

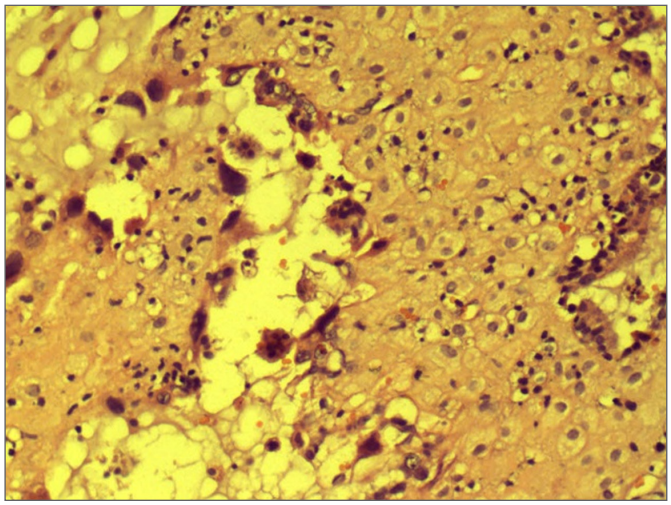

Figure 2. Atypical cells showed striking variability among themselves, and some cells had frightening atypia (x20, H&E).

DISCUSSION

Here, we describe the frightening cytological changes due to AS reaction that we observed in the endocervical polyp in the abortion material of a pregnant patient. AS reaction was first described by Arias-Stella in 1954 in endometrial glands (1). Later, Arias-Stella himself reported that these changes may also occur outside the endometrium (2). AS-related changes in the endocervical glands have been described in many studies in the literature and atypical cells have been described in the smears of these women (3,4). AS-related changes in an endocervical polyp are extremely rare and were first reported by Cariani et al. (5) in 1966. In 1995, McCormick et al. (6) reported tripolar mitosis secondary to AS reaction in an endocervical polyp. In our case, there were terrible cytological changes due to AS reaction in an endocervical polyp. Due to its rarity and cytological changes, our case makes an important contribution to the literature.

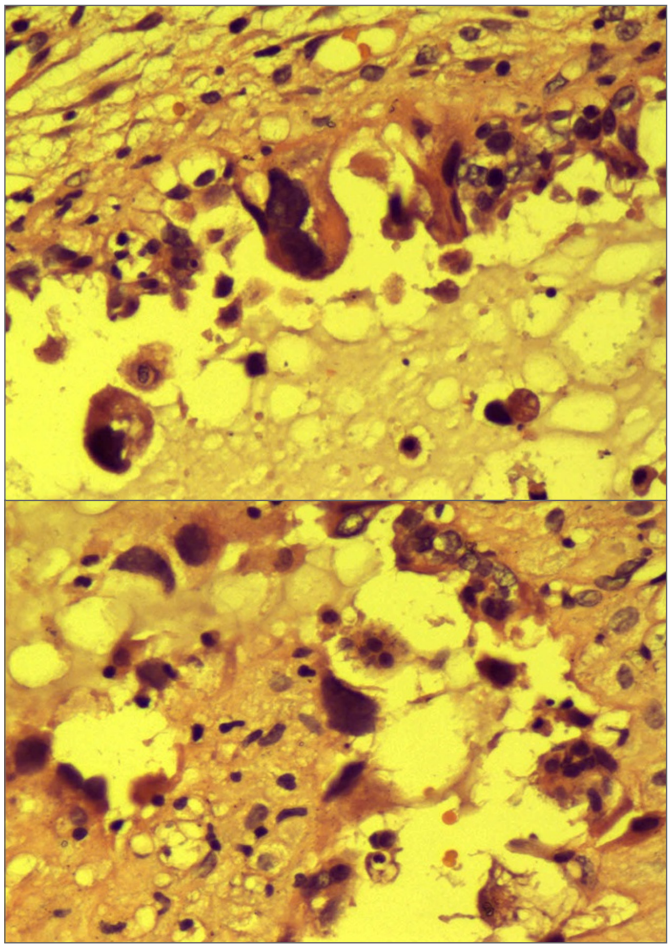

Figure 3,4. Despite this frightening appearance in atypia, there was no increase in mitotic activity and changes in nuclear chromatin were degenerative (x40, H&E).

Five different histological and cytological variants of AS reaction have been reported to date. These are minimal atypia, early secretory pattern, secretory or hypersecretory pattern, proliferative or nonsecretory pattern, and monster cell pattern (1,2). The secretory or hypersecretory pattern, which is the most frequently encountered one and defined as the classical pattern, is characterized by diffuse cytoplasmic vacuolization in the glands and hyperchromasia in the nuclei (2). Monster cell pattern, on the other hand, is the least encountered and the most difficult to diagnose variant, characterized by the presence of highly pleomorphic, large and odd nuclei containing inclusions (7). The AS reaction in endocervical glands often shows a monster cell pattern, further increasing the diagnostic difficulties (7,8). This pattern was also widely observed in our case and the following criteria were used to overcome the diagnostic pitfalls.

The histological diagnosis of AS reaction should be made independently of the organ in which it is seen and is possible by microscopic analysis of routine hematoxylin-

eosin stained sections. The cytological features of the AS reaction seen in the endocervical glands are generally similar to the endometrium, but it is typical that cells that appear strikingly pleomorphic are located between cells with normal morphology (9-13). Napsin, Ki-67 and p53 can be preferred for immunohistochemical study. The benefit of estrogen and progesterone is limited (11). Although the histopathological analysis of our case had some difficulties due to the small size of the polyp, the diagnosis was made safely with the following clinicopathological criteria. First, atypical cells were located focally interspersed between normal glands. Second, there was marked variation among atypical cells, and the atypia in some cells was quite frightening. Third, despite this apparent atypia, the nuclear changes were stained, that is, degenerative/regenerative, and there was no mitotic activity. Fourth, the stroma under the pleomorphic glands was quite smooth without desmoplastic reaction and there was evidence of decidualization in the surrounding stromal cells. Finally, while Napsin positivity was present in atypical cells, Ki-67 and p53 staining were not observed. When the clinical pregnancy history of the case was added to these findings, the morphological changes were interpreted in the context of AS.

Of the lesions of the endocervix to be confused with AS, two entities should be noted: microglandular hyperplasia and clear cell adenocarcinoma (14). Although the AS reaction in the endocervical region is focal, it has been described in 10% of pregnancies. It is often focal and is observed in the superficial glands of the cervical canal (14,15). Histologically, it consists of cells with highly atypical and hyperchromatic nuclei, with eosinophilic and vacuolated cytoplasm, similar to those in the endometrium. Typically, these pleomorphic cells are located between normal-appearing cells and mitosis is rare (15,16). The relationship between microglandular hyperplasia and hormonal status remains unclear. Morphologically, it is characterized by densely packed, irregularly shaped glands with varying degrees of cystic dilation (17). These glands contain mucin and are vacuolated. Although focal atypia is observed, cells are generally similar in size and shape, and mitotic activity is low (17,18). Although clear cell carcinoma is often associated with diethylstilbestrol exposure in utero, it can occur without a history of this exposure (19). It often presents with a mass. Morphologically, it exhibits an infiltrative and irregular growth pattern. It is very useful to evaluate this pattern at small magnification (19, 20). At low magnification, the glands of the AS reaction will show a structure compatible with the regular distribution of normal endocervical glands, while the glands of clear cell carcinoma will show an irregular distribution (20). In addition, cells in clear cell carcinoma exhibit a solid and papillary pattern, and mitotic activity is increased. Rare tumours that can be included in the differential diagnosis include metastatic renal cell carcinoma, mesonephric hyperplasia, and steroid cell tumours. Clinical, morphological and immunohistochemical studies are very useful in distinguishing these tumours (21).

CONCLUSION

Although AS reaction is very common in daily practice, especially in pregnant women, it is very important to keep in mind and diagnose these seemingly simple changes outside of the endometrial glands, as misdiagnosis of lesions included in the differential diagnosis can lead to severe consequences.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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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Case Report

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Candidemia due to *Candida glabrata* in a non-immunosuppressed hospitalized patient

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ABSTRACT

Opportunistic fungal infections due to Candida species in immunosuppressed patients appearas significant causes of mortality and morbidity. Candida infections and candidemia can also be encounteredamong immunocompetent patients with underlying predisposing factors. This paper presents a 72-year-old diabetic male patient who developed candidemia due to *Candida glabrata* complex without any underlying immunosuppressive disease. The patient fully recovered after a total of 23 days of anidulafungin treatment.

Keywords: Immunocompetent patient, *Candida glabrata* complex, candidemia, case report

Poster presentation at the 22nd Turkish Clinical Microbiology and Infectious Diseases (KLIMIK) Congress on March 9-12, 2022 in Antalya.

INTRODUCTION

Candidemia and invasive candidiasis are among the significant causes of mortality and morbidity, and the increase in the number of immunosuppressed patients, unfortunately, contributes to the prevalence of the disease. The five main Candida species (spp.) (*Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei*) account for more than 90% of all cases. Frequencies of Candida spp. vary by patient group, geographical region, previous antifungal treatment, and age (1).

Opportunistic mycoses caused by Candida spp. are very rare in non-immunosuppressed patients. This paper presents a 72-year-old diabetic male patient who developed candidemia due to *Candida glabrata* complex (*C. glabrata* complex) without any underlying immunosuppressive disease.

CASE

A 72-year-old male patient presented to the emergency department with complaints of nausea, vomiting, and painful urination that started 1.5 months ago and fatigue lasting for ten days. It was learned that he presented to another health institution a week ago with the same complaints and was prescribed to use ciprofloxacin 2×750 mg orally for seven days upon the preliminary diagnosis of urinary system infection. He had a history of diabetes mellitus (DM), coronary artery disease, benign prostatic hypertrophy, and lumbar herniation. On physical examination, his fever was 37.2°C, and abdominal examination yielded suprapubic tenderness and right costovertebral angle tenderness. Considering his laboratory findings, leukocyte count was 14,000/mm³ (reference (ref): 4.000-10.500/mm³), C-reactive protein was 175 (ref.: 0-5 mg/dL), AST was 39 IU/L (ref.: 0-40 IU/L), ALT was 55 IU/L (ref.: 0-40 IU/L), creatinine was 0.94 mg/dL, and glomerular filtration rate was 80 ml/min. The result of the abdominal ultrasound (USG) in the emergency department was reported as "The echogenicity of the kidney parenchyma increased (grade I). The bladder wall was diffusely thick (9 mm), and the prostate gland volume was measured as 32 cc."

The patient was admitted to the infectious diseases clinic with a preliminary diagnosis of complicated upper urinary tract infection. In the examination on the first day of his hospitalization, he was in good condition, conscious, oriented, and cooperative and had suprapubic tenderness and right costovertebral angle tenderness in his abdomen. Other system examinations were normal. With the preliminary diagnosis of urinary system infection, we started ertapenem 1×1 gr

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intravenous (I.V.) treatment. In the follow-ups, he had a fever of 38.6 °C on the 4th day of his hospitalization; thus, blood and urine cultures were taken. Examination of the peripheral blood smear was normal .Patient did not have central venous catheter or urine catheter. *C. glabrata* complex growth in his blood culture and 104 cfu/ml non-albicans Candida growth in urine culture and his blood culture, respectively. Non-albicans Candida isolated from urine culture was not identified as species. Antifungal susceptibility was determined by broth microdilution test according to Clinical and Laboratory Standards. Institute (CLSI). Antifungal susceptibility of the agents were reported as susceptible to micafungin, amphotericin B respectively by using broth dilution method. The minimum inhibitory concentration (MIC) for micafungin was ≤0.06 µg/ml, and MIC for amphotericin B was 1 µg/ml. Ertapenem treatment was discontinued and anidulafungin treatment was started as 200 mg loading and then 1×100 mg I.V according to the IDSA guidline for the management of Candidiasis (2). Blood cultures were obtained from the patient every 48 hours and found no growth on his 9th day of hospitalization. The treatment was prescribed to continue for 14 days after a negative blood culture result. The patient was then discharged, providing follow-up visits.

DISCUSSION

Candidemia is the most common form of invasive candidiasis, and the research often mentions an increase in the worldwide frequency of candidemia due to Candida spp. other than *Candida albicans* (3). Candidemia is among the most significant cause of mortality; the Candidemia-associated mortality rate is reported to be between 40-60% (3,4). Factors, such as the increase in the number of immunosuppressed and critical patients and the widespread use of invasive medical devices (e.g., central venous catheter, urinary catheter) and broad-spectrum antibiotics, contribute to the increase of its frequency (5).

In a 16-year study in a tertiary hospital in Lebanon, the rate of candidemia due to non-albicans Candida spp. (NAC) was reported to be significantly higher than that due to *Candida albicans* (64.7% and 35.3%, respectively).

Other than candidemia, *C. glabrata* complex associated catheter infection, meningitis, brain abscess, endocarditis, and osteomyelitis are reported in literature (6,10).

The main risk factors identified for candidemia in non-neutropenic patients are severe sepsis or septic shock, recent Clostridium difficile infection, diabetes mellitus (DM), total parenteral nutrition, chronic obstructive pulmonary disease (COPD), concurrent intravenous glycopeptide therapy, presence of a peripheral central catheter, previous antibiotic therapy, and immunosuppressive therapy . A Taiwan-based study showed cancer and DM as the most prevalent underlying diseases in patients with candidemia. The most common risk factors for candidemia were previously reported as broad-spectrum antibiotic use, central venous catheterization, and Candida colonization (11). The risk factors for candidemia in our patient were DM, Candiduria, previous use of antibiotics (ciprofloxacin), and the use of broad-spectrum antibiotics (ertapenem). In our case, Candida may be come from urinary tract infection. It is interesting that the patient developed *C. glabrata* complex -related candidemia despite not having an underlying immunosuppressive disease.In present case completely recovered following twenty-three days of anidulafungin treatment.

CONCLUSION

Overall, it should be kept in mind that fungemia due to *C. glabrata* complex and other Candida spp. may develop in patients who do not have an underlying immunosuppressive disease but have risk factors for Candida infections such as DM and the use of broad-spectrum antibiotics.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Case Report

ANATOLIAN CURRENT MEDICAL

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A newborn case of split choroid plexus supposed to have intraventricular hemorrhage by bedside cranial ultrasound

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ABSTRACT

Cranial ultrasound is a valuable bedside technique and procedure of choice to image the intraventricular hemorrhage (IVH). Moreover, anatomical variants of the neonatal brain should be known to avoid of misinterpretation. The term of split choroid plexus was described as a cleft in the choroid plexus, which could be partial or complete in the anterior portion, giving a lobular appearance. We presented the case of split choroid plexus in a late premature infant and we aimed draw attention to the fact that it can be confused with IVH.

Keywords: Intraventricular hemorrhage, prematurity, split choroid plexus, cranial ultrasound

INTRODUCTION

Intraventricular hemorrhage (IVH) is primarily seen in premature infants, and the risk is greater with increasing immaturity. However, IVH can be seen in late preterm and term babies, it is extremely rare in that population and associated with birth injury or asphyxia (1).

Cranial ultrasound (CUS) is a valuable bedside technique and procedure of choice to image the IVH (2). With ultrasonography largely available in neonatal units, routine ultrasonography is performed mostly by neonatologists to the high-risk infants during hospitalization (3). On the other hand, anatomical variants of the neonatal brain should be known to avoid of misinterpretation (4).

The patterns of the choroid plexus (CP) are described as lobular choroid, drumstick-shaped choroid and choroid cysts (2,4,5). The term of split CP was indicated as a cleft in the CP, which can be complete or partial in the anterior portion, giving a lobular appearance by Enriquez et al (2). Although variations in CP shape are known, there is no published case or case series on split CP mimicking IVH in the English literature. Here, we presented the case of split CP in a late premature infant and we aimed draw attention to the fact that it can be confused with IVH.

CASE

A 2010 g female newborn was delivered via cesarean section due to preeclampsia to a 25 years old mother from first pregnancy at 34 weeks and 4 days of gestation with no respiratory problems and discharged on the postnatal day two. On the postnatal 8th day of life, she was admitted to newborn follow up clinic with jaundice and poor sucking. Her vital signs along with the physical and neurological examination were all unremarkable, except for jaundice and purulent, foul-smelling drainage from the umbilical cord. Complete blood count, [white blood cells=7.170 /μL (lymphocytes ratio=18.7%, neutrophil ratio: 74.4%), hemoglobin=16.9 g/L, hematocrit=51.8%, platelet count=268.000/uL)]. C-reactive protein was 16.1 mg/dl (reference range: 0-5 mg/L). Total and direct bilirubin levels were 17 and 1.2 mg/dl respectively. Cranial ultrasound was performed due to prematurity and sepsis, about 19x5 mm echogenic image in the mildly dilated left lateral ventricle was found, suggesting grade 3 IVH. Left and right lateral ventricle atrial widths were 5 and 2.8 mm respectively.

The patient was admitted to our neonatal unit with a diagnosis of indirect hyperbilirubinemia, omphalitis and grade III IVH. Vitamin K was given via intramuscularly. Prothrombin time, partial thromboplastin time and international normalized ratio were in normal ranges

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according to gestational age. After pus culture from umbilicus and peripheral blood culture were obtained, antibiotic therapy and phototherapy were started. Upon further discussion with neuroradiology, CUS was performed again before discharge. It was determined that what was seen as possible IVH, was in fact split CP in the left lateral ventricle (**Figure**). Indirect hyperbilirubinemia and omphalitis resolved within 1 week. The patient was discharged home without any sign and symptoms. After a month, CUS was checked and split CP confirmed. Her growth and development were appropriate for her postnatal age during 4 months of follow.

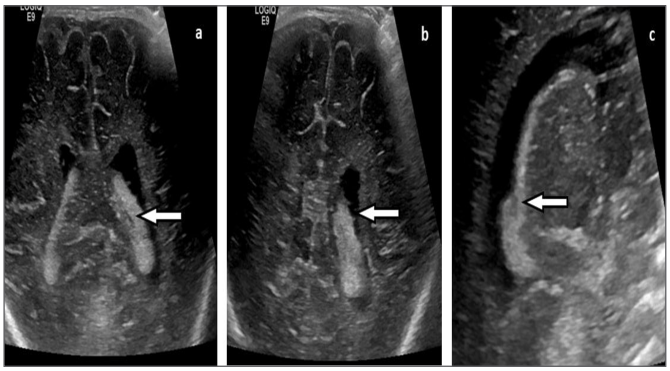

Figure. (a) Hypoechoic line (arrow) dividing the left choroid plexus in two, was seen in axial transfontanel ultrasonography section. (b) Thickening of the left choroid plexus and choroid plexus cyst (arrow) were observed in axial transfontanel ultrasonography section. (c) Lobulation in the left choroid plexus (arrow) was seen in sagittal transfontanel ultrasonography section.

DISCUSSION

Intraventricular hemorrhage is classically due to the rupture of micro-vessels in germinal matrix, but less commonly, it may also originate from the CP (3,6). According to the Papile grading system, IVH ranges in severity from grade I to grade IV. Grades III or IV IVH considered to have a robust correlation with worse neurodevelopmental prognosis (7,8). Therefore, monitoring of cranial bleeding by CUS is crucial for the neonatologists.

Cranial ultrasound is the most common used technique for imaging the intraventricular and parenchymal brain pathologies for neonatal brain because of low cost, accessibility, and safety (9). Congenital or acquired anomalies of the neonatal brain and the frequently occurring patterns of brain injury are detected by CUS in both preterm and full-term neonates. (2,3). However, evaluation of parenchymal, subarachnoid and subdural abnormalities are limited on sonographic examination. In addition, quality of imaging depends on the abilities and experience of the radiologists (10,11). In our unit, CUS was routinely performed in preterm infants ≤$34^{6/7}$ weeks of gestation with/without unexplained hyperbilirubinemia, sepsis and hemodynamic instability etc.

The CP is highly echogenic and has a smooth, sharply defined contour. In the sagittal view, it assumes a semicircular form around the thalamus and thickens at the ventricular atrium to form the glomus (12). It is found along the roof of the third ventricle and extends through the foramen Monro into the lateral ventricles (4,9). The CP does not extend from the caudothalamic grooves to the frontal horns or from the ventricular atrium to the occipital horns (4). Echogenic material anterior to the caudothalamic groove or in the dependent portions of the occipital horns suggests germinal matrix and intraventricular hemorrhage, respectively (4). Correa et al. (3) found that, posterior fontanelle sonography provided greater certainty in detecting IVH in the neonatal brain and it showed size, contours and echogenicity of choroid plexus more accurately. In addition, posterior fontanelle sonography was applicable for more accurate detection of intraventricular content and to assess marked lateral ventricle asymmetry (3). If the clues were used that mentioned in the above statements for our case, a clarifying of diagnosis could be made during the first CUS. Additional imaging methods, such as magnetic resonance of brain or cranial tomography, were not recommended by division of neuroradiology because CUS was sufficient if performed by experienced radiologists (2).

CONCLUSION

As in our case, cranial ultrasonographic evaluation should be repeated by more experienced ultrasonographers to avoid inappropriate management, especially for unexpected cases of IVH. In conclusion, neonatologists should be aware of variations in choroid plexus shape because it can mimic intraventricular hemorrhage.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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