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Research article

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Comparing the supine and lateral positions for proximal femoral nail use in the treatment of intertrochanteric femoral fractures

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Ethics Committee Approval
Ethical approval was obtained from Malatya clinical research ethics committee (approval no. 2021/110).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The management of unstable intertrochanteric fractures (ITF), which are becoming more common, is still a significant issue for public healthcare systems. As a result, successful fracture therapy is becoming a more crucial aspect of orthopedic practice. To treat older patients who have an ITF, this study compared the therapeutic outcomes and side effects of proximal femoral nail anti-rotation (PFNA) conducted in lateral decubitus and supine postures.

Methods: One-hundred twenty patients between the ages of 65 and 90 who underwent PFNA surgery as a result of an unstable femoral ITF brought on by low-energy trauma were included in the study, which was conducted as a retrospective cohort study. Two groups of patients were established: (1) Group L, consisting of patients who underwent surgery in the lateral decubitus position and (2) Group S, consisting of patients who underwent surgery in the supine position. Several patient characteristics were compared: (1) demographic information, (2) length of hospital stay, (3) length of surgery, (4) intra-operative blood loss, (5) incision length, (6) number of intra-operative fluoroscopies, (7) duration of activity outside of bed, (8) duration of clinical recovery of fracture, (9) surgical complications, (10) patient outcomes, and (11) Harris hip scores (HHS).

Results: Group L (60 patients) consisted of patients who underwent surgery in the lateral decubitus position, while Group S (60 patients) underwent surgery in the supine position (60 patients). The average hospital stay for patients receiving PFNA was 8.2 days for those in the supine position compared to 8.0 days for those in the lateral decubitus position. The difference between the operative times was significant (P<0.001) with 48.6 and 59.7 min in Groups L and S, respectively. Intra-operative blood losses in Groups L and S were 129.2 and 151.5 mL, respectively. Compared to Group S, Group L's mean incision length was much lower at 6 cm (as compared to 8 cm in Group S). The difference between the mean intra-operative radiation exposure times for Groups L and S was considerable at 9.38 versus 12.5 min. The mean times for fracture union and the HHS were not statistically different between the two groups after 12 weeks of treatment.

Conclusion: ITFs in elderly patients can be successfully treated with PFNA in either the lateral decubitus or supine position. Surgical duration, blood loss, intra-operative X-ray exposure, and incision lengths were all reduced with PFNA performed in the lateral decubitus position. As a result, treatment of ITFs in older individuals may involve PFNA fixation in the lateral decubitus position. Particularly for people with a muscular gluteal region or obese patients, the lateral decubitus position is advised.

Keywords: anti-rotation proximal femoral nail, intertrochanteric fractures, supine, lateral decubitus

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Introduction

Intertrochanteric fractures (ITF) are those that involve both the trochanter major and minor and are outside the joint capsule. A prominent worry for doctors nowadays is the management of unstable ITFs, which have become more common as a result of osteoporosis and longer life expectancies [1–3]. Therefore, effective management of these fractures is a crucial component of orthopedic medicine.

Different therapeutic approaches have been developed as a result of the lengthy prosthetic surgical process, excessive tissue damage caused by a wider incision, and an abundance of comorbidities. These complicated fractures can now be treated with a variety of procedures and implants [4]. Numerous clinical and biomechanical investigations examined the outcomes of several implants, including the proximal femoral nail, the dynamic hip screw, and the gamma nail (PFN). Complications, such as cut-out, implant fracture, implant-induced femoral shaft fracture, and reduction loss, have all been linked to the use of these implants [5–7]. Recent research has demonstrated successful clinical outcomes in unstable ITFs that were treated with PFNA [8–11]. The most preferable technique in this situation is the proximal femoral nail anti-rotation (PFNA). Due to its benefits, which include simplicity of usage, smaller incisions during surgery, and quicker recovery times, this approach is frequently used. However, it is essential to have adequate training and expertise in this surgical procedure.

The surgical approach used with the PFNA has been the subject of a small number of studies in the literature. These studies only follow patients for a brief period of time; therefore, obtaining sufficient data on long-term complications and survival and revision rates is not possible. For treatment of senior patients with an ITF, we compared the clinical results and side effects of PFNA performed in the in lateral decubitus and supine postures in the current study.

Materials and methods

A retrospective cohort design was used for creating the study. The study consisted of 120 patients with unstable femoral ITFs caused by low-energy trauma, aged 65 to 90, who underwent PFNA surgery between January 2015 and January 2018. Two groups of patients were established. Group L (60 patients) consisted of patients who underwent lateral decubitus surgery, while Group S consisted of patients who underwent supine surgery (60 patients). After receiving the go-ahead from the regional ethics committee and receiving patients' informed consent, the study was launched. The Malatya Turgut Özal University Clinical Research Ethics Committee gave their approval for this work under protocol number 2021/33.

The American Society of Anesthesiologists (ASA) classification system scores used in pre-operative evaluation were collected together with demographic data about the patients, fracture type according to AO/OTA classification, and two groups were homogenized to avoid selection bias.

Inclusion criteria:

1. Patients 65 to 100 years old
2. Patients in whom radiographic imaging revealed a fracture
3. Patients who experienced a fracture within 21 days
4. Patients who were active prior to the fracture
5. Patients who signed their own or a first-degree relative's informed consent
6. Patients who could participate in the examination and treatment while conscious and alert.

Exclusion criteria:

1. Patients with fractures that were older than 21 days
2. Patients with pathological fractures
3. Individuals with an open fracture
4. Patients who experienced multiple fractures or injuries
5. Patients who could not have surgery because of conditions, such as severe decompensated heart failure, liver failure, and/or kidney failure
6. Patients with recent or ongoing infections
7. Individuals undergoing chemo and/or hormone therapy
8. Patients with inadequate follow-up intervals
9. Individuals who previously underwent hip surgery
10. Patients who were pregnant.

Evaluation

An impartial researcher evaluated the patients' clinical and functional status at the two-year post-operative follow-up. The results in the therapy groups were assessed using the Harris hip score (HHS), a metric that is frequently used to gauge functional improvement in the management of hip issues and includes parameters for range of motion, discomfort, deformity, and hip function. Demographic information was compared to length of hospital stay, length of surgery, intra-operative blood loss, incision length, time spent using fluoroscopy during surgery, time spent getting out of bed, clinical fracture recovery time, and surgical complications.

Surgical technique

The same surgical team, which included two surgeons, operated on all of the patients. Both patient groups underwent surgery while under general or local anesthesia. Each operation was carried out under fluoroscopy supervision.

The patients in the group in the supine position were left in that position, but a height was added under the hips to create a slope of 10 to 15 degrees. Once the fracture was reduced, a trochanter major-type 3.2 mm guide wire was inserted intramedullarily. The entry to the nail was widened by sending a 17 mm reamer over the guiding wire. A standard PFNA with a diameter of 10-11-12 mm and a height of 240 mm (Orthopedic Designs; MEDGAL Sp. Inc., Bialystok, Poland) was inserted. Compression was accomplished via fluoroscopy after one neck screw and two lock screws were inserted into the neck at a 130º angle. For distal locking, a screw was also provided. By offering compression that was managed by fluoroscopy, the procedure could then be completed.

The patients' positions were maintained while they were in the lateral decubitus posture, which put the afflicted limb on top. The healthy limb's hip and knee flexion were maintained during surgery to obtain lateral hip fluoroscopy. A pillow was placed between the legs. A 3.2 mm trochanter major type guide wire was then inserted intramedullarily after the fracture was reduced. The entry to the nail was widened by sending a 17 mm reamer over the guiding wire. A standard PFNA with a diameter

of 10-11-12 mm and a height of 240 mm (Orthopedic Designs; MEDGAL Sp. Inc., Bialystok, Poland) was inserted. Fluoroscopy was used to achieve compression after one neck screw and two lock screws were inserted into the neck at a 130º angle. Additionally, a screw was given for distal locking. By offering compression under fluorescence control, the procedure was ended.

In this trial, all patients received 2 g of cefazolin before and after surgical intervention as part of an antibiotic prophylaxis regimen. In addition, the patients received 0.4 ml of low molecular weight heparin once a day for 14 days. On the first post-operative day, vigorous and passive quadriceps exercises were introduced to both patient groups. On the first day following surgery, patients with good bone quality who underwent successful fracture repair were mobilized with full load. Depending on their capacity for bone repair, other patients were mobilized with a gradual increase in weight. All patients were instructed to stroll with walkers.

Statistical analysis

The ideal patient count was determined via power analysis. The ideal count was examined within the context of the study utilizing the G*Power 3.1 application. The required minimum sample size was determined to be 60 patients in each group and a total of 120 patients in the study for the outcome variables of supine and lateral decubitus positions, while the amount of Type I error (alpha) was 0.05, the power of the test (1-beta) was 0.8, the effect size was 0.5 (medium effect), the distribution ratio of the groups was 1. The alternative hypothesis (H1) included a two-tailed, two-variable independent sample t-test [12].

SPSS Statistics software 19 (SPSS Inc., an IBM Company, Somers, NY) was used for the statistical studies. Clinical information was presented as a number, a percentage, or a mean (standard deviation [SD]). Two categorical variables were compared using the Wilcoxon and Pearson Chi-Squared tests ($\chi 2$). We used the Student's t-test for continuous variables. Statistics were deemed significant at $P<0.05$.

Results

Table 1 displays age, gender, broken side, and AO type. No discernible variations in the fundamental traits between the groups in the supine and lateral decubitus positions were found.

Table 1: General characteristics of the lateral decubitus and supine position groups

	Group L (n = 60)	Group S (n = 60)	*P*-value
Age (years)	86.4 (74–101)	85.76 (71–102)	0.950⁎
Sex (male/female)	28 / 32	27 / 33	0.573⁎⁎
Injured side (left/right)	36 / 24	37 / 23	0.745⁎⁎
AO type			
31-A1	12	14	
31-A2	44	43	0.872⁎⁎
31-A3	4	3	

⁎Wilcoxon-test; ⁎⁎Pearson Chi-Squared, Group L: the lateral decubitus position, Group S: the supine position

Table 2 displays information about hospital stay duration (days), operation duration (min), blood loss (mL), incision length (cm), X-ray fluoroscopy exposure time, activity time spent outside of bed (h), Harris values, and bone union duration. In patients receiving PFNA, the average length of hospital stays was 8.0 days in the lateral decubitus position and 8.2 days in the supine position ($P<0.001$). The disparity between the operating times of 48.6 min for Group L and 59.7 min for Group S was substantial. Intra-operative blood loss in Group L was 129.2 mL while in Group S it was 151.5 mL. Group L's incision was 6 cm long, which was much shorter than 8 cm in Group S. Compared to Group S patients, participants in Group L received significantly less intra-operative radiation (9.38 versus 12.5 min). The HHS and average fracture union times were not statistically different between the two groups after 12 weeks of treatment.

Table 2: Operative and clinical parameters of the lateral decubitus and supine position groups

	Position	Mean	SD	*P*-value⁎
Hospital stays (day)	L S	8.0 8.2	2.49 3.85	0.954
Operation time (min)	L S	48.6 59.7	26.3 20.1	<0.001
Length of incision (cm)	L S	6.0 8.0	1.4 1.7	<0.001
X-ray fluoroscopy exposure time (min)	L S	9.38 12.50	1.9 2.7	<0.001
Harris values	L S	84.1 83.8	4.466 4.280	0.451
Union time (week)	L S	12.0 11.9	2.784 2.899	0.788

⁎ Wilcoxon-test, Group L: the lateral decubitus position, Group S: the supine position, SD: standard deviation

A total of three clinical problems were seen in each of the two groups (Table 3) and included deep vein thrombosis and both superficial and deep wound infections. One supine patient experienced a superficial wound infection that was treated with intravenous antibiotics. Two problems occurred in the group that had been in the lateral decubitus position. One patient experienced a severe wound infection that was treated with intravenous antibiotic treatment and debridement. Another patient received three months of treatment with the vitamin K antagonist, warfarin, for a deep vein thrombosis that was detected by color Doppler sonography in the first post-operative week.

Table 3: Complications in the lateral decubitus position and supine position groups after treatments

Complication	Group S (n = 60)	Group L (n = 60)
Deep vein thrombosis	0	1
Superficial wound infection	1	0
Deep wound infection	0	1

Group L: the lateral decubitus position, Group S: the supine position

Discussion

The incidence of intertrochanteric fractures has been increasing in recent years as a result of an increase in life expectancy resulting from improved health care and quality of life. For the purpose of treating intertrochanteric fractures, numerous approaches have been suggested [4,5]. Among these, PFNA was created using a simpler and easier procedure than other implants to obtain greater fixation strength in the presence of osteoporotic bone. By compressing the bone, the neck screw used in PFNA achieves a precise fit and necessitates less bone removal than a single screw. The neck screw is more resistant to cut-out than other frequently used screw systems, according to bio-mechanical testing [13–16].

Minimally invasive techniques have recently become more popular in orthopedic surgery. Positive operative outcomes, such as significant operation time extension, excessive fluoroscopy exposure, and subpar clinical outcomes, have been reduced to a minimum as a result of increasing clinical experience and data from biomechanical and clinical studies. Most recent studies have reported that minimally invasive surgical techniques result in better radiological and clinical outcomes with shorter surgical times [6,8,15,17–19]. For all patients in our study, we favored a minimally invasive approach. We obtained superior clinical results, earlier patient mobilization, and fewer surgical complications. These findings are in line with those in the

literature, and we believe that elderly patients should undergo minimally invasive procedures.

Clinics can use the PFNA technique in a variety of positions. Both the lateral decubitus and supine positions are suitable for nailing the femur. The anesthesiologist is more physiologically comfortable when the patient is in the supine posture. Additionally, this position is favored in patients with significant lung distress, additional lower limb fractures, and spinal injuries. Obese people have more difficulty getting to the trochanter major when they are supine, but [20–24]. To reach the trochanter major, the extremities should be provided with adduction and internal rotation, especially in patients with a muscular gluteal area or those who are obese. These two patient characteristics could result in a substantial trochanter fracture, loss of reduction in the fracture, changes in neck shaft angle, and anteversion. Even with a decent anterior-posterior view of the proximal femur during the fluoroscopy, it may be challenging to get a good lateral image [20,21,24]. Therefore, a need to improve surgical procedure knowledge and experience is present. The supine position is suggested in a very small number of studies. In one of these investigations, Ding et al. [25] used the supine position to treat 45 patients with femoral ITFs. These authors came to the conclusion that closed reduction and anti-rotational intramedullary nailing in the supine position, which have the advantages of minimal trauma and low complications with excellent clinical outcomes, are safe and feasible ways to treat femoral ITFS. In the current investigation, traction of the extremity was carried out during the surgical intervention for reduction purposes in patients who underwent surgery while lying on their backs. Additionally, a radiolucent table was used for supine patients who were undergoing surgery. Although we were able to obtain a decent anterior–posterior image of the proximal femur in our patients during fluoroscopy, we had trouble obtaining a good lateral image. We spent less time preparing for the procedure when the patient opted for the supine position. Our lateral decubitus incision was less extensive than in Ding's study [25]. Our difficulties were comparable. Our clinical results, HHS, and bone union times were all comparable to the Ding study. The supine posture did not significantly outperform the lateral decubitus position according to the study's findings.

The lateral decubitus position eliminates the need for a traction table, facilitates conversion to open surgery when necessary, and provides a good lateral view of the proximal femur [20,21,26]. It also makes it simpler to locate and prepare the entry point for the intramedullary nail. Possible traction table side effects are avoided, including crush syndrome, pudendal, sciatic, and femoral nerve palsies, perineal injuries, compartment syndrome, and avulsion of the inferior epigastric artery in the opposite extremity [27]. Studies on surgical positions for patients with intertrochanteric femur fractures were reviewed by Xue et al. [28]. They discovered that PFNA in the lateral decubitus position, as opposed to PFNA in the supine position, was associated with a shorter operation times, less hospital stays, blood losses, the number of intra-operative X-rays, length of the incision, and activity outside of bed, indicating that the intervention should be performed in the lateral position. Similar to Xue [28], Li et al. [26] studied both techniques in their research and reached the same conclusions in which performing the procedure in the lateral decubitus position was preferable. According to the author, patients treated with PFNA in the lateral decubitus position as opposed to the supine position experienced significantly better intra-operative parameters after 12 weeks of treatments (operation time, incision length, intra-operative blood loss, and intra-operative radiation exposure). Nevertheless, the final functional results of the older patients' intertrochanteric fracture treatments did not significantly differ from one another.

Although PFNA fixation in the lateral decubitus position was demonstrated to be a useful choice for the treatment of ITFs, more conclusive studies on early surgery and longer follow-up time are required to justify its use. The treatment of intertrochanteric fractures in elderly patients who cannot endure the lateral decubitus posture with PFNA has significant limitations. Our study is restricted by its retrospective study design, small patient population, and brief follow-up period. Future research must include more cases and longer follow-up periods.

Conclusion

The findings of this study demonstrate that treating intertrochanteric fractures in older individuals with PFNA in the lateral decubitus and supine positions was successful. However, PFNA performed in the lateral decubitus position resulted in reduced blood loss, a lower intra-operative X-ray count, and a shorter incision. As a result, the treatment of ITFs in older individuals may involve PFNA fixation in the lateral decubitus position. The lateral decubitus position offers a similar number of advantages as the supine position.

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The modified Glasgow prognostic score (MGPS) and the mortality prediction model II (MPM II) can predict mortality in patients with breast cancer admitted to intensive care: A retrospective cohort study

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Breast cancer is the second most common cause of cancer-related death in women worldwide. Predicting the prognosis in breast cancer with very high mortality is important in terms of disease treatment and increasing life expectancy. In our study, we aimed to examine the importance of some inflammatory markers and scoring systems in predicting prognosis in patients with breast cancer who were hospitalized in the intensive care unit.

Methods: This retrospective cohort study was conducted in the Department of Medical Oncology and Intensive Care Unit between 2014 and 2020. Breast cancer patients who were admitted to the intensive care unit at any stage of their treatment during the study and followed up and treated in the medical oncology department of the hospital were included in the study. All data were compared between groups (discharged or exitus) based on survival status. Socio-demographic information, laboratory findings (hemoglobin, leukocytes, neutrophils, lymphocytes, platelets, eosinophils, monocytes, C-reactive protein [CRP], albumin, lactate dehydrogenase [LDH], clinical status [co-morbidities, length of stay in intensive care, mechanical ventilation, and reason for hospitalization in the intensive care unit]), and survival data of the patients were collected retrospectively from hospital medical records. We also recorded treatment-related data and relapse/progression information. Neutrophil–lymphocyte, platelet–lymphocyte, and lymphocyte–monocyte ratios (NLR, PLR, and LMR, respectively) were calculated.

Results: Thirty-seven (52.1%) patients died and 34 (47.9%) patients survived. The NLR (P=0.021), Modified Glasgow Prognostic score (P<0.001), APACHE II score (P<0.001) and mortality probability model (MPM II) upon admission (P<0.001) were significantly higher in the exitus group than in the survivors. The lymphocyte_monocyte ratio (P=0.030) and prognostic nutritional index (P=0.004) were significantly higher in the discharged group than in the death group. When we evaluated performance of the prognostic scores to predict mortality, we found that the APACHE II score (area under the curve [AUC]: 0.939, 95% confidence interval [CI]: 0.888–0.990), MPM II-Admission (AUC: 0.936, 95% CI: 0.880–0.992), and modified Glasgow Prognostic Score ([mGPS] AUC: 0.727, 95% CI: 0.600–0.854) had the highest area under curve values. Multivariable regression revealed that longer chemotherapy duration (≥2 weeks), an mGPS score of two points, and high MPM-II (≥36 points) were independently associated with mortality.

Conclusion: Among the inflammatory markers and scores examined, mGPS and MPM-II were found to be independently associated with mortality in breast cancer patients who were hospitalized in the intensive care unit. In addition, patients with longer chemotherapy duration had a higher risk of mortality, but this result was limited by various possible confounders.

Keywords: intensive care unit, breast cancer, inflammation, clinical scoring, mortality

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Introduction

Breast cancer has become an increasingly important and preventable public health problem [1]. More than two million women worldwide were diagnosed with breast cancer in 2020. It is estimated that the cancer type with the highest prevalence in the last five years is breast cancer [2]. It is also the most common cancer in women in Turkey and constitutes 25% of all female cancers. [3].

Some risk factors for the development of breast cancer have been identified and include obesity, sedentary lifestyle, unhealthy diet, alcohol consumption, prolonged hormone replacement therapy, and various medications [4]. Although these factors may also affect the course of disease in those who are diagnosed with breast cancer, they have little role in quantifying the prognosis. Screening, preliminary treatments, and early diagnosis are critical for preventing breast cancer development and mortality; however, prediction of prognosis and survival in patients diagnosed with breast cancer is also a crucial matter to consider, particularly in relation with decisions regarding treatment [5]. It is known that inflammatory processes play an active role in the initiation, progression, and metastasis of cancer during almost all stages [6]. Based on these features, many studies have investigated the role of inflammation markers in predicting prognosis in different cancer types [7-9]. In studies concerning breast cancer, it was revealed that inflammatory parameters, such as the modified Glasgow Prognostic Score (mGPS), neutrophil–lymphocyte, platelet–lymphocyte, and lymphocyte–monocyte ratios (NLR, PLR, and LMR, respectively), and Systemic Immune-Inflammation Index (SII) are associated with prognosis and mortality [10–14].

The number of studies investigating inflammatory markers has increased in recent years; however, the number of comprehensive studies, including scoring systems such as Prognostic Nutrition Index (PNI), Mortality Probability Models (MPM II), Acute Physiology and Chronic Health Assessment II (APACHE II), especially in hospitalized patients requiring intensive care, is still quite limited [15–17]. As such, no consensus on the use of clinical scoring and inflammatory markers in predicting breast cancer prognosis can be found. This study aimed to determine the role of inflammatory parameters in predicting mortality in breast cancer patients hospitalized in the intensive care unit (ICU).

Materials and methods

This retrospective cohort study was conducted in the Medical Oncology Department and Intensive Care Unit of Medipol University Faculty of Medicine between 2014 and 2020. Approval was obtained from the ethics committee of Medipol University for the study (Date: 18/11/2021, decision no: E-10840098-772.02-5922).

Study population

Patients with breast cancer who were admitted to the ICU at any stage of their treatment were included. Patients with systemic inflammatory disease in addition to breast cancer or with another malignancy at the same time were excluded from the study.

Laboratory and clinical records

Socio-demographic information, laboratory findings (hemoglobin, leukocytes, neutrophils, lymphocytes, platelets, eosinophils, monocytes, C-reactive protein [CRP], albumin, lactate dehydrogenase [LDH], clinical status [comorbidities, hospitalization duration in the ICU, mechanical ventilation, and reason for hospitalization in the ICU]), and survival data of the patients were collected retrospectively from the medical records. In addition, we recorded treatment-related data and recurrence/progression information. The NLR, PLR, and LMR were calculated by dividing the absolute values of the laboratory parameters.

Data collection and scoring tools

SII was obtained by multiplying the platelet count by the neutrophil count and dividing the obtained value by the lymphocyte count. A high value indicates a poor prognosis [19].

The PNI was obtained by multiplying the serum albumin (g/L) with the total lymphocyte count (10^9/L). Results are divided into two according to a threshold of 45, with higher values given a score of zero and lower values a score of [20]. Zero indicates normal, and 1 point indicates severe malnutrition. PNI has been shown to be an independent prognostic indicator in various cancers [21–23].

The MPM II is a prognostic scoring system that evaluates determinants thought to be effective in prognosis. Variables include the patient's level of consciousness, hospitalization in the ICU, malignancy, infection, cardio–pulmonary resuscitation, systolic arterial pressure, and age. For each variable, a score of zero or one is given based on presence/absence or threshold. Evaluation of MPM is done by probability calculation, which was independent of the total score [24]. Physiological variables evaluated in APACHE II include age, temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, venous HCO3, sodium, potassium, serum creatine, hematocrit, leukocytes, and Glasgow Coma Score (GCS). The highest value in the APACHE II score is 71 points, and mortality increases to 80% at 35 points and above [25].

Of the scores, MPM II was calculated upon the first admission of the patient to the ICU, while APACHE II was calculated after the patient completed the first 24 h in the ICU. All other laboratory values were obtained from the blood results at the initial ICU admission of the patient. Mortality was defined as the primary outcome for prognostic assessment.

High CRP (>10 mg/dL) and hypoalbuminemia (<3.5 mg/dL) were used to calculate mGPS [18]. Two points were given to those with two abnormalities, one point to those with one abnormality, and zero points if none were present. A high score indicated a poor prognostic indicator.

Statistical analysis

All analyses were performed on SPSS v25 (SPSS Inc., Chicago, IL, USA). Normality in continuous variables was checked using the Shapiro–Wilk test. According to these results, data concerning continuous variables were given as mean ± standard deviation or median (1^{st}–3^{rd} quartile), while categorical data were expressed as frequency and percentage values. Comparisons between the two groups were performed with either the independent samples t-test (when fulfilling parametric

assumptions), or the Mann–Whitney U test (non-parametric). Appropriate chi-squared tests were used to assess significance regarding categorical distributions. Prediction performances were evaluated by using a receiver operating characteristic (ROC) curve analysis by calculating the area under curve (AUC) and sensitivity and specificity values. Multiple logistic regression analysis (forward conditional method) was performed to identify the best prognostic factors influencing mortality. Finally, *P*-values of <0.05 were accepted as statistically significant.

Results

We evaluated 71 patients (70 females and one male) in our study. The median age was 58 (range 33–90) years. Thirty-seven (52.11%) patients died, and 34 (47.89%) were discharged.

The percentage of having undergone ≥4 weeks of chemotherapy was significantly higher in the exitus group than in the discharged group (*P*=0.003).

Neutrophil lymphocyte ratio (*P*=0.021), mGPS (*P*<0.001), APACHE II score (*P*<0.001), and MPM II upon admission (*P*<0.001) were significantly higher in patients who had died compared to survivors. The LMR (*P*=0.030) and prognostic nutritional index (*P*=0.004) were significantly higher in subjects who had been discharged compared to the exitus group. We found no significant differences between the groups in terms of PLR and SII index (Table 1).

In our study, APACHE II (94.59%), MPM II upon admission (89.19%), and mGPS (83.78%) were found to have the highest sensitivities in determining mortality. Specificity values were highest with the MPM II upon admission (84.85%), SII (79.41%), and APACHE II scores (78.79%). Curve analyses revealed that the highest AUC values were achieved based on the APACHE II score (AUC: 0.939, 95% confidence interval [CI]: 0.888–0.990), MPM II upon admission (AUC: 0.936, 95% CI 0.880–0.992), and mGPS (AUC: 0.727, 95% CI: 0.600–0.854) scores. The predictive performance of PLR and SII was not significant (Table 2, Figures 1 and 2).

According to multiple logistic regression analysis, we found long chemotherapy duration (≥2 weeks), an mGPS score of 2 points, and high MPM-II score (≥36) were independently associated with mortality (Table 3). Patients with an mGPS score of two points had a 19.694-fold higher risk of death (odds ratio [OR]: 19.694, 95% CI: 1.444–268.636; *P*=0.025). Patients with an MPM II (admission) score of ≥36 points had a 86.965-fold higher risk of death than those with lower scores (OR: 86.965, 95% CI: 6.930–1091.341; *P*=0.001). Other variables included in the model, including age (*P*=0.245), cancer status (*P*=0.716), reason for admission (*P*=0.107), NLR (*P*=0.400), PLR (*P*=0.388), LMR (*P*=0.929), SII (*P*=0.631), PNI (*P*=0.585), and APACHE II score (*P*=0.077) were found to be insignificant.

Table 3: Significant prognostic factors of the mortality, multiple logistic regression analysis

Prognostic Factors	B coefficient	*P*-value	OR	95.0% CI for OR	
Chemotherapy (≥2 weeks)	3.192	0.013	24.349	1.960	302.435
mGPS (2)	2.980	0.025	19.694	1.444	268.636
MPM II-Admission (≥36)	4.466	0.001	86.965	6.930	1091.341
(Constant)	-6.465	0.002	0.002		

Dependent Variable: Mortality, Nagelkerke R^2: 0.775, Correct prediction: 89.66%, OR: Odds ratio, CI: Confidence Interval, mGPS: Modified Glasgow prognostic score, MPM II: Mortality Probability Models

Figure 1: Receiver operating characteristic curve of the neutrophil–lymphocyte, platelet–lymphocyte, and lymphocyte–monocyte ratios (NLR, PLR, and LMR, respectively) and SII to predict mortality

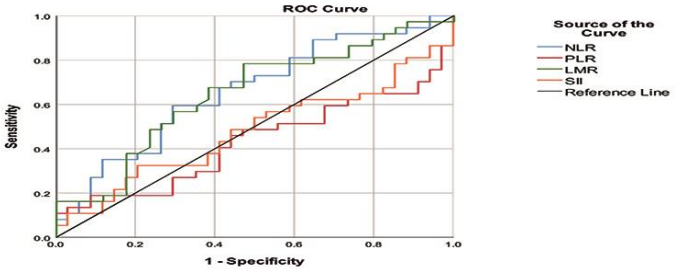
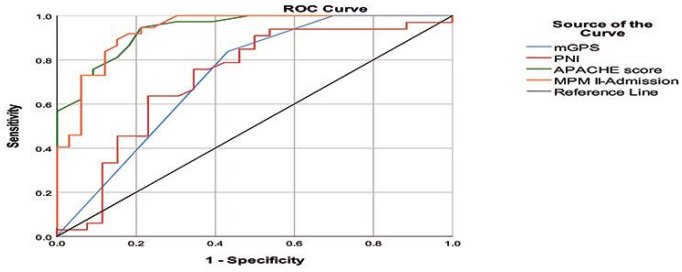


Figure 2: ROC curve of the modified Glasgow Prognostic Score (mGPS), Prognostic Nutritional Index (PNI), Acute Physiology and Chronic Health Assessment II (APACHE II) score, and Mortality Probability Models (MPM II)-Admission to predict mortality



Discussion

Breast cancer is the second most common cause of cancer-related deaths in women [26]. It is very valuable for clinicians to be able to predict the prognosis in cancer with such a high mortality. In this study, in which the significance of some inflammatory markers and scoring in predicting breast cancer prognosis was examined, higher mGPS score and MPM-II (≥36) were found to be associated with higher mortality. Moreover, having undergone chemotherapy for at least two weeks was associated with an increase in mortality.

It has been established that mGPS is an important inflammatory marker reflecting the prognostic status in breast and various other cancers. In this scoring system, albumin and CRP, which are biochemical tests that can be easily examined in blood, are evaluated in a combined way [18]. CRP, one of these components, is known to have a critical prognostic value as an inflammation marker in breast cancer patients [27]. Another component, hypoalbuminemia, may occur as a result of impaired nutrition secondary to an ongoing systemic inflammatory response [28]. Hypoalbuminemia has also been used to determine the prognosis of the disease in various cancer types [29,30]. The association of mGPS with poor clinical outcomes in patients with breast cancer was demonstrated in a study [31]. In addition, many studies have revealed that mGPS is associated with survival in other organ cancers [28,32–34]. In our study, mGPS was shown to be an important prognostic marker for mortality in breast cancer patients at the first admission in ICU. The mGPS values in our study were calculated from the blood taken at the time of a patient's first admission to the intensive care unit. When we look at the literature, no article reporting that the prognostic value of mGPS calculated at admission to the ICU in breast cancer patient is available. This lack of information should be viewed as important data that should be added to literature.

Table 1: Summary of patients characteristics and laboratory measurements with regard to groups

		Status		
Characteristics	**Total (n=71)**	**Exitus (n=37)**	**Discharged (n=34)**	***P*-value**
Age	58 (45–67)	58 (47–65)	55.5 (45–70)	0.982
Sex				
Female	70 (98.59%)	36 (97.30%)	34 (100.00%)	1.000
Male	1 (1.41%)	1 (2.70%)	0 (0.00%)	
Comorbidities	29 (40.85%)	14 (37.84%)	15 (44.12%)	0.767
Diabetes mellitus	11 (15.49%)	6 (16.22%)	5 (14.71%)	1.000
Hypertension	20 (28.17%)	10 (27.03%)	10 (29.41%)	1.000
Ischemic heart diseases	3 (4.23%)	2 (5.41%)	1 (2.94%)	1.000
COPD	2 (2.82%)	1 (2.70%)	1 (2.94%)	1.000
Hypothyroidism	3 (4.23%)	1 (2.70%)	2 (5.88%)	0.604
Atrial fibrillation	7 (9.86%)	3 (8.11%)	4 (11.76%)	0.703
Chronic renal failure	6 (8.45%)	2 (5.41%)	4 (11.76%)	0.417
Chemotherapy				
None	6 (8.57%)	2 (5.56%)	4 (11.76%)	0.003
< 2 weeks	22 (31.43%)	5 (13.89%)	17 (50.00%)	
2–4 weeks	6 (8.57%)	5 (13.89%)	1 (2.94%)	
> 4 weeks	36 (51.43%)	24 (66.67%)	12 (35.29%)	
Malignancy status				
Controlled / Remission	4 (5.63%)	1 (2.70%)	3 (8.82%)	0.024
Newly diagnosed	8 (11.27%)	1 (2.70%)	7 (20.59%)	
Recurrence / Progression	59 (83.10%)	35 (94.59%)	24 (70.59%)	
Stage				
Stage I	3 (6.38%)	1 (3.85%)	2 (9.52%)	0.717
Stage II	2 (4.26%)	1 (3.85%)	1 (4.76%)	
Stage III	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Stage IV	42 (89.36%)	24 (92.31%)	18 (85.71%)	
Reason of ICU admission				
Respiratory problems	20 (28.17%)	11 (29.73%)	9 (26.47%)	0.002
Neurological problems	11 (15.49%)	7 (18.92%)	4 (11.76%)	
Sepsis	20 (28.17%)	15 (40.54%)	5 (14.71%)	
Postoperative	15 (21.13%)	1 (2.70%)	14 (41.18%)	
Others	5 (7.04%)	3 (8.11%)	2 (5.88%)	
Length of stay in ICU	3 (2–7)	5 (2–8)	2 (2–4)	0.010
MV	52 (73.24%)	36 (97.30%)	16 (47.06%)	<0.001
Invasive MV	34 (47.89%)	32 (86.49%)	2 (5.88%)	<0.001
Hemoglobin	10.77 (1.87)	10.65 (2.04)	10.91 (1.68)	0.553
Platelet (x1000)	146 (95–223)	105 (56 - 164)	219 (135–257)	<0.001
WBC	9360 (6240–14820)	9250 (6240 - 14820)	10685 (6410– 14150)	0.917
Neutrophil	7570 (5160–13000)	7430 (5340 - 13320)	7600 (5160– 11970)	0.917
Lymphocyte	610 (410 –1160)	530 (270–880)	735 (490–1640)	0.037
Eosinophil	10 (0–20)	0 (0 - 10)	15 (0–40)	0.011
Monocyte	410 (240–830)	480 (310–790)	370 (240–850)	0.604
CRP	85.63 (40.24–189.05)	118.28 (53.98– 198.84)	67.22 (5.35– 122.05)	0.030
Albumin	2.94 (0.67)	2.73 (0.56)	3.21 (0.72)	0.005
LDH	479 (285–782)	636 (285–1612)	439 (392–672)	0.755
NLR	11.41 (5.07–20.38)	14.71 (6.88–24.54)	8.09 (3.85–17.00)	0.021
PLR	218.03 (100.8–371.19)	192.16 (61.54–351.16)	218.67 (113.33– 390.24)	0.306
LMR	1.39 (0.75–2.71)	1.03 (0.70–1.70)	1.85 (0.98–3.56)	0.030
SII	1570.70 (556.07–3338.57)	1570.70 (334.15–3950.69)	1482.58 (646.19– 3138.67)	0.747
mGPS				
0	9 (13.43%)	0 (0.00%)	9 (30.00%)	<0.001
1	14 (20.90%)	6 (16.22%)	8 (26.67%)	
2	44 (65.67%)	31 (83.78%)	13 (43.33%)	
PNI	34.40 (28.75 - 40.65)	31.45 (27.85– 35.20)	38.15 (33.45 - 43.35)	0.004
APACHE II score	17 (11–27)	27 (19–32)	9 (7–14)	<0.001
MPM II-Admission	40.5 (23–77)	70 (49–92)	23 (8–26)	<0.001

Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, MV: Mechanical ventilation, WBC: White blood cell, CRP: C-Reactive protein, LDH: Lactate dehydrogenase, NLR: Neutrophil–lymphocyte ratio, PLR: Platelet–lymphocyte ratio, LMR: Lymphocyte–monocyte ratio, SII: Systemic immune-inflammation index, mGPS: Modified Glasgow prognostic score, PNI: Prognostic nutritional index; APACHE: Acute Physiology and Chronic Health Assessment II, MPM II: Mortality Probability Models

Table 2: Performance of prognostic scores for predicting mortality

Prognostic Scores	**Cut-off**	**Sensitivity**	**Specificity**	**Accuracy**	**PPV**	**NPV**	**AUC (95.0% CI)**	***P*-value**
NLR	≥12.6	59.46%	70.59%	64.79%	68.75%	61.54%	0.659 (0.532–0.786)	**0.021**
PLR	≥240	45.95%	55.88%	50.70%	53.13%	48.72%	0.429 (0.294–0.564)	0.306
LMR	<1.8	78.38%	52.94%	66.20%	64.44%	69.23%	0.649 (0.520–0.778)	**0.030**
SII	≥3200	32.43%	79.41%	54.93%	63.16%	51.92%	0.478 (0.342–0.614)	0.747
mGPS	2	83.78%	56.67%	71.64%	70.45%	73.91%	0.727 (0.600–0.854)	**0.002**
PNI	<35	72.73%	65.38%	69.49%	72.73%	65.38%	0.720 (0.581–0.859)	**0.004**
APACHE II score	≥15	94.59%	78.79%	87.14%	83.33%	92.86%	0.939 (0.888–0.990)	**<0.001**

MPM II is a prognostic scoring system used in ICU patients to predict mortality risk [35]. Most of the studies using MPM II were conducted to estimate the mortality of patients hospitalized in the ICU regardless of disease [24,36]. In a few studies conducted in cancer patients, it was shown that MPM II showed a performance than other scoring systems in predicting mortality [17,37]. Contrary to the literature, our study revealed that MPM II appears to be a significant prognostic marker in predicting the mortality of patients with breast cancer. Because the MPM II is calculated at the time of ICU admission, it mostly depends on the variables defined at the time of ICU admission or in the period immediately prior to admission. The most likely factor that could explain the conflicting results between our study and those in the literature may be the criteria for ICU admission. Differences in the admission criteria could be responsible for variations regarding patients' baseline characteristics, which could influence patient prognosis and treatment-related decisions, ultimately leading to considerable changes in outcome or other prognostic features.

In addition, inflammatory markers (NLR, PLR, LMR, SII) and scoring systems, such as PNI and APACHE II, were also examined to ascertain their value in predicting breast cancer prognosis in our study. Although different studies have shown that these markers and scoring systems have an important role in predicting breast cancer prognosis [12,16,38–41], in the multivariate analysis performed in our study, it was found that these parameters were not independently associated with breast cancer mortality. However, it should be noted that when sensitivity and specificity values were assessed, APACHE II score demonstrated relatively high values in both measures.

Another result of our study was that undergoing chemotherapy for a longer period of time was associated with increased risk of mortality and remained significant in multivariable analyses. This situation can be interpreted to be related to chemotherapy toxicity and side effects; however, it is evident that treatment decisions and length of therapy are based on relevant criteria, and therefore, these results should be evaluated cautiously and should not be generalized due to various biases and confounding factors that must be taken into account, including diagnosis, cancer stage, co-morbidities, planned duration of chemotherapy, and/or adjunct treatments. As such, it would be more appropriate to evaluate the effects of chemotherapy duration together with relevant factors, such as cancer type, time since diagnosis, chemotherapy protocol(s), last chemotherapy session, and patient-related characteristics.

Limitations

Our study has some limitations which include its single-centered, retrospective nature and small sample size. Since survival was defined as discharge from the ICU, longer-term survival data are not available and thus, detailed survival analyses could not be performed. In addition, data, such as time of diagnosis, chemotherapy protocol, time until chemotherapy initiation, use of additional treatments, and alternative therapies, were not assessed. These factors and various others may have affected prognosis. Our findings should therefore be interpreted cautiously and with these limitations in mind.

Conclusion

In this study, it was found that mGPS and MPM-II scores in breast cancer patients hospitalized in the intensive care unit were significant in determining mortality based on a multivariate analysis. Comprehensive, multicenter, prospective studies are needed to determine whether these parameters (or others) can be used to assess prognosis in breast cancer patients requiring intensive care during their treatment.

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Clinical outcomes of pediatric extracorporeal life support: Single center experience

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Ethics Committee Approval
This study was approved by Ege University Faculty of Medicine clinical research ethics committee (number: 21-2T/18, 19.02.2021). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The use of extracorporeal life support (ECLS) in children has notably increased over the last two decades, the indications for its use are expanding. According to the Extracorporeal Life Support Organization (ELSO) 2016 report, the rate of pediatric extracorporeal membrane oxygenation (ECMO) runs was 24% among all ECMO patients. A relationship between higher ECMO volume and mortality for neonates and adult patients supported with ECLS was reported. Different mortality rates were reported for different diagnostic and age groups for ECMO patients. The objective of this study was to describe our experience with pediatric ECMO.

Methods: A retrospective cohort study was conducted on patients between 1 month and 18 years who underwent ECMO treatment in a pediatric intensive care unit from January 2015 to June 2022. Patients' characteristics, outcomes, and complications were recorded.

Results: A total of 22 children underwent ECMO during the study period. The median age of the patients was 4.5 years (ranging from 2 months to 18 years). Eight (36.4%) patients required venoarterial (VA) ECMO, and 14 patients (63.6%) required venovenous (VV) ECMO. Among the eight children who underwent VA ECMO, central cannulation was performed in 62.5% of cases. Seven children who required VV ECMO were cannulated with a double lumen catheter (42.8%). Thirteen (59.1%) patients were successfully weaned from ECMO. Weaning rates were 25% and 78.5% for VA and VV ECMO, respectively. Among 22 patients, overall hospital mortality was 72.7%. Mortality rates were 87.5% and 64.2% for VA and VV ECMO. Five patients (22.7%) survived to hospital discharge.

Conclusion: Extracorporeal life support is one of the life-saving treatment modalities. This study found that the children requiring VA ECMO had a higher mortality rate than children requiring VV ECMO, a result that is consistent with the ELSO registry report. In our study, children requiring VV ECMO had a higher weaning rate than the ELSO registry data. However, they had a lower survival to discharge rate than the ELSO registry data. We feel that by describing this case series, the spread of ECMO practice may be supported in Turkey.

Keywords: extracorporeal life support, children, heart failure, respiratory failure, intensive care

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Introduction

Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) is a treatment modality used in patients with severe respiratory and/or heart failure [1,2]. The first successful case of neonatal ECMO support was implemented in 1976 [3]. According to the Extracorporeal Life Support Organization (ELSO) 2016 report, the rate of pediatric ECMO runs was 24% among all ECMO patients (9.6% respiratory, 10.6% cardiac, and 3.8% ECLS to support cardiopulmonary resuscitation) [4].

ECMO is basically implemented in two different ways: (1) venovenous ECMO (VV-ECMO) or (2) venoarterial ECMO (VA-ECMO). While the main purpose in VV-ECMO is to support lung function, the main purpose in VA-ECMO is to provide both respiratory and cardiac support. Both VA and VV ECMO can be applied to pediatric patients who are experiencing respiratory failure, but VV ECMO is preferred primarily to avoid systemic thromboembolic complications. While an increase in the frequency of VV ECMO has been observed in this patient population in recent years, it is thought that increasing availability for double lumen cannula is associated with this condition.

Survival rates for ECMO patients have been reported with a variety of ranges among different patient age groups and different indications. Neonatal respiratory patients have the highest survival rates, while extracorporeal cardiopulmonary resuscitation (ECPR) patients have the lowest [5]. In children with severe multi-organ failure, survival is 43%–47% [6,7]. The rate of survival to discharge is 61% for pediatric respiratory ECMO cases and 44%–54% for neonatal and pediatric congenital heart disease patients [8,9].

In this study, we aimed to describe the patient demographics, indications, complications and outcomes in children requiring VV or VA ECMO.

Materials and methods

A retrospective cohort study was conducted on patients between one month and 18 years supported with ECMO in a 17-bed tertiary pediatric intensive care unit (PICU) at Ege University Children's Hospital from January 2015 to June 2022. The study was approved by the Ethics Committee of Ege University Faculty of Medicine (2021-2T/18). We retrospectively analyzed the medical records from 22 children. Incomplete medical records were excluded. Patient's demographics, primary diagnosis, comorbidities, pre-ECMO/post-ECMO laboratory analysis, ECMO variables, cannula size, duration of ECMO support, vasoactive inotropic score (VIS), weaning from ECMO, and complications were evaluated. The Pediatric Risk of Mortality (PRISM) score, Pediatric Logistics Organ Dysfunction (PELOD) score, length of PICU stay, and in-hospital mortality was recorded.

Cannulation is performed at the bedside for VV ECMO and both peripheral and central VA ECMO by the cardiovascular surgeon. Unfractionated heparin infusion was given with the goal of reaching an activated clotting time within 180 to 220 s. The ECMO flow was set to maintain adequate tissue perfusion pressure; for VA ECMO, 80–150 ml/kg/min and for VV ECMO, 60–120 ml/kg/min. A central venous oxygen saturation > 70%, normal arterial lactate, adequate mean arterial blood pressure indicated adequate tissue perfusion.

ECMO indications included a reversible cause of respiratory and/or circulatory failure with persistent inadequate gas exchange and/or high need for vasoactive inotropic medications [10,11].

Statistical analysis

We performed descriptive analysis on the data using SPSS 22 for statistical calculations. Continuous values are presented as medians with interquartile range (IQR). The Mann–Whitney U test was used for continuous data. Chi-squared analysis and Fisher's exact test were used for categorical data. *P*-value <0.05 was considered significant.

Results

A total of 22 children underwent ECLS during the study period. The median age of the patients was 4.5 years (ranging from 2 months to18 years), and 54.5% of participants were female. Eight (36.4%) patients required VA ECMO, and 14 patients (63.6%) required VV ECMO. Among the eight children who underwent VA ECMO, central cannulation was performed in 62.5% of cases. Six children who required VV ECMO were cannulated using a double lumen catheter. Nine children (40.9%) had an underlying medical condition, of which acquired immune deficiencies (5/22, 22.7%), and congenital immune deficiencies (2/22, 9%) were the most common. Among VV ECMO patients, one child was diagnosed with pediatric acute respiratory distress syndrome due to coronavirus 2019 (COVID-19)-associated pneumonia. The demographic data of the patients are given in Table 1.

The median PRISM score was 20, and the median PELOD score was 21. Inotropic support was needed in 78.2% of cases. The median vasoactive inotrope score was 62.1 (range, 0–440). The median oxygenation index was 33 (range 7.8–100.1) in VV ECMO patients and 24 (range 2.7–29.5) in VA ECMO patients. The median duration of ECMO support was 15.2 days (ranging from 4 h to 53 days). The median length of stay in the PICU was 30 days (range 1–139 days). Oxygenators were changed in 26% of patients without adverse effects.

A comparison of VV and VA ECMO patients is shown in Table 2. VVECMO patients had a longer duration of mechanical ventilation days (36.5 [30.7–70.7] versus 13.5 [4.5–24.2]; P=0.004), longer ECMO duration (16 [11.7–36] versus 7.5 [3.5–14.5] day; P=0.035), longer PICU length of stay (43.5 [30.7–71.7] versus 17 [7–24] days; P=0.006), and longer hospital stays (64 [30.7–83] versus 17 [7 –24] days; P=0.002). The other variables showed no significant differences between the two groups.

Anticoagulation-related complications were diagnosed in 68.1% of children (15/22). Among patients, four children had major bleeding (three patients with intracranial hemorrhage and one patient with a gastrointestinal system hemorrhage). The lower gastrointestinal system hemorrhage, which developed in a double lumen VV ECMO patient, was managed by correction of coagulopathy, intestinal resection, and a jejunostomy procedure. Limb ischemia developed in a patient with peripheral VA ECMO managed by perfusion cannulation.

Table 1: Patients demographics and outcomes

Patient	Age (year)	Weight (kg)	Pre-existing condition	Comorbidities	ECMO modality	Decanulated from ECMO	Alive at discharge
1	9	52	Posterior mediastinal mass	B Cell ALL	VV	Yes	Yes
2	14	40	Heart failure		VA	No	No
3	2.5	10	Trauma, PARDS		VV	Yes	No
4	12	50	Pneumonia, air leak	Langerhans cell histiocytosis	VV	Yes	No
5	14	47	Dilated cardiomyopathy		VA	No	No
6	2	10	Fulminant hepatitis	Liver transplantation atypical HUS	VV	No	No
7	4	12	Myocarditis		VA	Yes	No
8	11	36	PARDS	Cystic fibrosis	VV	No	No
9	18	70	Postpartum cardiomyopathy		VA	No	No
10	15	47	Calcium channel blocker intoxication		VA	Yes	Yes
11	0.5	6	Cardiopulmonary arrest		VA	Yes	No
12	1.5	12	PARDS		VV	Yes	No
13	4.5	15	PARDS		VV	Yes	Yes
14	12	78	Septic shock	AML M2	VV	Yes	No
15	16	30	Dilated cardiomyopathy		VA	No	No
16	2.5	4.5	Myocarditis		VA	No	No
17	0	3.7	Bacterial pneumonia, PARDS	LAD	VV	No	No
18	2	12	Viral Pneumonia, PARDS	Common B ALL	VV	Yes	Yes
19	3	19	Viral Pneumonia, PARDS	B Cell ALL	VV	No	No
20	3	15	COVID-19 pneumonia, PARDS	SCID	VV	No	No
21	11	47	Hydrocarbon inhalation, PARDS		VV	Yes	Yes
22	1.3	10	Viral pneumonia, PARDS		VV	Yes	Yes

ECMO: Extracorporeal membrane oxygenation, ALL: Acute lymphoblastic leukemia, PARDS: Pediatric acute respiratory distress syndrome, HUS: Hemolytic uremic syndrome, AML: Acute myeloid leukemia, LAD: Leukocyte adhesion deficiency, COVID-19: Coronavirus disease-2019, SCID: Severe combined immunodeficiency

Table 2: Clinical characteristics of patients with VV-ECMO and VA-ECMO

	VV-ECMO (n = 14)	VA-ECMO (n = 8)	*P*-value
Gender; Male, n (%)	7 (50)	3 (37.5)	
Age (years), median (IQR)	4.2 (1.4–11.2)	8.5 (2.1–14.7)	0.402
Weight (kg), median (IQR)	15 (11.5–46.2)	29.5 (10–47)	0.868
PRISM score, median (IQR)	16 (13.5–21)	23 (15.7–30.7)	0.095
PELOD score, median (IQR)	16.5 (11.7–22.2)	22 (13.5–23)	0.365
Peak VIS in first 24h of sepsis, median (IQR)	40 (5.0–86)	75 (50–130)	0.067
Duration of MV (days), median (IQR)	36.5 (30.7–70.7)	13.5 (4.5–24.2)	0.004
Hospital days prior ECMO, median (IQR)	3.5 (2–4.2)	2.5 (1–8.5)	0.616
ECMO duration, median (IQR)	16 (11.7–36)	7.5 (3.5–14.5)	0.035
PICU length of stay (days), median (IQR)	43.5 (30.7–71.7)	17 (7–24)	0.006
Hospital length of stay (days), median (IQR)	64 (30.7–83)	17 (7–24)	0.002
Mortality, n (%)	9 (64.2)	7 (87.5)	0.613

VV-ECMO: Venovenous extracorporeal membrane oxygenation, VA-ECMO: Venoarterial extracorporeal membrane oxygenation, IQR: Interquartile range, PRISM: Pediatric risk of mortality, PELOD: Pediatric Logistic Organ Dysfunction, VIS: Vasoactive inotropic score, MV: mechanical ventilation, PICU: Pediatric intensive care unit

Table 3: Comparison between survivors and non-survivors

	Survivors (n = 6)	Non-survivors (n = 16)	*P*-value
Gender; Male, n (%)	2 (33.3)	8 (50)	0.646
Age (years), median (IQR)	6 (1.8–12)	4.2 (1.6–13.5)	1.000
Weight (kg), median (IQR)	29.5(11.5–56.5)	17.5 (10–45.2)	0.449
ECMO modality **VV ECMO, n (%)** **VA ECMO, n (%)**	 5 (35.7) 1 (12.5)	 9 (64.3) 7 (87.5)	
PRISM score, median (IQR)	19 (14–24)	18.5 (12.5–24.2)	0.747
PELOD score, median (IQR)	16.5 (11.7 - 22.2)	21.5 (11–23)	0.858
Pre-ECMO lactate (mmol/L)	6.5 (2.9–18)	2.2 (0.8–7.6)	0.083
Requirement of CRRT, *n* (%)	2 (33.3)	8 (50)	0.646
Peak VIS in first 24h of sepsis, median (IQR)	20 (5.0–88.7)	50 (15–90)	0.381
Duration of MV (days), median (IQR)	36.5 (26.5–57.5)	28 (14.2–60.2)	0.367
Hospital days prior ECMO, median (IQR)	2.5 (1.7–4)	3.5 (1.2–5.7)	0.494
ECMO duration, median (IQR)	11.5 (8–44.5)	15 (5.2–27.2)	1.000
PICU length of stay (days), median (IQR)	43.5 (29.5–61.2)	28 (15.5–60.2)	0.407
Hospital length of stay (days), median (IQR)	75.5 (49–83)	28 (15.5–60.2)	0.098

IQR: Interquartile range, ECMO; extracorporeal membrane oxygenation, VV: venovenous, VA: venoarterial, PRISM: Pediatric risk of mortality, PELOD: Pediatric Logistic Organ Dysfunction, CRRT: continuous renal replacement therapy, VIS: Vasoactive inotropic score, MV: mechanical ventilation, PICU: Pediatric intensive care unit

All patients required mechanical ventilation support. Ten patients required continuous renal replacement treatment (CRRT) during ECMO support, and pre-existing acute kidney injury was present in five patients. Three patients underwent plasmapheresis due to coagulopathy and multiple organ failure. All central cannulations were performed bedside in the intensive care unit, and no patient developed mediastinitis.

Thirteen (59.1%) patients were successfully weaned from ECMO. The weaning rate was 25% for VA ECMO and 78.5% for VV ECMO. Among 22 patients, overall hospital mortality was 72.7%. Five patients (21.7%) survived to hospital discharge. The mortality rates of VA ECMO and VV ECMO were 87.5% and 64.2%, respectively. No differences in terms of disease severity scores, peak VIS, pre-ECMO lactate levels, ECMO duration, and lengths of PICU and hospital stays between the survivors and non-survivors were found (Table 3). The mortality rate attributed to ECMO was 27.2% (6/22 patients). The two non-survivors who underwent bronchoscopy were considered to have developed irreversible lung damage on the basis of progressive pulmonary fibrosis.

Discussion

The use of ECMO in patients with cardiac and pulmonary failure has increased over the last three decades despite optimal medical treatment [1]. VV ECMO indications in children, especially, cover a broad range of lung diseases. In our case series of 22 patients, ECMO was applied to cases with different diagnoses due to respiratory and cardiac failure.

According to the ELSO report, pediatric respiratory ECLS has a 58% rate of for survival to discharge. Among pediatric cardiac ECLS patients, cardiogenic shock has a rate of 42% survival to discharge [3,4]. In our patient population, we found a lower survival to discharge rate, especially for the VA ECMO group. Among eight patients who underwent cardiac ECLS, five had dilated cardiomyopathy, two had myocarditis, and one had cardiogenic shock due to intoxication. Our patients with end-stage heart failure, whose only chance was a heart transplant, could not survive because they could not be bridged to transplantation.

Our patient population did not include the children with congenital heart disease who underwent VA ECMO to wean them from cardiopulmonary bypass following cardiac surgery. In our hospital, PICU is located in a different building from the cardiovascular and pediatric surgery departments. This situation results in ECMO runs for patients with congenital heart disease

and congenital diaphragmatic hernia to be performed outside the PICU.

Previous studies have reported that higher annual ECMO patient volume is associated with a lower mortality rate [12,13]. It has also been speculated that higher ECMO volume is associated with better patient outcomes. ELSO registry reported that higher age group specific ECMO volume was associated with lower mortality rates for neonates and adults. They reported no relationship in the pediatric population [4]. Pediatric specific analysis revealed that the relationship between mortality and higher patient volume is present only in pediatric patients requiring cardiac ECMO [12]. We think that the high mortality rates in our study, especially for VA ECMO patients, may be related to the fact that our patient population did not include congenital heart surgery patients.

In developing countries, such as ours, with limited human and financial resources, it is important to identify new ECMO centers, establish ECMO teams, and organize their training. ECMO education and training should be provided for all healthcare professionals who are responsible for caring for ECMO patients. Providing the best outcome for ECMO patients depends on a multidisciplinary team of well-educated and experienced surgeons, intensivists, nurses, and perfusionists.

Limitations

Our study has several limitations, mainly as a result of retrospective study design. Our patient cohort has a small population similar to those in previously reported single center studies. In our study, children requiring ECMO after congenital heart surgery were not included in the cohort. For this reason, we think that the mortality rates of VA ECMO patients are higher than the previously reported rates.

Conclusion

Extracorporeal life support is one of several lifesaving treatment modalities. This study found that the children requiring VA ECMO had higher mortality rates than children requiring VV ECMO, a finding that is consistent with the ELSO registry report. In our study, children requiring VV ECMO had higher weaning rates than the ELSO registry data. However, they had a lower survival to discharge rates than the ELSO registry data. We feel that by describing this case series, the spread of ECMO practice may be supported in Turkey.

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A correlation of the ratio of left atrial volume to left ventricular ejection fraction in predicting atrial fibrillation in ischemic stroke

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Ethics Committee Approval
This study was approved by the Non-Interventional Clinical Research Ethics Committee of Sancaktepe Şehit Professor Doctor İlhan Varank Training and Research Hospital before the initiation of the study (Decision No: 2021/197, Date: 29.09.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The enlargement of left atrial volume index (LAVI) in diastolic dysfunction (DD) may predispose one to atrial fibrillation (AF) and is an important etiological reason for ischemic stroke (IS). The ratio of LAVI increase to left ventricular ejection fraction (LVEF) is a new parameter, and this work investigates the correlation between DD parameters, LAVI, LAVI/LVEF ratio, and AF in patients with sinus rhythm presenting with IS.
Methods: Here, 108 consecutive individuals who were diagnosed with IS were included in the case-control study. The patients were divided into two groups: Those with AF events on rhythm Holters (AF group, n=57) and those without (control group, n=51). LAVI was calculated from the apical four- and two-chamber views before the mitral valve was opened. LVEF was calculated by Simpson's method.
Results: The mean age of the AF group was 73.9 (6.3) years, and the control group was 72.1 (3.9) years. Hypertension, diabetes mellitus, glucose, HbA1c, CHA_2DS_2-VASc score, and previous stroke were higher in the AF group (P<0.05). LAVI (35.7 [25.3-38.2] vs 29.6 [27.7-30.9], P<0.001), the LAVI/LVEF ratio (0.7 [0.63-0.77] vs 0.5 [0.50-0.54], P<0.001), and the E/é ratio (14.6 [13.9-15.0] vs 10.7 [9.0-11.8], P<0.001) were higher in patients with AF. Multivariable analyses showed that LAVI (OR:7.985, 95%CI [2.586-4.767], P<0.001) and the LAVI/LVEF ratio (OR:0.010, 95% CI [0.000-0.007], P=0.015) were potential independent risk factors for AF events. A positive correlation was found between the CHA_2DS_2-VASc score and LAVI (P=0.032, r=0.407) and LAVI/LVEF ratio (P=0.041, r=0.253).
Conclusion: We concluded that the increase in LAVI and LAVI/LVEF ratio increases the risk of IS by increasing the tendency to AF. These parameters are useful in predicting IS.

Keywords: ischemic stroke, atrial fibrillation, left atrial volume, ejection fraction

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Introduction

Ischemic stroke (IS) is one of the leading causes of mortality and morbidity worldwide [1]. Cardiovascular diseases, diabetes mellitus (DM), hypertension (HT), and atrial fibrillation (AF) are the strongest risk factors for thromboembolism leading to acute ischemic stroke [2]. Having AF enhances the risk of IS five-fold [2, 3]. AF is the most common rhythm problem specifically in elderly patients, and many factors play a role in its etiology [2]. The enlargement of the left atrium as well as metabolic and hormonal factors pave the way for the formation of AF. In addition, one of the most important factors causing left atrial enlargement is left ventricular diastolic dysfunction (DD) [4, 5].

The dilatation of left atrial volume in DD may predispose one to AF which is one of the major etiological reasons for ischemic stroke. However, DD is not considered an etiological factor for ischemic stroke when making the current risk score calculation. However, the increased left atrial volume index (LAVI) is an important diagnostic indicator for the echocardiographic definition of DD [4]. The increasing ratio of LAVI to left ventricular ejection fraction (LVEF) is a new parameter and is being investigated in terms of efficacy in predicting AF. In this study, we investigated the correlation between DD parameters, LAVI, LAVI/LVEF ratio, and AF in patients with sinus rhythm presenting with IS.

Materials and methods

We included 108 consecutive individuals received to our hospital with IS. All subjects underwent 24-hour rhythm Holter recording and echocardiographic imaging within the first 72 hours after hospitalization. All patients were divided into two groups: those patients with newly diagnosed AF events on rhythm Holters (atrial fibrillation group) and those without (control group). The two groups were checked in terms of demographic, clinical, and echocardiographic characteristics.

Exclusion criteria: Patients with carotid artery disease, those diagnosed with heart failure and LVEF ≤40, patients with moderate or severe mitral/aortic stenosis or regurgitation, and patients who had previously diagnosed AF or received invasive or non-invasive treatment for AF were excluded.

Diagnosis of ischemic stroke: The diagnosis of IS was made based on the recommendations of the American Stroke Association after a detailed history, physical examination, and brain imaging [1]. Neurological examination was performed according to the National Institute Health Stroke Scale (NIHSS). [1]. Venous blood specimens were taken from all patients after at least 8 hours of fasting, and biochemical and hematological analyzes were performed using standard laboratory methods.

24-hour rhythm Holter and diagnosis of atrial fibrillation: A 24-hour rhythm Holter was performed on all patients diagnosed with ischemic stroke within the first 72 hours after hospitalization. Holter recordings were analyzed with Cardioscan 12.0 (DM Software Inc., Stateline, NV, US) software. All recordings were made in accordance with ISHNE-HRS expert opinions, and these results were interpreted by two different cardiologists [6]. The diagnosis of AF was made according to the recommendations of the current guidelines [7]. Standard 12-lead ECG registering or single-lead ECG trace ≥30 sec with an absence of recognizable repetitive P waves and non-uniform RR intervals (when the atrioventricular transmission is not impaired) were considered diagnostic for clinical AF.

Echocardiography: The Society of American Echocardiography recommendations were considered during echocardiography. All individuals visited a transthoracic echocardiographic consultation with an available trading device (Wisconsin, GE Vingmed, Milwaukee, Vivid 9 Pro, USA). Images were taken in the lateral left decubitus position [8]. All common measurements (LA end-systolic diameter, LV end-systolic/diastolic diameters, etc.) were taken from the apical four-chamber and parasternal long-axis views. Simpson's method was used for calculating LVEF. A single-lead electrocardiogram was continually registered.

Measurements were taken for LAVI from the apical two- and four-chamber view before the mitral valve was opened. According to DD guidelines, the LA volume was measured in custom views maximizing LA length and transverse diameters. When applying PW Doppler, the mitral peak E-wave (cm/s) velocity was acquired from color imaging of the apical four chambers for optimal alignment with blood flow (1-3 mm axial size) between the mitral leaflet tips. A PW Doppler velocity (cm/s) sample volume (mostly 5-10 mm axial size) in the mitral lateral and septal regions was measured in the apical four-chamber view; the mean and velocity were calculated. To attain the highest Doppler velocity aligned with the CW, the jet velocity (m/s) of tricuspid regurgitation (TR) was obtained using CW Doppler from apical four-chamber and parasternal view with color flow imaging. Echocardiographic data were reviewed by two diverse cardiologists blinded to the patients' characteristics [8].

Ethics committee approval

(Decision No: 2021/197, Date: 29.09.2021) was obtained from the Non-Interventional Clinical Research Ethics Committee of Sancaktepe Şehit Professor Doctor İlhan Varank Training and Research Hospital before the initiation of the study. Written and verbal consent was obtained from all participants. The Declaration of Helsinki was followed in the application of the ethical rules of the study.

Statistical analysis

The SPSS 20.0 (Armonk, IBM Corporation, USA) program was used for statistical analysis. Continuous factors are shown as the mean (standard deviation [SD]) or median (25-75 percentile), and categorical factors are presented as percentages (%) and n (number). Due to the number of cases in the groups, normality assumptions were examined with Kolmogorov-Smirnov tests. Student's t-test was used for continuous variables, and Pearson's x^2 test was used for categorical factors. The Mann-Whitney U test was used to compare two free groups (LVEF, LAVI, LAVI/LVEF, E/é, Mitral inflow E, E/a) when the variable was not normally distributed. Multivariable and univariable logistic regression analyses were used to study the relationship between AF and other risk factors. Pearson's correlation coefficient (r) analyses were used to investigate the strength of the association between LAVI, LAVI/LVEF ratio, and CHA_2DS_2-VASc score. A *P*-value below 0.05 was considered significant in all statistical results.

Results

The mean age of the patients in the AF group (n=57) was 73.9 (6.3) years, and the control group (n=51) was 72.1(3.9) years (*P*=0.265). There was no difference between the two groups in terms of gender, systolic and diastolic blood pressures, heart rates, current smoking, dyslipidemia, coronary artery disease, serum cholesterol levels, and renal functions.

HT (61.4% vs 41.1%, *P*=0.017), DM (50.8% vs 35.2%, *P*=0.008), serum glucose level (132.9 [31.7] vs 118.1 [28.6], *P*< 0.001), HbA1c level (7.2 [1.2] vs 6.6 [1.1], *P*=0.004), CHA_2DS_2-VASc score (5.6 [1.2] vs 4.2 [2.5], *P*<0.001), previous stroke episode (24.5% vs 7.8%, *P*=0.001) were higher in the AF group (Table 1).

Table 1: Clinical characteristics of patients with ischemic stroke with atrial fibrillation and control group

Variables	Atrial fibrillation group (n=57)	Control group (n=51)	*P*-value
Age (years)	73.9 (6.3)	72.1 (3.9)	0.265
Gender (male), n (%)	30 (52.6)	27 (52.9)	0.548
Systolic BP (mmHg)	132.6 (22.5)	128.7 (20.6)	0.158
Diastolic BP (mmHg)	82.9 (15.6)	77.8 (14.2)	0.458
Heart rate beats/min	74.4 (13.5)	75.7 (13.7)	0.450
Hypertension, n (%)	35 (61.4)	21 (41.1)	0.017
Diabetes mellitus, n (%)	29 (50.8)	18 (35.2)	0.008
Dyslipidemia, n (%)	16 (28.1)	14 (27.4)	0.578
Current smoking, n (%)	12 (21.1)	13 (22.8)	0.420
Coronary artery disease, n(%)	14 (24.5)	12 (23.5)	0.196
Previous stroke/TIA, n (%)	14 (24.5)	4 (7.8)	0.001
CHA_2DS_2-VASc score	5.6 (1.2)	4.2 (2.5)	0.000
Glucose (mg/dL)	132.9 (31.7)	118.1 (28.6)	0.014
HbA1c (%)	7.2 (1.2)	6.6 (1.1)	0.004
Creatinine (mg/dL)	0.9 (0.3)	0.9(0.5)	0.789
EGFR, ml/min/1.73 m^2	76.7 (38.7)	77.8 (40.4)	0.568
LDL cholesterol (mg/dL)	121.5 (34.5)	128.9 (36.7)	0.895
HDL cholesterol (mg/dL)	42.4 (19.5)	41.6 (15.5)	0.758
Triglyceride (mg/dL)	159.7 (45.6)	152.8 (42.8)	0.695

EGFR: Estimated glomerular filtration rate, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TIA: Transient ischemic attack.

Left ventricular wall thicknesses, systolic and diastolic diameters, and LVEF were not different between the two groups (*P*>0.05), LAVI (35.7 [25.3-38.2] vs 29.6 [27.7-30.9], *P*<0.001), the LAVI/LVEF ratio (0.7 [0.63-0.77] vs 0.5 [0.50-0.54], *P*<0.001). The E/é ratio (14.6 [13.9-15.0] vs 10.7 [9.0-11.8], *P*<0.001) was higher in patients with AF (Table 2).

Table 2: Echocardiographic features of patients ischemic stroke with atrial fibrillation and control group

Variables	Atrial fibrillation group (n=57)	Control group (n=51)	*P*-value
IVST, mm	1.1 (0.5)	1.1 (0.4)	0.752
LVPWT, mm	1.1 (1.7)	1.1 (1.7)	0.525
LVDD, mm	4.8 (0.3)	4.7 (0.3)	0.857
LVSD, mm	3.2 (0.5)	3.0 (0.4)	0.458
LAVi, ml/m^2	35.7 (25.3-38.2)	29.6 (27.7-30.9)	<0.001*
LVEF, %	55 (52.5-58.0)	57.0 (55.0-60.0)	0.067*
LAVI/LVEF ratio	0.7 (0.63-0.77)	0.5 (0.50-0.54)	<0.001*
Mitral inflow E, m/s	0.78 (0.62-0.85)	0.82 (0.71-0.93)	0.487*
E/A ratio	0.87 (0.75-1.18)	0.81 (0.71-0.98)	0.254*
E/é, mean	14.6 (13.9-15.0)	10.7 (9.0-11.8)	<0.001*
Peak TR velocity (m/s)	2.8 (0.9)	2.7 (0.7)	0.187

E/A: the ratio between mitral E- and A-wave flow velocity, IVST: Interventricular septal thickness, LVPWT: Left ventricular posterior wall thickness, LAVI: Left atrial volume index LVEDD: Left ventricle diastolic diameter, LVEF: Left ventricular ejection fraction, LVSD: Left ventricle systolic diameter, TR: Tricuspid regurgitation. *: Mann-Whitney U test

The relationship between AF events and other risk factors was examined by logistic regression analysis. Univariable regression analyses showed DM (OR: 2.754, 95% CI [1.737-6.122], *P*=0.014), serum glucose (OR: 1.017, 95% CI [1.003-1.032], *P*=0.018) , HbA1c (OR: 1.981, 95% CI [1.213-3.325], *P*=0.006), previous stroke episode (OR: 5.875, 95% CI [1.842-18.739], *P*=0.003), CHA_2DS_2-VASc score (OR: 1.474, 95% CI [1.154-1.882], *P*=0.002), the E/é ratio (OR: 2.495, 95% CI [1.818-3.422], *P*<0.001), LAVI (OR: 3.23, 95% CI [1.951-5.359], *P*<0.001), and the LAVI/LVEF ratio (OR: 8.1, 95% CI [1.052-6.351], *P*<0.001) were related to AF events. Multivariable analyses showed that only LAVI (OR: 7.985, 95% CI [2.586-4.767], *P*<0.001) and the LAVI/LVEF ratio (OR: 0.010, 95% CI [0.000-0.007], *P*=0.015) are potential independent risk factors for AF events with ischemic stroke patients (Table 3). A considerable positive correlation was found between the CHA_2DS_2-VASc score, LAVI, and the LAVI/LVEF ratio (Figure 1, 2).

Table 3: The association between AF and other risk factors with logistic regression analysis

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
HT	1.051 (0.439-2.513)	0.199		
DM	2.754 (1.737-6.122)	0.014		
Glucose	1.017 (1.003-1.032)	0.018		
HbA1c	1.981 (1.213-3.235)	0.006		
Previous stroke	5.875 (1.842-18.739)	0.003		
CHA_2DS_2-VASc	1.474 (1.154-1.882)	0.002		
E/é	2.495 (1.818-3.422)	<0.001		
LAVI	3.23 (1.951-5.359)	<0.001	7.985 (2.586-4.767)	<0.001
LAVI/LVEF	8.10 (1.052-6.351)	<0.001	0.010 (0.000-0.007)	0.015

DM: Diabetes Mellitus, LAVI: Left atrial volume index, LVEF: Left ventricle ejection fraction, HT: Hypertension.

Figure 1: The correlation between CHA_2DS_2-VASc score and left atrial volume index

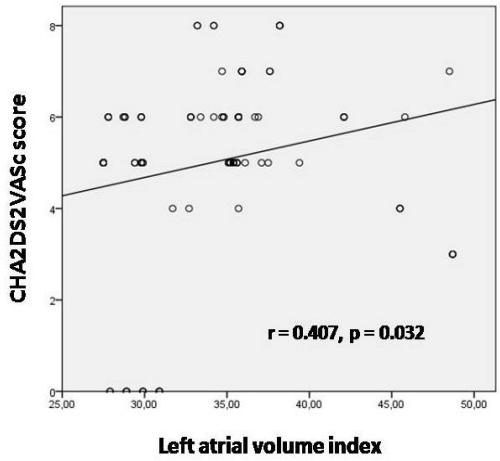
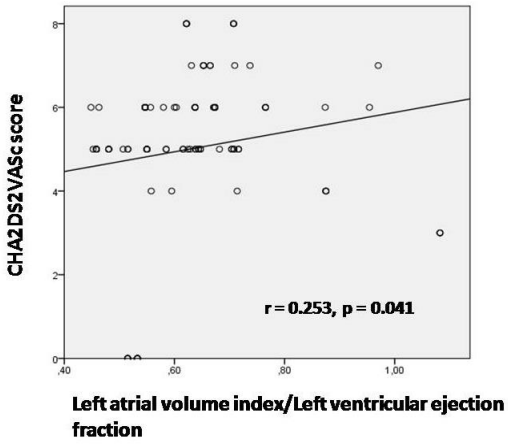


Figure 2: The correlation between CHA_2DS_2-VASc score and left atrial volume index/Left ventricular ejection fraction



Discussion

We found that an increase in LAVI and the LAVI/LVEF ratio was related to the AF events in patients with ischemic stroke with sinus rhythm. The LA/LVEF ratio was positively correlated with the CHA_2DS_2-VASc score and increased LAVI and the LAVI/LVEF ratios were independent risk factors for AF in patients with IS. To the best of our

knowledge, the LAVI/LVEF has not been evaluated previously in predicting AF with patients of IS.

AF incidence is the most common rhythm problem worldwide and increases with age. AF may be secondary to many underlying diseases or may occur alone. The most prominent anatomical feature in AF is left atrial or bi-atrial dilatation as defined by imaging. In DD, impaired left ventricular myocardial relaxation and increased LV chamber stiffness leads to high cardiac filling pressures [8, 9]. Increased pressure and volume in the left ventricle lead to atrial enlargement over time. Structural remodeling emerges when atrial pressure increases, which in turn leads to atrial fibrosis. This is moderated at the cellular plan by stimulation of various pro-fibrotic factors including transforming growth factor-beta, Ang II, and a platelet-derived growth factor that can act individually or synergistically to encourage fibrosis [5,10].

One of the important studies on the association between diastolic dysfunction and ischemic stroke outcomes was accomplished by Ryu et al. [11]; 503 patients with ischemic stroke and LVEF ≥ 50% were included in that study, and DD-related outcomes were investigated by measuring tissue Doppler values. They found an independent relation between DD, functional outcomes, and mortality after ischemic stroke. In particular, patients with an E/e' >14 had a four-fold higher mortality risk compared to patients with an E/é ≤8.8. In our study, the mitral E/é ratio was higher in the AF group [11]. In addition, we found that increased LAVI and LAVI/LVEF values were independent risk factors for the presence of AF versus the mitral E/é ratio.

Strahrenberg et al. [12] performed a 7-day Holter follow-up in patients with sinus rhythm and IS. Patients diagnosed with paroxysmal AF were evaluated by echocardiography, and the left atrial diameter, left atrial volume index, LAVI/A, and LAVI/a' were greater in these patients. A similar study was later performed by Walden et al. LAVI and the ventricular and atrial septum LAVI/a' ratio were higher in patients who had a stroke/TIA and developed AF during their follow-up [13]. Similarly, LAVI values were higher in the AF group in our study. Differently, the ratio of LAVI/LVEF, a new parameter, was found to be higher in the AF group. This parameter was also found to be correlated with the CHA_2DS_2-VASc score. The ratio of LAVI value to LVEF could be a useful new marker, like LAVI, in predicting DD and AF in patients with ischemic stroke.

The Framingham Offspring Study showed that left atrial functional index (LAFI) was associated with incidence AF and CVD [14]. The formula for LAFI is (LA emptying fraction x LVOT-VTI/ LA max index). These measurements need a quality image, and their measurement takes more time to collect. Compared to previous studies and complex formulas, the measurement of LAVI and LAVI/LVEF seems practical and time-saving for physicians.

The LA capacity volume index reflects the accumulative effects of increased LV filling pressure. Increased LAVI is an independent risk factor for heart failure, AF, death, and ischemic stroke. It is associated with an unfavorable prognosis [15]. A prior study evaluated LAVI values with three-dimensional echocardiography and found that the left ventricular volume (LVV)-to-LAV ratio decreased with age [16]. On the contrary, LAV increases more than left ventricular volume (LVV) with aging; the LAV/LVV ratio thus increases. Increased LAV values may increase both the frequency of AF and the incidence of ischemic stroke. Compared to a prior study, which showed that the LAV enlarges with aging using three-dimensional echo, our study evaluated the LAVI/LVEF ratio using a two-dimensional echocardiography. In this study, we tried to demonstrate the role of diastolic dysfunction parameters and a new parameter, the LAVI/LVEF ratio, in the etiology of ischemic stroke using two-dimensional echocardiography. In recent years, there have been new developments in imaging modalities, and measurements are made with more sophisticated devices. However, these devices are not readily available everywhere and using the device and interpreting images require experience. Two-dimensional echocardiography is easy to access and use, and many important parameters can be obtained quickly and reliably.

Limitation

One of the most main limitations of this study is the small number of patients. Another limitation is that the accurate diagnosis of DD was made by cardiac catheterization. However, our patients were newly diagnosed with acute IS, and catheterization could not be performed considering the current conditions. Another limitation is that left atrial volumes were evaluated with two-dimensional echo, and comparisons could not be made with methods such as three-dimensional echo or cardiac MRI. The retrospective nature of our study and the lack of long-term follow-up are controversial in terms of the usefulness of these parameters. It is known that a 72-hour rhythm Holter is more acceptable for the diagnosis of post-stroke AF. Our findings need to be validated prospectively and benchmarked against other means of risk stratification including two-week ambulatory ECG monitoring and cardiac MRI.

Conclusion

LAVI and the LAVI/LVEF ratios increased in subjects with AF events. LAVI and the LAVI/LVEF ratios were correlated with the CHA_2DS_2-VASc score. In the absence of significant structural heart and valvular disease, DD is the most likely cause of increased LAVI. Although DD does not directly cause IS events, it has important effects on left atrial dilatation and AF development. Although DD has not yet played a part in the risk factors involved in estimating ischemic stroke, larger studies will likely be conducted in the future to shed light on this issue.

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Health literacy levels and affecting factors among adults in Northeast Anatolia

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This study was approved by the Non-Interventional Clinical Research Ethics Committee of Atatürk University (decision no. 27.12.2018-8/21)..
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Abstract

Background/Aim: Health literacy is individuals' wishes and capacities to develop their own opinions and make decisions regarding health services, their ability to maintain and promote their health, access health-related information, and interpret those messages and information correctly. Although health literacy began being discussed in the 1980s, its importance has become more apparent in recent years. However, greater research with regional and local data is still needed in this field. The purpose of this study was to determine levels of health literacy among adults in central districts of the Erzurum province, Turkey, and to examine the factors affecting these.

Methods: This cross-sectional study was performed with 864 individuals from the 15–65 age group living in Erzurum. The questionnaire employed in the research consisted of two parts: a personal information form and the Turkish Health Literacy Scale-32. The questionnaire was applied following receipt of participant consent. SPSS v 24 was used to enter and analyze the data. Descriptive statistics were expressed as percentage, mean, standard deviation, minimum, and maximum values. The chi-square test, Spearman's correlation analysis, and regression analysis were applied. Statistical significance was set at $P<0.05$.

Results: The mean age of the participants was 35.6 (13.0) years, and 55.8% were women. Additionally, 23.6% (n=204) of participants were educated to a primary school level or were uneducated, and 56.0% were not working in income-generating employment. Health literacy levels were inadequate in 24.1% of participants, problematic in 31.6%, adequate in 27.7%, and perfect in 16.6%. Health literacy levels varied significantly depending on participants' age groups ($P<0.001$), sex ($P=0.007$), education levels ($P<0.001$), possession of health insurance ($P<0.001$), presence of chronic disease in themselves or first-degree relatives ($P=0.002$ and $P<0.001$, respectively), and history of hospitalization exceeding 15 days ($P=0.026$).

Conclusion: The incidence of inadequate/problematic health literacy was 55.7%. Although it is not an expected rate for health literacy, this rate shows that only half of the population has a sufficient level and a significant inadequacy in health literacy. This shows that insufficient health literacy is widespread in Erzurum and that interventions aimed at health literacy are required in the province as in the country as a whole. Understanding the factors affecting health literacy is important in terms of improving health, health services planning, and intervention in these spheres.

Keywords: health literacy, THLS-32, health promotion

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Introduction

Health literacy is related to general literacy and refers to individuals' wishes and capacities to develop their own opinions and make decisions regarding health services throughout their lives, their ability to maintain and promote their health, to access health-related information in order to improve their quality of life and to correctly interpret those messages and information [1,2].

Health literacy is a concept defined within the framework of health improvement. It first appeared in a paper titled 'Health Education as Social Policy' by Scott Simonds in 1974. The concept of health improvement was defined at the International Conference on Health Promotion held in Canada in 1986 as 'enabling individuals to increase their control over and improve their health.' The concept of 'health literacy' was introduced to include the learning and perception of factors affecting health (health determinants) in addition to social, political, and economic conditions [3].

Health literacy allows individuals to acquire information, personal skills, and a level of self-confidence that encourages behavior that will improve their own health and that of the community by altering their lifestyle and living conditions [4]. It reinforces more effective use of existing health services, improved quality conditions in health services, and the individuals' competence in terms of their and the community's health [5,6]. Research has shown that inadequate health literacy is associated with increased hospitalization, greater use of emergency department services, less use of preventive health services, irregular drug use, poor comprehension of health-related messages, and a low level of health, particularly in the elderly [7,8].

Only 12% of adults in the USA are reported to possess sufficient health literacy [9]. A systematic review from 2009 examining 10 international studies reported prevalences of health literacy between 34% and 59% [10]. The 'Research into Turkish Health Literacy levels and Related Factors' in 2017 reported an insufficient literacy rate of 30.9% and a problematic-limited literacy rate of 38% [11].

Although health literacy began being discussed in the 1980s, its importance has become more apparent in recent years. The benefits of improving health literacy are now well-known worldwide. Various international scales measuring health literacy recently began being employed in Turkey [12–14]. However, greater research with regional and local data is still needed in this field.

This study aimed to determine levels of health literacy among adults in central districts of Erzurum province, Turkey, and to examine the factors affecting them.

Materials and methods

SThis descriptive, cross-sectional study was performed between May and September 2018 with the approval of the Atatürk University Non-Interventional Clinical Research Ethical Committee (decision no 27.12.2018–8/21).

The study population consisted of 348,217 individuals aged 15–65 living in central districts based on the 2017 Turkish Statistical Institute (TSI) data for Erzurum. A study sample of 630 individuals was calculated on Epi Info software based on a 30% prevalence of sufficient or perfect health literacy at a 95% confidence interval and a 3% margin of error. The sample size was increased by 25% against possible data losses, and we aimed to reach a total of 890 individuals. The study was performed using simple random sampling in 13 Family Health Centers (FHCs). Participants were enrolled from the FHCs in proportion to their population densities. Participants represented individuals presenting to FHCs and agreeing to take part.

Inclusion criteria were literacy, speaking Turkish, ability to communicate, and age between 15 and 65 years. Exclusion criteria were working in any health-related profession or occupation and inability to complete the questionnaire due to any health problem.

The data collection tool consisted of two parts: a personal information form and the Turkish Health Literacy Scale-32 (THLS-32). The dependent variable in the research was health literacy level, while independent variables included age, sex, education level, working in income-generating employment, health insurance, monthly family income, presence of chronic disease, presence of chronic disease in a first-degree relative, hospitalization for 15 days or longer, and receipt of education in health-related subjects.

THLS-32 was developed through the adaptation of the European Health Literacy Survey (HLS-EU) into the Turkish language by Okyay et al. [15] THLS-32 is structured as a 2 x 4 matrix with two domains (treatment and service, and protection from diseases/improvement of health) and four processes (access to health-related information, information understanding, information evaluation, and information use/application). THLS-32 consists of 32 five-point Likert-type propositions (1. Very easy, 2. Easy, 3. Difficult, 4. Very difficult, and 5. Don't know). As in the HLS-EU study, the indices are standardized between 0 and 50 at evaluation [Index=(mean-1) x (50 / 3)]. Health literacy is classified into four classes depending on the scores calculated (0–25=inadequate health literacy, 25–33=problematic / threshold health literacy, 33–42=adequate health literacy, and 42–50=perfect health literacy). The scale was validated by Okyay et al. [15], with a Cronbach alpha coefficient of 0.93 for the total scale, 0.88 for the first domain, and 0.86 for the second.

Statistical analysis

SPSS v.24 software was used for data entry and statistical analysis. Descriptive statistics were expressed as percentage, mean, standard deviation, minimum, and maximum values. The normal distribution of data was assessed using the Kolmogorov-Smirnov test. The χ^2 test, Spearman correlation analysis, and binary logistic regression analysis were applied. Independent variables included in the binary logistic regression analysis were selected from variables yielding significant results at univariate regression analysis and found to be significant in the relevant literature. The "Backward logistic regression (LR)" method was employed in regression analysis. *P*-values <0.05 were regarded as statistically significant.

Results

Eight hundred and sixty-four individuals were included in the study, a participation rate of 97.0%. The mean age of the participants was 35.6 (13.0) years (min=15, max=65), and 55.8% (n=482) were women. In terms of education levels, 23.6% (n=204) of participants were educated to a primary school level or were else uneducated. Fifty-six percent (n=484) of the study population was not in income-generating employment. The highest proportion of participants had sufficient income to meet their expenditures (44.3%). At least one chronic disease was present in 22.3% (n=193) of participants and in first-degree relatives of 36.1% (n=312). In addition, 13.3% (n=115) of participants had been hospitalized for 15 days or more, and 24.0% (n=207) had received education on a health-related subject. Participants' 16.2% sociodemographic and health-related characteristics are shown in Table 1.

Table 1: Distribution of participants' sociodemographic and health-related characteristics

Characteristic	No.	Percentage
Age group		
15 – 24	214	24.8
25 – 34	221	25.6
35 – 44	198	22.9
45 – 54	133	15.4
55 – 64	98	11.3
Sex		
Male	382	44.2
Female	482	55.8
Education level		
Primary school or below	204	23.6
Middle school	135	15.6
High school	260	30.1
Vocational school of higher education	52	6.1
University/school of higher education	178	20.6
Master's	29	3.4
Employment		
Not working	484	56.0
Occasional work	43	5.0
Working	337	39.0
Health Insurance		
No	94	10.9
General health insurance	762	88.2
Other	8	0.9
Income		
Less than outgoings	337	39.0
Equal to outgoings	383	44.3
Greater than outgoings	144	16.7
Presence of chronic disease		
Yes	193	22.3
No	671	77.7
Presence of chronic disease in a first-degree relative		
Yes	312	36.1
No	552	63.9
Hospitalization status		
Yes	115	13.3
No	749	86.7
Receipt of health education		
Yes	207	24.0
No	657	76.0

Cronbach alpha values of 0.90 for the THLS-32 'treatment and service' subdomain, 0.91 for the 'protection from diseases and improvement of health' subdomain,' and 0.94 for the total scale were determined in this study. Based on THLS-32 general scale scores, 24.1% (n=209) of the individuals participating in this study had inadequate health literacy, 31.6% (n=273) problematic health literacy, 27.7% (n=239) adequate health literacy, and 16.6% (n=143) perfect health literacy levels. Health literacy levels based on THLS-32 categories are shown in Figure 1.

Adequate/perfect health literacy levels were most prevalent in the 25 – 44 (55.2%) and 15 – 24 (53.7%) age groups, and significant differences were determined in health literacy distribution levels between age groups (χ^2=62.8, P<0.001). On the other hand, a weak, negative correlation was observed between participants' ages and index scores (r=-0.232, P<0.001). In terms of gender, the incidence of women with perfect health literacy levels (16.8%) was higher than that of men (16.2%), and health literacy distributions by gender were significantly different (χ^2=11.9, P=0.007). In terms of education levels, the incidence of adequate/perfect health literacy levels was highest among individuals educated to university level or above (60.0%), while the incidence of inadequate health literacy was highest among individuals educated to primary school levels or lower and with insufficient income (37.3%). Health literacy level distributions differed significantly in education levels (χ^2=73.8, P<0.001). In terms of employment status, the incidence of adequate/perfect health literacy levels was higher among individuals with income-generating employment (50.5%) compared to the unemployed (40.3%) and occasional workers (39.5%). However, participants' health literacy level distributions by employment status were similar (χ^2=12.4, P=0.053). The incidence of adequate/perfect health literacy levels was 52.8% among participants regarding their income as exceeding their outgoings, 42.9% among those with income equal to outgoings, and 42.1% among those with income less than outgoings. There was no statistically significant difference in health literacy level distributions regarding income status (χ^2=11.4, P=0.074). The incidence of adequate/perfect health literacy levels was higher among participants with health insurance (44.0%) than in those without (45.8%), and distributions differed significantly (χ^2=32.2, P<0.001).

The incidence of adequate/perfect health literacy levels among participants with at least one chronic disease (32.1%) was lower than that among individuals with no chronic disease (47.7%), and health literacy level distributions differed significantly (χ^2=14.9, P=0.002). The incidence of adequate/perfect health literacy levels among participants with chronic disease in a first-degree relative (33.0%) was lower than that in individuals with no chronic disease in first-degree relatives (50.6%), and the difference between distributions was statistically significant (χ^2=25.6, P<0.001). The incidence of adequate/perfect health literacy levels among participants with a history of hospitalization exceeding 15 days (37.4%) was lower than that in individuals with no history of hospitalization (45.3%), and the difference between health literacy levels was statistically significant (χ^2=9.2, P=0.026). The incidence of adequate/perfect health literacy levels among participants who had received health education on any subject (58.5%) was higher than that among individuals with no such education (39.8%), and the difference between health literacy levels was statistically significant (χ^2=26.0, P<0.001). A comparison of health literacy levels in terms of participants' sociodemographic and health-related characteristics is shown in Table 2.

Figure 1: Participants' health literacy levels based on THLS-32 categories

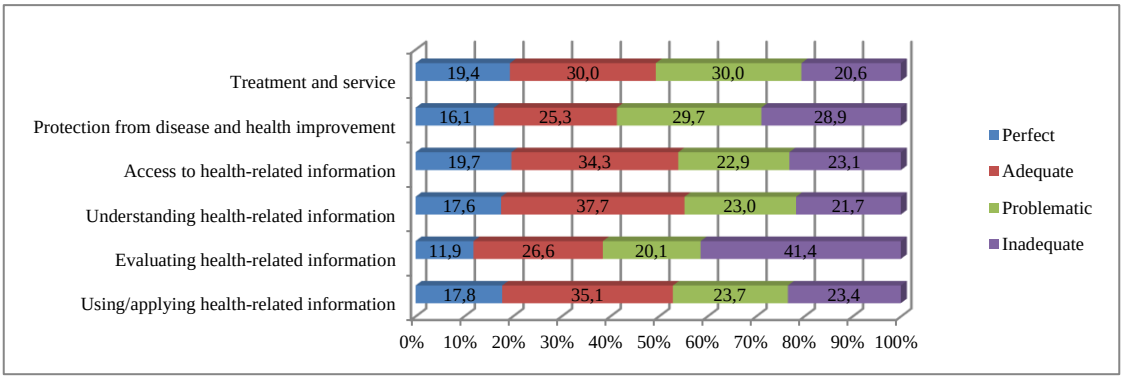

Table 2: A comparison of participants' health literacy levels by sociodemographic and health-related characteristics

		Inadequate		Problematic		Adequate		Perfect				
		n	%	n	%	n	%	n	%	Total	%	Statistics
Age groups	15–24	45	21.1	54	25.2	63	29.4	52	24.3	214	100	χ^2=62.8
	25–34	47	21.3	52	23.5	71	32.1	51	23.1	221	100	*P*<0.001
	35–44	43	21.7	71	35.8	62	31.4	22	11.1	198	100	
	45–54	41	30.8	55	41.4	23	17.3	14	10.5	133	100	
	55–64	33	33.7	41	41.8	20	20.4	4	4.1	98	100	
Sex	Female	98	20.3	171	35.5	132	27.4	81	16.8	382	100	χ^2=11.9
	Male	111	29.1	102	26.7	107	28.0	62	16.2	482	100	*P*=0.007
Education	Primary school or below	76	37.3	77	37.7	37	18.1	14	6.9	204	100	χ^2=73.8
	Middle school	36	26.7	39	28.9	32	23.7	28	20.7	135	100	*P*<0.001
	High school	64	24.6	84	32.3	78	30.0	34	13.1	260	100	
	University or above	33	12.5	73	27.5	92	34.7	67	25.3	265	100	
Health Insurance	Yes	178	23.1	253	32.9	227	29.5	112	14.5	770	100	χ^2=32.2
	No	31	33.0	20	21.2	12	12.8	31	33.0	94	100	*P*<0.001
Chronic disease	Yes	59	30.6	72	37.3	39	20.2	23	11.9	193	100	χ^2=14.9
	No	150	22.3	201	30.0	200	29.8	120	17.9	671	100	*P*=0.002
Chronic disease in first-degree relative	Yes	93	29.8	116	37.2	68	21.8	35	11.2	312	100	χ^2=25.6
	No	116	21.0	157	28.4	171	31.0	108	19.6	550	100	*P*<0.001
Receipt of health education	Yes	29	14.0	57	27.5	73	35.3	48	23.2	207	100	χ^2=26.01
	No	180	27.4	216	32.8	166	25.3	95	14.5	657	100	*P*<0.001

Discussion

In this research, 24.1% of participants had inadequate health literacy levels based on THLS-32 scores, while 58.5% had either inadequate or problematic literacy. In the Research into Turkish Health Literacy levels and Related Factors study, the incidence of inadequate health literacy was 30.9%, and that of inadequate/problematic literacy was 68.9% [11]. These findings show the widespread nature of inadequate/problematic health literacy representing an important public health problem. Inadequate/problematic health literacy levels between 48.2% and 82.8% have been reported in studies involving patients presenting to FHCs in different regions of Turkey [18,19]. Studies performed using the Test of Functional Health Literacy in Adults (TOFHLA) of individuals presenting to primary health institutions in Kosovo and Belgrade have reported inadequate health literacy levels of 86.6% and 46.4% [20,21]. The use of different scales by which health literacy levels are assigned to different categories in different studies makes direct comparison problematic. However, inadequate health literacy levels vary considerably depending on the communities involved.

The frequency of inadequate and inadequate/problematic health literacy categories in the protection from disease and improvement of health category in the present study was higher than that in the treatment and service dimension. Similarly to the present research, the Research into Turkish Health Literacy levels and Related Factors and studies performed in countries taking part in the Health Literacy Europe Research exhibited similar health literacy subdimension patterns among themselves, and inadequacy was again more frequent in the improvement of health subdomain [2, 11]. This may be related to services and interventions in the area of health improvement being more recent than health services. On the other hand, this may result from information sources intended to emphasize the relationship between health behaviors and outcomes or to bring about a change in health behaviors being perceived as more complex than information sources regarding the use of health services. The highest frequency of inadequate/problematic health literacy in terms of health-related information categories was determined in the evaluation category. This is consistent with all regions in the Research into Turkish Health Literacy Levels and Related Factors and different studies from Turkey [11,16–19]. Nevertheless, individuals with sufficient access to health-related information and with sufficient ability to apply existing information experience difficulty in evaluating health-related information, one component of health literacy. In order to overcome this difficulty, in addition to reliable and comprehensible sources of health information, they also require the self-sufficiency with which to assess it.

The elderly naturally constitute a significant part of the disease burden and health service use, and this burden is increasing as life expectancies increase. Health literacy levels, therefore, become more important with age. The incidence of inadequate/problematic health literacy levels in this study was 4.3% in the 15 – 24 age group but rose to 75.5% in the 55 – 64 age group. Two nationwide studies from Turkey also observed that mean health literacy scores decreased with age [11,22]. Findings from the HLS-EU and studies of adult health literacy in the USA similarly show that advancing age is a risk factor for health literacy [2,9]. The HLS-EU identified age as a powerful predictor of health illiteracy. A powerful negative correlation was observed between age and health illiteracy in Greece, Bulgaria, Poland, and Spain [2]. Paasche-Orlow et al.'s [23]

review of the data from 85 studies reported that studies with low mean ages had the lowest prevalences of inadequate health literacy. The fact that the elderly constitute a risk group for inadequate health literacy increases their vulnerability in different areas of health.

Gender is today regarded as one of the social determinants of health. Research shows that inadequate health literacy levels in men (29.1%) are higher than in women (20.3%), and literacy category distributions also differ between the sexes. Studies comparing health literacy in terms of gender have reported inconsistent findings, with some reporting better health literacy levels among men (20%). In contrast, others have reported that the female gender significantly increases the probability of an adequate level of health literacy [2,21]. The Research into Turkish Health Literacy Levels and Related Factors study and the Turkish Health Literacy Study reported that women were at a disadvantage in terms of adequate health literacy [11,24]. The HLS-EU determined that gender has a weak effect on health literacy and that levels were higher in women than in men in Holland, where the effect was greatest [2]. Paasche-Orlow et al.'s [23] review study reported no association between health literacy levels and sex. The fact that no relationship was revealed between health literacy and sex may be due to study populations having different characteristics (such as mean ages, education levels, and socioeconomic factors) and to societal gender variations.

Education is a precondition for health, although health is also a precondition for education. The incidence of inadequate/problematic health literacy was highest among participants educated to primary level or lower (75%) in this study, while that of adequate/perfect health literacy was highest among individuals educated to a university level or above (60%). Different studies from Turkey and elsewhere agree that education is important determinant of health literacy, with such literacy levels increasing in line with age [9,11,15,25]. Van der Heide et al. set out to explain the relationship between education and health literacy and to investigate the probable contribution of education to health literacy. Those authors noted the effect of education and health literacy on the role of three health indicators (declared health status, physical health status, and mental health status). That study presented powerful evidence that, while education and health literacy both affect health, health literacy is also affected by education [26]. The relationship between a low education level and poor health status can be explained by health literacy.

Regular income and employment is another important determinant of health status. No significant difference was determined in the present study between health literacy category distributions depending on working in income-generating employment and income status, although individuals with regular jobs and a better level of income also had higher health literacy levels. National and regional studies from Turkey have shown that individuals with regular jobs have higher levels of health literacy and that literacy levels rise in line with income [11,16,27]. Research involving individuals presenting to first-tier health services in Serbia showed that the working group comprised 8.7% of individuals with inadequate health literacy levels but 61.3% of those with adequate levels and that health literacy categories differed depending on employment status [21]. In the HLS-EU, full- and part-time workers had higher levels of health literacy than others, and limited health literacy levels were common among individuals with low social status [2]. Consistent with both domestic and international research, our study findings also show that the absence of regular income-generating employment and a low level of income are socioeconomic phenomena constituting risk factors in terms of health literacy.

The incidence of inadequate health literacy was higher (33.0%) among participants without health insurance in this research than among those with health insurance (23.1%). Domestic and regional studies from Turkey have also determined higher health literacy levels among individuals with health insurance than those without [11,27]. The fact that lack of health insurance is an important and one of the main factors restricting access to health services also increases the probability that this at-risk group will be disadvantaged in terms of health literacy.

Chronic diseases today result in more deaths than all other causes. Eighty-seven percent of deaths in Turkey between the ages of 30 and 70 derive from non-infectious diseases [11]. In the present study, inadequate/problematic levels of health literacy were more common (67.9%) among participants with chronic disease than among those without (52.3%). Inadequate/problematic levels of health literacy were also more common (67.0%) among individuals with chronic diseases in first-degree relatives than in those without (49.4%). Different studies from Turkey have also reported lower levels of health literacy among individuals with chronic diseases [11,16,27]. In the HLS-EU, the relationship between long-term health problems and general health illiteracy was assessed as important for seven countries other than Holland, and individuals with chronic diseases also had lower general health literacy index scores [2]. Studies from Germany and America have also found that inadequate health literacy is independently associated with poor physical and mental health [28,29]. Consistent with previous research, our findings also show an association between health literacy and the presence of chronic disease. Individuals with chronic diseases have lower health literacy. This may be due to lower mean age and higher education levels among individuals without chronic disease. On the other hand, there are also studies reporting that poor health literacy levels are associated with poor health outcomes even when demographic variables are brought under control [7]. All these findings show that the relationship between the presence of chronic disease and health literacy levels is a two-way interaction.

Inadequate health literacy also constitutes a risk factor for inefficient use of health services. The incidence of inadequate/problematic health literacy levels was higher (62.6%) in this research among individuals with histories of hospitalization exceeding 15 days than among individuals with no such history (54.7%). The HLS-EU determined a negative correlation between health literacy level and hospitalization, clinic presentation, and emergency department use [2]. Low health literacy levels are linked to a greater risk of hospitalization. Two review studies in the field of health literacy also concluded that inadequate levels of health literacy were associated with increased rates of hospitalization [30,31]. These

studies all show that inadequate health literacy is an obstacle to the appropriate and sufficient use of health services in all areas and tiers.

In the present study, the sufficient sample number calculated using an appropriate method in the 15 – 65 age group living in the province of Erzurum was achieved by weighting central district populations. In addition, the THLS-32 scale, with proven validity and reliability and an adaptation to the Turkish language and society of the HLS-EU scale widely used worldwide in this field, was used to measure participants' health literacy levels. However, because this study involved individuals presenting to FHCs, the results cannot be generalized to the entire community.

Conclusion and recommendations

The incidence of adequate/perfect health literacy in this study was 44.3%, while that of inadequate/problematic health literacy was 55.7%. This shows that insufficient health literacy is widespread in our community and that interventions aimed at health literacy are required in our province, and the country as a whole. The frequency of inadequate/problematic health literacy being greater in the field of protection from disease and health improvement (54.6%) than in that of treatment and service (50.6%) indicates that limited health literacy is a greater problem in the area of health improvement and that areas of intervention should be directed toward that field. Among the processes concerning health-related information, the frequency of inadequate/problematic health literacy was highest (54.0%) in the information evaluation process. This shows the importance of health education, which is central to all these endeavors and closely related to the improvement of health to achieve a sufficient ability to evaluate health-related information. Differences in health literacy levels that may vary between the genders among communities can be overcome by establishing gender equality in all societies and by men and women enjoying equal rights and opportunities. In addition, priority should be attached to measures aimed at older individuals with low education levels and chronic diseases in themselves or first-degree relatives, constituting a risk for low health literacy.

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Evaluation of osteoporosis and related factors and quality of life of patients with juvenile idiopathic arthritis and burnout status of parents

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Ethics Committee Approval
This study was approved by the Ethics Committee of Dr. Sami Ulus Gynecology and Childhood Health and Diseases Training and Research Hospital (Approval number: 06.2009/047).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Juvenile idiopathic arthritis (JIA) can negatively influence the lives of children and parents. Because it is a chronic disease, a complete recovery is not expected; additionally, children with JIA and their parents must cope with problems such as chronic pain, physical disability, school absenteeism, and social communication disorders. Children's quality of life (QoL) may be affected by all these problems. Also, prolonged exposure to stress and failure to cope with stress may cause burnout syndrome in parents. The study aims to evaluate osteoporosis, QoL of children with JIA and the burnout status of caregivers.

Methods: In this prospective, cross-sectional study, 30 patients aged 4–18 years, who were followed up for at least 6 months with the diagnosis of JIA, were included. Demographic, clinical, and laboratory characteristics were recorded retrospectively. Daily dietary calcium intake and daily activity levels were questioned. The patients' bone mineral densities (BMD) were measured by the Dual Energy X-ray Absorptiometry method. Z scores below -2 were classified as the osteoporosis group, and those above -2 were classified as the non-osteoporosis group. The Turkish Pediatric Quality of Life Inventory validated and reliable in Turkish children was used to evaluate the QoL. Maslach Burnout Inventory was used to evaluate the burnout status of parents.

Results: The mean age of patients was 12.6 (4.3) years. Osteoporosis was detected in 46.7% (n=14) cases. The mean age was higher (14.5 [3.7] in the osteoporosis group and 10.9 [4.1] in the non-osteoporosis group) (P=0.032) and the rate of oligoarticular JIA (7.1%), daily calcium intake (288 [168-456] mg/kg), and duration of activity (3 [2-6] hours) were lower in the osteoporosis group (P=0.039, P=0.043, P<0.001, respectively). Among the QoL indicators, the physical health total score was the lowest. Emotional functionality scores decreased as the age increased (P=0.037) and increased as the BMD z-score increased (P=0.024). Emotional burnout, one of the parental burnout indicators, increased as the duration of illness increased (P=0.003), and the BMD z-score decreased (P=0.003). Depersonalization increased as the age increased (P=0.010) and the duration of the disease prolonged (P<0.001) and increased as daily activity duration (P=0.032) and BMD z-score values decreased (P=0.002). Personal achievement decreased as the age increased (P=0.025) and the duration of illness (P=0.014), and the time spent watching television increased (P=0.030). Emotional exhaustion and depersonalization of the parents increased as the scores in any of the indicators of QoL decreased (P<0.05 for each). The personal success of the parents increased as the scores in any of the indicators of QoL increased (P<0.05 for each). All QoL indicators, except for social functionality and psychosocial health total score, were significantly lower in the group with osteoporosis. In addition, parents of children with osteoporosis had higher emotional burnout and depersonalization scores and lowered personal achievement scores (P<0.05 for each).

Conclusion: In the current study, we observed a decrease in the QoL of the children and burnout syndrome in the parents. It was found that the deterioration in children's QoL indicators affected the burnout indicators of parents, and the presence of osteoporosis affected both QoL and parental burnout. Awareness of modifiable risk factors in children with JIA is very important. The disease and osteoporosis secondary to this disease can impair children's QoL and cause burnout in parents.

Keywords: osteoporosis, quality of life, burnout syndrome, juvenile idiopathic arthritis

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Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory, rheumatic disease that can result in permanent joint deformities and physical disability [1]. A complete recovery is not expected in JIA. Children with JIA experience absenteeism from school due to frequent hospital admissions decreased participation in activities, impaired peer communication, and deterioration of quality of life [2,3]. Children with JIA may feel incompetent regarding self-esteem, social acceptance, physical competence, and attractiveness, even after controlling disease severity [4].

Quality of life is described as the feeling of satisfaction of an individual about his/her life. On the other hand, health-related quality of life refers to the patient's perception of the effect of the illness and treatment process on their life [5]. 'Pediatric Quality of Life Inventory (PedsQL) is a quality of life scale. The validity and reliability studies have been conducted for all age groups in Turkish children. It is used to analyze children's and parents' perceptions of physical health, emotional functionality, social functionality, school functionality, and psychosocial health [5-7].

The parents feel stressed due to being diagnosed with a chronic disease to their child, the long treatment period, the unknown disease process, and frequent hospital visits [8]. Prolonged exposure to stress and failure to cope with stress may result in burnout syndrome [9]. Emotional exhaustion is the feeling of being overwhelmed with responsibilities, and depersonalization is the alienation of the person to whom he or she serves. The personal achievement dimension is used to evaluate the individual's feeling of inadequacy and helplessness in the face of his/her responsibilities [10].

Burnout syndrome was previously evaluated in professional groups such as teachers and nurses [11,12]. The literature has also described it in parents who care for children with diseases such as autism and brain tumors [13,14]. To our knowledge, there is no study evaluating burnout in parents caring for children with JIA.

This study aims to evaluate the presence of osteoporosis and related factors in children with JIA to examine the quality of life of children and the burnout of caregivers.

Materials and methods

In this study, 30 patients aged 4–18 years who were followed up for at least 6 months with the diagnosis of JIA in the Pediatric Nephrology Clinic of Dr. Sami Ulus Gynecology and Childhood Health and Diseases Training and Research Hospital were included. The age, gender, comorbidity and fracture history of the patients were recorded. Disease type, age at diagnosis, duration of disease, and the use of corticosteroids, calcium, vitamin D, and bisphosphonate were obtained from hospital records. Daily calcium intake was calculated by evaluating the food frequency questionnaire. The average daily time spent sleeping, watching TV, and on the computer and the average daily activity were questioned. Participation in physical education classes, the duration of participation, and if the children were occupied with any branch of sports regularly, the type of sports and the duration and interval of the sportive activity were questioned.

In the physical examination, height measurements were made with a stadiometer standing up, and body weight measurements were measured with a 100 g sensitive digital adult weight meter. In laboratory examinations, serum calcium, phosphorus, ALP, parathormone, and 25 OH vitamin D levels were measured. Bone mineral densities of the patients were measured by Dual Energy X-ray Absorptiometry (DXA) method. Those with a z-score below -2 were considered osteoporosis, those between -1 and -2 were considered below the normal limit (osteopenia), and those above -1 were considered normal. While performing the statistical analysis, those with a z-score below -2 were classified as the osteoporosis group, and those above -2 were classified as the non-osteoporosis group.

Evaluation of quality of life

The Turkish Pediatric Quality of Life Inventory (PedsQL), which has been validated for all age groups in Turkish children, was used to evaluate the patients' quality of life. The inventory includes self-report and parent forms prepared according to age groups. The questions measuring problems in physical, social, emotional, and school functionality are answered on a five-choice Likert-type response scale (0: never, 1: rarely, 2: sometimes, 3: often, 4: always). The scores procured from the items are converted to a value between 0 and 100 points (0: 100, 1: 75, 2: 50, 3: 25, 4: 0). Higher scores indicate higher quality of life.

Evaluation of burnout syndrome

The burnout status of caregiving parents was evaluated by Maslach Burnout Inventory (MBI). The scale evaluates burnout in three areas: emotional exhaustion, depersonalization, and lack of personal accomplishment. Items in the inventory are answered on a five-choice Likert-type response scale (a: never, b: several times a year, c: several times a month, d: several times a week, e: every day where a is scored as zero, b as 1, c as 2, d as 3, and e as 4 points). A high score in the areas of depersonalization and emotional exhaustion and a low score in the area of personal achievement is defined as burnout.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Dr. Sami Ulus Gynecology and Childhood Health and Diseases Training and Research Hospital Ethics Committee (Approval number: 06.2009/047). An informed consent form was obtained from the patients and their parents.

Statistical analysis

The data were analyzed by using SPSS for Windows 11.5 package program. The normality of the distribution of the continuous variables was tested using the Shapiro-Wilk test. Descriptive statistics were given as mean (standard deviation) or median (minimum-maximum) for continuous variables and the number of cases and percentage (%) for categorical variables.

When 30 individuals were included in this study, it was determined that the expected differences between the groups could be shown significantly with 84% power and 0.5 alpha value. Student's t-test evaluated the significance of the difference between the groups in terms of means, the significance of the difference between two groups in terms of median values was evaluated by the Mann-Whitney U test, and when the number of

independent groups was more than 2, the Kruskal Wallis test was used. When the difference was found to be significant according to the Kruskal-Wallis test, a non-parametric multiple comparison test was used to detect the situations that caused the difference.

Nominal variables were evaluated by using Pearson's Chi-Square or Fisher's Exact Chi-Square test. Spearman's correlation test was applied to evaluate whether there was a statistically significant correlation between continuous variables.

The significance of the change in BMD level with calcium intake over time was evaluated using the Analysis of Variance in Repeated Measurements. Bonferroni Corrected Multiple Comparison test was used to determine the follow-up times that caused the statistical difference. A value of $P<0.05$ was considered statistically significant.

Results

The evaluation was made of 30 patients who met the study criteria, comprising 15 females and 15 males. The mean age was 12.6 (4.3) years. Osteoporosis was detected in 14 (46.7%) patients. Demographic and clinical features of the cases according to osteoporosis groups are shown in Table 1. The mean age of the group with osteoporosis was significantly higher compared to the group without osteoporosis ($P=0.032$), while the height SDS was significantly lower in the group with osteoporosis ($P=0.019$). The disease duration was longer in the group with osteoporosis compared to the group without osteoporosis; however, the difference was not statistically significant ($P=0.117$). When the groups were compared according to disease type, it was found that the rate of oligoarticular JIA was significantly lower in the osteoporosis group ($P=0.039$). In addition, daily dietary calcium intake was also significantly lower in the osteoporosis group ($P=0.043$). When the groups were compared according to physical activity status, it was determined that the osteoporosis group was less active, and in terms of the duration of daily activity, the difference was statistically significant ($P<0.001$) (Table 1).

Descriptive statistics of child quality of life and parental burnout indicators of all cases are shown in Table 2. It was observed that the emotional functionality score decreased as the age increased (r=-0.382 and $P=0.037$) and increased as the BMD z-score increased (r=0.417 and $P=0.024$). There was no statistically significant correlation between other child quality of life indicators and clinical and demographic data ($P>0.05$). When the parental burnout indicators were evaluated, it was found that the emotional burnout score increased as the duration of illness was prolonged (r=0.531 and $P=0.003$), and the BMD z-score decreased (r=-0.517 and $P=0.003$). The depersonalization score increased as the age increased ($P=0.010$) and the duration of disease prolonged ($P<0.001$) and increased as daily activity duration ($P=0.032$) and BMD z-score decreased ($P=0.002$). Personal achievement scores decreased as the age increased ($P=0.025$), the duration of illness prolonged ($P=0.014$), and the time spent watching television daily increased ($P=0.030$). The correlation coefficients and significance levels between child quality of life, parental burnout indicators and age, duration of illness, duration of physical activity, and BMD z-score are shown in Table 3.

Table 1: Demographic and clinical characteristics of the patients with and without osteoporosis

Variables	Osteoporosis (-)	Osteoporosis (+)	*P*-value
Age, Mean (SD)	10.9 (4.1)	14.5 (3.7)	0.032*
Age of diagnosis, Mean (SD)	7.1 (4.0)	8.8 (2.7)	0.190
Height SDS, Mean (SD)	-0.88 (1.58)	-2.72 (1.80)	0.019*
Weight SDS, Mean (SD)	-0.40 (1.31)	-2.03 (3.39)	0.119
BMI SDS, Mean (SD)	0.36 (1.17)	-0.69 (1.87)	0.086
Gender, n (%)			
Male	8 (50%)	7 (50%)	1.000
Female	8 (50%)	7 (50%)	
Comorbidity, n (%)	2 (12.5%)	6 (42.9%)	0.101
History of fracture, n (%)	1 (6.3%)	1 (7.1%)	1.000
Disease type, n (%)			
Enthesitis related	-	3 (21.4%)	0.090
Systemic	1 (6.3%)	5 (35.7%)	0.072
Polyarticular	8 (50%)	5 (35.7%)	0.431
Oligoarticular	7 (43.8%)	1 (7.1%)	0.039*
Use of Medication, n (%)			
Corticosteroid	14 (87.5%)	14 (100%)	0.485
NSAID	15 (93.8%)	14 (100%)	1.000
DMARD	15 (93.8%)	14 (100%)	1.000
Calcium	4 (25%)	12 (85.7%)	<0.001*
Activity status, n (%)			
Regular sportive activity	8 (50%)	4 (28.6%)	0.232
Active participation in physical education classes	8 (50 %)	4 (28.6 %)	0.232
Activity evaluation, Median (min-max)			
Daily sleeping time (hours)	8 (6-10)	8 (5-11)	0.525
Daily activity time (hours)	5.5 (3-9)	3 (2-6)	<0.001*
Daily time spent on watching Tv	4 (1-5)	4 (2-6)	0.257
Daily time spent on computer	0.5 (0-4)	2 (0-4)	0.580
Duration of illness	4 (1-9)	6 (1-12)	0.117
Cumulative Dosage of corticosteroids (mg)	8,062.5 (2,100-19,500)	13,237.5 (1,800-22,500)	0.150
Cumulative Dosage of corticosteroids (mg)	217.3 (78-696)	303.1 (56-1,032)	0.401
Dietary calcium intake (mg/kg)	455 (120-830)	288 (168-456)	0.043

* $P<0.05$ was accepted as statistically significant. SD: standard deviation, DMARD: Disease Modifying Anti-Rheumatic Drug, NSAID: Non-steroidal anti-inflammatory drug

Table 2: Descriptive statistics of pediatric quality of life and parental burnout indicators of all cases

Variables	Mean	SD	Median	Minimum	Maximum
Pediatric Quality of Life					
Physical health total score	55.6	19.7	54.7	12.5	96.9
Emotional functioning	62.7	20.9	65.0	5.0	100.0
Social functioning	70.8	15.7	70.0	35.0	100.0
School functioning	62.0	14.1	60.0	40.0	100.0
Psychosocial functioning	64.4	13.5	63.2	43.3	93.3
Total scale score	61.7	13.7	62.5	42.3	94.6
Parental burnout					
Emotional exhaustion	13.7	9.0	13.0	0.0	30.0
Depersonalization	5.8	5.6	3.0	0.0	18.0
Personal accomplishment	20.5	8.2	20.0	4.0	36.0

Emotional exhaustion ($P=0.002$ for physical health total score, $P<0.001$ for emotional functioning, $P=0.023$ for social functioning, $P<0.001$ for school functioning, $P=0.006$ for psychosocial functioning, $P<0.001$ for total scale score) and depersonalization of the parents ($P<0.001$ for physical health total score, $P=0.015$ for emotional functioning, $P=0.014$ for social functioning, $P<0.001$ for school functioning, $P=0.012$ for psychosocial functioning, $P=0.003$ for total scale score) increased as the scores in any of the child quality of life indicators decreased. As the scores increased in any of the child quality of life indicators (except for the social functionality score), the personal success score of the parents increased ($P=0.002$ for physical health total score, $P=0.002$ for emotional functioning, $P=0.057$ for social functioning, $P=0.002$ for school functioning, $P=0.004$ for psychosocial functioning, $P=0.002$ for total scale score). The correlation coefficients and significance level between parent burnout level and child quality of life indicators are shown in Table 4.

Table 3: Correlation coefficients and significance levels between child quality of life and parental burnout indicators and age, duration of illness, duration of physical activity and BMD z-score

Variables		Age	Duration of illness	Duration of sportive activity	Duration of sleeping	Duration of activity	Duration of watching Tv	Duration spent on computer	BMD z-score
Physical health total score	r	-0.193	-0.294	-0.234	0.103	0.133	-0.136	-0.106	0.341
	P	0.307	0.115	0.214	0.590	0.484	0.474	0.576	0.066
Emotional functioning	r	-0.382	-0.249	-0.114	0.185	0.219	-0.107	0.311	0.412
	P	0.037*	0.184	0.550	0.328	0.245	0.573	0.094	0.024*
Social functioning	r	-0.042	-0.258	-0.142	0.020	0.035	-0.334	0.134	-0.038
	P	0.827	0.169	0.453	0.917	0.855	0.071	0.480	0.841
School functioning	r	-0.025	-0.228	-0.061	0.210	0.120	-0.114	-0.009	0.417
	P	0.896	0.233	0.752	0.275	0.536	0.557	0.961	0.024
Psychosocial functioning	r	-0.279	-0.219	-0.103	0.096	0.155	-0.221	0.241	0.221
	P	0.136	0.244	0.590	0.612	0.414	0.240	0.200	0.241
Total scale score	r	-0.192	-0.280	-0.290	0.251	0.121	-0.105	0.090	0.280
	P	0.309	0.134	0.20	0.181	0.523	0.581	0.637	0.133
Emotional exhaustion	r	0.330	0.531	0.091	-0.291	-0.289	0.313	0.221	-0.517
	P	0.075	0.003*	0.633	0.119	0.122	0.092	0.240	0.003*
Depersonalization	r	0.466	0.631	0.012	-0.158	-0.392	0.339	0.311	-0.550
	P	0.010	<0.001	0.951	0.405	0.032	0.066	0.094	0.002
Personal accomplishment	r	-0.407	-0.444	-0.184	0.399	0.216	-0.397	-0.093	0.492
	P	0.025	0.014	0.331	0.029	0.252	0.030	0.626	0.006

* *P*<0.05 was accepted as statistically significant

Table 4: Correlation coefficients and significance levels between parental burnout levels and child quality of life indicators

Variables	Emotional exhaustion		Depersonalization		Personal accomplishment	
	r	*P*-value	*r*	*P*-value	*r*	*P*-value
Physical health total score	-0.539	0.002*	-0.558	<0.001*	0.550	0.002*
Emotional functioning	-0.573	<0.001*	-0.440	0.015*	0.534	0.002*
Social functioning	-0.414	0.023*	-0.443	0.014*	0.352	0.057
School functioning	-0.724	<0.001*	-0.563	<0.001*	0.543	0.002*
Psychosocial functioning	-0.490	0.006*	-0.452	0.012*	0.504	0.004*
Total scale score	-0.636	<0.001*	-0.526	0.003*	0.549	0.002*

* *P*<0.05 was accepted as statistically significant

When the child quality of life and parental burnout level scores of the patients with and without osteoporosis were compared, all child quality of life indicators were significantly lower in the group with osteoporosis compared to the group without osteoporosis, except for social functionality and psychosocial health total scores (*P*=0.013 for physical health total score, *P*=0.007 for emotional functioning, *P*=0.697 for social functioning, *P*=0.003 for school functioning, *P*=0.085 for psychosocial functioning, *P*=0.017 for total scale score). In addition, parents of children with osteoporosis had higher emotional burnout (*P*<0.001) and depersonalization scores (*P*<0.001) and lower personal achievement scores (*P*=0.002) (Table 5).

Table 5: Comparison of child quality of life and parental burnout level in terms of osteoporosis

Variables	Osteoporosis	Median	Minimum	Maximum	*P*-value
Physical health total score	No	64.1	12.5	96.9	0.013*
	Yes	48.4	25.0	81.2	
Emotional functioning	No	75.0	5.0	100.0	0.007*
	Yes	55.0	30.0	90.0	
Social functioning	No	70.0	35.0	100.0	0.697
	Yes	70.0	50.0	90.0	
School functioning	No	65.0	50.0	100.0	0.003*
	Yes	52.5	40.0	75.0	
Psychosocial functioning	No	68.8	43.3	93.3	0.085
	Yes	57.5	45.0	80.0	
Total scale score	No	68.9	43.4	94.6	0.017*
	Yes	54.9	42.3	71.7	
Emotional exhaustion	No	6.5	0.0	24.0	<0.001*
	Yes	18.5	6.0	30.0	
Depersonalization	No	1.0	0.0	12.0	<0.001*
	Yes	10.0	0.0	18.0	
Personal accomplishment	No	26.0	13.0	36.0	0.002*
	Yes	14.5	4.0	33.0	

* *P*<0.05 was accepted as statistically significant.

Discussion

In our study, the prevalence of osteoporosis was 46.7%. Patients with osteoporosis have a higher average age and lower daily dietary calcium intake and activity level. Osteoporosis is significantly lower in the oligoarticular type. The factors affecting child quality of life and parental burnout indicators at varying rates include the child's age, duration of illness, daily activity level, daily television watching, and BMD z-score. The level of parental burnout is affected by the quality of life of children, and osteoporosis negatively affects both the child and the parents.

Children with JIA are exposed to many factors that negatively affect bone mineral density during childhood and adolescence when peak bone mass should be reached [15]. Many factors, such as age, duration of illness, disease activity, and inflammation processes, are responsible for osteoporosis development. It has been reported that osteoporosis starts earlier and progresses more severely when JIA starts at an early age [16,17]. In our study, contrary to the literature, the mean age of the group with osteoporosis was significantly higher than the group without osteoporosis, and the age of onset was greater. Although not statistically significant, this contradiction can be attributed to the fact that the group with osteoporosis had been exposed to disease activity for a longer duration due to the longer duration of the disease, and they received corticosteroid therapy for a longer period and at high doses. In addition, the significantly lower dietary calcium intake in the osteoporosis group is one of the factors contributing to this contradiction.

In children with JIA, significant losses in bone mass have been reported with DEXA in all subgroups. In addition, the lower bone mass has been reported, especially in patients with polyarticular JIA compared to the oligoarticular type [15,18]. In our study, when osteoporosis was evaluated according to the disease types, the difference between the types was significant only in the oligoarticular type. The osteoporosis rate was lower in children with oligoarticular JIA.

It has been shown in many studies that adequate physical activity during childhood positively affects cortical bone acquisition [19]. In the current study, the osteoporosis group's daily physical activity level was significantly lower than the group without osteoporosis. This result supports the positive effect of physical activity on bone mineralization in children with JIA.

In addition to its physical effects, JIA also affects the lives of children and their families psychologically and socially. Oliveira et al. reported that the health-related quality of life of children with JIA was worse regarding physical and psychosocial aspects than healthy children [20]. The current study determined the lowest mean of the quality-of-life indicators in the total physical health score. Emotional functionality scores decreased as age increased. We attribute this to the fact that functional limitations can be perceived better as age progresses. Being a parent of a child with a chronic illness can have various psychological consequences. Lindström et al. [21] reported that parents of children with chronic diseases experienced burnout at a higher rate than those of healthy children. Norberg [13] reported that burnout syndrome developed in parents caring for children with brain tumors, and Weiss [14] reported that burnout developed in parents caring for children with mental retardation and autism. We could identify no studies in the literature evaluating the burnout status of parents of children with JIA. In our study, we found that as the duration of illness increased, the parents' emotional exhaustion and depersonalization scores increased, and the personal achievement scores decreased. These results indicate those caregiver parents of children with JIA experience burnout, like other chronic diseases. In JIA, a long disease process and uncertainty may cause the families to lose hope that their children will get better and have longer exposure to problems, such as the restriction of social interaction due to frequent hospital admissions. Eventually, this may cause burnout symptoms to develop. In addition, it was found that the parents' emotional exhaustion and depersonalization scores increased as the scores in any of the child's quality of life indicators decreased and the personal success scores of the caregivers increased as the scores of the child's quality of life increased. Our findings show that the quality of life of children negatively affects both the children and the caregivers. Considering caregivers' contribution in treating children with JIA, we propose that patients should be evaluated together with their families.

In our study, the emotional functionality score of the children increased as the BMD z-score value increased, and the emotional exhaustion and depersonalization levels of the parents increased as the BMD z-score value decreased. In addition, it was determined that quality of life scores, especially in the children's physical health, emotional functionality, and school functionality, were lower, and the burnout and depersonalization levels of the parents were higher in the osteoporosis group compared to those without osteoporosis. In the adult literature, although it has been reported that osteoporosis negatively affects the quality of life of postmenopausal women, there is no study on the effect of osteoporosis on the quality of life of children with JIA [22].

Limitations

One of the limitations of our study was that no statistically significant results could be obtained in terms of some risk factors associated with osteoporosis due to the small sample size. In addition, the children's quality of life and the parents' burnout status were not compared with the healthy control group. There is a need for randomized controlled studies with a larger sample.

Conclusion

It is important to increase the quality of life in patients with JIA and to prevent the development of indifference and exhaustion in families over time. Minimizing the modifiable risk factors for osteoporosis may be important in improving patients' quality of life, increasing the perception of personal success, and reducing burnout symptoms in families.

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Effect of the using a pupillometer on recovery and early cognitive functions in anesthesia management for endoscopic retrograde cholangiopancreaticography in geriatric patients

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Ethics Committee Approval
The study was approved by the Local Ethical Committee of Necmettin Erbakan University, Meram Faculty of Medicine (Number: 126-2021/3107). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive procedure used for the diagnosis and treatment of pancreaticobiliary pathologies. Because it is an invasive procedure that is difficult to tolerate by the patient and takes a long time, it is preferable to use it under deep patient sedation and even under general anesthesia in some cases. This study aimed to evaluate the effects of using a pupillometer versus the Ramsey sedation scale (RSS) during anesthesia management for ERCP on recovery and return of cognitive functions in the geriatric patient population.

Methods: A mini-mental test was applied to evaluate the pre-operative cognitive functions of the cases before the intervention. The included patients were divided into groups using the sealed-envelope method. Management of the depth of anesthesia was evaluated by Ramsey sedation scale; in group R and was evaluated by pupillometer in group P. The infusion dose of dexmedetomidine was changed to 0.1 µg/kg/h according to the results of the evaluation.

Results: Sixty cases were included in the study. No difference between the groups in terms of age (P=0.246), gender (P=0.797), American Society of Anesthesiologists (ASA) score (P=0.197), comorbidity (P=0.748), anesthesia duration (P=0.397), midazolam doses (P=0.561), propofol doses (P=0.677), and intra-operative hemodynamic values (P=0.668) were found. Intra-operative dexmedetomidine dose was statistically significantly lower (P=0.004), and recovery was faster in group P (P<0.001). While no differences between the groups in the pre-operative mini-mental test scores (P=0.140) were found, the post-operative scores were statistically significantly lower in group R (P=0.025).

Conclusion: In this study, it was observed that the pupillometer led to a reduction in the use of dexmedetomidine and cognitive functions were better during the post-operative recovery period. As a result, depth of anesthesia can be monitored with a pupillometer. Although the use of pupillometer in endoscopic interventions in the geriatric patient group does not make a hemodynamic difference when compared with the RSS, the pupillometer leads to accelerated recovery from anesthesia, improvement in the return of cognitive functions, and reduction in drug consumption.

Keywords: geriatric anesthesia, endoscopic retrograde cholangiopancreatography, pupilometer, mini-mental test, post-operative cognitive dysfunction

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Introduction

Endoscopic retrograde cholangiopancreaticography (ERCP) is an invasive modality used for the diagnosis and management of pancreaticobilliary pathologies. Due to procedure invasiveness and patient intolerance during conscious sedation, general anesthesia is usually preferred for this lengthy and complicated procedure. Adequate sedation and patient cooperation are essential for successful and safe ERCP. While deep sedation may result in airway obstruction, aspiration, respiratory depression, and hemodynamic instability, conscious sedation is associated with significant patient discomfort and intolerance during endoscopic procedures. Thus, achieving adequate and regular sedation without increasing the rate of cardiorespiratory depression is intended [1–4].

Evaluating the depth of anesthesia during induction and maintenance is a challenging issue [5]. The Ramsay sedation scale (RSS) is a simple and reliable scoring system that is frequently used today for the evaluation of sedation [6]. Technological advances and emerging modalities have facilitated anesthesia depth assessment. Pupil diameter measurement with a pupillometer can be used for the evaluation of intra-operative depth of Anesthesia [7,8]. Standardized measurement methods for a pupillometer have enabled objective comparisons of serial measurements [9]. Pre-operative evaluation of geriatric patients should include accurate assessment of their functional capacity, cognitive status, and comorbidity; finally, appropriate peri-operative management is essential.

In this study, we evaluated recovery of consciousness and cognitive functions using pupillometer when compared with RSS during anesthesia management for ERCP procedures in geriatric patients.

Materials and methods

Setting and participant

Ethical approval for this study was obtained from (Necmettin Erbakan University, Meram Faculty of Medicine, Ethics Committee) (Number: 126-2021/3107) according to the declaration of Helsinki. Power analysis was performed to determine the number of samples. A sample size of 60 was determined to be sufficient assuming that α was 0.05, effect size was 0.50, and power was (1 β) 0.80. G*power (Version 3.1.9.6) was used for this calculation. Sixty patients older than 65 years with American Society of Anesthesiologists (ASA) class II/III physical status who underwent ERCP procedures under deep sedation between April and December 2021 in the gastrointestinal endoscopy unit were enrolled in this study. Patients with orientation and cooperation disorders, severe psychiatric disorders, cardiac dysrhythmia and heart failure history, drug dependence, intra-operative inotropic drug use, emergent patients, and patients who refused to participate in the study were excluded. Informed consent was obtained from all patients before inclusion in the study.

Anesthetic management

Demographic data of the participants were recorded and randomized using the sealed envelope method. Patients were grouped as group R for patients managed with Ramsay sedation scale and group P for those managed with pupillometer device. Minimental test was applied for the evaluation of the preoperative cognitive functions of the participants before the procedure. Hemodynamic measurements, such as heart rate, echocardiographic (ECG) monitoring, non-invasive arterial blood pressure and pulse oximetry were recorded. All patients received bolus midazolam (0.15 mg/kg), propofol (1 mg/kg), and dexmedetomidine (0.5 µg/kg) infusion for anesthesia induction. Dexmedetomidine (0.2–0.7 µg/kg/h) was applied for maintenance. Dexmedetomidine dose was changed by 0.1 µg/kg/h after evaluating the depth of anesthesia at 5-min intervals.

While evaluating the depth of anesthesia, RSS scores of 3 to 4 were included in group R; serial measurements of pupil diameter were recorded and compared to first pupil diameter measurement after induction in group P. Dexmedetomidine infusion dose was changed to 0.1 µg/kg/h based on changes in pupil diameter.

Once the procedure was completed, infusion was terminated, and the patient was awakened. The time from infusion termination to an Aldrete score of 9 was recorded as recovery time. The mini-mental test was repeated 30 min after infusion termination to evaluate for the cognitive functions.

Statistical analysis

Data was analyzed using SPSS 18.00 (Statistical Package for Social Sciences, Inc., Chicago, IL). Continuous variables were presented as mean (standard deviation) and percentages (%). Categorical variables were presented as numbers and percentages. Kolmogorov–Smirnov test was used for testing normal distribution of the data. Mann–Whitney U test was used for analyzing continuous variables. A chi-squared test was used for comparison and analysis of categorical variables between groups. *P*-values <0.05 were considered statistically significant.

Results

A total of 60 patients with 30 patients in each group, were included in the study. 14 (46.7%) female and 16 (53.3%) male patients were included in group P while 16 (53.3%) female and 14 (46.7%) male patients were in group R. Five (16.7%) patients in group P and 7 (23.3%) patients in group R had no comorbidities. No significant differences between both groups in terms of age (P=0.246), gender (P=0.797) and comorbidities (P=0.748) were found.

No statistically significant difference between both groups in terms of anesthesia duration was found (P=0.397). No difference between intra-operative propofol application (P=0.677) was observed. Dexmedetomidine use in group P was significantly lower than group R (P=0.004), and recovery time in group P was significantly faster than group R (P<0.001) as shown in Table 1. Figure 1 shows hemodynamic follow-up the both groups. With regard to mini-mental test results, no significant difference was observed between both groups during the pre-operative period (P=0.140), while a statistically significant difference in the post-operative period (P=0.025) was found (Table 2).

Table 1: Administered drugs and administration durations

	Group P (n=30) Mean (SD)	Group R (n=30) Mean (SD)	*P*-value
Anesthesia duration (min)	39.20 (13.72)	41.70 (8.32)	0.397
Midazolam (mg)	1.93 (0.25)	1.97 (0.18)	0.561
Propofol (mg) (induction)	67.00 (25.88)	79.67 (23.56)	0.052
Propofol (mg) (total)	133.00 (61.42)	140.33 (73.79)	0.677
Dexmedetomidine (mg)	14.94 (7.49)	21.23 (8.90)	0.004*
Recovery time (min)	18.33 (6.74)	26.50 (7.79)	<0.001*

* *P*<0.05 statistically significant

Figure 1: Comparison of intra-operative parameters of heart rate (HR), peripheral oxygen saturation (SPO2), systolic (SPB) and diastolic (DPB) blood pressures between groups.

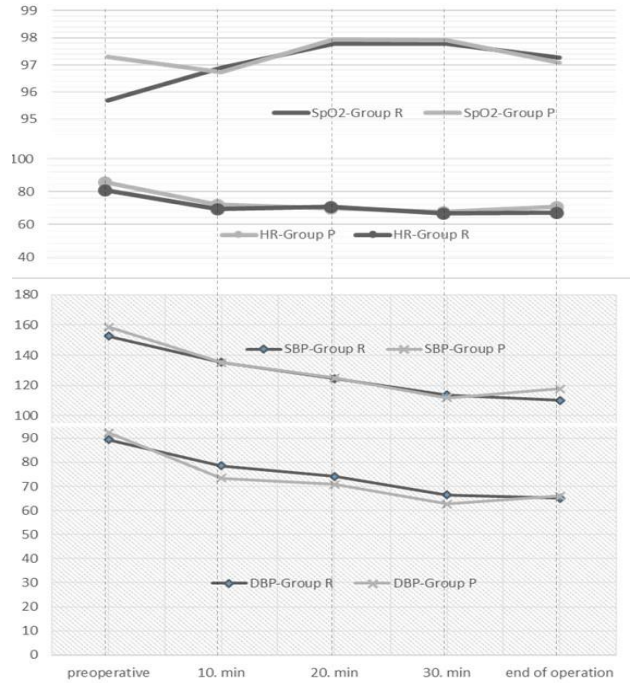

Table 2: Mini-mental test scores

	Group P (n=30) Mean (SD)	Group R (n=30) Mean (SD)	*P*-value
Pre-operative	19.37 (4.87)	21.10 (4.08)	0.140
Post-operative	18.90 (4.92)	16.23 (3.99)	0.025*

* *P*<0.05 statistically significant

Discussion

By applying pupillometer parameters and Ramsay scores as references in the management of intra-operative depth of anesthesia, we observed that pupillometer usage led to a reduction in the use of dexmedetomidine and resulted in better cognitive functions in the postoperative recovery period. There is an increase in the number of therapeutic endoscopic procedures in geriatric patients due to population aging. Development of a personalized sedation strategy that takes into account a patient's general condition, underlying disease, and estimated surgical difficulty during ERCP procedure in geriatric patients has important implications toward a patient's prognosis [10]. Although deep sedation increases patient's comfort during the procedure, this type of sedation is associated with airway obstruction, aspiration, respiratory depression, and hemodynamic instability; in contrast, patients may suffer from pain under inadequate sedation. The primary goal of sedation management is to maintain adequate and regular sedation without causing an increase in the risk of cardiac or respiratory depression. Thus, the dose of conscious sedation agents used should be titrated well and patients should be monitored closely [11]. Monitoring the depth of anesthesia reduces the dose and cost of the drugs used and accelerates recovery [12–15].

Nociception monitoring is one of the biggest current challenges in anesthesiology. Inadequate sedation can result in potentially harmful hemodynamic variations. Clinical parameters, such as heart rate and/or blood pressure changes, are frequently used to evaluate intra-operative analgesia. Since these parameters' reliability and specificity are questionable in most cases, other physiological indices and measurements may be useful for providing more accurate clinical feedback on depth of anesthesia.

Different physiological approaches and noninvasive modalities have been developed to monitor intraoperative nociception stimuli. Individualization of the intra-operative drug doses is the main goal to avoid both under and over dosing [16]. Among these modalities, a pupillometer appears to be a reliable tool. Pupillary diameter increase in patients under anesthesia after nociceptive stimuli is known as "pupillary dilation reflex". The amplitude of pupillary dilation reflex is proportional to the intensity of nociceptive stimulus and inversely proportional to the amount of administered drug [17–20].

Intra-operative pupillary diameter is a dynamic indicator of pain; however, no previous studies have evaluated the potential clinical benefits of pupillometry-guided ERCP. In our study, dexmedetomidine was preferred for induction, while propofol was used for maintenance. Propofol is preferred in ERCP and other endoscopic procedures due to its short duration of action, rapid awakening, and easy titration. Dexmedetomidine is desirable in procedural sedation as it induces cooperative sedation, analgesia and rapid recovery without causing respiratory depression [21,22]. In this study, RSS was used as an objective method to determine sedation level in our control group. Patients in the control group were maintained at a goal Ramsay sedation score of 4. Ceylan et al. [22] investigated the effects of propofol and dexmethodimidine sedation on the hemodynamic and cognitive functions of patients during ERCP procedures. Ramsay sedation scores of 3 to 4 were associated with adequate levels of sedation without producing any negative impact on recovery scores, hemodynamic, and/or respiratory parameters. These findings are compatible with our results regarding hemodynamic parameters. Bispectral index (BIS)-based depth of anesthesia monitoring was associated with improved early recovery in previous studies [23–25].

Although Adequacy of Anesthesia (AoA) monitoring did not lead to a reduction in the occurrence of unwanted events, it did produce a reduction in the amount of medications used and helped accelerate recovery [26,27]. Similarly, the use of Smart Pilot View (SPV) improved recovery and drug consumption [28,29]. Post-operative recovery time was significantly lower in the pupillometer group when compared with the RSS group.

The cognitive reserve of the brain decreases while sensitivity to stress and the risk of postoperative cognitive dysfunction increase with aging [30]. Careful evaluation and documentation of the cognitive status of geriatric patients before surgery is critical for the diagnosis of post-operative cognitive dysfunction (POCD), which is a common occurrence after surgery. Pre-operative cognitive impairment may be a key indicator of risk for postoperative delirium [31–33].

Many factors have a negative impact on early post-operative cognitive functions and time for recovery of

consciousness and cognition after anesthesia, including type of surgery, anesthetic agents, and anesthetic auxiliary drugs (such as steroids, anticholinergics), duration of anesthesia, level and duration of pre-operative hypotension, hormone levels (thyroid stimulating hormone [TSH], sex hormones), sedative and anxiolytic premedication, and patient's age and underlying diseases [34–37]. Post-operative cognitive dysfunction is associated with prolonged hospitalization, increased mortality, and functional decline. Peri-operative multidisciplinary and multi-modal approach, antipsychotic use, depth of anesthesia monitoring, and dexmedetomidine were found to be associated with a reduction in post-operative cognitive dysfunction in non-cardiac elective surgery patients [38]. Dexmedetomidine may alleviate POCD by producing a decrease serum tumor necrosis alpha and interleukin 6 (TNF-α and IL-6, respectively) levels [39]. In our study, dexmedetomidine was preferred for sedation maintenance in both groups. Besides, post-operative mini-mental test scores were higher in the pupillometer group.

Limitations

In this study, we compared anesthesia management by using the pupillometer and RSS methods. Lack of comparison with other monitoring methods and evaluation challenges due to undesirable/adverse post-operative events in our study can be considered as limitations.

Conclusion

Depth of anesthesia can be monitored with a pupillometer. Although no difference in hemodynamic parameters when compared with the RSS, pupillometer monitoring causes acceleration of anesthesia recovery, improvement in the return of cognitive function, and reduction in drugs used during endoscopic procedures in geriatric patients.

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Anti-inflammatory and anti-apoptotic potential of beta-glucan on chemotherapy-induced nephrotoxicity in rats

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Abstract

Background/Aim: Cyclophosphamide (CP) is an anti-cancer agent that mediates nephrotoxicity. Beta (β)-glucan has restorative effects on kidney toxicities through its antioxidant potential; however, the effects of β-glucan on CP-induced renal injury remain unknown. In an experimental nephrotoxicity model using rats, we sought to examine the potential protective action of β-glucan on kidney histomorphology, apoptosis, and TNF-α expression.

Methods: Male albino Wistar rats were divided equally into four groups: control, CP, β-glucan, and CP+β-glucan. The kidney tissues of the rats were examined for TNF-α and caspase-3 immunostaining to evaluate inflammation and apoptosis, respectively. Hematoxylin and eosin (H&E) and periodic acid–Schiff (PAS) staining were used for histopathological analyses.

Results: The CP group showed severe histopathological damage in the renal tissues of rats.

In the renal tissue of the CP group, immunoreactivities for TNF-α (1.25 [0.079] and caspase-3 (1.506 [0.143] were also higher than the control group (0.117 [0.006] and 0.116 [0.002], respectively; $P<0.001$). In the CP+β-glucan group, the histopathological changes significantly improved.

Conclusion: Beta-glucan has therapeutic potential against CP-induced nephrotoxicity in rat kidney.

Keywords: β-glucan, nephrotoxicity, oxidative stress, caspase-3, TNF-α

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Ethics Committee Approval
The study was approved by the Local Animal Experiments Ethical Committee of Kahramanmaras Sutcu Imam University, Protocol no: 2022/02. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Introduction

Cyclophosphamide (CP), an alkylating drug, is frequently used as an immunosuppressant during organ transplantation and is used against many types of cancers, autoimmune disorders, and other conditions [1, 2]. However, the therapeutic use of CP is restricted due to the side effects it produces, such as nephrotoxicity, cardiotoxicity, and hepatotoxicity [3]. Renal damage induced by CP includes apoptosis and necrosis of tubular epithelial cells [3], inflammation [4], fibrosis [5], and decreased lysosomal enzyme activity [6]. The toxic mechanism of CP is attributed to its main metabolites, phosphoramide mustard and acrolein, which cause an increase in free radicals [7]. Acrolein is responsible for inducing the reactive oxygen species (ROS) production that is crucial for DNA interstrand cross-links and the activation of multiple signaling molecules and inflammatory markers, specifically tumour necrosis factor-alpha (TNF-α) and interleukins (ILs); IL-1β and IL-6 [8,9]. It also leads to mitochondrial and endoplasmic reticulum dysfunction, as well as cell membrane disruption, resulting in apoptosis [10].

Beta (β)-glucans are beneficial and natural food ingredients that can be found in yeast, cereal, seaweed, and mushroom [11]. Its many biological properties, such as anti-inflammatory [12], antioxidant [13], anticancer [14], ROS-scavenging [11], and immune-modulating properties [15], have been reported. As evidenced by previous reports, β-glucan exhibited cytoprotective action against uranyl acetate–induced nephrotoxicity [16], chronic nicotine toxicity [17], and renal ischemia-reperfusion injury [18] in rodents.

TNF-α is a crucial mediator produced during inflammatory processes in acute and chronic kidney diseases. Blocking TNF-α with neutralizing antibodies or specific antibodies has been highly effective in the treatment of inflammatory disorders [19]. Previous studies have shown that dietary β-glucan reduces inflammation in various tissues by reducing the expression of pro-inflammatory cytokines [20,21].

The preventive properties of β-glucan against CP-induced renal damage have not, as far as we know, been studied. The purpose of this investigation was to determine whether β-glucan would help protect rats from CP-induced kidney injury by doing a histopathological analysis and utilizing an immunohistochemistry technique to quantify TNF-α and caspase-3 levels.

Materials and methods

Experimental procedures and groups

Twenty-eight male albino Wistar rats (200–250 g) from the Kahramanmaras Sutcu Imam University Animal Care and Research Unit (Kahramanmaras, Turkey) were housed under optimal laboratory conditions (12 h of light, 12 h of darkness, temperature of 22±2 °C) and had water and standard rodent food available *ad libitum*. The Kahramanmaras Sutcu Imam University's Ethics Committee granted permission for the animal experimentation procedure (Approval number: 2022/02-01). The four groups (n=7 each) were the control, CP, β-glucan, and CP+β-glucan groups. The control group was given no treatment for 7 days. On day 2, the CP group received a single intraperitoneal (i.p.) dosage of 200 mg/kg CP to induce nephrotoxicity [8]. β-glucan group received β-glucan dissolved in distilled water at a dose of 50 mg/kg by oral gavage (o.g.) [22] for 7 days. The CP+β-glucan group, however, was given 200 mg/kg (i.p.) CP on day 2 and 50 mg/kg (o.g.) β-glucan, both as a single dose, for 7 days.

On the eighth day, the animals were sacrificed under anesthesia using ketamine/xylazine HCl (75/10 mg/kg, i.p.). All kidney tissues were collected for histomorphological analysis and fixed in 10% buffered formalin solution.

Histopathological examination

The fixed kidney tissues were processed, and 5 µm thick sections were stained with hematoxylin–eosin (H&E) and periodic acid–Schiff (PAS) for histopathological evaluation. The prepared slides were examined by an observer in a blind manner under a light microscope (Carl Zeiss Axio Imager A2 microscope, Germany) with ×20 magnification. The following degenerative changes were scored within each slide in 10 histological fields [4]: 0=no damage, 1=10% of the histopathology damage, 2=10–25% damage, 3=25–50% damage, 4=50–75% damage, 5=>75% damage.

Immunochemistry

Sections taken on adhesive slides were deparaffinized and boiled by a microwave oven in Tris-EDTA buffer for antigen retrieval. The slides were treated with 3% H_2O_2 solution and then blocked with normal goat serum. The slides were incubated with primary antibodies against anti-TNF-α (1: 200, ab220210, Abcam) and anti-caspase-3 (1: 200, ab184787, Abcam) at +4 °C overnight. The slides were rinsed with PBS before being incubated for 30 minutes with anti-rabbit IgG secondary antibody (1: 200, 65-6140, Thermo Scientific), washed, and incubated for 10 minutes with horseradish peroxidase (HRP; 1: 200, 43-4323, Thermo Scientific). After placed in diaminobenzidine (DAB), the slides were counterstained with Mayer's hematoxylin. The histoscore was calculated using the following rating scale: 0.1: <25%, 0.4: 26–50%, 0.6: 51–75%; 0.9: 76–100%, and intensity of immunoreactivity as 0: unstained, +0.5: very low, +1: low, +2: moderate, +3: severe. The score was calculated using the staining intensity × prevalence [23].

Statistical analysis

The software SPSS v. 25.0 was used to conduct statistical analysis (IBM, Chicago, IL). The Shapiro–Wilk test was used for data with a normal distribution. One-way analysis of variance (ANOVA) or the Kruskal–Wallis test were applied to compare the groups, as necessary. For the significant group comparisons, Tukey's multiple range test or the Mann–Whitney *U* test were used, with the Bonferroni correction and an adjusted α value (5C2=0.05 / 10=0.005). The results were presented as mean (standard deviation [SD]) or a median (min–max). Statistics were deemed significant at $P<0.05$.

Results

Effects of β-glucan on renal histological changes

The kidney sections in the control and β-glucan groups showed typical tubular and glomerular histoarchitecture (Figures 1a and 1b). The CP group revealed degenerative changes including desquamation of tubular epithelial cells, hyaline casts, cellular vacuolization, focal inflammatory cells, tubular

degeneration, and coagulation necrosis of some tubular epithelium (Figures 1c and 1d). However, these histopathological changes were markedly attenuated with concomitant treatment by β-glucan (Figure 1e). As shown in Table 1, the injury score showed significant increase in the CP group compared to the control group (P<0.001). The tubular injury score in the CP+β-glucan group was significantly lower than in the CP group (P<0.001).

Figure 1: Photomicrograph of H&E stained renal sections. The control (a) and ß-glucan (b) groups show typical glomerule (g), proximal (p) and distal (d) tubule. (c,d) Sections from the CP group show degeneration in tubule epithelial cells (black asterisks), hyaline cast (black arrow), tubular lumen with sloughed epithelial cells (black arrowhead), cellular vacuolation (white arrow), coagulation necrosis of tubular epithelium (curved arrow). (e) CP+β-glucan group, (a,b,c,d X400).

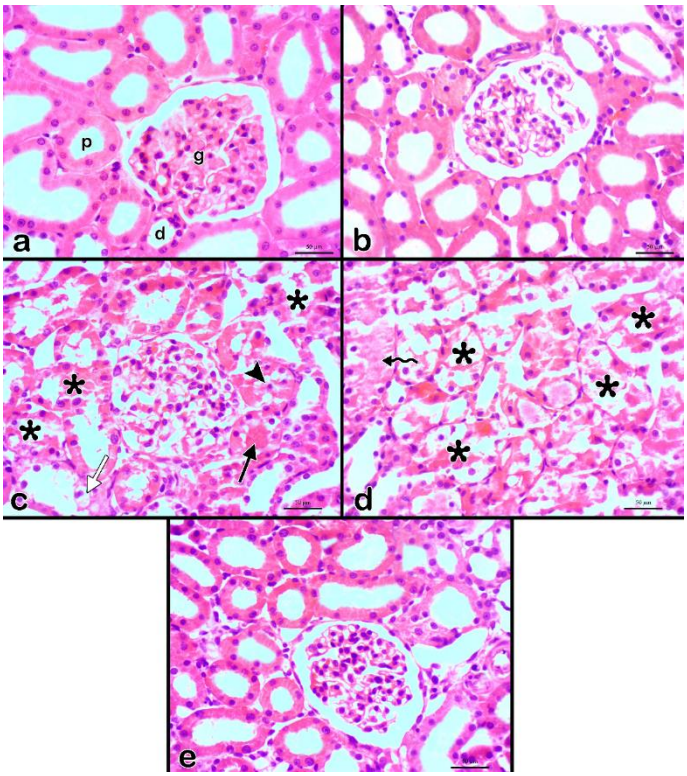


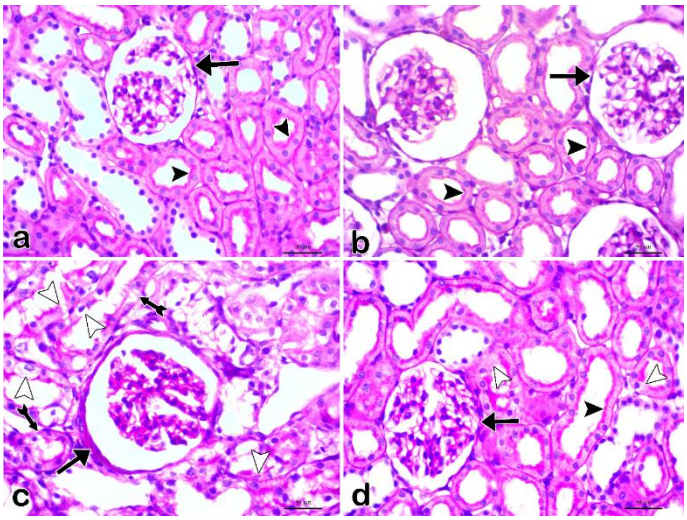
Table 1: Histopathological scores of all groups in renal tissues

Groups	Median (min-max)
Control	0[a] (0-1)
β-glucan	0[a] (0-1)
CP	4[b] (3-5)
CP+β-glucan	1[c] (0-2)
***P*-value [Θ]**	<0.001

[Θ]: Kruskal Wallis H test was used. Mann Whitney U Test was used to pairwise comparisons and an adjusted alpha value for Bonferroni correction was 0.008. [a]: The control and β-glucan groups did not differ significantly (P=0.189). [b]: Significant difference observed between control, β-glucan, CP+β-glucan and CP groups (P<0.001). [c]: Significant difference observed between control, β-glucan and CP+β-glucan groups (P<0.001)

PAS-stained slides from the control and β-glucan groups showed PAS-positive reaction of the brush border of the proximal tubule and parietal layer of Bowman's capsule (Figures 2a and 2b). The basal lamina of a parietal layer of Bowman's capsule thickened in the CP group. The proximal tubules had a disrupted brush border, and irregularity and disruption of proximal basal lamina was determined (Figure 2c). The CP+β-glucan group displayed nearly normal basal lamina of tubules and parietal layer of Bowman's capsule and the brush border for PAS reaction as compared to the CP group. However, some proximal tubules showed only a mild reaction along their brush border (Figure 2d).

Figure 2: Photomicrograph of PAS-stained renal sections. The parietal layer of Bowman's capsule (black arrow) and the brush border (black arrowheads) of the proximal tubule both show strong PAS positive reactions in the control (a) and (b) ß-glucan groups. The CP group (c) exhibits disruption of the proximal basal membrane (tailed arrows), strong PAS positive reactions in the parietal layer of the Bowman's capsule that is thickened (black arrow), and a weak reaction along the disrupted brush border of the proximal tubules (white arrowheads). (d) CP+β-glucan group shows strong positive reaction in the brush border of nearly most of proximal tubules (black arrowhead), along parietal layer of Bowman's capsule (black arrow) and also weak reaction along the disrupted brush border of some proximal tubules (white arrowheads), (a,b,c,d X400).



Immunohistochemical findings of TNF-α and caspase-3 for kidney

Figure 3 and Table 2 show that the CP group had significantly higher TNF-α and caspase-3 expression than the control group (P<0.001). The administration of β-glucan along with CP led to the decreased expression of these proteins when compared to the group that had only received CP (P<0.001).

Figure 3: Representative images of TNF-α (a-d) and caspase-3 (e-h) immunostained kidney sections. (a,e) Control group, (b,f) β-glucan group, and (c,g) CP group: Intense TNF-α and caspase-3 expression (black arrows), respectively. CP+β-glucan group (d,h): Mild TNF-α and caspase-3 expression (black arrows), respectively, (a-h X400).

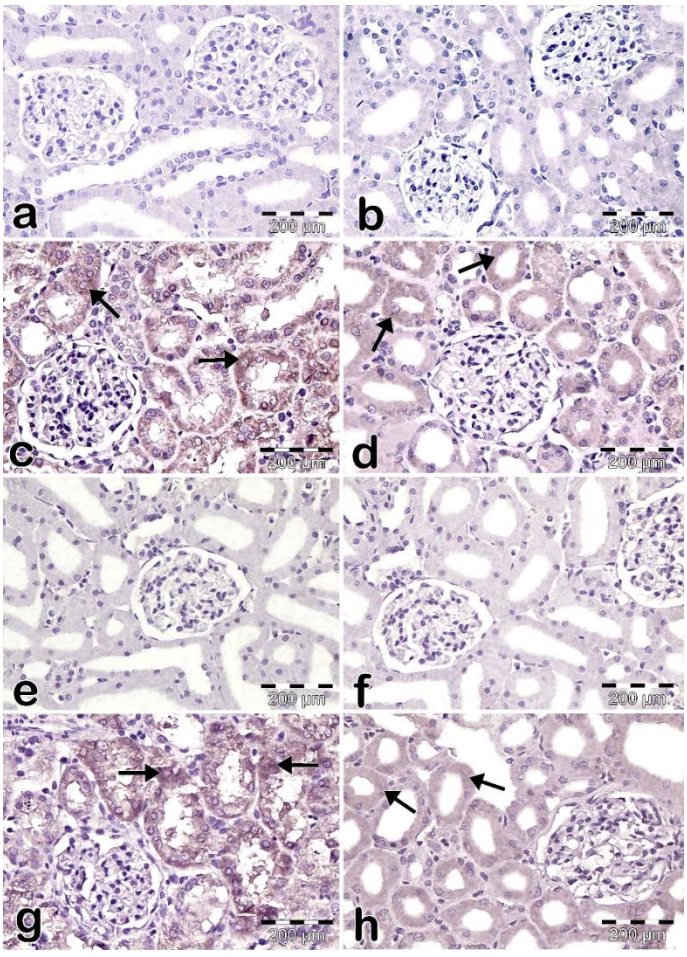


Table 2: Histoscores of TNF-α and caspase-3 immunoreactivity of all groups

Groups	TNF-α Mean (SD)	Caspase-3 Mean (SD)
Control	0.117[c] (0.006)	0.116[c] (0.002)
β-glucan	0.110[c] (0.010)	0.893[c] (0.030)
CP	1.250[a] (0.079)	1.506[a] (0.143)
CP+β-glucan	0.75[b] (0.114)	1.31[b] (0.07)
***P**-values**	< 0.001	< 0.001

*: One Way ANOVA; Tukey test was used to pairwise comparisons, SD: Standard deviation. In terms of differences for TNF-α and caspase-3 immunoreactivity; [a]: CP group was significantly higher in all groups (P<0.001); [b]: CP+β-glucan group was higher than both control and β-glucan (P<0.001); [c]: Control and β-glucan groups did not differ significantly (P=0.998).

Discussion

Kidneys play a fundamental role in basal metabolism in addition to maintaining homeostasis and eliminating toxins and drugs [24]. The antineoplastic drug CP, which is used to manage chemotherapy [25], is known to cause serious nephrotoxicity. CP toxicity has been reported to cause degenerative changes to the kidney, worsened renal injury markers, and oxidative stress parameters in rats [10].

A previous study indicated that CP causes necrosis, Bowman's capsule injury, and inflammatory cells [6]. Another study on rats found inflammatory cell infiltration, congestion, glomerular and tubular distortion, along with thickening of Bowman's capsule, of the wall of blood vessels, and of the tubular basal lamina [26]. These outcomes are consistent with the nephrotoxicity observed in the renal tissues of rats treated with CP in the current study. Several natural and other antioxidants are beneficial and effective source for preventing renal damage [27]. Previous studies have revealed the beneficial potential of β-glucan, a natural product on kidney [16-18]. Additionally, β-glucan has been reported to exhibit beneficial effects on gut microbiota, intestinal barrier function, and enhanced signaling in significant brain regions of C57BL/6 J male mice with cognitive impairment [20].

In the current study, β-glucan administration reduced CP-induced nephrotoxicity, due to its antioxidant activity, when combined with CP [13]. The results of this research, therefore, support the therapeutic benefit of β-glucan in the treatment of CP-induced nephrotoxicity.

The accumulation of CP in the cell may disrupt the antioxidant defense mechanisms and increase the generation of reactive compounds. In the course of CP metabolism and degradation of its metabolites, there is production of ROS encompassing superoxide anions, hydroxyl radicals, and hydrogen peroxide [28]. The production of oxidative stress leads to the activation of inflammatory cascades in damaged renal tissue [3,29]. ILs and TNF-α are important inflammatory mediators in the pathogenesis of CP-mediated inflammation [1]. TNF-α levels in rat renal tissues were found to be significantly higher after CP administration, according to previous research [8, 30]. In the current study, rats with CP-induced kidney damage had higher expression of the pro-inflammatory cytokine TNF-α than did control rats. Beta-glucan has anti-inflammatory activities and numerous studies have shown the positive effects of dietary β-glucans on various tissues [21,31,32]. Different types of inflammatory mediators, including TNF-α, ILs, nitric oxide, interferon gamma, and the non-cytokine mediator prostaglandin E2, play important roles in the anti-inflammatory effects of β-glucans [33]. Consistent with previous research, we found that β-glucan induced an anti-inflammatory effect by significantly reducing the expression of TNF-α in the kidney tissue of the CP+β-glucan group compared to the CP group.

Kidney inflammation and apoptosis have been linked to CP toxicity [30]. Apoptosis is crucial for maintaining tissue homeostasis by removing damaged or infected cells, and caspases, which are sensitive to the redox state of the cell, play a major role in the apoptotic process [34]. CP significantly increased caspase-3 expression in rats compared to controls in the current study. This finding corroborates the reports that CP-induced oxidative stress leads to apoptosis through caspase-3 activation in kidney tissues of rats [8,30].

In contrast, the anti-apoptotic properties of β-glucan [22,35,36] protected against apoptosis by inhibiting caspase-3 expression and significantly reduced its activity relative to the CP-treated rats. We believe that this is the first work to demonstrate the anti-apoptotic properties of β-glucan against CP-induced apoptosis in rat kidney tissues.

Conclusion

In conclusion, β-glucan restored CP-induced nephrotoxicity in rats by improving histopathological damage, suppressing the TNF-α and apoptosis, allowing for the possibility of blocking nephrotoxicity mediated by the anti-inflammatory and anti-apoptotic properties of β-glucan. Combining β-glucan with chemotherapy is encouraged to reduce the nephrotoxicity caused by CP in kidney tissue.

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Is there a risk of early relapse in patients with acute lymphoblastic leukemia presenting with bone-associated symptoms?

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Abstract

Background/Aim: Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. Patients usually present with fatigue, pallor, weight loss, and joint and/or bone findings. However, the effects of bone-associated symptoms on prognosis remains controversial. We aimed to demonstrate whether bone-associated symptoms affect prognosis in children with ALL.
Methods: This retrospective cohort study included the data from 268 patients with ALL who were diagnosed and treated between January 2011 and December 2020. The patients were divided into two groups as those with and without bone-associated symptoms. We compared the groups in terms of age, gender, immunophenotyping, day 8 prednisolone response, and risk groups, in addition to minimal residual disease (MRD), relapse, and survival rates.
Results: Eighty-five out of 268 (32%) children had bone-associated symptoms at the time of diagnosis, whereas others (n=183) had none of these symptoms. The relapse rate in children with bone-associated symptoms was found to be higher than the others (17.6% versus 12%), but the difference was not significant (P=0.24). However, children with bone findings developed earlier relapse when compared with the others (18.6 versus 28.6 months; P<0.001).
Conclusion: Therefore, we suggest that bone-associated symptoms at the time of diagnosis could be considered a warning sign for earlier relapse, and these children should be carefully followed.

Keywords: leukemia, childhood, bone involvement

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Introduction

Acute leukemia is the most common malignancy in childhood [1]. Although the most common complaints at presentation are fatigue, pallor, and weight loss, more than one-third of children may present with complaints of refusal to walk, bone pain, and arthralgia. These complaints are due to leukemic cell infiltration of the periosteum, bone, and joints [2]. Such findings may be confused with growing pains or sometimes with rheumatological diseases thus prolonging the time for initiation of the correct diagnostic process [3]. The effects of bone and joint findings on prognosis remain controversial [4,5]. In this study, we investigated the demographic characteristics, prognosis, and survival of patients (children) who presented with bone-associated symptoms and acute lymphoblastic leukemia (ALL).

Materials and methods

Data from 268 children diagnosed with ALL between January 2011 and December 2020 were retrospectively analyzed. The patients' ages at diagnosis, gender, symptoms at presentation, time from symptom onset to diagnosis, radiographic findings, laboratory findings, immunophenotypes, risk groups, and survival analyses were evaluated. The information was obtained from patients' files. The time from symptom onset to diagnosis was determined from the patient's anamnesis. At the time of diagnosis, chest, vertebral, and limb/wrist x-rays were routinely performed in all patients. In cases with localized bone complaints, magnetic resonance images (MRI) were obtained. The patients were divided into two groups, namely those with and without bone complaints. The treatment risk groups of 118 out of 268 patients were evaluated according to the polymerase chain reaction (PCR)-based minimal residual disease (MRD), and in the others (n=150), the ALLIC BFM 2009 risk group stratification was used. Patients were treated according to the ALLIC BFM 2009 protocol. We divided the relapsed patients into groups A and B. Group A consisted of relapsed patients with bone-associated symptoms (bone pain, arthralgia, arthritis, limping, and traumatic fracture), whereas in group B, relapsed patients did not have any of these complaints.

Statistical analysis

The data analysis was performed using the SPSS v. 22.0. The Kolmogorov–Smirnov test was conducted to check the normality of data distribution in groups. The chi-squared and t-tests were used to compare categorical and laboratory data, respectively. The survival analyses were done using the Kaplan–Meier test. The differences between the groups were analyzed with the log-rank test. $P<0.05$ was considered significant.

Results

Of the 268 patients diagnosed with ALL, 102 (38.1%) were female, and 166 (61.9%) were male. Their mean age (standard deviation) was 6.35 (4.5) years (range, 3 months–17.8 years). According to immunophenotyping at diagnosis, 236 children (87.7 %) had an immunophenotype compatible with B-cell, and 33 (12.3%) had a T-lineage compatible with ALL. Of all patients, 31.7% (n=85) had bone-associated symptoms at the time of the first presentation. These complaints were bone pain (arm, leg, waist, and back pain), arthralgia, arthritis, limping, and traumatic fracture (Table 1).

Table 1: Bone-associated symptoms at the time of diagnosis

	n (%)
Complaints at presentation	n=85/268 (31.7%)
Bone pain	36 (42.3)
Arthralgia	20 (23.5)
Limping	15 (17.6)
Arthritis	12(14.1)
Spontaneous fracture	2 (2.4)

It was observed that 24 (9%) of the 268 patients had radiological findings consistent with ALL. Of these cases, 22 were in the group presenting with bone-associated symptoms (25.8%; n=22/85) while two were asymptomatic. Of these 24 patients, a total of 32 ALL-related radiological findings were defined, mostly observed in upper extremities and vertebrae (n=15/32, 68%). The most frequent radiographic findings were focal, osteolytic, and osteosclerotic lesions, and related details are given in (Table 2). All patients with radiographic findings had B-cell ALL.

Table 2: Radiographic findings

Radiographic findings	n=32 (%)
Focal, osteolytic, and osteosclerotic lesions	8 (25)
Vertebral height loss (not compression fracture)	6(18)
Periosteal reaction	6(18)
Osteopenia, density loss, osteoporosis	3 (9)
Increased signal intensity (T2 MR)	3 (9)
Increased lucency	2 (6)
Metaphyseal radiolucent band	2 (6)
Fracture	2 (6)

The patients with and without bone-associated symptoms were compared in terms of age, gender, immunophenotyping, whole blood count, day 8 prednisolone response, risk group, and MRD results. The demographic characteristics of the patients based on study group are given in Table 3.

Table 3: Demographic characteristics of the patients

	Group A n=85	Group B n=183	*P*-value	Total n=268
Gender				
Girl	35(41.2%)	67 (36.6%)	0.28	102(38.1%)
Boy	50(58.8%)	116 (63.4%)		166(61.9%)
Age, mean (SD) (years)	6.09 (3.9)	6.47 (4.8)	0.53	6.35 (4.5)
Immunophenotype				
B-cell	79 (92.9%)	156 (85.2%)	0.05	236 (87.7%)
T-cell	6 (7.1%)	27 (8%)		33 (12.3%)
Laboratory findings				
Leukocyte	29.983	45.937	0.02	40.768
Hemoglobin	8.74	8.3	0.21	8.45
Platelet	112.923	75142	0.002	87.110
Day 8th prednisolone response				
Good	68 (80%)	142 (77.6%)	0.1	210 (78.4%)
Poor	13 (15.3%)	39 (21.3%)		52 (19.4%)
Mature B-cell ALL	4 (4.7%)	2 (1.1%)		6 (2.2%)
Risk group				
SRG	8 (9.4%)	15(8.2%)	0.3	23 (8.6%)
MRG	43 (50.6%)	95(51.9%)		138(51.5%)
HRG	34 (40%)	73(39.9%)		107(39.9%)
Relapse	15 (17.8%)	22(12%)	0.24	37 (13.8%)
Resistant disease		3(1.6%)		3 (1.1%)
Time to diagnosis (days) mean (SD)	31.18 (4)	15.9 (1.6)	<0.001	20.8 /1.8

Group A: patients with bone-associated symptoms, Group B: patients without bone-associated symptoms, SRG: Standard risk group, MRG: Moderate risk group, HRG: High-risk group

Risk stratification was done according to PCR-based MRD in 118 (44%) children. In the remaining 150 (56%) cases, classification was defined according to the ALLIC BFM 2009. When the patients with and without bone-associated symptoms were compared, no significant differences in terms of age and gender ($P=0.28$ and $P=0.53$, respectively) were found. The leukocyte count was significantly lower, and the platelet count was significantly higher in the group presenting with bone-associated symptoms ($P=0.02$ and $P=0.002$, respectively).

Although the relapse rate was higher (17.6%) in children with bone-associated symptoms, the difference was not significant (*P*=0.24). The time from the onset of complaints to diagnosis was significantly longer in the symptomatic group (*P*<0.001).

Relapse was seen in 15 (17.6%) of the 85 patients who presented with bone-associated symptoms and 22 (12%) of the 183 patients without these complaints (*P*=0.24). Of the 37 relapsed patients, 17 had genetic abnormalities (9p21 deletion, t (12;21), t (9;22)). Table 4 shows the demographic data of the relapsed cases in the two groups.

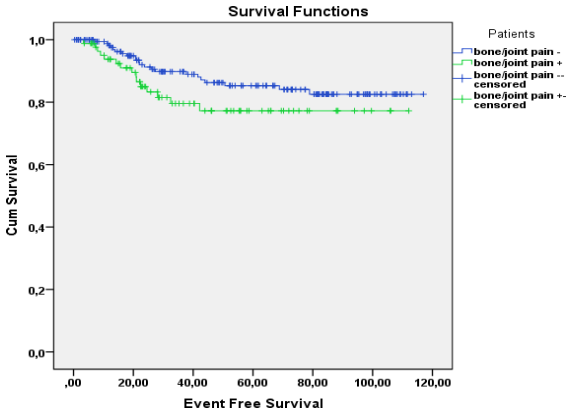
Table 4: Characteristics of relapsed patients

	Group A n=15/85 (17.6%)	**Group B n=22/183 (12%)**
Age, mean (SD) (years)	6.55 (4.1)	7.69 (5.2)
Gender		
Girl	8 (53.3%)	8 (36.4%)
Boy	7 (46.7%)	14 (63.4%)
Relapse region	Bone marrow, n=12 Combined relapse, n=3	Bone marrow, n=13 Combined relapse, n=6 Extramedullary (CNS), n=2 Extramedullary (testis), n=1
Immunophenotype		
B-cell ALL	13 (86.6%)	18 (81.8%)
T-cell ALL	2 (13.4%)	4 (18.2%)
Time to relapse (months) mean (SD)	18.6 (10.5)	28.6 (19.06)

Group A: relapsed patients with bone-associated symptoms Group B: relapsed patients without bone-associated symptoms, ALL: acute lymphoblastic leukemia *P<0.05 CNS: central nervous system

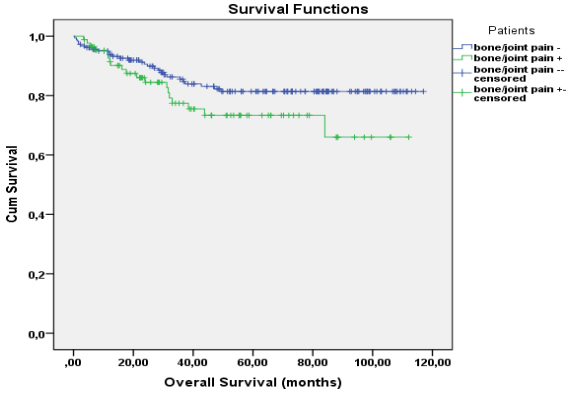
The patients presenting with bone-associated symptoms relapsed significantly earlier than the other group (*P*=0.04). The mortality rate in the whole group was 17.5% (47/268). The causes for mortality were relapse 59.5% (n=28), infection 34% (n=16), and resistant disease 6.5% (n=3). The death rates in group A and B were similar (22%: n=19/85 versus 15%: n=28/183; *P*=0.19). The overall survival rates of the patients with and without bone-associated symptoms were found to be 77.6% and 84.8%, respectively (*P*=0.109) while the event-free survival rate was 82.4% and 88%, respectively (Figures 1 and 2).

Figure 1: Event-free survival of patients with and without joint and/or bone pain complaints



Bone/joint pain -: patients without bone/joint pain, bone/joint pain +: patients with bone/joint pain

Figure 2: Overall survival of patients with and without joint and/or bone pain complaints



Bone/joint pain -: patients without bone/joint pain, bone/joint pain +: patients with bone/joint pain.

Discussion

Acute leukemia patients often present with fatigue, pallor, weight loss, and bleeding. However, other complaints, such as joint and/or bone pain, arthritis, and limping, are not uncommon. In the current study, 31.7% had bone-associated symptoms. Pain in the long bones was the most frequently reported complaint (n=36, 42.3%). Its frequency varies between 14% and 55% as reported in previous studies [6–10]. Although joint and/or bone pain is common in childhood, parents often delay doctor visits since they associate these complaints with benign growing pains or children's activities. The children presenting with joint and/or bone pain are usually treated with anti-inflammatory agents and can be misdiagnosed as rheumatological diseases [3]. Therefore, the diagnosis of leukemia is usually delayed . In the current data, three children received anti-inflammatory treatment before diagnosis, and the average time to diagnosis from the onset of first clinical symptoms was found to be significantly longer compared to the children without bone complaints. Clinicians should consider ALL rather than rheumatological diseases in the presence of hepatomegaly, splenomegaly, and lymphadenopathy in patients who present with osteoarticular findings [1]. In the literature, the duration of the diagnostic process varies between 42 and 80 days [4–8]. In our sample, one of the patients was diagnosed with rheumatoid arthritis and used methotrexate and prednisolone for one year before a correct diagnosis was obtained. Patients who used steroids before the diagnosis of ALL may have a poor prognosis [11].

Imaging technics performed on patients at the stage of diagnosis differs in previous studies. In a study by Zhou et al. [12], scanning was performed with single photon-emission computed tomography (PET/CT). In another study, only the bone radiographs of the patient were examined [6]. We examined the radiographic images of all patients, and if the patient had pathological findings, we performed MRI. In the literature, the frequency of radiographic findings varies between 18% and 55% [5,6,12,13]. We observed that 9% (n=24) of children had ALL-related radiographic findings. The most common radiographic findings in ALL are metaphyseal radiolucent bands, periosteal reaction, osteolytic lesions, and osteopenia [6,13,14]. In our data, the most frequent ALL-related findings were osteolytic, osteosclerotic, and focal lesions (25%). Metaphyseal radiolucent bands were present in only two patients.

Of our patients, 87.7% had B-cell ALL. At the time of presentation, bone complaints were higher among those with B-cell ALL, but this finding might be related to the low incidence of T-cell ALL. Similarly, in previous studies, more bone complaints were observed in patients diagnosed with B-cell ALL [7,15]. We also did not observe any radiographic findings in our patients with T-cell ALL who presented with bone complaints.

In the current study, no differences in age and gender between the two groups were found. The literature suggests that patients presenting with bone-associated symptoms have low leukocyte levels and high hemoglobin and platelet levels at the time of diagnosis. Consistent with the literature, we also found significantly low leukocyte and high platelet counts in symptomatic patients, but no difference was found in terms of the hemoglobin values [16]. Tragiannidis et al. [15] also reported

no difference in the hemoglobin values between patients with and without bone involvement.

In terms of the current data, the distribution of risk groups in two groups was found to be similar. Although the number of patients with relapse was higher in the group with bone- associated symptoms, the difference was not significant. The relapse rate was also not significantly different in terms of children's bone radiographic findings. While some studies in the literature report that the risk of relapse increases as the number of radiographic findings increases, others do not indicate such a risk [5,6,12,13].

The most important prognostic factor in childhood ALL is MRD [17]. We did not find a significant difference in the PCR MRD results of our patients with and without bone- associated symptoms. In the survival analysis, we found that the overall and event-free survival rates of the patients presenting with bone complaints were lower than the other group. However, these differences were not significant. In a study by Kang et al. [4], no significant difference in the overall survival between the patients with and without musculoskeletal complaints was found. In the literature, it was reported that the survival rate of patients with severe radiographic findings is significantly better than those without these findings [4,13].

Although the relapsed rate was found to be similar, in the children with bone complaints, relapse time occurred significantly earlier than in the other group. However, we did not find any related data in the literature that compared this finding. In our study, the distribution of risk groups and day 8 prednisolone response in both groups were similar. Since we were previously not able to do advanced genetic evaluations, such as next-generation sequencing, we cannot comment further on this finding.

Conclusion

In conclusion, we did not find any significant difference in terms of survival and relapse rates in children with bone-associated symptoms when compared with the children without bone-associated symptoms. However, relapse time in this group occurred significantly earlier than in the other group. Although we were not able to perform advanced genetic testing, the distribution of risk groups was found to be similar within the two groups. Therefore, we suggest that bone-associated symptoms at the time of diagnosis could be considered a warning sign for earlier relapse and these children should be carefully followed. Many factors, including treatment, early treatment response, and genetics, contribute to relapse, In the absence of these details, it is not possible to attribute bone and joint symptoms as an independent risk factor for early relapse. In addition, cases presenting with joint/bone pain should be carefully examined, and the diagnosis of leukemia should be included in the differential diagnosis.

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Research article

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One-year results of the national breast and cervical cancer screening program: Giresun province in the black sea region

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Ethics Committee Approval
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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Increasing the survival rate of patients with breast and cervical cancers is possible by early diagnosis through screening individuals for cancer in the asymptomatic period. Especially during the COVID-19 pandemic period, the possibility of early diagnosis in breast and cervical cancers has decreased due to the decrease in cancer screening applications. The aim of cancer screening is to increase the survival of patients by detecting precancerous lesions early. The purpose of our study is to evaluate the application and results of breast and cervical cancer screening in the Black Sea region's Giresun province.

Methods: This is a cross-sectional and descriptive study. The results of patients who were admitted to the Giresun Early Diagnosis Cancer Screening and Education Center between July 1, 2021, and June 28, 2022, were examined. The mammography report results of women aged 40–69 years who applied to the cancer screening center for breast cancer screening, and the HPV and Pap smear results of the patients aged 30–65 years who applied for cervical cancer screening, were evaluated retrospectively through the public health management system. Mammography results were evaluated with BIRADS (Breast Imaging Reporting and Dated System) scoring. The type of HPV and the cytology results from cervical swab samples were analyzed for cervical cancer screening.

Results: A total of 3567 people underwent mammography. Per the mammography results, the percentage of those with BIRADS 0 was 7.7% (n=278), the percentage of those with BIRADS 1–2 was 91% (n=3256), the percentage of those with BIRADS 4 was 0.7% (n=25), and the percentage of those with BIRADS 5 was 0.14% (n=5). HPV-DNA and cervical cytology examinations were performed for cervical cancer screening in 2326 patients. As a result of cervical cancer screening, HPV positivity was found in 6.44% (n=150) patients, and 14 different HPV types were found in the positive samples. When HPV types were examined, the two most common types were HPV type 16 (13.6%) and type 56 (11.9%). When the HPV types were examined in the positive samples, the two most common types were HPV type 16 (13.6%) and type 56 (11.9%). HPV type 18 was the least detected HPV type in patients (3.7%). When the Pap smear screening results of the 150 cases with positive screening results were examined, 3.33% were ASC-US (atypical squamous cells of undetermined significance), 22% were reported as infection, and 62.6% were normal.

Conclusion: The role of primary care physicians directing patients registered in their coverage area to cancer screening programs is especially effective in raising society's awareness and education on the issue. As a result, it is important that primary care physicians and related specialist physicians, together with cancer early detection and screening centers, adopt a supportive stance towards these programs in order for them to be implemented effectively.

Keywords: breast cancer screening, women's health, human papilloma virus, cervical cancer screening

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Introduction

Breast cancer is the most common type of cancer detected among women worldwide. Approximately one in four cancer diagnoses is breast cancer, and breast cancer ranks first among the causes of cancer-related death for women in many countries [1]. In Turkey, amongst all causes of death, cancer-related causes rank second [2]. Early diagnostic methods are important and effective tools for addressing complex disease processes such as cancer [3]. With early diagnosis, survival increases significantly. In developed countries, the 5-year survival rate for breast cancer has risen to 90% by detecting and treating breast cancer at an early stage [4].

Although it varies according to sociocultural and economic factors, cervical cancer is the fourth most common type of cancer observed in women [5,6]. In Turkey, it ranks ninth among cancer types in women according to 2017 data [7]. Human papillomavirus (HPV) is sexually transmitted, and more than 200 subtypes have been described [6]. HPV type 16 and HPV 18 are involved in the etiology of the majority of cervical cancers [8]. Cervical cancers are a type of cancer that can be prevented by, first, preventing HPV transmission, then by detecting the infection before it reaches the precancerous stage [9]. The World Health Organization (WHO) recommends performing cancer screening with community-based, accepted, and easy-to-apply methods for the early detection of breast and cervical cancer [10]. It has been accepted that 70% of the population should be screened in order for the cancer screening program to be deemed successful [11]. In our country, at community-based cancer early detection screening and education centers, women aged 40–69 years receive mammography every 2 years for breast cancer screening, and women aged 30–65 years receive HPV DNA and Pap smear tests every 5 years for cervical cancer screening. Opportunistic screenings are performed during outpatient admissions to secondary and tertiary institutions [12].

This study aims to evaluate the application and results of breast and cervical cancer screening in the Black Sea region's Giresun province.

Materials and methods

This study is a descriptive and cross-sectional community-based study. The study examines the screening results of female patients aged 30–69 years who applied to the Giresun Cancer Early Diagnosis Screening and Education Center (CEDSEC) for cervical cancer and breast cancer screening between July 1, 2021, and June 28, 2022. The results were evaluated retrospectively through the public health management system used in primary care in Turkey. The results of mammography imaging performed for breast cancer screening were reported at the national evaluation center with the BIRADS (Breast Imaging Reporting and Dated System) scoring system. Cervical cancer screening is performed by collecting cervical swab samples distributed through barcoded kits, after which cytology and HPV DNA analysis are performed on the samples sent by our institution to the national central laboratory. This study analyzed the age, HPV type, and cervical cytology results of mammography report results and HPV DNA–positive patients who applied to CEDSEC in the last year.

The study was approved by the Scientific Research Ethics Committee of Ordu University (decision date: 02/9/2022, decision no: 2022/201). The research conforms to the principles set forth in the Declaration of Helsinki. Informed consent was not obtained from patients due to the retrospective nature of the study.

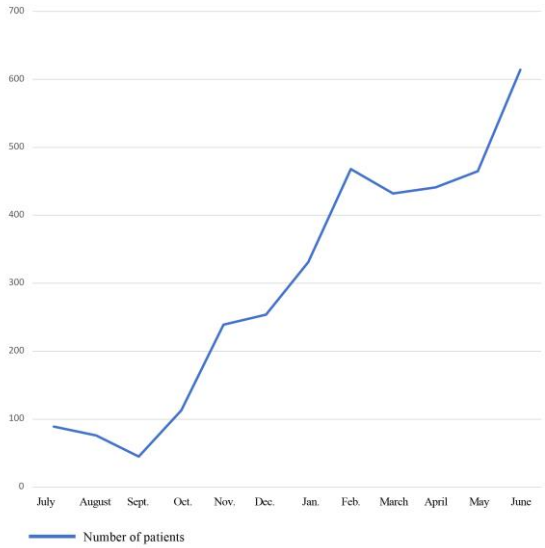
Statistical analysis

Data were transferred to the SPSS v. 22.0 (IBM; Chicago, IL) software program for analysis. Descriptive statistical methods (mean, standard deviation, percentage) were used while evaluating the data. HPV type and cytology results were detected after cervical cancer screening of women, results of mammography for breast cancer screening were evaluated, and their frequency and percentage were determined.

Results

A total of 3567 people received a mammogram within the scope of the breast cancer screening program in the cancer early diagnosis screening and education center in our province. Based on the mammography results, 7.7% (278) of the patients were BIRADS 0, 91% (3256) were BIRADS 1–2, 0.7% (25) were BIRADS 4, and 0.14% were BIRADS 5 (5). The mammography results of three people were inconclusive due to insufficient imaging. At the time of the study, the effects of the COVID-19 pandemic manifested as a decrease in patient applications for cancer screening. In the last 6 months of the 1-year period in which the study was conducted, patient applications for breast cancer screening increased compared to the first 6 months (Figure 1).

Figure 1: Distribution of patient admissions for mammography over a one-year period



The mean age of the 2326 patients who applied for cervical cancer screening was 48.53 years. The scan result was positive in 6.44% (n=150) of the patients, and in 0.38% (n=9), it was reported as insufficient material and required re-screening. When the HPV types detected were examined, the two most common types were HPV 16 at a rate of 13.6% and HPV 56 at a rate of 11.9%. HPV 18 was the least detected HPV type in patients, at a rate of 3.7% (Table 1). When the Pap smear cytology results of women with positive screening results were examined, 3.33% (n=5) were found to have atypical squamous cells of uncertain significance (ASC-US), 22% were found to

have infection, 62.6% (n=18) were found to be normal, and 12% had insufficient material.

Table 1: Distribution of HPV types detected in cervical cancer screening

HPV type	n	%	HPV type	n	%
16	33	13.6	33	11	4.5
31	15	6.19	58	13	5.8
51	21	8.6	68	13	5.3
52	25	10.3	35	10	4.1
56	29	11.9	45	12	4.9
39	18	7.4	59	11	4.5
18	9	3.7	other	22	9.09

More than one type of HPV was detected in patients. Other: HPV types other than the 13 types included in the table.

Discussion

District health directorates, CEDSECs community health centers, and family medicine units work together to reach the target population for cancer screening in Turkey. Family physicians and family health workers in primary care play an active role in informing the community about cancer screenings because they are in direct communication with patients.

In this study, 2326 people applied for cervical cancer screening in a 1-year period. The number of patients who applied for cervical cancer screening was less than the number of patients who applied for mammography. This difference may be related to the cultural structure and beliefs in Turkey. According to the results of a breast cancer screening program between 2016 and 2017 that included 15,294 women, BIRADS 4–5 was found in 0.6% of their sample, BIRADS 0 in 3.9%, and the others were reported as BIRADS 1–2 [13]. Again, in a study conducted with 3758 participants in Istanbul, the rate of BIRADS 0 was found to be 18.4% and the rate of BIRADS 4–5 was found to be 0.5% [14]. In a study conducted by Tuncez et al. [15], the rate of patients with BIRADS 0 in mammography was 9.7%, the rate of patients with BIRADS 1–2 was 87.5%, and the rate of patients with BIRADS 4–5 was 0.9%. In our study, in the breast cancer screening results of 3567 patients who were screened in total, the rate of those with BIRADS 1–2 was 91%, those with BIRADS 0 was 7.7%, those with BIRADS 4 was 0.7%, and those with BIRADS 5 was 0.14%. These findings are similar to other studies in the literature. It is important that patients with BIRADS 4–5 are referred to tertiary health institutions for further examination.

The number of patients who applied for breast cancer screening in the first 6 months of the 1-year period in which the study was conducted was less than the last 6 months. 77.1% of the applications were made in 2022. In this context, the long-term effects of the pandemic may have reduced the frequency of cancer screening in the first period of my study. In addition, this situation may have prevented reaching the target population, limiting the generalizability of our screening results to the general population.

Some HPV types have a very high risk of developing into cervical cancer. The purpose of screening for early diagnosis worldwide is to search for HPV infection and, if HPV is found, to clarify the type and apply the referral algorithm appropriate to the risk level [16].

In a study conducted in the United States evaluating Pap smear test results, abnormal cytology was found in 5.5% of the patients, of which 3.3% were found to have ASC-US (atypical squamous cells of uncertain significance) [17]. In studies conducted in our country for cervical cancer screening, abnormal Pap smear test results varying between 2.3% and 5.3% were found, most of which were determined as ASC-US at a rate of 1.9%–4.2%, and low-grade squamous intraepithelial lesion (LSIL) at a rate of 0.3%–0.8% [18]. In a study by Tuncez et al. [15], abnormal cytology was detected in 10.6% of the Pap smear test results, 7.1% of which were ASC-US and 2.6% of which were LSIL. In another study, 39.6% Pap smear test positivity was found, and the rate of referral to an advanced center for colposcopy was 4.6% [19]. In a study including 14,899 people in Brazil, ASC-US was found in 3.4% of cervical swabs [20]. In that study, when the Pap smear cytology results of women with positive screening results were examined, 3.33% (n=5) were ASC-US and 22% were found to have infection, which is similar to the literature. In our study, 62.6% (n=18) of Pap smear test results were normal and 12% had insufficient material. In Turkey, the Pap smear test and HPV-DNA test are performed together as a co-test as part of the National cancer screening program. Accordingly, cervical cancers that will require further examination can be detected more practically. Additionally, the detection of high cervical cancer risk factors of HPV 16 and HPV 18 types in the primary care setting followed by a referral to a gynecologist with cytology saves time.

In a study to examine the distribution of HPV types in China, HPV 52, HPV 16, and HPV 58 were the most frequently observed HPV types, at rates of 20.31%, 16.81%, and 14.4%, respectively. The same study found HPV positivity to be 79.56% [21] in 2950 cases. In the ATHENA research conducted in 2015, the most common HPV type detected in a detailed examination according to age groups is HPV 16, and in order of frequency, HPV 52, HPV 31, HPV 18 are the most common types [22]. In a systematic study in which data between 2005 and 2019 were analyzed, the most frequently detected HPV types were HPV 16, HPV 52, HPV 35, HPV 18, and HPV 56 [23]. When the HPV types seen in this study are examined, the two most common types are HPV 16 at 13.6% and HPV 56 at 11.9%. HPV 18 was the least detected human papillomavirus type in patients, at a rate of 3.7%. The fact that HPV 16, which increases the risk of cervical cancer, is the most common type in this study supports screening programs. This method allows for referring the patients from primary care to the gynecologist in the early period and to take them under observation before precancerous lesions occur. In the literature are studies showing that approximately 13 million new cervical cancer cases can be prevented by 2070 with both HPV immunization and cervical cancer screening algorithm after 2020, and that cervical cancer cases can be almost completely eradicated in some countries [24].

Limitations

Some of the dates of the study coincide with the period where the effects of the COVID-19 pandemic continued to manifest. This may have contributed to the lower number of patient applications for cancer screening than in previous years and may have limited the generalizability of our results. Due to the disruptions in the referral chain, seasonal migration, and the fact that this study was conducted in an agricultural and difficult-to-access area, adequate feedback could not be provided regarding further investigations after tertiary referrals.

Conclusion

Both breast and cervical cancer have high rates of survival if diagnosed early. In this sense, the high awareness of healthcare professionals about cancer screenings will benefit both the healthcare system and female patients by increasing breast and cervical cancer screenings. Community health centers in primary care positions throughout Turkey organize educational programs to raise awareness about health screenings in remote regions. Making these educational programs increasingly available can raise awareness in the community and increase participation in cancer screenings. In addition, after the outcome evaluation in cancer screening programs, when necessary, patients should be referred to tertiary healthcare institutions for further examination, and the results should be followed. Finally, reaching the target population in breast and cervical cancer screenings in our country will be possible primarily by supporting health professionals working in health institutions with in-service training.

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Comparison of the effectiveness of connective tissue massage and myofascial release technique in young adult women with primary dysmenorrhea

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Ethics Committee Approval
This study was approved by Istanbul Aydın University Clinical Research Ethics Committee (Date: 19.09.2019, Decision Number 2019/157).
The authors stated that the written consent was obtained from the patient presented with images in the study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Dysmenorrhea can restrict daily living activities and the overall productivity of women, thereby negatively affecting quality of life and causing absenteeism in students and loss of workdays in working women. Medical treatment is frequently used in clinics, but alternative approaches are needed when currently available treatment options are not effective. The aim of this study is to investigate and compare the acute effects of two manipulative methods, connective tissue massage (CTM) and myofascial release technique (MRT), on menstrual pain, fatigue, pain threshold, and menstrual symptoms in young adult women with primary dysmenorrhea (PD).

Methods: Forty young adults diagnosed with PD and scoring ≥4 in menstrual pain intensity according to the Visual Analog Scale (VAS) were included in the study. Menstrual pain and fatigue severity was evaluated by using VAS, pain threshold by algometer device from six unique points, and menstrual symptom severity using the Menstrual Symptom Questionnaire. Participants were randomly divided into two groups and evaluated in their first menstrual cycles. In Group 1, 10 sessions of CTM were applied between the first and second menstrual cycles, and in Group 2, a single session of MRT was applied on the most painful day of the second menstrual cycle. After the application, all participants were re-evaluated on the most painful day of their second menstrual cycles.

Results: No statistically significant difference was found between the groups in terms of age, BMI, menarche age, menstrual cycle, and menstrual bleeding duration. In both groups, a significant decrease was found in pain, fatigue, and menstrual symptom severity, and a significant increase was found in pain threshold (P=0.001). MRT was found to be more effective at improving the pain threshold at all points except the first point (1st point P=0.098, 2nd point P=0.034, 3rd point P=0.037, 4th point P=0.041, 5th point P=0.009, 6th point P=0.001).

Conclusion: It was found that CTM and MRT were effective at improving pain, fatigue, pain threshold, and menstrual symptoms in PD, and MRT was found to be more effective at increasing pain thresholds compared to CTM.

Keywords: primary dysmenorrhea, connective tissue massage, myofascial release, menstrual pain

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Introduction

Dysmenorrhea, which is a physiological event, is one of the most common and important problems experienced during menstruation [1]. It can restrict daily living activities and the overall productivity of women, thereby negatively affecting quality of life and leading to absenteeism in students and loss of workdays in working women [2]. While the rate of dysmenorrhea worldwide is 45–95%, studies conducted in Turkey in recent years reported a rate approximating 60% [3,4].

Primary dysmenorrhea (PD) is a painful condition without an underlying pelvic pathology that begins just before or during menstruation, lasts 12–72 hours, and progresses as cramps in the lower abdomen [2].

PD is mostly seen in young adult women and begins 1–2 years after menarche [5]. The main symptom of pain may accompanied by headache, dizziness, sweating, nausea, palpitations, fatigue, emotional disorders, and gastrointestinal disturbances such as vomiting and diarrhea [6].

The main purpose in dysmenorrhea treatment is to relieve pain by affecting physiological mechanisms or alleviating symptoms [2]. Three approaches are used to treat dysmenorrhea: medical, surgical, and conservative. Physiotherapy methods used in dysmenorrhea treatment include local heat agents, electrical stimulations (e.g., transcutaneous electrical nerve stimulation [TENS]), interferential current), massage, exercise, manipulative therapy, and connective tissue massage (CTM) [2,7].

Generating cutaneous stimulation CTM stimulates the skin and then the mechanical receptors in the connective tissue. The resulting stimulus reaches the radix posterior of the spinal cord via afferent nerves, where it stimulates the release of opioids; thus, pain carried by small-diameter fibers is inhibited [8, 9]. Studies indicate that menstrual pain decreases as a result of CTM [7,10].

Myofascial release technique (MRT) is a technique that focuses on the myofascial complex, and its main purposes are inhibition of pain and improvement of function [11]. MRT is thought to reduce stress in pain-sensitive structures by restoring fascial mobilization. One study found that MRT has positive effects on pain in PD [12].

Based on data from the literature, alternative and more effective, conservative treatment approaches for PD could be implemented. Therefore, the aim of this study is to investigate acute effects of CTM and MRT on menstrual pain, fatigue, pain threshold, and menstrual symptoms in women with PD and to determine which technique is superior.

Materials and methods

Participants

This study was conducted between September 2019 and January 2020 on women who were studying at Istanbul Gelisim University Health Services Vocational School. Comprehensive information was given to all participants about the purpose and duration of the study, assessment tools, and interventions, and written consent was obtained from all participants.

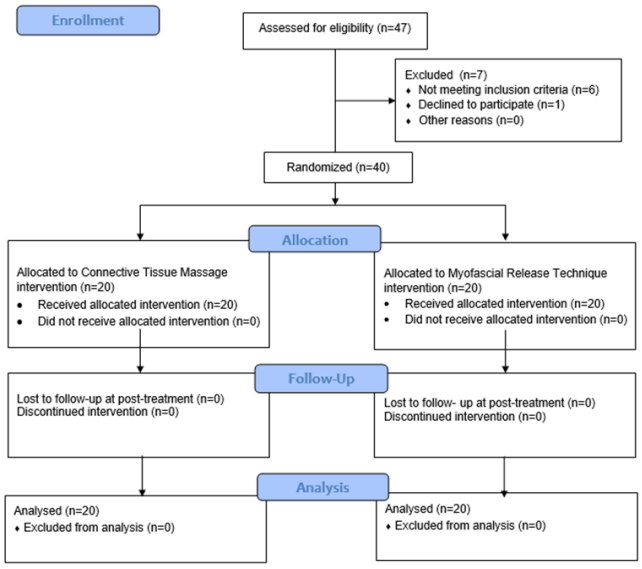
Istanbul Aydın University Clinical Research Ethics Committee approved this study (decision no. 2019/157, taken on Sept. 19, 2019).

Individuals who were ≥18 years, were diagnosed with PD by a gynecologist, had regular menstruation in the last 6 months, had menstrual pain between 40–100 mm according to the VAS, and volunteered to participate in the study were included.

Individuals who have secondary dysmenorrhea, who have an irregular menstrual cycle, who have a menstrual cycle duration <21 days or >35 days, who have a previous birth or pregnancy history, who are pregnant, who are using intrauterine or oral contraceptives, anti-inflammatory, analgesic, and psychotherapeutic medication, who have pelvic pathology or pelvic surgery history, and who have any neurological or systemic disease were excluded from the study.

When we compared the VAS values before and after the treatment in terms of primary outcome measurement, it was calculated that at least eight cases should be included in each sample group in order to find a significant difference between the measurements. Calculations were made using the G*Power v. 3.1.9.4 software program, considering type I error α=0.05 and 95% power value (1-β)= 0.95 [13,14]. Considering possible data loss, 20 female participants were included for each group. Individuals who met the inclusion criteria were randomly divided into two groups, CTM (n=20) or MRT (n=20), using the Research Randomizer website (Randomizer.org, 2019) (Figure 1).

Figure 1: Flow diagram



Assessment tools

Sociodemographic assessment

An evaluation form was completed for all individuals, containing information such as age; weight; height; smoking, alcohol, and exercise habits; age of menarche; duration, type, and intensity of menstruation; medications used for menstrual pain; amount of medication used for menstrual pain; other pain coping methods for menstrual pain; family history of dysmenorrhea; presence of systemic disease; and a history of surgery.

Pain and fatigue assessment

The VAS was used to measure pain intensity. Individuals were asked to mark the degree of pain they felt during evaluation on a 100-mm line. One end represents 0 (no pain), and the other end represents 10 (unbearable pain). Then, the point that was marked was measured with a ruler, and the

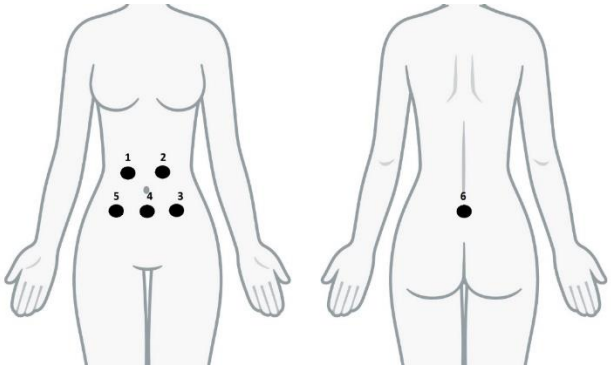
numerical value of pain intensity was recorded [15]. VAS was also used to assess severity of fatigue.

Pain threshold assessment

For pain threshold assessment, deep tissue hyperalgesia was measured using a Baseline® pressure algometer (Fabrication Enterprises Inc., New York, NY). Measurement was performed using a 1-cm^2 pressure probe, by holding the algometer perpendicular to the measurement point [16].

Measurements were made from six different points, 4 cm to right and left of the umbilicus (point 1 and 2), 4 cm below these two points (point 3 and 5), 4 cm below the umbilicus (point 4), and the middle of S2–S4 vertebrae spinous processes (point 6) (Figure 2). Two measurements were taken from each point, and we waited 30 seconds between both measurements. In cases where measurements were inconclusive, a third measurement was taken from same point [16]. Then, the average of these measurements was calculated and recorded as lbs/cm^2. The assessment was performed by gradually increasing the intensity of pressure, and individuals were told to state the moment when pressure caused pain, using the verbal indicator "okay".

Figure 2: Pain threshold measurement points



Menstrual symptom assessment

To evaluate menstrual symptoms, the Menstrual Symptom Scale was used, which was developed by Chesney and Tatso and whose Turkish validity study was conducted by Güvenç et al.. An increase in the total score of the scale indicates an increase in the severity of menstrual symptoms [17,18].

Interventions

Connective tissue massage

CTM was applied to pelvic areas, including the sacral, lumbar, lower thoracic, and anterior pelvic regions. Application was started on the 14th day, following ovulation, and 5 sessions/week were performed, totalling 10 sessions, until the next menstrual cycle. During manipulation, both long (Figure 3a, points 2, 4, 6, 9, and 10; Figure 3b, all points) and short strokes (Figure 3a, points 1, 3, 5, 7, and 8) were used. Each stroke was applied three times on the right side and then three times on the left side. Each session was concluded with long strokes on bilateral iliac crests and subcostal regions.

Treatment of sacral, lumbar, and lower thoracic regions was performed in upright sitting position. Treatment of the anterior pelvic region was performed in the supine position. The total session was completed in approximately 10 minutes [19].

Figure 3a: Direction of strokes in sacral, lumbar and lower thoracic regions (only one side shown)

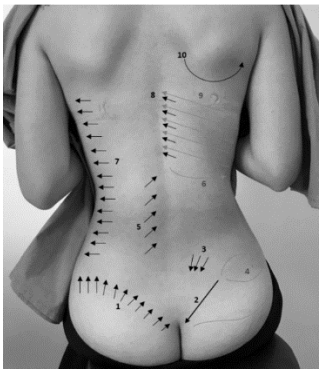
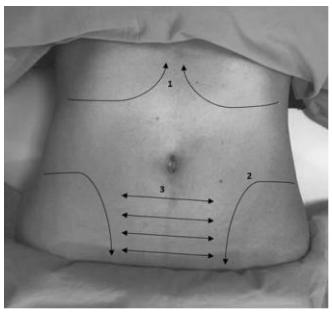


Figure 3b: Direction of strokes in anterior pelvic region



Myofascial release technique

During application, fingers or hands were first placed on treatment area. Pressure was applied to soft tissue until a restricted layer was felt. Then, the fascia was moved along the substrate surface while maintaining contact with substrates. Tension was applied for approximately 60–90 seconds, until relaxation was felt [20].

Individuals were placed in a supine position for antero-lateral (fascia superficialis, fascia transversalis, fascia extraperitonealis) abdominal wall (Figure 4a), then in a prone position for posterior (fascia thoracolumbalis, erector spine) abdominal wall (Figure 4b) [12].

Figure 4a: Antero-lateral abdominal wall relaxation

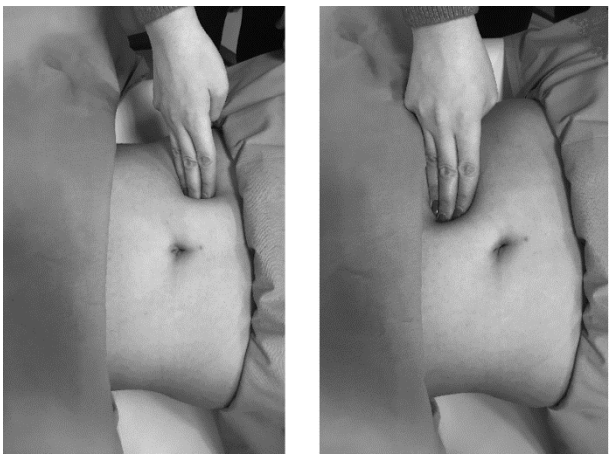
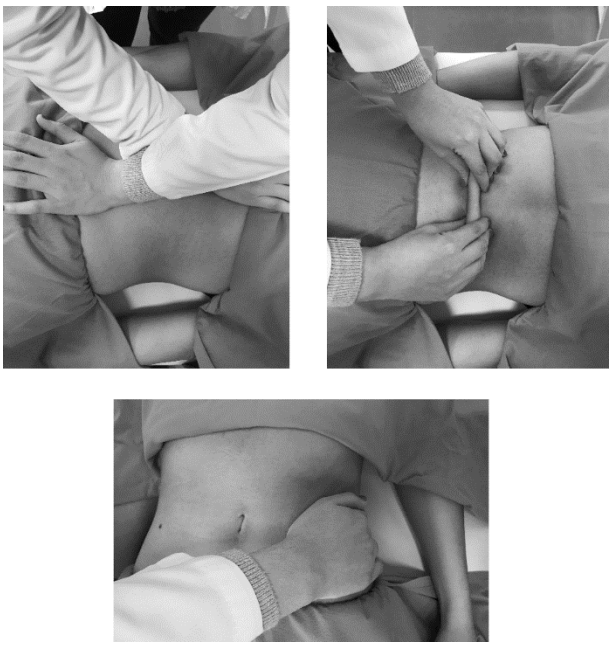


Figure 4b: Posterior abdominal wall relaxation



Statistical analysis

For statistical analysis of data, the software program SPSS v. 24.0 (IBM, Armonk, NY) was used. The Shapiro–Wilk test for normality was used to determine the conformity of data to a normal distribution. If there was a normal distribution in data before and after treatment within-group, the paired samples *t*-test was used; if the data were not normally distributed, the non-parametric Wilcoxon test was used. In intergroup evaluation, if data were suitable for normal distribution independent samples *t*-test was used; if not, the non-parametric Mann–Whitney *U* test was used. The chi-squared test was used to analyze relationship between categorical variables. For statistical significance, data were interpreted at the $P<0.05$ level.

Results

In our study, a total of 40 individuals—20 in the CTM group and 20 in the MRT group—were examined. All participants were evaluated on the most painful day of their first menstrual cycle. Group 1 received 10 sessions of CTM 5 days/week following ovulation (14th day) between the first and second menstrual cycles. Group 2 received one session of MRT on the most painful day of the second menstrual cycle. Following the end of treatments, on the most painful day of the second menstrual cycle, evaluations were re-applied to all participants as outcome measures implied.

The mean age of individuals was 21.70 (2.71) years in the CTM group and 20.75 (2.02) years in the MRT group. The mean BMI of the CTM group was 22.56 (3.15) kg/m^2 and of the MRT group was 21.53 (3.77) kg/m^2. Individuals in the CTM and MRT groups were found to be similar in terms of age ($P=0.31$) and BMI ($P=0.291$). In the CTM group, the mean menarche age of patients was 12.80 (1.36) years and 12.95 (1.60) years in the MRT group. When age of menarche ($P=0.868$), duration of menstrual cycle ($P=0.483$), and menstruation cycle length ($P=0.532$) were examined, both groups had similar values and were within normal limits (Table 1).

Table 1: Sociodemographic characteristics of the groups

	CTM (n=20) Mean (SD)	MRT (n=20) Mean (SD)	z	*P*-value
Age	21.70 (2.71)	20.75 (2.02)	-1.016	0.310
BMI (kg/m^2)	22.56 (3.15)	21.53 (3.77)	-1.055	0.291
Menarche age (years)	12.80 (1.36)	12.95 (1.60)	-0.166	0.868
Cycle length (days)	28.15 (1.63)	28.45 (2.08)	-0.702	0.483
Menstruation length (days)	5.45 (1.53)	5.75 (1.77)	-0.625	0.532

P<0.05: Statistically Significant Difference, Mean: Arithmetic Average, SD: Standard Deviation, z: Mann Whitney U Test Value

There was no difference between groups in terms of pain ($P=0.561$), fatigue ($P=0.394$), and menstrual symptom severity ($P=0.168$) before treatment. However, there was a significant difference in terms of pain intensity (CTM, $P=0.001$; MRT, $P=0.001$), fatigue intensity (CTM, $P=0.001$; MRT, $P=0.004$), and menstrual symptom severity (CTM, $P=0.007$; MRT, $P=0.001$) values in both the CTM and MRT groups after treatment. There was no difference between groups in terms of pain ($P=0.342$), fatigue ($P=0.824$), and menstrual symptom severity ($P=0.148$) after treatment (Table 2).

Table 2: Comparison of pain, fatigue and menstrual symptom severity values of groups before and after treatment

		CTM (n=20) Mean (SD)	MRT (n=20) Mean (SD)	t	*P*-value
Pain intensity (cm)	BT	7.20 (1.43)	6.92 (1.58)	0.586	0.561[a]
	AT	3.94 (2.32)	2.90 (2.21)	-0.962	0.342[a]
	P	0.001[b]	0.001[b]		
	t	5.644	7.476		
Fatigue intensity (cm)	BT	6.79 (1.85)	6.27 (1.96)	0.862	0.394[a]
	AT	4.21 (2.71)	3.90 (2.76)	0.224	0.824[a]
	P	0.001[b]	0.004[b]		
	t	4.305	3.284		
Menstrual symptom severity	BT	76.90 (14.40)	83.10 (13.47)	-1.406	0.168[a]
	AT	64.45 (12.93)	77.10 (14.45)	1.478	0.148[a]
	P	0.007[b]	0.001[b]		
	t	3.025	4.140		

P<0.05: Statistically Significant Difference, Mean: Arithmetic Average, SD: Standard Deviation, BT: Before Treatment, AT: After Treatment, a: Independent Samples T Test, b: Paired Samples T Test, t: Test Value

Before treatment, there was no difference in pain threshold values between groups (1st point $P=0.265$, 2nd point $P=0.166$, 3rd point $P=0.178$, 4th point $P=0.184$, 5th point $P=0.272$, 6th point $P=0.559$). After treatment, at all points in both groups, a significant increase was observed in pain threshold, and MRT was superior to CTM at all points except point 1 (1st point $P=0.098$, 2nd point $P=0.034$, 3rd point $P=0.037$, 4th point $P=0.041$, 5th point $P=0.009$, 6th point $P=0.001$; Table 3).

Table 3: Comparison of groups' pain threshold values before and after treatment

			CTM (n=20) Mean (SD)	MRT (n=20) Mean (SD)	t/z	*P*-value
Pain threshold (lbs/cm^2)	Point 1	BT	2.47 (1.40)	2.95 (1.41)	z=-1.115	0.265[c]
		AT	4.75 (1.13)	6.29 (1.69)	z=-1.654	0.098[c]
		P	0.001[a]	0.001[a]		
		Z	z=-3.847	z=-3.925		
	Point 2	BT	2.39 (1.50)	2.93 (1.13)	z=-1.386	0.166[c]
		AT	4.84 (1.41)	6.58 (1.31)	z=-2.125	0.034[c]
		P	0.001[a]	0.001[a]		
		Z	z=-3.826	z=-3.922		
	Point 3	BT	1.81 (1.43)	2.43 (1.54)	z=-1.346	0.178[c]
		AT	4.30 (1.42)	6.00 (1.33)	z=-2.089	0.037[c]
		P	0.001[a]	0.001[a]		
		z	z=-3.935	z=-3.923		
	Point 4	BT	1.83 (1.42)	2.38 (1.31)	z=-1.328	0.184[c]
		AT	4.16 (1.04)	5.81 (1.29)	z=-2.046	0.041[c]
		P	0.001[a]	0.001[a]		
		z	z=-3.811	z=-3.826		
	Point 5	BT	2.00 (1.73)	2.53 (1.19)	t=-1.114	0.272[d]
		AT	4.40 (1.06)	6.33 (1.48)	t=-2.748	0.009[d]
		P	0.001[b]	0.001[b]		
		t	t=-6.490	t=-10.709		
	Point 6	BT	5.27 (2.73)	5.71 (1.87)	t=-0.590	0.559[d]
		AT	8.58 (2.82)	11.35 (2.53)	t=-3.906	0.001[d]
		P	0.001[b]	0.001[b]		
		t	t=-8.316	t=-12.700		

P<0.05: Statistically Significant Difference, Mean: Arithmetic Average, SD: Standard Deviation, BT: Before Treatment, AT: After Treatment, a: Wilcoxon Test, b: Paired Samples T Test, c: Mann Whitney U Test, d: Independent Samples T Test, t: Paired Samples T Test and Independent Samples T Test Value, z: Wilcoxon and Mann Whitney U Test Value

Discussion

The effectiveness of CTM and MRT treatments on pain, fatigue, pain threshold, and menstrual symptoms in PD were examined. It was found that CTM and MRT treatments decreased menstrual symptoms, menstrual pain, and fatigue and increased pain thresholds. When two treatment methods were compared, it was determined that MRT was superior at increasing pain thresholds.

CTM can create presynaptic and postsynaptic inhibition and close the "pain gate" by stimulating cutaneous–visceral reflexes through mechanoreceptors in skin and the autonomic nervous system as a result of stretching force [21]. Also, CMT provides an increase in endogenous opioid release [22], and CTM creates vasodilation as a result of local mechanical effect, and then increases parasympathetic activity [23]. Therefore, our

study shows that CTM is an effective method for pain relief in PD treatment.

Increased prostaglandin levels in PD lead to an increase in intrauterine pressure, which leads to a decrease in uterine blood flow and to ischemia. This ischemia also results in pain [24]. The increase in venous blood flow provided by MRT may lead to a reduction in pain by eliminating ischemia. In addition, some studies implied that activation of the sympathetic nervous system and cortisol levels decrease with MRT [25]. In our study, a decrease in abnormal sympathetic activity may be an explanation for reduced pain. In addition, pressure applied with MRT releases endorphins and other inhibitory neurotransmitter substances [26]. This may also be effective at reducing PD pain.

CTM has positive effects on fatigue, including effects such as general body relaxation, reduction of muscle spasm, increase of plasma β-endorphins, and vascularization [21]. In addition, the beneficial effects of touch and massage on different systems, especially sympathetic nervous system activity, hypothalamic–pituitary–adrenocortical activity, and stress hormones reducing effects play a role in the reduction of fatigue [27]. In our study, we believe that the reasons for the decrease found in fatigue with CTM are relaxation of body, increase in vascularization and β-endorphins, decrease in excessive sympathetic activity, and the presence/increase in stress hormones.

It is known that MRT increases energy and relieves physical tension [20]. No studies in the literature were found examining the effect of MRT on fatigue in women with PD; our study is the first such study.

Our study found a significant improvement in fatigue level of individuals with MRT, which we believe is due to positive effects of touch obtained with massage-like applications and with relaxation effect provided by MRT.

In a study with 88 dysmenorrhea patients, effects of thermotherapy and TENS were examined, revealing that pain threshold increased in application groups in abdominal region and increased in each group, including the placebo group, in the lumbar region [16]. Our study found a significant increase in pain threshold values after application at all points in both groups. The reasons for this increase may be decrease of individuals' pain perception, decrease in sensitivity of cutano-visceral regions according to gate-control theory, and decrease in sympathetic activity. In addition, when we compared groups after treatment, it was seen that MGT was more effective in increasing pain threshold at all points except point 1. The reason for this result may be that MGT can reduce sensitivity by relaxing fascia and contribute to increased myometrial blood flow. Our results support the literature and corroborate the idea that reducing pain leads to an increase in pain threshold by decreasing sensitivity.

Demirtürk et al. [10] applied reflexology and CTM to students with PD, and they found that menstrual symptoms decreased significantly with both approaches, but no difference was found between approaches. In a study examining short-term effects of CTM, Özgül et al. [19] found a significant improvement in menstrual symptoms of individuals compared to controls. In our study, although there was a significant improvement in menstrual symptom severity in both groups, no significant difference was found between groups. We think that positive effects of both approaches on menstrual symptoms are due to reasons such as decreased pain and sensitivity, decreased sympathetic activity, increased dopamine and serotonin release, and increased vascularization.

Limitations

Since there was no control group in our study, the potential for a placebo effect from the applications could not be eliminated. Because the pre- and post-treatment evaluations of individuals were made on the most painful day of their menstrual cycles, difficulties were encountered in reaching individuals on these days. Also, it was not possible for both applications to be blinded. Although the sample size was calculated with G power using the sample article, our statistical analyses would yield more accurate results if a larger sample size is used.

Conclusion

Both treatment approaches—CTM and MRT—can be used in clinics as an alternative to medication to reduce severity of pain and fatigue, increase pain threshold, and alleviate menstrual symptoms. Also, these two techniques can be used in combination. Studies examining prostaglandin levels and changes in hormones can be planned in order to better understand the mechanism of action of treatment approaches. Studies that compare the effectiveness of CTM and MRT with different approaches (e.g., spinal manipulation, classical massage, relaxation exercises, reflexology, TENS, acupressure, local heat application, phytotherapy, vitamin-mineral supplements, physical activity) can be conducted in individuals with PD. Our study evaluated the short-term effects of CTM and MRT. Future studies are encouraged to use longer-term treatment programs. Placebo-controlled studies can be conducted with larger samples, involving individuals of different age groups.

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Urogynecological symptoms of the retroverted gravid uterus in the first half of the pregnancy: A retrospective cohort study of an underestimated, underdiagnosed and underreported issue

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Ethics Committee Approval
The approval was taken from the Ethics Committee of Istanbul Professor Doctor Cemil Taşçıoğlu State Hospital (date: July 1, 2019, number: 48670771-514.10).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Urogynecological symptoms, including pelvic pain, lower backache, feeling of bearing down, frequency, nocturia, urgency, stress incontinence, and urge incontinence, are common during pregnancy. But little has been reported regarding possible changes in lower urogenital tract anatomy and its effects in pregnancy. Therefore, the subject of this study is whether the incidence of urogynecological symptoms is higher when the uterus is retroverted in pregnancy.

Methods: We enrolled 1432 pregnant women examined before the 20th week of pregnancy between January 2018 and March 2022. Patients were allocated into two groups according to whether the uterus was retroverted (n=226 (15.7%)) or anteverted (n=1206 (84.3%)). These two groups were compared regarding pelvic pain, lower backache, the feeling of bearing down, frequency, nocturia, urgency, stress incontinence, and urge incontinence.

Results: Retroverted gravid uterus was noted in 11.8% (n=41) of nulliparae and 17% (n=185) of multiparae (*P*=0.021), with an overall prevalence of 15.7%. Of 1432 patients, the overall prevalence for frequency, urgency, nocturia, urge incontinence, stress incontinence, lower backache, pelvic pain, and feeling of bearing down were 31%, 26.7%, 18.2%, 5.4%, 7.5%, 6.9%, 56.4% and 7.5%, respectively. Between both groups, there were differences in frequency, urgency, nocturia and lower back pain. There were two patients with incarcerated gravid uterus with urinary retention.

Conclusion: Patients with a retroverted uterus are more likely to experience the symptoms of lower back pain, frequency, nocturia, and urgency in the first half of pregnancy.

Keywords: retroverted uterus, pregnancy, lower back pain, lower urinary tract symptoms

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Introduction

The retroverted uterus has been reported as a normal variant, and its prevalence has been documented as 20% in the general population and up to 15% in pregnancies in the first trimester [1-3]. In most cases, retroversion spontaneously returns to a normal axial position by the 14th week of gestation when the gravid uterus grows into the abdominal cavity. Increased glomerular filtration rate, increased urinary output, and dilation of the upper urinary tract, which are the effects of pregnancy on renal function, have been well documented. On the other hand, relatively little has been reported regarding possible changes in lower genital tract anatomy and its effects during pregnancy. Cystoscopically, it was revealed that an enlarged gravid uterus could cause an indentation on the bladder dome that may affect lower urologic symptoms [4]. Urogynecological symptoms are common during pregnancy, including pelvic pain, lower backache, the feeling of bearing down, frequency, nocturia, urgency, stress incontinence, and urge incontinence.

During pregnancy, the genitourinary system undergoes anatomical and physiological alterations because of hormonal effects and the gravid uterus. The thought that a retroverted gravid uterus has an additional effect on urogynecological symptoms is reasonable sense. Therefore, the subject of this study is whether the incidence of urogynecological symptoms is higher when the uterus is retroverted in pregnancy.

Materials and methods

This trial was carried out in the Obstetrics and Gynecology Department of the University of Health Science, Istanbul Professor Doctor Cemil Taşçıoğlu State Hospital. We enrolled 1432 pregnant women that were examined before 20 weeks of gestational age between January 2016 and June 2019. Ethics Committee approval was taken from the same institution's Ethics Committee (date: July 1, 2019, number: 48670771-514.10). All procedures in this trial, including human participants, were conducted following the 1964 Helsinki Declaration and its later amendments.

Patient data were extracted from a computer system, and files were retrospectively evaluated. Maternal age, parity, gestational age, the complaints (pelvic pain, lower backache, feeling of bearing down, frequency, nocturia, urgency, stress incontinence, urge incontinence), and clinical and sonographic findings at presentation were noted. The exclusion criteria included urinary tract infection, leiomyoma, adnexal mass, congenital Mullerian anomaly, endometriosis, and urological and gastrointestinal diseases.

Patients were allocated into two groups according to whether the uterus was retroverted (n=226 (15.7%)) or anteverted (n=1206 (84.3%)). These two groups were compared in terms of mentioned findings above. Then, the retroverted group was divided into two subgroups: 12 weeks and below and above 12 weeks. These two subgroups were compared in terms of the symptoms of frequency, nocturia, urgency, and lower back pain.

Frequency is at least 7-day voids and one night-time void [5]. Nocturia is depicted as at least three night-time voids [6]. Urgency is defined as a sudden, compelling desire to pass urine which is difficult to defer [7].

Statistical analysis

All analysis was performed using SPSS software (Statistical Package for the Social Sciences, version 25.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate the eligibility of the data for normal distribution. While an independent t-test or Mann-Whitney U test was used for continuous variables, data with categorical variables were compared using the chi-square test. Descriptive statistics were used to calculate each variable's frequency, central tendency (mean, median), and dispersion (SD, maximum - minimum) when appropriate. In other words, if the variables follow the normal distribution, it was stated as mean (SD); if not, it was noted as median and minimum–maximum). A *P*-value <0.05 has been considered statistically significant.

Results

The retroverted gravid uterus was noted in 11.8% (n=41) of nulliparae and 17% (n=185) of multiparous (*P*=0.021), with an overall prevalence of 15.7%. Median values of gestational ages were the same in both groups; 12 (5–20). The proportions of subjects in gestational age groups were similar (*P*=0.647) (Table 1). The mean maternal age at diagnosis was 29.38 (6.48) and 29.37 (6.06) weeks in retroverted and anteverted groups, respectively (*P*=0.997). Median values of parity in retroverted and anteverted groups were 1 (0–4) and 1 (0–5), respectively (*P*=0.026). The median value of body mass indices was 23.4 (21.7-29.8) and 23.2 (22.5–26.8) in retroverted and anteverted groups, respectively, and there was no statistical significance between the groups (*P*=0.949).

Table 1: The proportions of subjects in gestational age groups.

Gestational age (weeks)	Retroverted group n (%)	Anteverted group n (%)	Total n (%)
5	8 (3.5)	32 (2.7)	40 (2.8)
6	8 (3.5)	34 (2.8)	42 (2.9)
7	7 (3.1)	42 (3.5)	49 (3.4)
8	16 (7.1)	90 (7.5)	106 (7.4)
9	20 (8.8)	114 (9.5)	134 (9.4)
10	16 (7.1)	80 (6.6)	96 (6.7)
11	26 (11.5)	118 (9.8)	144 (10.1)
12	27 (11.9)	145 (12)	172 (12)
13	33 (14.6)	188 (15.6)	221 (15.4)
14	20 (8.8)	119 (9.9)	139 (9.7)
15	12 (5.3)	73 (6.1)	85 (5,9)
16	13 (5.8)	78 (6.5)	91 (6.4)
17	5 (2.2)	23 (1.9)	28 (2)
18	6 (2.7)	28 (2.3)	34 (2.4)
19	4 (1.8)	22 (1.8)	26 (1.8)
20	5 (2.2)	20 (1.7)	25 (1.7)
Total	226	1206	1432

Of 1432 patients, the overall prevalence for frequency, urgency, nocturia, urge incontinence, stress incontinence, lower backache, pelvic girdle pain and feeling of bearing down were 31%, 26.7%, 18.2%, 5.4%, 7.5%, 6.9%, 56.4%, and 7.5%, respectively. Between both groups, there were differences in frequency, urgency, nocturia, and lower back pain (Table 2). Table 3 depicts the frequency, urgency, nocturia, and lower back pain in patients with retroverted gravid uterus under the gestational age of 12 weeks and above.

There were two patients with incarcerated gravid uterus with urinary retention, both of which were corrected by intervention. Both were *in vitro* fertilization pregnancies. One of them was a triplet pregnancy at the gestational age of 13. The

other subject was a 15-week twin pregnant. This gives an incidence of 1.4 in 1000 for incarcerated gravid uterus.

Table 2: Lower urinary tract symptoms in both groups.

		Retroverted group n=226 (15.7%) n (%)	Anteverted group n=1206 (84.3%) n(%)	*P*-value
Frequency	(-)	123 (54.4)	865 (71.7)	<0.001
	(+)	103 (45.6)	341 (28.3)	
Nocturia	(-)	170 (75.2)	1001 (83)	0.005
	(+)	56 (24.8)	205 (17)	
Urgency	(-)	145 (64.2)	905 (75)	0.001
	(+)	81 (35.8)	301 (25)	
Urge incontinence	(-)	213 (94.2)	1141 (94.6)	0.826
	(+)	13 (5.8)	65 (5.4)	
Stress incontinence	(-)	211 (93.4)	1113 (92.3)	0.575
	(+)	15 (6.6)	93 (7.7)	
UTI	(-)	206 (91.2)	1096 (90.9)	0.896
	(+)	20 (8.8)	110 (9.1)	
Lower back pain	(-)	199 (88.1)	1134 (94)	0.001
	(+)	27 (11.9)	72 (6)	
Pelvic girdle pain	(-)	94 (41.6)	530 (43.9)	0.512
	(+)	132 (58.4)	676 (56.1)	
Feeling of bearing down	(-)	203 (89.8)	1122 (93)	0.092
	(+)	23 (10.2)	84 (7)	

Table 3: Frequency, urgency, nocturia, and lower back pain in patients with retroverted gravid uterus under gestational age of 12 weeks and above.

		Gestational age of 12 weeks and below n=128 (56.6%) n(%)	Above gestational age of 12 weeks n=98 (43.4%) n(%)	*P*-value
Frequency	(-)	60 (46.8)	63 (64.3)	<0.001
	(+)	68 (53.2)	35 (35.7)	
Nocturia	(-)	84 (65.6)	86 (87.7)	0.552
	(+)	44 (34.4)	12 (12.3)	
Urgency	(-)	80 (62.5)	65 (66.3)	0.001
	(+)	48 (37.5)	33 (33.7)	
Lower back pain	(-)	106 (82.8)	93 (94.9)	0.006
	(+)	22 (17.2)	5 (5.1)	

Discussion

Uterine retroversion is considered a normal variant. In our study, 226 subjects with a retroverted gravid uterus were seen out of 1432 pregnant women, submitting a total prevalence of 15.7%. This is consistent with other studies which have indicated a prevalence of up to 15% [1-3].

Lower backache/pelvic pain is a common symptom during pregnancy. It has been documented that between 20% to 90% of pregnant women have some type of pregnancy-related lumbopelvic pain [8-11]. Moreover, pregnant women often express that lumbopelvic pain affects their daily activities [12]. On the other hand, this pain can be underestimated and dismissed by healthcare providers considering the pain during pregnancy is a transient, self-limiting condition and is not an important health risk to the fetus and mother [12-13]. At 12 to 18 weeks gestation, the prevalence of low back pain/pelvic pain during pregnancy was reported as 62%, with 33% experiencing pelvic girdle pain, 11% having lower back pain, and 18% expressing both [14]. In our study, the overall prevalence of lower back and pelvic girdle pain were 6.5% (n=99) and 56.4% (n=808), respectively. Regarding lower back pain, patients in the retroverted group had a higher prevalence (11.9%) in our study.

The feeling of bearing down is one of the commonest complaints of patients with a retroverted uterus. Crichton [15] reported in his study that 56.4% of the subjects (n=808) had feelings of bearing down. In our study, 23 cases (10.2%) in the retroverted group had the complaint, and this number in the anteverted group was 84 (7%). Although it looks higher in the retroverted group, it has not reached statistical significance.

Frequency and nocturia are the commonest lower urinary tract symptoms in pregnancy [16]. Non-pregnant women void 4–6 times a day and none or once at night. Van Brummen et al. [17] revealed that the prevalence of frequency at the 12th week of pregnancy was 74%. Francis [5] reported the prevalence of frequency for early, mid, and late pregnancies as 59%, 61%, and 81%, respectively. Parboosingh and Doig [6] reported that 66% of pregnant women had nocturia by the third trimester. Our study's overall prevalences of frequency and nocturia were 31% and 18.2%, respectively. When we evaluated the groups separately, these values were 45.6% and 24.8% in the retroverted group and 28.3% and 17% in the anteverted group, respectively. Patients in the retroverted group were more likely to encounter frequency and nocturia. Besides, within the retroverted group, subjects under 12 weeks of pregnancy had a prevalence of 53.2% and 34.4% for frequency and nocturia, respectively, whereas these values were 35.7% and 12.3% in patients above 12 weeks. We believe this disparity was caused because most of the retroversion corrects itself and goes out from the hollow of the sacrum circa 12 weeks of pregnancy.

Urgency and urge incontinence prevalence increases during pregnancy. Cutner et al. [18] reported that 62% of patients had urgency, and 18% experienced urge incontinence throughout the pregnancy. Chen et al. [19] reported that the prevalence of urge incontinence for early, middle, and late pregnancy was 31.5%, 42.9%, and 48.8%, respectively. Chaliha et al. [20] demonstrated that 22.9% of patients had urgency, and 8% experienced urge incontinence during pregnancy. Daly et al. [21] revealed that the prevalence of urge incontinence during pregnancy was 4%. The urgency and urge incontinence etiology was explained by detrusor instability and low compliance [18-22]. In our study, the overall prevalence of urgency and urge incontinence were 26.7% and 5.4%, respectively. In the retroverted group prevalence of urgency and urge, incontinence was 35.8% and 5.8%, respectively. In the anteverted group, 25% of patients had urgency, and 5.4% of subjects had urge incontinence. Prevalences of both groups for urge incontinence were similar, but patients in the retroverted group were more likely to encounter urgency. Within the retroverted group, subjects under 12 weeks of pregnancy had a prevalence of 37.5% for urgency, whereas this value was 33.7% in patients above 12 weeks. The disparity can be explained by spontaneous correction of retroversion circa 12 weeks of pregnancy.

During pregnancy, stress incontinence has been reported in up to 84% of women [23-26]. Francis [5] revealed that 16% of women had stress incontinence in the first half of the pregnancy. Stanton et al. [27] concluded that 36% of subjects experienced stress incontinence at 32 weeks of gestation. Huebner et al. [26] reported the prevalence of stress incontinence in the first half of the pregnancy as 3.6%. In our study, the overall prevalence of stress incontinence was 7.5%, and there was no difference between the groups.

We observed two patients having incarcerated retroverted gravid uterus with acute urinary retention submitting a prevalence of 1.4 in 1000 pregnancies. Incarceration of the retroverted gravid uterus is a rare condition seen mainly in the second trimester. Patients with difficulties in micturition or acute urinary retention can be associated with symptoms [28]. Generally, spontaneous correction of the retroversion occurs between 12 and 16 weeks, but in 1.4% of subjects, this fails, and

the uterus is trapped in the hollow of the sacrum [29]. The cervix is displaced anteriorly when the retroverted uterus becomes incarcerated in the pelvic cavity. As a result, complete urethral obstruction might be seen with acute urinary retention [29]. The condition's prevalence has been reported as 1 in 3000 pregnancies [30]. Our study's higher prevalence of incarcerated gravid uterus may be because multiple pregnancies *after in vitro* fertilization procedures have risen in the last decades. Both cases were conceived by *in vitro* fertilization and had multiple pregnancies. Symptoms of frequency, nocturia, and urgency were present in both patients before the urinary retention occurred. We believe that most of the cases are not reported in the literature.

Limitations

The first limitation of our article is the study design since it is retrospective. Second, diagnoses of stress incontinence and urge incontinence were solely based on the signs and symptoms, not confirmed by urodynamics.

Conclusion

In conclusion, patients with a retroverted uterus are more likely to experience the symptoms of lower back pain, frequency, nocturia, and urgency in the first half of pregnancy. Especially if they persist after the twelfth week of pregnancy, one should confirm the uterine position with physical and imaging examinations for early diagnosis of uterine incarceration. We believe uterine position and related symptoms during pregnancy are underestimated, underdiagnosed and underreported. We suggest that pregnant women having a retroverted uterus in the first trimester of pregnancy should have repeat pelvic examinations in the second trimester. We also recommend physicians give special attention to lower urinary tract symptoms in pregnancy and examine the uterine position.

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Comparison of selenium levels between diabetic patients with and without retinopathy

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Ethics Committee Approval
The study was approved by Health Sciences University, Samsun Research and Training Hospital Ethical Committee, date: 21.03.2017 number: 2017-5-37.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Diabetic retinopathy is a common ailment that causes visual impairment among adults, and evidence suggests that oxidative stress plays a significant role in its pathogenesis. The objective of this study was to examine the potential association between selenium deficiency and an increased risk of diabetic retinopathy among individuals with type 2 diabetes mellitus.

Methods: This study was a prospective case-control study. 115 patients with a diagnosis of type 2 diabetes mellitus were included. The patients were divided into groups with and without retinopathy. No subgroups were made according to the level of retinopathy. The aim was to compare the serum selenium level of patients between groups. Therefore, other variables that may contribute to the development of retinopathy were also recorded. The duration of diabetes, medications used, and glycosylated hemoglobin levels were recorded. The retinopathy group included 47 patients, and the non-retinopathy group included 68 patients. Selenium levels were measured in plasma samples.

Results: The mean selenium level of the retinopathy group (70.11 [17.28] µg/l) was significantly lower than that of the non-retinopathy group (80.20 [19.10] µg/l) (P=0.005). The median duration of diabetes mellitus was significantly higher in the retinopathy group than in the non-retinopathy group (10 [1-25] and 6 [1-21], respectively; P=0.002). Logistic regression analyses showed that higher levels of blood selenium were independent preventive factors against the occurrence of retinopathy (OR [95% CI]: 0.965 [0.939-0. 991]). The duration of diabetes mellitus was an independent risk factor for retinopathy occurrence (OR [95% CI]: 1.131 [1.050-1.219]). One unit increase in selenium level was associated with a unit decrease in diabetic retinopathy of 0.965 (0.939-0.991).

Conclusion: Our research revealed a correlation between the duration of diabetes and the incidence of diabetic retinopathy. Furthermore, a notable difference was observed in blood selenium levels between patients with diabetic retinopathy and those without it. Specifically, patients with diabetic retinopathy had lower plasma selenium levels compared to the control group. These findings have potential implications for the treatment or prevention of diabetic retinopathy, but more research is needed to determine the efficacy of selenium supplementation for diabetic patients with or without microvascular complications. Future studies should investigate the effect of selenium deficiency on different subtypes of diabetic retinopathy and the impact of selenium supplementation in this patient population.

Keywords: diabetes mellitus, diabetic retinopathy, free radicals, microvascular complication, oxidative stress, selenium

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Introduction

Diabetes mellitus (DM) is a significant public health issue affecting over 460 million people globally [1]. The worldwide prevalence of both the disease and its complications is steadily increasing. Diabetic retinopathy, a common microvascular complication of DM, is an important cause of visual loss among adults [2]. The level of hyperglycemia and the duration of DM are major determining factors for the development of this microvascular complication [3]. The Diabetes Control and Complications Trial showed that normalization of hyperglycemia in patients with type 1 DM is related to a 76% risk reduction for the occurrence of diabetic retinopathy and a 54% risk reduction for its progression [3]. Other factors that increase the risk of diabetic retinopathy are being studied to prevent morbidity.

Research has shown that increased levels of reactive oxygen species in the vitreous fluid are correlated with the progression of diabetic retinopathy [4]. Hyperglycemia leads to the accumulation of advanced glycation end products in various tissues, which plays a crucial role in the development of microvascular complications in DM [5]. The mechanism behind diabetic retinopathy is well understood, and it is recognized that multiple factors contribute to its development. Some of these factors are related to hyperglycemia, while others are not directly connected to it [6]. The accumulation of free radicals in the retina along with oxidative stress results in thickening of the basal membrane, endothelial pericyte loss, leukocyte adhesion, DNA damage, retinal inflammation, and an increase in vascular permeability [7-9].

Selenium is a component of the enzyme glutathione peroxidase (GPx), which catalyzes the reduction of hydrogen and organic peroxides to alcohol and water. Selenomethionine is the depot form of selenium and cannot be synthesized in vivo, so it must be taken either in food or as a supplement. Selenium has an important role in cleaning reactive oxygen species by decreasing lipid peroxidation. For this reason, selenium supplementation is thought to be a preventive factor for some complications of DM [10].

Although this mechanism is important for the progression of diabetic retinopathy, there is still doubt about whether antioxidant nutrients improve diabetic retinopathy. On the other hand, the relationship between trace element deficiency and diabetic retinopathy is among the topics that have been frequently studied recently. Therefore, we measured selenium levels in vivo and interpreted the results. The aim of this study was to investigate whether selenium deficiency is related to an elevated risk of diabetic retinopathy among patients with type 2 DM.

Materials and methods

This study was a prospective case-control study. The patients were selected from patients who were treated at Samsun Research and Training Hospital Internal Medicine outpatient clinics between November 2019 and November 2020. Patients who are older than 18 years old with a diagnosis of type 2 DM were included. Although the patients were already being treated with antidiabetic medications, the diagnosis was retrospectively confirmed according to the recent algorithms of the American Diabetes Association for each patient [11]. Power analysis was done according to 80% power and a 95% confidence interval, and the minimum patient number that must be included in each group was calculated as 46 for detecting a true difference in means [12].

Patients were excluded from the study if they were younger than 18 years of age, pregnant or lactating, being treated with glucocorticoids or selenium supplements, or immunocompromised. Furthermore, patients were also excluded if they were taking drugs that could interfere with selenium levels. Age, sex, and the duration of DM were noted. The duration of diabetes was calculated based on the records in the insurance system and by asking the patients. All patients were examined by the same ophthalmologist to determine whether diabetic retinopathy was found or not.

Fundus photographs were taken for each patient to confirm the diagnosis. Best-corrected visual acuities were obtained, and dilated fundus examinations were performed for each patient after applying cyclopentolate drops. Diabetic retinopathy was diagnosed according to the Early Treatment Diabetic Retinopathy Study [13].

The study group included a total of 115 patients comprising 47 patients with type 2 DM and diabetic retinopathy (retinopathy group), and the control group included 68 patients with type 2 DM without retinopathy (non-retinopathy group). Plasma samples were collected from the patients, and serum selenium levels, fasting plasma glucose levels, and glycosylated hemoglobin (HbA1c) levels were measured. HbA1c levels were measured using the high-performance lipid chromatography technique with a Trinity Biotech Premier Hb9210 device. Fasting plasma glucose levels were measured by the hexokinase method, which was adapted to automatized devices. Reduced nicotinamide adenine dinucleotide phosphate is proportional to the glucose levels and measured by absorbance differences at 340 nm.

Selenium levels were measured in plasma using the inductively coupled plasma – mass spectrometer method. This method has the following stages: the sample is heated to 10000K by electromagnetic induction and ionized by argon plasma. Ionized elements are separated by a mass spectrometer, and finally, levels of elements are measured using a detector. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was approved by Health Sciences University, Samsun Research and Training Hospital ethics committee with protocol number 2017-5-37.

Statistical analysis

A statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) Version 20.0. Continuous variables that were normally distributed were represented as the mean (standard deviation [SD]), while non-normally distributed continuous variables were represented as the median (min-max). Categorical variables were expressed as numbers and percentages (%). The student's t-test and Mann-Whitney U test were used for comparisons of continuous variables, while the chi-squared test was used for comparisons of categorical variables. Logistic regression analysis was utilized to

evaluate independent risk factors. A *P*-value of less than 0.05 was considered statistically significant.

Results

The study included a total of 115 patients comprising 62 (53.9%) females and 53 (46.1%) males. There were 47 patients in the study group (those with retinopathy) and 68 patients in the control group (those without retinopathy). The group with retinopathy had 26 female and 21 male patients, while the other group had 36 female and 32 male patients. The mean age in the retinopathy group was higher (Table 1). However, this difference was not statistically significant. Similarly, no statistically significant difference was found between the groups in terms of gender distribution.

Table 1: Demographic properties and selenium levels of two groups

	Non-retinopathy (n=68)	Retinopathy (n=47)	*P*-value
Age, mean (SD), years	53.2 (9)	56.5 (10)	0.070
Female sex, n(%)	36 (52.9)	26 (55.3)	0.801
Fasting plasma glucose, mean (SD), mg/dl	192 (90)	214 (97)	0.218
HbA1c, mean (SD)	8.1 (2.3)	8.9 (2.3)	0.087
Duration of DM, median (min-max), years	6 (1-21)	10 (1-25)	0.002
Selenium, mean (SD), µg/l	80.2 (19.1)	70.1 (17.3)	0.005

HbA1c: glycosylated hemoglobin, SD: standard deviation

The mean levels of fasting plasma glucose of the study group and the control group were 214 (97) mg/dl and 192 (90) mg/dl respectively. The mean levels of HbA1c were 8.9% (2.3) for the retinopathy group and 8.1% (2.3) for the non-retinopathy group. The mean fasting plasma glucose level and mean HbA1c level were higher in the retinopathy group compared to the non-retinopathy group. However, these differences were not significant statistically (*P*=0.218 and *P*=0.087, respectively).

The median duration of DM was significantly higher in the retinopathy group compared to the non-retinopathy group (Table 1). The mean selenium level was significantly lower in the retinopathy group (70.1 [17.3] µg/l) compared to the non-retinopathy group (80.2 [19.1] µg/l) (*P*=0.005). When age, gender, HbA1c levels, selenium levels, and the duration of DM were used as independent variables in the logistic regression analysis, a higher blood selenium level was an independent preventive factor against the occurrence of retinopathy (OR [95% CI]: 0.965 [0.939-0. 991]) while the duration of DM was an independent risk factor for retinopathy occurrence (OR [95% CI]: 1.131 [1.050-1.219]).

Discussion

Diabetic retinopathy is one of the major causes of visual disturbance among adults worldwide and the leading cause of visual loss in developed countries [14]. Screening diabetic patients for this complication has resulted in improvement in the quality of vision in this population, but unfortunately, the prevalence of diabetic retinopathy is still higher than 40%. Globally, 93 million people have diabetic retinopathy [15].

The pathogenesis of diabetic retinopathy associated with hyperglycemia includes oxidative stress, polyol activity, and the hexosamine pathway [6]. It has been demonstrated that diabetic patients are more susceptible to oxidative stress due to impaired defense mechanisms [16]. Recent research has indicated that oxidative stress is linked to retinopathy in both diabetic patients and non-diabetic individuals [17]. There have been numerous studies exploring the use of dietary antioxidant supplements for the prevention or treatment of diabetic retinopathy. One study found that oxidative stress in DM results in retinal activation of caspase-3 and apoptosis of endothelial cells and pericytes. An antioxidant supplement mixture was used and showed potential for improving patient management [18].

Kähler et al. [19] investigated antioxidant treatments in diabetic microvascular complications and reported that selenium and D-alpha-tocopherol supplementation improves neuropathic symptoms. In another trial, Gonzalez de Vega et al. [20] showed that selenium supplementation improves GPx activity even in hyperglycemic conditions. This study was an in vitro analysis of oxidative pathways and antioxidative supplements [20]. In one of the oldest studies on the subject, selenium levels were measured in pediatric diabetic children and were significantly higher in the diabetic group. However, the relationship of this condition with microvascular complications was not mentioned because none of the children in that study had diabetic complications [21].

In our study, the fasting plasma glucose levels of the study group were higher than that of the control group, but this result did not reach statistical significance. This condition may be related to the small sample size. But there was a significant difference between the two groups according to the duration of DM. Longer duration of diabetes was related to an increased risk of diabetic retinopathy (OR [95% CI]: 1.131 [1.050-1.219]). This is compatible with the results of similar studies on risk factors of diabetic retinopathy [3].

The comparison of two groups according to selenium levels showed that plasma selenium levels were lower in patients who had diabetic retinopathy. Regression analysis showed that elevated plasma selenium levels were an independent preventive factor against the occurrence of retinopathy (OR [95% CI]: 0.965 [0.939-0.991]), while a longer duration of DM was an independent risk factor for the occurrence of retinopathy. Selenium levels of aging populations may decrease because of low intake [22]. This is compatible with our results, which show that the retinopathy group had a higher mean age and lower selenium level.

One study from China that included 135 patients investigated the role of serum trace elements and heavy metal levels in diabetic retinopathy [23]. The study found that the serum concentrations of manganese (Mn) and zinc (Zn) were significantly lower in the diabetic retinopathy group, while cadmium (Cd) and cesium (Cs) levels were higher [23]. However, only selenium levels were measured in the study and not other trace elements.

Some other studies have explored the effect of other factors such as protein and lipoprotein glycosylation and their impact on diabetic retinopathy severity. Research has shown that both glycation and oxidative processes play a role in the development of diabetic retinopathy, and changes in the concentrations of Cd, Se, chromium (Cr), Zn, and copper (Cu) can affect the progression of the disease [24]. An animal study conducted in 2015 investigated the effect of chromium supplementation on diabetic retinopathy and found that chromium histidinate (CrHis) supplementation had beneficial effects on the retinas of diabetic rats [25]. Another study found that chromium levels had a predictive value for the occurrence of

diabetic retinopathy at 15.2 μg/L (sensitivity: 70%; specificity: 60.5%) [26].

All these studies measured the levels of trace elements or metals in a cross-sectional timeline, so the results may be affected by the nutrition status of the participants. For example, in our study, all of the participants were living in the same region in the central Black Sea region of Turkey and had similar dietary habits. All participants were offered a Mediterranean-type diet containing balanced macronutrients for weight and age. Fish, grains, eggs, and beans are foods that include high selenium levels and are easily accessible foods in this region. In a study from Black Sea region, the average of selenium level in honeybee pollen was 0.422-0.722 mg kg^{-1} dry pollen. Measurement of trace element levels in regional honeybee pollen is one way to show food sources specific to the regions in which they are collected [27]. In another recent study, selenium levels in fish were enough for daily intake in the Black Sea region (Samsun, Trabzon, and Sinop) and selenium/mercury levels were within permissible limits according to the WHO [28].

Some researchers have studied the effect of trace elements in diabetes control but did not study their effect on microvascular complications. For example, Sonkar et al. [29] showed that the mean levels of zinc, copper, selenium, and magnesium were significantly lower in patients with T2DM than the control cases. Another study from China demonstrated that a higher dietary intake of vitamin E and selenium seems to have a preventive effect on diabetic retinopathy [30].

The OR of our study was compatible with another study. We found that one unit increase in selenium level was associated with a unit decrease in diabetic retinopathy of 0.965 (0.939-0.991). The other study showed that one unit increase in selenium level was associated with a unit decrease in diabetic retinopathy of 0.98 (0.96, 1.00) [31].

Our findings may improve choices to prevent diabetic retinopathy. Preventive efforts are important along with intravitreous treatment options in the management of diabetic retinopathy. Good glycemic control and high blood pressure control are the cornerstones of prevention of diabetic retinopathy [31]. Besides controlling hyperglycemia and high blood pressure, we can measure blood selenium levels of patients with diabetic retinopathy and provide supplements if deficient. A recent animal study showed that sodium selenite can increase insulin secretion levels in pancreatic β cells of type 1 DM mice and improve diabetic retinopathy [32]. A recent review on the subject summarized that insufficient zinc as well as excessive copper levels are associated with increased oxidative stress levels, which can worsen microvascular lesions in DM. These abnormalities are correlated with the duration of diabetes and higher levels of HbA1C, as in our study [33].

Limitations

The main limitation of this study is that since the main setup of the study was to compare patients with and without retinopathy, and they were not divided into subgroups. The study was also conducted during the COVID-19 pandemic, so we could not reach as many patients. We suggest that future studies be done to analyze the effect of selenium deficiency on diabetic retinopathy by separating the patients according to retinopathy types. The sample size was not enough to apply these results to all the diabetic patients. We think that new studies with larger sample sizes could be more definitive to identify the relationship between the occurrence of diabetic retinopathy and selenium deficiency.

Selenium deficiency is associated with thyroid diseases, thyroid nodules, cancer, weakened immune function, and pregnancy, which could have been significant confounders to our study. For this reason malignancy, pregnancy, and immunosuppression were exclusion criteria in our study. Furthermore, patients who were taking drugs that could interfere with selenium levels were excluded. But we could not analyze whether the patients had thyroid disease or nodules. However, people receiving thyroid hormone replacement were not included in the study from the beginning as it could have been a confounding factor. Therefore, we think that excluding patients receiving thyroid-related treatment minimizes the effect of this factor.

Conclusion

In our study, a significant difference was found between patients with diabetic retinopathy and the non-retinopathy group in terms of blood selenium levels. These findings may be important for treatment or the prevention of diabetic retinopathy. Nevertheless, we still need more evidence for selenium supplementation for diabetic patients with or without microvascular complications. Future studies are needed to investigate the effect of selenium supplementation in this patient group.

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Top 50 cited articles on cardiac rehabilitation: A bibliometric and altmetric analysis study

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Ethics committee approval was not required as the data used in this study were obtained from published articles.
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Abstract

Background/Aim: Cardiovascular disease (CVD) is the leading cause of death globally, with an estimated 18.6 million deaths each year. Cardiac rehabilitation (CR) has positive effects on reducing the mortality and morbidity of CVD, so there is a growing interest in this field. The aim of this study was to analyze the top 50 cited articles in the field of CR.

Methods: The Web of Science (WoS) database was searched for articles published between 1986 and 2021. A record was made of the following information for the bibliometric analysis: article title, year of publication, number of authors and their names, number of citations, citation index, journal of publication, impact factor, type of article, and source of funding. The altmetric attention score (AAS) was recorded using automatic software calculation.

Results: The majority of articles were published in the journal "Circulation" (n=14) and the "Journal of the American College of Cardiology" (n=8). The country with the highest number of articles was the US (n=27), and the most cited author was P.A. Ades. Studies evaluating exercise-based rehabilitation, key components of CR, and secondary prevention were among the top cited articles. In terms of AAS, in addition to the titles mentioned, mobile health services that rely on communication technologies have also received attention.

Conclusion: This study provides useful information for researchers interested in CR, including trends, topics of interest in the field, and potential research collaborations. It is intended to guide future, more comprehensive, and in-depth studies on CR.

Keywords: cardiac rehabilitation, bibliometric analyses, altmetric analyses, citation

Introduction

Cardiovascular diseases (CVDs) remain a major cause of mortality and morbidity globally. In 2019, over 18.6 million people died from CVD, representing a 17.1% increase from the previous decade [1]. There were also more than 523.2 million cases of CVD in 2019, a 26.6% increase compared to 2010. Experts predict that the global burden of CVD will continue to grow in the coming years due to the long-term effects of the COVID-19 pandemic [2]. According to the National Burden of Disease Study, 8% of the total burden of disease in 2004 was due to CVD, and CVD was the leading cause of morbidity among adults in Turkey [3]. Ischemic heart disease in particular has been the leading cause of the increasing global burden of disease in the past 30 years. Therefore, preventing the occurrence and recurrence of CVD should be a top priority in reducing the burden on public health systems worldwide.

Cardiac rehabilitation (CR) has been shown to improve cardiopulmonary function, reduce cardiovascular risk and mortality, decrease relapses and hospitalizations, and improve quality of life [4-12]. Hence, the steady increase of scientific evidence showing the positive effect of CR on the mortality and morbidity of CVD has attracted the attention of many clinicians in recent years. However, the availability and capacity of CR programs varies greatly by region and country, and many patients do not have access to the benefits of participation [13].

Another study investigating the availability and distribution of CR in Europe found that 90.9% of European countries had a CR program. However, only one spot is available for every seven patients in need, although this density is quite good compared with other regions of the globe [14]. In Turkey, it is estimated that the economic burden of CVD, including direct healthcare costs and indirect costs from loss of productivity, will double to $19.4 billion by 2035 [15].

Bibliometric analysis is a statistical method that can be used to identify trends and changes within a research field, to profile publications on a subject, and to improve the quality of science through a systematic and reproducible review process [16,17]. Bibliometric analysis is a quantitative research technique based on bibliographic data that provides information about the general perspective of a research field based on articles, authors, and journals [18]. In the bibliometric analysis method, a wide variety of analysis techniques, including citation-based and performance-based analysis, are used to classify publications according to countries, universities, research groups, or authors [19]. In recent years, bibliometric analysis has been used to analyze various diseases in different branches of medicine.

When searching for the most valuable articles on a specific topic, researchers usually consider criteria such as the journal of publication, current impact factor, h-index, and number of citations. However, with the widespread use of the internet and social media platforms in recent years, platforms such as Facebook, Linkedin, Twitter, and blogs have become important tools that contribute to the promotion of medical literature [20-22]. Altmetric analysis is used to gather quantitative data and determine the metrics of a particular article on these platforms. In this study, we analyzed the 50 most cited (T50) articles on CR between 1985 and 2021 using these techniques and evaluated the relationship between the total number of citations/citation index and AAS. The aim was to contribute to the development of new study goals and methodologies by providing data on current issues in the field of CR, the most interesting research areas, and any deficiencies.

Materials and methods

The Clarivate Analytics Web of Science (WoS) database (Philadelphia, USA) was used to identify the top 50 articles related to CR. The database was searched using the keywords "Cardiac Rehabilitation" to identify articles published between 1985 and 2021 in English as of December 31, 2021. The articles were then ranked according to the number of citations from highest to lowest using the "Number of citations" option. Ethics committee approval was not needed for this study as the data analyzed were taken from published articles.

The top 50 articles were identified through a search of the WOS database by two reviewers, who searched abstracts and full texts according to the study type and subject. Only original articles and reviews were included as publication types, while letters to the editor, editorial material, corrections, and other types of publications were excluded. Only articles with CR as the main focus were included, whereas articles with a core topic other than CR were also excluded, even if they included information on CR. In cases where the two reviewers had differing opinions, a third reviewer was consulted to reach a consensus. During the bibliometric analysis, the information recorded included the citation index, title of the article, number of authors, names of authors (first authors and corresponding authors), country, publication year, number of citations, type, subject, and funding sources, Q classification of the publication, h-index, and impact factor. If the authors of the article came from multiple countries, the corresponding author's country was considered as the country of origin for the article.

The AAS was used to determine the impact of an article by taking into account the number of citations and the level of engagement on internet-based social platforms, including views and downloads. The "Altmetric it" function on the website https://www.altmetric.com was used to calculate the AAS. The AAS is calculated based on three primary factors: volume, sources, and authors. The number of citations an article receives from different authors is directly related to the AAS.

More references to an article result in a higher submetric attention score. Different citation sources, such as Facebook, blogs, Twitter, and LinkedIn, have varying levels of influence on the score. The characteristics of the authors citing the article also factor into the calculation of the AAS. More information about how the AAS is calculated can be found on the Altmetric website (https://www.altmetric.com).

Statistical analysis

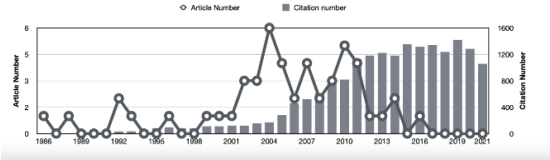
All statistical analyses were conducted using the software IBM SPSS Statistics v. 21.0. The Shapiro-Wilk test was used to determine the distribution of variables. Descriptive statistics were expressed in the form of mean (standard deviation [SD]) for quantitative variables and in the form of "frequency and percentage (n [%])" for categorical variables. Spearman's rank correlation analysis was used to evaluate correlations

between non-normally distributed variables. Relationships were considered highly correlated when the correlation coefficient (r) was ≥0.60, moderately correlated when r was between 0.30 and 0.59, and weakly correlated when r was ≤0.29. A *P*-value of <0.05 was considered statistically significant.

Results

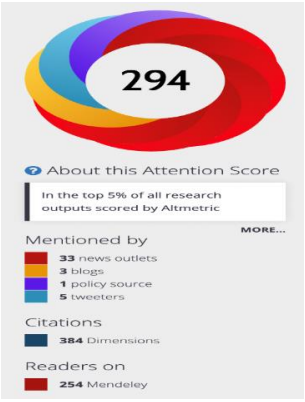
The search yielded 16,971 articles on CR published between 1986 and 2021 in the WoS database. Table 1 shows the top 20 most cited articles from the top 50 articles obtained (#1 and #100 in the supplemental material). The top 50 articles had citation counts ranging from 169 to 1509 with an average of 390.82 (638.36) and a median value of 258.5. The number of articles and citations of the top 50 articles between 1985 and 2021 is shown in Figure 1.

Figure 1: The number of articles and citations of the top 50 articles between 1985 and 2021



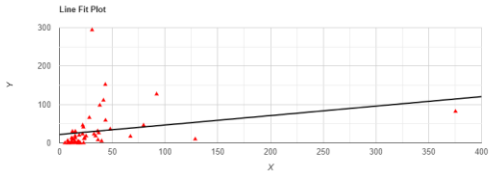
The AAS ranged from 1 to 294. The AAS could not be determined for 12 articles. The average AAS was 22.1 (47.7) with a median value of 8. The most cited article in the top 50 was "Exercise-based rehabilitation for patients with coronary heart disease (CHD): Systematic review and meta-analysis of randomized controlled trials" (#1), which was published by Taylor et al. in 2004. "Exercise-based cardiac rehabilitation for CHD" (#2), another study published by Taylor et al. in 2011, ranked first in the citation index score, although it ranked second in the total number of citations. The study with the highest AAS was "Referral, Enrollment, and Delivery of Cardiac Rehabilitation/Secondary Prevention Programs at Clinical Centers and Beyond: A Presidential Advisory From the American Heart Association" (#15), which was by Balady et al. and published in 2011 (Figure 2).

Figure 2: Altmetric donut of the study entitled "Referral, Enrollment, and Delivery of Cardiac Rehabilitation/Secondary Prevention Programs at Clinical Centers and Beyond A Presidential Advisory From the American Heart Association"



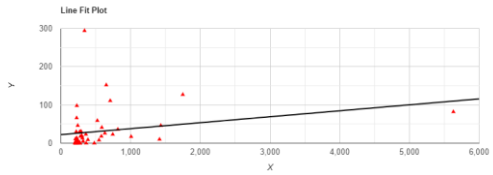
When examining the articles in the top 50 list, it was determined that the most cited were studies examining the three basic components of CR: education, exercise training, psychological support, and secondary prevention [23-25]. The AAS values for the most prominent topics related to CR were highest for referral systems, enrollment and utilization, smartphone-based home care models, and the basic components of CR [26,27]. Exercise-based rehabilitation (n=15), secondary prevention (n=14), and participation and referral to CR (n=7) were the most frequently analyzed topics in the top 50 articles. A significant correlation was found between the citation index and the AAS (P<0.05, r=0.259) (Figure 3). Similarly, a significant correlation was observed between the total number of citations and the AAS (P<0.05, r=0.245) (Figure 4).

Figure 3: Correlation Graphic of Citation Index and The Altmetric Attention Score



Results of the Pearson correlation indicated that there is a non-significant small positive relationship between X and Y, (r(48)=0.259, P=0.069).r=0.2594

Figure 4: Correlation graphic of total number of citations and the altmetric attention score



Results of the Pearson correlation indicated that there is a non-significant small positive relationship between X and Y, (r(48)=0.245, P=0.086).r=0.2454

The most cited articles on CR were mainly published in 2004 (n=6) and 2010 (n=5) (Figure 1). No articles published after 2016 were included in the top 50 list. The top 50 articles were published in 18 journals, with two or more articles published in 10 journals (Table 2). Most of the articles were published in the journal “Circulation” (n=14), the “Journal of the American College of Cardiology” (n=8), and “the European Heart Journal” (n=4) (Table 3).

The countries that contributed the most to T50 articles were the USA (n=27), the United Kingdom (n=8), and Italy (n=8). The number of authors of T50 articles ranged from 1 to 24. The majority of the articles (n=35) had 5 or more authors. P.A. Ades and N. Oldridge were the most frequent authors. Oldridge was also the most highly cited author with a total of 4407 citations. Furthermore, he was the first and corresponding author in one article and contributed to six articles in total.

Table 2: Journals of the T100 articles (n≥2)

Journal	Number of articles
Circulation	14
Journal of The American College of Cardiology	8
European Heart Journal	4
European Journal of Preventive Cardiology	3
Heart	3
American Journal of Medicine	2
European Journal of Cardiovascular Prevention & Rehabilitation	2
JAMA-Journal of The American Medical Association	2
Archives of Internal Medicine	2
Cochrane Database of Systematic Reviews	2

Table 3: Journals with T50 articles, ranked according to times cited

Journal name	Number of articles	IF	H - Index	Q Classification
Circulation	14	6.16	607	Q1
Journal Of The American College Of Cardiology	8	4.75	431	Q1
European Heart Journal	4	5.87	293	Q1
European Journal of Preventive Cardiology	3	1.49	101	Q1
Heart	3	1.33	183	Q1
American Journal of Medicine	2	1.37	229	Q1
European Journal of Cardiovascular Prevention & Rehabilitation	2	1.49	101	Q1
JAMA-Journal of The American Medical Association	2	11.48	680	Q1
Archives of Internal Medicine	2	5.21	342	Q1
Cochrane Database of Systematic Reviews	2	1.31	273	Q1
BMJ-British Medical Journal	1	6.27	429	Q1
British Journal of Health Psychology	1	0.97	88	Q1
Journal of Psychosomatic Research	1	0.80	156	Q1
New England Journal of Medicine	1	26.14	1030	Q1
Stroke	1	1.81	319	Q1
Clinical Rehabilitation	1	1.39	110	Q1
Mayo Clinic Proceedings	1	2.16	179	Q1
American Heart Journal	1	1.11	187	Q1

*IF: Impact factor, Q Classification: Quarter classification of Journal

Table 1: Top 20 cited articles

Title	Authors	Source Title	PY	TC	CI	AS	AT
1-Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and meta-analysis of randomized controlled trials	Ref#25	American Journal of Medicine	2004	1509	83.83	46	Meta-Analysis
2-Exercise-based cardiac rehabilitation for coronary heart disease	Ref#24	Cochrane Database of Systematic Reviews	2011	1479	134.45	10	Meta-Analysis
3-Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol - Consensus statement of the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology	Ref#23	European Heart Journal	2005	851	50.06	36	Review
4-Cardiac Rehabilitation After Myocardial Infarction - Combined Experience Of Randomized Clinical-Trials	Oldridge et al.	JAMA-Journal of The American Medical Association	1988	774	22.76	23	Meta-Analysis
5-Core components of cardiac rehabilitation/secondary prevention programs: 2007 update -	Ref#36	Circulation	2007	704	46.93	152	Guideline
6-Cardiac rehabilitation and secondary prevention of coronary heart disease - An American Heart Association Scientific Statement from the Council on Clinical Cardiology in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation	Leon et al.	Circulation	2005	689	40.53	26	Review
7-Recommendations for competitive sports participation in athletes with cardiovascular disease -	Pelliccia et al.	European Heart Journal	2005	604	35.53	18	Review
8-Statement on exercise: Benefits and recommendations for physical activity programs for all Americans - A statement for health professionals by the committee on exercise and cardiac rehabilitation of the council on clinical cardiology, American Heart Association	Fletcher et al.	Circulation	1996	602	23.15	41	Guideline
9-Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery	Suaya Jose et al	Circulation	2007	562	37.47	8	Research Article
10-Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation	Piepoli Massimo et al	European Journal of Cardiovascular Prevention & Rehabilitation	2010	554	46.17	7	Review
11-Medical progress: Cardiac rehabilitation and secondary prevention of coronary heart disease.	Ades	New England Journal of Medicine	2001	501	23.86	0	Review
12-Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: A systematic review and meta-analysis of randomized controlled trials	Ref#32	American Heart Journal	2011	397	36.09	23	Meta-Analysis
13-Statement On Exercise – Benefits, And Recommendations For Physical-Activity Programs For All Americans	Fletcher et al	Circulation	1992	394	13.13	9	Guideline
14-Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation	Kavanagh et al	Circulation	2002	380	19	0	Research Article
15-Referral, Enrollment, and Delivery of Cardiac Rehabilitation/Secondary Prevention Programs at Clinical Centers and Beyond A Presidential Advisory From the American Heart Association	Ref#26	Circulation	2011	355	32.27	294	Guideline
16-Cardiac Rehabilitation and Survival in Older Coronary Patients	Suaya, Jose et al	Journal Of The American College of Cardiology	2009	334	25.69	13	Research Article
17-Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards, and outcome measures for referral and delivery	Piepoli, Massimo et al.	European Journal of Preventive Cardiology	2014	331	41.38	5	Guideline
18-Relationship Between Cardiac Rehabilitation and Long-Term Risks of Death and Myocardial Infarction Among Elderly Medicare Beneficiaries	Hammill, Bradley et al.	Circulation	2010	327	27.25	18	Research Article
19-Action plans and coping plans for physical exercise: A longitudinal intervention study in cardiac rehabilitation	Sniehotta et al.	British Journal of Health Psychology	2006	303	18.94	20	Research Article
20-Global Secondary Prevention Strategies to Limit Event Recurrence After Myocardial Infarction Results of the GOSPEL Study, a Multicenter, Randomized Controlled Trial From the Italian Cardiac Rehabilitation Network	Giannuzzi, Pantaleo et al.	Archives of Internal Medicine	2008	282	20.14	0	Research Article

PY: Publication year, TC: Total citations, AS: Altmetric score, CI: Citation index, AT: Article type

Discussion

Bibliometric analysis is a scientific evaluation method that quantitatively evaluates articles published within a certain time period and the relationships between them. It provides comprehensive information about parameters such as global publication efficiency, trends over the years, the status of countries, and citation data [28]. Altmetric analysis takes into account the impact of a publication on social media and the internet and can be used as a supplement or alternative to traditional evaluation methods such as the impact factor [29]. Altmetrics track the online activity related to research output, allowing us to evaluate the immediate social impact of an article through real-time analysis of its online presence and dissemination. Few studies have used altmetric analysis to evaluate the impact of research on social media and the internet, and to the best of our knowledge, no study has combined bibliometric and altmetric analysis to evaluate the impact of research on CR. In this study, we aimed to present a broad perspective on the field of CR through both bibliometric and altmetric analyses of the top 50 articles in the field of CR.

Bibliometric assessments often involve analyzing the number of citations received by articles, which is a crucial aspect of evaluating the impact and influence of research. Although the article investigating exercise-based rehabilitation in patients with CHD published in 2004 was the most cited article in this study, the article investigating exercise-based cardiac rehabilitation for CHD published in 2011 had the highest citation index. This article is also the second most cited article [24,25]. Along with these two articles, exercise-based rehabilitation was the most frequently researched topic with a total of 15 articles in the T50 list. Exercise is one of the three core modalities of CR, along with education and psychological support, as outlined in international guidelines and expert consensus [30].

High-quality systematic reviews provide important data and scientific evidence for the use of exercise-based CR specifically in the CVD population and confirm that it reduces cardiovascular risk and mortality, as well as reinfarction after myocardial infarction and hospitalizations due to heart failure [24,25,31,32]. Exercise training has been shown to have direct benefits on the heart and blood vessels supplying the heart, including reduction of the heart's oxygen needs, improvement of endothelial function and autonomic tone, modification of coagulation and inflammatory markers, and promotion of the growth of coronary collaterals [33]. However, a previous review of the research on exercise-based CR for CHD found that the decreased mortality rates associated with CR may be due to the indirect effects of exercise, such as improved risk factors for clogged arteries [34]. International guidelines recommend exercise-based CR as a crucial part of comprehensive care for individuals with CHD and heart failure, but a large number of patients globally do not receive this treatment.

The article that received the most attention according to AAS was a guideline that examined the referral, enrollment, and delivery of CR and secondary prevention [26]. "Core components of cardiac rehabilitation/secondary prevention programs: 2007 update" and "Exercise-based cardiac rehabilitation for CHD 2016" ranked second and third,

respectively [35,36]. Although the article with the highest number of citations ranked fifth, the articles that received the most attention according to the altmetric analysis were not those with the most citations. The publications with the top two AASs ranked 15th and 5th in terms of the number of citations they received.

These results illustrate the contrast between bibliometric and altmetric analyses. The T50 list included studies on key components of CR, such as secondary prevention, referral, enrollment and delivery to CR, and the impacts of CR on mortality, a smartphone-based home care model, and home and center-based CR. In particular, studies based on exercise, which is among the main components of CR, were emphasized (n=15). These studies emphasized the efficacy and importance of CR in the prevention of CVD and the reduction of mortality. In recent years, with the widespread use of technology and the internet by patients, smartphone-based CR programs and activities have come to the forefront [27].

Another important issue studied in the top 50 articles was patients' referrals and participation in CR. A few developed Western countries, such as the United States, the United Kingdom, and Canada, have developed mature and well-established CR propulsion systems, as well as systematic and standardized CR models. Despite this, CR awareness and participation are generally low in most developing countries and regions. An international study investigating the worldwide availability of CR found it to be present in 111 of 203 countries [13]. According to data from the World Health Organization, CR programs can be found in the majority of European countries (80.7%), a substantial number of countries in the Americas (70.0%), over half of the countries in Southeast Asia and the Eastern Mediterranean Region (54.5% in both regions), just under half of the countries in the Western Pacific region (42.7%), and a small number of countries in Africa (17.0%) [13].

The articles included in the T50 list, which were drawn from the period of 1986 to 2021, were predominantly published between 2004 and 2010 (n=26). The increase in publications during this period can be explained by the contribution to the development of CR of the physical activity and exercise guideline in CVD patients published by the AHA in 2003, followed by the systematic guideline on CR published jointly by the AHA and AACPR in 2007. No article published after 2016 could enter the T50 list. This is an understandable result as the quoting process is time-consuming. Chen et al. [37] have shown that an article can reach its maximum number of citations in about 3 years from the date of publication. Therefore, the citation counts for articles published in 2016 or more recently may not be accurately reflected in the database search conducted in this study.

Nearly all of the articles with high AASs were published after 2004, with the exception of the 1996 American Heart Association article titled, "Benefits and recommendations for physical activity programs for all Americans." AAS could not be determined for 12 articles, which were mostly published before 2003. This occurred because altmetric analysis has only been actively used for a relatively short period of time, so less data are available for articles published earlier. The AAS of current articles can be expected to be higher. A broad range of data sources were analyzed to identify the T50 articles, and by including more recent articles, this study also evaluated publications that have not yet had the opportunity to receive a significant number of citations. This is believed to be the reason for the moderate to poor correlation observed between the citation index or number of citations and altmetric scores. This factor should be kept in mind when interpreting the study results.

The country that contributed the most to the T50 list was the USA, with 27 articles, as in many branches of medicine. The USA was followed by the UK and Italy with 8 articles each. In bibliometric analyses conducted on different subjects in the field of medicine, the USA is generally the first country. These findings may be the result of the significant number of articles published in the United States, as well as the nation's high level of scientific excellence, or the preponderance of journals based in the United States and Canada in which the articles were published. Previous bibliometric studies have suggested that journals tend to publish articles that originate from their own regions [38,39].

The funding rate for articles on CR was low. Almost all of the funders were public institutions, and almost all of the funded articles were from the USA. This suggests that economic resources may play a significant role in the production of articles that are likely to generate high-quality scientific interest.

The prevalence of CVD is increasing rapidly all over the world due to the aging and growth of populations. There are also increases in survival rates after CVD, depending on both the advances in healthcare and the widespread access of patients to health services [1,4,7]. There is accumulating evidence in the literature that CR, a supervised program that typically includes exercises, health education, and psychological intervention, improves mortality, morbidity, and quality of life for patients following a cardiac event [5,7-12,40]. Despite the positive effects of CR in increasing the quality of life of patients and reducing the health cost burden of countries, its application is not widespread worldwide. Except for a few developed countries (USA, UK, and Canada), few countries have referral and treatment systems with established applicability and efficiency. In our study, both the most highly cited publications and those with the highest altmetric scores were also from these countries. Furthermore, most of the journals in which these publications were published were based in these countries.

Keyword clustering analysis and co-citation analysis of references reflect CR's trends and hotspots. Early studies of CR focused on mainly the efficacy of CR and the disease groups to which it would be applied. With the steady increase of evidence regarding the positive effects of CR on CVD, studies seem to focus more on referral, enrollment, delivery of CR, and secondary prevention. Current hotspots are the three core components of CR that focus on exercise prescription for CR: training, exercise training, and psychological support. In addition, with the spread of the internet and its ease of accessibility, patient-centered remote health applications have also started to emerge and become popular. Since COVID-19 entered our lives in 2019, none of the studies on CR in this field have yet reached the number of citations to enter the T50 list. However, CR is likely to be critically important in the treatment of CVD caused by COVID-19 [41-43].

Limitations

One of the limitations of the study is that the study was based on only a search in the WoS database. Other databases (Scopus, Google Scholar) and articles written in different languages were not included in the analysis. In addition, cross-country citation interaction and dimensions of self-citation have not been explored.

Conclusion

Exercise-based rehabilitation was found to be the most frequently studied topic in the top 50 articles related to CR. The most cited articles were mainly from 2004 and 2010 and were published in journals such as “Circulation”, “the Journal of the American College of Cardiology”, and “the European Heart Journal”. The study found that the countries that contributed the most to the top 50 articles were the USA, the United Kingdom, and Italy. The study also found that there is a correlation between the citation index and the AAS. The results suggest that more research on CR is needed to improve the availability and capacity of CR programs worldwide and to reduce the burden of cardiovascular disease. Additionally, bibliometric and altmetric analysis can provide a more comprehensive view of the state of a particular research area than traditional methods and guide further studies in these areas.

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Evaluation of Nd:YAG laser capsulotomy results in patients who underwent cataract extraction and intraocular lens implantation with the endocapsular phacoemulsification method

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Ethics Committee Approval
This study was approved by the Ethics Committee of Harran University, 01.06.2006/4.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Posterior capsular opacification (PCO) is a common complication that develops after cataract surgery, and it can be treated neodymium-doped yttrium aluminum garnet (Nd:YAG) laser capsulotomy. In this study, we aimed to investigate the effects of different intraocular lenses (IOLs) on the development of posterior capsule opacification (PCO), to determine the time between surgery and Nd:YAG laser capsulotomy, and to evaluate the efficacy, effectiveness, and complications of capsulotomy in patients who underwent cataract surgery with the phacoemulsification method and subsequently developed PCO.

Methods: The cohort study included one eye of each of 153 cases (63 males, 90 females) who underwent cataract surgery with the phacoemulsification method in our clinic from August 1, 2006, through August 1, 2008, and subsequently developed PCO. According to the type of IOL implanted, the cases were divided into three groups: polymethylmethacrylate IOL (Group 1), hydrophilic acrylic IOL (Group 2), and hydrophobic acrylic IOL (Group 3). The control examinations of the patients who underwent Nd:YAG laser capsulotomy were undertaken before capsulotomy and at the first week, first month, and third month after capsulotomy.

Results: Visual acuity improvement was detected in 96.7% of the 153 cases. It was determined that 9.1% of the cases had an intraocular pressure (IOP) increase of more than 5 mmHg at the third hour after capsulotomy and approached baseline values at the end of 1 week. The mean total energy used in all the cases was 37.20 (14.70) mjl. The mean total energy used in 14 patients with an IOP elevation of above 5 mmHg was 71.07 (10.59) mjl. Nd:YAG laser capsulotomy was performed at an average of 6.29 (4.91) months in Group 1, 7.81 (4.35) months in Group 2, and 17.7 (12.35) months in Group 3. After capsulotomy, clinically significant cystoid macular edema was observed in 1.9% of the cases, IOL damage in 3.9%, and vitreous hemorrhage in 0.6%.

Conclusion: In this study, the incidence of PCO development was found to be lower in the patients who underwent hydrophobic acrylic IOL implantation; therefore, this type of lens should be preferred for implantation. Although Nd:YAG laser capsulotomy is an outpatient treatment method that can be applied quickly and can increase visual acuity, it can also lead to complications. To eliminate most of these complications, it would be beneficial to minimize the energy used during the laser procedure.

Keywords: posterior capsular opacification, intraocular lens, Nd:YAG laser, capsulotomy, endocapsular phacoemulsification

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Introduction

Posterior capsular opacification (PCO) is a common long-term complication that develops after cataract surgery and causes findings such as decreased visual acuity, photophobia, and glare [1–3]. The incidence of PCO after cataract surgery has been reported to vary between 2.5% and 50% [4].

PCO occurrence may depend on patient-related factors, the surgical technique applied, or the characteristics of the intraocular lens (IOL) implanted [2–5]. Not only the material of IOL, but also its edge profile and localization, are important in the formation of PCO [4,5]. Other predisposing factors for the development of PCO include younger age, surgical complications, trauma, uveitis, and diabetes mellitus (DM) [5].

PCO can be treated surgically or with a less invasive method—neodymium-doped yttrium aluminum garnet (Nd:YAG) laser capsulotomy—which is performed to improve visual acuity and obtain a good fundus image [4,6,7]. Nd:YAG laser posterior capsulotomy is a highly safe and painless method compared to surgical capsulotomy that can be applied in outpatient settings [8].

Although Nd:YAG laser posterior capsulotomy is less invasive and easier to perform, complications are possible. Major anterior segment complications include elevated intraocular pressure (IOP), corneal endothelial damage, tyndallization, IOL damage, and iris hemorrhage, while the main posterior segment complications include retinal detachment (RD), vitreous prolapse, cystoid macular edema (CME), and anterior hyaloid rupture [8,9].

In this study, we aimed to investigate the effect of IOLs on the formation of PCO, to evaluate the time elapsed between surgery and Nd:YAG laser capsulotomy, and to determine the efficacy, effectiveness, and complications of capsulotomy in patients who underwent cataract surgery with the phacoemulsification (PE) method and subsequently developed PCO.

Materials and methods

Ethical approval for this study was obtained from the Ethics Committee of Harran University (Jan. 6, 2006, decision no. 4). The patients participating in the study provided informed consent in accordance with the principles of the Declaration of Helsinki. The study included one eye of each of 153 cases (63 males, 90 females) that had undergone cataract extraction and IOL implantation with the endocapsular PE method in our clinic from Aug. 1, 2006, through Aug. 1, 2008, had developed PCO in the postoperative period and underwent Nd:YAG laser capsulotomy. The ages of the cases varied between 36 and 82 years, with a mean of 62.64 (9.72) years (Table 1).

Table 1: Age and gender distribution of cases according to the groups

	IOL type					
	PMMA		Hydrophilic acrylic		Hydrophobic acrylic	
Gender	Male	Female	Male	Female	Male	Female
n	16	23	30	36	17	31
%	33.4	66.6	45.45	54.55	35.41	64.59
Age, mean (SD)	61.12 (10.55)	60.43 (8.00)	61.83 (9.68)	64.75 (7.12)	63.88 (10.27)	62.70 (12.59)

IOL: intraocular lens, PMMA: polymethylmethacrylate, SD: standard deviation

In the eyes that had undergone PE and IOL implantation, a side-entry was made following the induction of local anesthesia. After filling the anterior chamber with viscoelastic material, a 2-mm corneal tunnel incision was made, followed by 5.0–5.5-mm capsulorhexis and hydrodissection. Then, PE was performed with the stop and chop technique. Cortex material was cleaned with irrigation and aspiration. After filling the capsule and anterior chamber with viscoelastic material, a hydrophilic acrylic IOL (Eyecryl 600, biconvex, 6.0–12.5 mm, biconvex design, 5° haptic angle, round-sedged, foldable; India) and a hydrophobic acrylic IOL in 48 (Sensar AR40e, biconvex design, 6–13 mm, 5° haptic angle, sharp-edged, foldable; Advanced Medical Optics, USA). In the remaining 39 patients, before IOL implantation, the corneal incision was enlarged to 5.5 mm, and a polymethylmethacrylate (PMMA) IOL (Clear Vision, biconvex, 5.5–12.5 mm, 5° haptic angle, round-edged; India) was placed into the capsule. The corneal incision was sutured with 2 or 3 10/0 monofilaments. The viscoelastic material was cleaned with irrigation and aspiration, and the anterior chamber entrances were inflated with a balanced eye solution.

The patients were called for controls at the first week, first month, third month, sixth month, 12th month, 24th month, and 48th month after PE surgery.

Patients with decreased visual acuity; those with photophobia, glare, or loss of contrast sensitivity due to PCO; those in which the fundus could not be visualized; and those with diplopia development due to PCO were included in the sample. Cases with uncontrollable IOP, in which the posterior capsule could not be seen (due to pathologies in the cornea or anterior chamber), those with no vision, patients diagnosed with neurological or psychiatric disease, those using drugs (e.g., atropine, pilocarpine, cyclopentolate) to prevent pupillary dilation and accommodation, and those who did not regularly attend their control examinations were excluded.

The cases were divided into the following three groups according to the type of IOL implanted:

- Group 1: PMMA IOL
- Group 2: hydrophilic acrylic IOL
- Group 3: hydrophobic acrylic IOL

Before posterior capsulotomy, the patients underwent a complete eye examination. It was noted when the cases had undergone cataract surgery. Visual acuity was determined using the Snellen chart, and IOP was measured with Goldmann's applanation tonometer. The cornea, anterior chamber, iris, pupil, IOL, posterior capsule, vitreous, and fundus examinations were undertaken with biomicroscopy, if possible, in the presence of PCO.

Before posterior capsulotomy, the eyes of the cases were dilated with 1% tropicamide (Tropamid®, Bilim Pharmaceuticals, Istanbul, Turkey) and 2.5% phenylephrine hydrochloride (Mydfrin®, Alcon Labs, Texas, USA) drops. As a topical anesthetic, 0.5% proparacaine hydrochloride (Alcaine®, Alcon-Couvreur, Puurs, Belgium) was used. Capsulotomies were performed using a Q-switched (Meridian Microruptor V, Berne, Switzerland) Nd:YAG laser device and a capsulotomy lens (Volk® Capsulotomy Lens, USA). The energy level of the laser device was adjusted according to the degree of PCO, and capsulotomies with a diameter of 3–4 mm were created in the posterior capsule center. During each application, starting from the lowest energy value, this value was increased or fixed

according to the potency. After laser capsulotomy, 1% brinzolamide (Azopt®, Alcon Labs, USA) and 1% dexamethasone (Maxidex®, Alcon Labs, USA) were dripped into the eye of each case.

At the end of the first, second, and third hours after the posterior capsulotomy procedure, IOP measurement and biomicroscopic anterior segment examination were performed. If IOP was below 22 mmHg, 1% dexamethasone (Maxidex®) (4x1) was applied, and if between 22 and 25 mmHg, 1% brinzolamide (Azopt®) (2x1) and 1% dexamethasone (4x1) were administered for a week. If IOP was above 25 mmHg, oral acetazolamide (250 mg, 4x1; Diazomid® tablets, Biofarma Istanbul, Turkey) and potassium citrate + potassium bicarbonate (8 mg, 1x1; Kalinor®, Farma-Tek, Istanbul, Turkey) were prescribed, and the patients were called for check-ups after 1 week. The patients were encouraged to attend follow-up evaluations at the first and third months.

In the follow-up examinations, visual acuity was evaluated according to the Snellen chart, IOP was measured with Goldmann applanation tonometry, and examinations of the cornea, anterior chamber, iris, pupil, intraocular lens, posterior capsule, vitreous, and fundus were performed with a biomicroscope. A visual acuity improvement of one line or more on the Snellen chart after capsulotomy was accepted as an increase in visual acuity.

Statistical analysis

The paired *t*-test, chi-square test, and Pearson correlation analysis were performed using the Statistical Package for the Social Sciences v. 11.5 (SPSS, Chicago, IL, USA) software package. Continuous variables that were normally distributed were represented as the mean (standard deviation [SD]), while non-normally distributed continuous variables were represented as the median (min-max). A *P*-value of less than 0.05 was considered significant.

Results

The best-corrected visual acuity (BCVA) scores of the cases before capsulotomy were found to vary between 3 mps and 0.8 mps. After Nd:YAG laser capsulotomy, visual acuity improved in 96.7% of all of the 153 cases, 96.7% of the 39 cases in Group 1, 97% of the 66 cases in the hydrophilic acrylic Group 2, and 98% of the 48 cases in Group 3. Among the five cases whose visual acuity did not improve following capsulotomy, diabetic maculopathy was found in two, myopic retinal degeneration in one, senile macular degeneration in one, and intravitreal hemorrhage in one.

When the BCVA levels of the cases before and after capsulotomy were compared, the mean BCVA increase was 0.3 (0.2) in all the cases, 0.3 (0.2) in Group 1, 0.4 (0.2) in Group 2, and 0.3 (0.2) in Group 3. In the statistical analysis performed with the paired *t*-test, the increase in BCVA was found to be statistically significant ($P<0.05$).

IOP measurements were performed before and after (first hour, second hour, third hour, first week, first month, and third month) Nd:YAG laser capsulotomy. When the IOP levels before capsulotomy and at the third hour were compared, the IOP elevation was less than 3 mmHg in 14.4% of the 153 cases, between 3 and 5 mmHg in 76.5%, and more than 5 mmHg in 9.1%. In Group 1, the IOP elevation was below 3 mmHg in 15.4% of the cases, between 3 and 5 mmHg in 74.4%, and above 5 mmHg in 10.2%, while these rates were determined to be 10.6%, 80.3%, and 9.1%, respectively, in Group 2, and 16.7%, 75%, and 8.3%, respectively, in Group 3. An IOP elevation above 10 mmHg was not detected in any of the cases (Table 2). When the mean IOP measurements of the patients before and after Nd:YAG laser capsulotomy were compared, the mean IOP increase at the third hour was 3.83 (1.81) mmHg in all the cases, 3.84 (1.86) mmHg in Group 1, 3.93 (1.23) mmHg in Group 2, and 3.69 (1.38) mmHg in Group 3. The paired *t*-test results revealed that the post-capsulotomy increase in IOP was significant within the groups ($P<0.001$). However, there was no statistically significant difference in the mean IOP increase between the groups ($P>0.05$).

Table 2: Mean IOP measurements of the cases before and after capsulotomy

IOL type	IOP before capsulotomy	IOP after capsulotomy					
		Hour 1	Hour 2	Hour 3	Week 1	Month 1	Month 3
Group 1	14.48 (3.20)	15.80 (3.10) x	17.17 (2.90) xx	18.33 (3.06) xxx	14.25 (3.08)	14.42 (3.08)	14.42 (3.14)
Group 2	14.06 (3.06)	15.46 (3.14) x	16.87 (3.24) xx	18.01 (3.43) xxx	14.28 (2.87)	14.06 (2.88)	14.01 (2.94)
Group 3	15.04 (2.72)	16.12 (2.86) x	17.50 (3.01) xx	18.72 (3.24) xxx	14.79 (2.66)	14.89 (2.62)	14.90 (2.68)
Total	14.47 (3.01)	15.77 (3.05) x	17.15 (3.09) xx	18.31 (3.27) xxx	14.28 (2.87)	14.41 (2.86)	14.39 (2.94)

x: $P<0.05$ xx: $P<0.01$ xxx: $P<0.001$, IOP: intraocular pressure, IOL: intraocular lens

The mean energy used in all cases that underwent capsulotomy was 2.36 (0.33) mjl/pulse, the total energy was 37.20 (14.70) mjl, and the mean number of shots was 15.92 (6.40). When examined according to the groups, the mean energy, total energy, and mean number of shots were determined as 2.49 (0.43) mjl/pulse, 39.15 (15.70) mjl, and 16.15 (7.20), respectively in Group 1, 2.30 (0.28) mjl/pulse, 37.27 (13.15) mjl, and 16.21 (5.57), respectively in Group 2, and 2.35 (0.30) mjl/pulse, 35.81 (15.90) mjl, and 15.35 (6.87), respectively in Group 3 (Table 3).

Table 3: Mean energy, total energy, and number of laser shots used during capsulotomy

Groups	Number of eyes n (%)	Mean energy (mjl/pulse)	Total energy (mjl)	Number of laser shots
Group 1	39 (25.5)	2.49 (0.43)	39.15 (15.70)	16.15 (7.20)
Group 2	66 (43.2)	2.30 (0.28)	37.27 (13.15)	16.21 (5.57)
Group 3	48 (31.3)	2.35 (0.30)	35.81 (15.90)	15.35 (6.87)
Total	153 (100)	2.36 (0.33)	37.20 (14.70)	15.92 (6.40)

When the relationship between total energy used in capsulotomy and IOP levels was examined, the total energy used was 22.04 (10.11) mjl in 21 cases with a post-capsulotomy IOP elevation <3 mmHg, 35.99 (8.52) mjl in 118 cases with a post-capsulotomy IOP elevation of 3–5 mmHg, and 71.07 (10.59) mjl in 14 cases with a post-capsulotomy IOP elevation >5 mmHg (Table 4).

Table 4: Total energy used according to IOP increase after capsulotomy

IOP increase	Group 1 Total energy (mjl)	Group 2 Total energy (mjl)	Group 3 Total energy (mjl)	Whole cohort Total energy (mjl)
<3 mmHg	19.66 (01.75)	22.14 (4.74)	24.62 (16.04)	22.04 (10.11)
3-5 mmHg	38.41 (08.32)	36.05 (8.37)	33.97 (8.50)	35.99 (8.52)
>5 mmHg	73.75 (12.09)	66.83 (8.08)	74.75 (11.06)	71.07 (10.59)

IOP: Intraocular pressure

In the correlation analysis between the mean IOP increase and the total energy levels used in all the cases and groups, it was observed that IOP elevation increased

significantly as the total energy used increased (P<0.001, r=867); however, there was no statistically significant difference between the groups (P>0.05).

The time between cataract surgery and Nd:YAG laser capsulotomy was 10.54 (9.25) months in all cases, 6.29 (4.91) months in Group 1, 7.81 (4.35) months in Group 2, and 17.7 (12.35) months in Group 3. Accordingly, it was determined that capsulotomy was performed earliest in the cases that underwent PMMA IOL implantation and latest in those that underwent hydrophobic IOL implantation, while the cases in the hydrophilic IOL group required capsulotomy later than the PMMA IOL group and earlier than the hydrophilic IOL group. There was a significant difference between the three groups in relation to time elapsed between cataract surgery and Nd:YAG laser capsulotomy (P<0.001).

After capsulotomy, IOL damage was detected in six (3.9%) cases in the whole cohort—three (7.7%) cases in Group 1, two (3%) cases in Group 2, and one (2%) case in Group 3. In addition, in the post-capsulotomy period, three patients had clinically significant macular edema, and one patient with DM developed intravitreal hemorrhage. Complications such as iris hemorrhage, vitreous prolapse, and RD were not observed in any of our cases after capsulotomy.

Discussion

Despite all the developments in cataract surgery, PCO remains one of the most important complications of cataract surgery. It has been reported that the incidence of PCO associated with standard cataract surgery ranges from 5% to 50% [5]. Current studies show that Nd:YAG laser capsulotomy is widely used in the treatment of PCO and significantly improves visual function in these patients [1,5,9,10]. Various studies have found a substantial increase in visual acuity after Nd:YAG laser capsulotomy performed in cases with PCO [6]. In the current study, the mean visual acuity increase was 0.4 in all cases.

In the literature, following Nd:YAG laser capsulotomy, visual acuity was reported not to have increased in 8.3% of cases by Menon et al. [11], 6.1% by Dawood et al. [12], and 2.5% by Javed et al. [13], which were all due to secondary eye events, such as maculopathy, diabetic retinopathy, and myopic retinal degeneration [11–13]. In our study, there was no visual acuity improvement in 3.3% of the cases after Nd:YAG laser capsulotomy. This lack of improvement was determined to be associated with diabetic retinopathy in two cases, myopic retinal degeneration in one, maculopathy in one, and intravitreal hemorrhage in one.

Studies have shown an increase in IOP after Nd:YAG laser posterior capsulotomy, which has been attributed to several mechanisms. First, outflow is prevented by the accumulation of capsular residues and inflammatory cells, blood elements, fibrin, and high–molecular-weight proteins in the inner wall of the trabecular mesh and Schlemm canal as a result of the Nd YAG laser capsulotomy procedure, leading to increased IOP [14]. Other mechanisms underlying IOP increase include the vitreous moving forward and causing pupillary block, laser shock waves damaging endothelial cells in the trabecular meshwork and resulting in edema, and trabecular cells being damaged by liberated inflammatory mediators or directly by the laser procedure itself [15,16].

In various studies, it has been reported that the mean increase in IOP is between 1.2 and 9.1 mmHg after Nd:YAG laser capsulotomy. In the literature, the mean IOP increase after capsulotomy was reported as 1.2 mmHg by Ge et al. [17], 2.1 mmHg by Cai et al. [18], 2.5 mmHg by Seong et al. [19], 3.0 mmHg by Maden et al. [20], 3.6 mmHg by Kraff et al. [16], 4.2 mmHg by Pollack et al. [21], 4.4 mmHg by Esgin et al. [22], and 9.1 mmHg by Gartaganis et al. [23]. In our study, the mean IOP increase after capsulotomy was found to be 3.8 mmHg.

Studies have shown that IOP elevation resulting from Nd:YAG laser decreases to pre-capsulotomy values within 24 hours to 1 week, through drugs used [18,24]. Our study determined that IOP decreased to the values before capsulotomy (i.e., baseline values) at the end of 1 week.

The relationship between the increase in IOP due to Nd:YAG laser capsulotomy and the total amount of energy used has also been previously investigated. Kraff et al. [16], Esgin et al. [22], and Leys et al. [25] reported no significant relationship between the increase in IOP and the total energy used, while Shetty [26] et al., Cumurcu et al. [27], and Rahul et al. [28] found a significant relationship between the increase in IOP and the total energy used. In the current study, the mean total energy used was 37.2 (14.7) mjl, and the mean energy used in the patients with an IOP increase over 5 mmHg was determined to be 71 (10) mjl, indicating a significant correlation between the increase in IOP and the total energy used.

According to previous studies, the time between surgery and Nd:YAG laser capsulotomy varies between 1 month and 38 months [21,29,30]. In our cases, this time interval was between 1 and 48 months, which is consistent with other studies.

Ram et al. [31] investigated the effect of PMMA, silicone, acrylic hydrophilic, and hydrophobic IOLs on PCO and found that the patients with PMMA IOLs developed PCO at a higher rate than the remaining groups over a 2–4-year follow-up period.

Suh et al. [32] evaluated the effect of hydrophilic and hydrophobic acrylic IOLs on PCO. Over the 3-year follow-up of cases, the authors reported that PCO developed in 20.3% of those who had undergone hydrophilic acrylic IOL implantation and 6.8% of those who had undergone hydrophobic acrylic IOL implantation, and they performed Nd:YAG laser capsulotomy in all of the cases that developed PCO. In another study comparing hydrophilic and hydrophobic acrylic IOLs, Kaya et al. [33] reported that the patients with hydrophilic acrylic IOLs had a higher rate of PCO development than those with hydrophobic acrylic IOLs during the 12-month follow-up period. In our study, we divided the patients into three groups according to the type of IOL implanted after cataract surgery. The mean time between surgery and Nd:YAG laser capsulotomy was 6.29 months in the PMMA IOL group, 7.81 months in the hydrophilic acrylic IOL group, and 17.7 months in the hydrophobic acrylic IOL group. These values are in agreement with previous studies.

PMMA and hydrophilic IOLs accelerate the proliferation of lens epithelial cells (LECs) due to their biomaterial structure. With its bioadhesive properties, the hydrophobic acrylic IOL adheres well to the lens capsule and

prevents the migration of LECs [34,35]. In addition to the biomaterial structure of this IOL, the edge characteristics also affect the formation of PCO. The sharp-cut edges found in this IOL create bends, preventing the migration of LECs and reducing the rate of PCO development [36,37]. In our study, the late appearance of PCO in Group 3 compared to the other two groups can be explained by the bioadhesive properties and sharp edges of the hydrophobic acrylic IOL used.

Studies have reported that RD occurs in 0.21–2.6% of cases after Nd:YAG laser capsulotomy [21,25,38]. It has been suggested that the incidence of RD increases after Nd:YAG capsulotomy in myopic patients, and that surgeons exercise greater caution and should use minimum energy when performing their surgeries. In contrast, Javed et al. [13], Şimsek et al. [39], and Khanzada et al. [40] found no RD development after Nd:YAG laser capsulotomy. We also did not observe RD development in any of our cases after capsulotomy.

In the literature, the rate of CME development following Nd:YAG laser capsulotomy was reported as 0.5% by Dawood et al. [12] and 3% by Raza et al. [41], while Esgin et al. [22] and Anil et al. [24] did not find CME development in any of their patients after this surgery. In the current study, 1.9% of the patients developed clinically significant CME. This was previously attributed to the release of prostaglandins as a result of damage to the vitreous after capsulotomy [42].

In previous studies, GIL damage following Nd:YAG laser capsulotomy was reported at a rate of 17.1% by Özkağnıcı et al. [43], 11.5% by Esgin et al. [22], 7.8% by Rahul et al. [28], 5.4% by Khanzada et al. [40] 3.3% by Javed et al. [13], and 0.5% by Dawood et al. [12]. Consistent with the literature, we determined that 3.9% of our patients had IOL damage after this surgery.

Conclusion

PCO is a complication that causes symptoms such as decreased visual acuity, photophobia, and decreased contrast sensitivity after cataract surgery. Many factors affect the development of PCO, such as DM and the type of IOL implanted. Based on our results, we recommend the use of hydrophobic acrylic IOLs during this surgery, since they result in less PCO development.

Although this is a highly safe and painless method compared to surgical capsulotomy that can be applied under outpatient clinic conditions, it also has certain complications, including elevated IOP, RD, CME, IOL damage, and vitreous prolapse. To eliminate the risk of most of these complications, it is necessary to minimize the energy used during the laser procedure.

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Frequency and type of arrhythmia in Holter electrocardiogram in patients undergoing hemodialysis

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Ethics Committee Approval
This study was approved by the ethics committee of İzmir Bakırçay University non-interventional clinical research with the decision number 2022/769.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: It is known that approximately 40% of chronic hemodialysis patients die due to cardiac arrhythmia and cardiovascular diseases. Determining whether the hemodialysis procedure poses a risk for arrhythmia is important in terms of prognostic follow-up of the patients. Therefore, we aimed to determine the underlying arrhythmia frequency and types with 24-hour Holter electrocardiogram (ECG) in patients receiving hemodialysis with normal baseline electrocardiography between the hemodialysis periods.
Methods: Between January 2018 and January 2022, 91 consecutive patients who received hemodialysis for chronic renal failure (CRF) and applied to the cardiology outpatient clinic with complaints of palpitation and sinus rhythm on ECG and evaluated with 24-hour rhythm Holter ECG were included in the study. Our study was designed as a retrospective cohort study.
Results: The mean age of the patient population was 65.78 (11.92) years, the mean systolic blood pressure was 143.71 (24.88) mmHg, and the mean heart rate was 83.43 (15.85) beats/min. Hypertension (HT) (n=44, 48%) and coronary artery disease (n=34, 37%) were the most common comorbid diseases. The most common arrhythmias detected on Holter ECG were ventricular extrasystole (VES) (n=18, 19.8%) and paroxysmal AF (n=8, 8.8%). Non-sustained ventricular tachycardia was detected in two patients.
Conclusion: Detecting arrhythmia in the interdialytic periods in patients receiving hemodialysis due to CRF is important for follow-up and treatment. Even if the baseline ECG is normal in hemodialysis patients with CRF, the frequency of the underlying arrhythmia that needs to be treated is high.

Keywords: arrhythmia, Holter ECG, hemodialysis, frequency

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Introduction

Compared to patients with normal renal function, a significant increase in patients undergoing hemodialysis due to end-stage renal disease was observed at a rate of approximately 180/1000 per year (according to the USA renal data system report) [1]. It is known that a high rate of approximately 40% of chronic hemodialysis patients die due to cardiac arrhythmia and cardiovascular diseases [2,3]. The relationship between sudden death and hemodialysis is tried to be explained by the change in serum electrolyte concentrations, which has not been clarified by traditional cardiovascular risk factors alone [4,5].

Many factors in the blood circulation, parathyroid hormone, aldosterone, fibroblast growth factor-23, angiotensin-2, endogenous cardiac glycosides, vitamin D, and angiogenesis inhibitors have been implicated in myocardial fibrosis and reduction of capillary density, but it has not been clarified enough. This pathophysiological process, which results in hypertrophic myocardium and reduced capillary density, can play a critical role in the development of arrhythmia by creating a temporary insufficiency in coronary oxygen delivery [6,7].

Determining whether hemodialysis is linked to arrhythmia in patients with chronic renal failure (CRF) is important for the diagnostic follow-up of patients. Detection and treatment of underlying treatable arrhythmias are effective ways to heal patients and are important in this regard [8–10]. In this respect, we aimed to detect and document arrhythmic events that could not be detected in the basal electrocardiography (ECG) between the hemodialysis periods with 24-hour Holter ECG.

Materials and methods

Patients (n=91) who applied to the cardiology outpatient clinic between January 2018 and January 2022 were receiving hemodialysis for CRF, and were evaluated with 24-hour rhythm Holter ECG were included in the study. Patients whose baseline ECG was not in sinus rhythm and known any arrhythmia, younger than 18 years of age, did not have routine transthoracic echocardiographic (TTE) measurements, and whose rhythm Holter ECG cannot be optimized were excluded from the study. In addition, patients who had malignancy, active infection, prosthetic valve disease, and cardiac pacing were excluded from the analysis.

The results of blood tests, ECG and TTE findings, and rhythm Holter ECG results were obtained from hospital records. The blood analysis results of these patients include the values after hemodialysis, and Holter ECG records were taken from 24-hour rhythm monitoring performed at least one day after receiving hemodialysis.

Our study was designed as retrospective and observational. Before the study, ethical approval was obtained from Izmir Bakırçay University Non-Invasive Clinical Research Ethics Committee. (Decision number: 2022/769).

Definitions

Non-sustained ventricular tachycardia (NSVT) was defined as ventricular-derived tachycardia with a wide QRS complex lasting more than three consecutive beats and lasting less than 30 seconds. Supraventricular tachycardia was defined as atrial origin tachycardia with a narrow QRS complex and regular RR distance. Paroxysmal AF (Atrial Fibrillation) was defined as atrial origin tachycardia attack with narrow QRS complex and irregular RR distance in rhythm Holter ECG. Multifocal atrial tachycardia (MAT) was defined as three or more different P waves in rhythm Holter ECG, variable P-P, P-R, R-R intervals, and atrial origin tachycardia (atrial rhythm 100–180/min) attack.

Statistical analysis

Analysis was done using the IBM SPSS Statistics 24.0 program. The normality distribution of numerical variables was determined by the Kolmogorov-Smirnov (n ≥50) test. Numerical variables are given as mean and standard deviation. Categorical variables were reported as numbers (n) and percentages (%).

Results

The mean age of the patient population was 65.78 (11.92) (min 41, max 90) years, with a 56% male sex ratio and 44% female sex ratio. The mean body mass index (BMI) was 25.19 (3.64) kg/m2. The mean systolic and diastolic blood pressure (BP) of the patients were 143.71 (24.88) mmHg and 82.24 (18.45) mmHg, respectively. The mean heart rate of the patients was 83.43 (15.85) beats/min. 30% of the patients had a history of smoking, and 4% had a history of alcohol use. The clinical and demographic data of the patients are summarized in Table 1.

Table 1: Clinic and demographic data

Variables	Findings, n=91
Age, year, mean (SD)	65.78 (11.92)
Male sex, n (%)	51 (56)
BMI, mean (SD)	25.19 (3.64)
Systolic BP, mmHg, mean (SD)	143.71 (24.88)
Diastolic BP, mmHg, mean (SD)	82.24 (18.45)
Heart rate, beat/min, mean (SD)	83.43 (15.85)
Smoking, n (%)	28 (30)
Alcohol use, n (%)	4 (4)
Hypertension, n (%)	44 (48)
CAD, n (%)	34 (37)
DM, n (%)	24 (26)
Anemia, n (%)	31 (34)
COPD, n (%)	8 (8)
Thyroid disease, n (%)	12 (13)
PTE history, n (%)	5 (5)

BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, PTE: pulmonary thromboembolism, SD: standard deviation, n: no. of patients

Hypertension (n=44, 48%) and coronary artery disease (n=34, 37%) were the most common comorbid diseases. These were followed by anemia (n=31, 34%), diabetes mellitus (n=24, 26%), thyroid disease (n=12, 13%), and chronic obstructive pulmonary disease (COPD) (n=8, 8%), respectively.

The mean values of blood parameters; hemoglobin 12.54 (2.01) g/dL, fasting glucose 114.54 (40.98) mg/dL, thyroid-stimulating hormone (TSH) 1.45 (1.12) mIU/L and creatinine 2.92 (1.12) mg/dL. The most commonly used drugs by patients before a rhythm Holter ECG were beta-blocker (n=25, 27%), oral iron preparation (n=16, 17%), non-dihydropyridine calcium channel blockers (non-dhp CCBs) (n=12, 13%), and oral vitamin B12 (n=12, 13%). The laboratory findings and drugs used by the patients are given in Table 2.

In echocardiographic findings, the mean left ventricular ejection fraction (LVEF) was n=51.66 (10.71%), and the mean left atrium diameter was 34.74 (4.25) mm. Moderately severe mitral regurgitation was found in 22% of the patients, moderately severe mitral stenosis in 7.7%, moderately severe tricuspid

insufficiency in 20.9%, and moderately severe aortic stenosis in 17.6% of the patients.

Table 2: Laboratory findings and medication of patients

Variables	Findings, (n=91) Mean (SD)
Fasting blood glukose, mg/dL	114.58 (40.98)
Urea, mg/dL	22.33 (13)
Creatinine, mg/dL	2.92 (1.12)
WBC, x 10^9/L	9.50 (2.44)
Hemoglobin, g/dL	12.54 (2.01)
Platelet, x10^9/L	254.06 (91.12)
TSH, mIU/L	1.45 (1.12)
Ferritin, ng/mL	52.99 (38.91)
Vitamin B12, pg/mL	261.74 (102.99)
Sodium, mEq/L	138.62 (2.95)
Potassium, mEq/L	4.55 (0.73)
Total cholesterol, mg/dL	208.16 (44.20)
Triglyceride, mg/dL	184.42 (83.78)
HDL, mg/dL	40.80 (9.97)
LDL, mg/dL	123.61 (31.78)
Medications, n(%)	
Betablocker therapy	25 (27)
Non-dihydropyridine CCBs	12 (13)
Oral iron preparation	16 (17)
Oral B12 preparation	12 (13)

WBC: white blood cell, TSH: thyroid stimulant hormone, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CCB: calcium channel blocker, SD: standard deviation, n: no. of patients.

The most common arrhythmias detected on Holter ECG were ventricular extrasystole (VES) (n=18, 19.8%) and paroxysmal AF (n=8, 8.8%). In addition, seven (7.7%) patients had a sustained ventricular tachycardia (SVT) attack, and six (6.6%) patients had supraventricular extrasystole. Non-sustained ventricular tachycardia was detected in two patients. TTE and Holter ECG findings of the patients are presented in Table 3.

Table 3: Echocardiography and Holter ECG findings of the patients

Variables	Findings, (n=91)
LVEF (%), mean (SD)	51.66 (10.71)
Mid-severe mitral regurgitation, n (%)	20 (21.9)
Mid-severe mitral stenosis, n (%)	7 (7.7)
Mid-severe tricuspid regurgitation, n (%)	19 (20.8)
Mid-severe aorta stenosis, n (%)	16 (17.6)
Left atrium diameter, mm, mean (SD)	34.74 (4.25)
VES, n(%)	18 (19.8)
PAF, n(%)	8 (8.8)
SVE, n(%)	6 (6.6)
NSVT, n(%)	2 (2.2)
SVT, n(%)	7 (7.7)
MAT, n(%)	2 (2.2)
AT, n(%)	4 (4.4)

LVEF: left ventricle ejection fraction, VES: ventricular extrasystole, PAF: paroxysmal atrial fibrillation, SVE: supraventricular extrasystole, NSVT: non-sustained ventricular tachycardia, SVT: supraventricular tachycardia, MAT: multifocal atrial tachycardia, AT: atrial tachycardia, SD: standard deviation, n: no. of patients.

Discussion

A 24-hour rhythm Holter ECG scan in patients receiving hemodialysis revealed that arrhythmia was detected in 51% (n=47) of the patients. The most common arrhythmia was VES, followed by paroxysmal AF in 1/5 of the patients.

Ventricular arrhythmias are common in renal failure patients treated with long-term hemodialysis. It is known that the risk of arrhythmia increases during hemodialysis treatment. Ventricular arrhythmias may be responsible for an important component of cardiovascular mortality in hemodialysis patients. Determining the prevalence and types of arrhythmias in dialysis patients is central to reducing cardiovascular morbidity and mortality [11]. The factors predicted for the formation of these arrhythmias in the literature range from hemodynamic changes to metabolic disorders caused by dialysis. It is known that the presence of left ventricular hypertrophy with arterial hypertension, which can occur frequently in renal failure due to volume overload, is a risk factor for the development of complex arrhythmias [11–13].

In a study of 152 patients to estimate the prevalence of arrhythmias and characterize the pattern of arrhythmic events associated with dialysis treatments in patients with renal failure treated with dialysis, early atrial and ventricular complexes were seen in almost all patients, and paroxysmal supraventricular tachycardia was detected in 41%. Clinically significant arrhythmias include persistent AF in 8.6% of patients, paroxysmal atrial fibrillation (PAF) in 3.9%, non-sustained ventricular tachycardia in 19.7%, bradycardia in 4.6%, and 1.3% of patients. Advanced second-degree atrioventricular block was detected in three patients, and third-degree atrioventricular blockes were detected in 2.6% of them. Early ventricular complexes were more common on dialysis days, while tachyarrhythmias were more common during and immediately after dialysis [14]. Because arrhythmias are common during dialysis, this may be one of the limitations of this study. In our study, this situation was avoided by using the interdialytic time interval, and the underlying true arrhythmia frequency and types were investigated in dialysis patients with normal baseline ECG.

In the study of Hamadou et al. [15] investigating the presence of cardiac arrhythmia in chronic hemodialysis patients, VES was observed as the most common arrhythmia, with a rate of 20%. Hypertension, diabetes mellitus, hyperlipidemia, CRF, male gender, and age, which are cardiovascular risk factors, can cause ventricular extrasystoles with their effects on ischemic heart disease [12,13]. The frequency of ventricular arrhythmias in patients with end-stage renal disease is between 13-38%. Bozbaş et al. [16] found the frequency of complex ventricular arrhythmias to be 37.2% in 94 hemodialysis patients. The prevalence of supraventricular arrhythmias is between 16–69% when we look at the [17], and similarly, in our current study, supraventricular arrhythmias other than paroxysmal AF were found to be approximately 20%.

As it is known, hypertension is the most common comorbid disease as a cause or consequence of CRF [18]. In our study, hypertension and coronary artery disease were the most common comorbid diseases.

Although ventricular arrhythmias pose a serious risk for sudden death, atrial arrhythmias, primarily AF, may also result in significant morbidity in patients with CRF receiving hemodialysis. The frequency of AF tends to increase in hemodialysis patients. In a study conducted on elderly dialysis patients, the incidence of AF was found to be 14.8%, and this rate increased from 11% to these levels in the last 15 years [19–21]. Recent studies have shown that arrhythmia is common in the long interdialytic interval, and AF was detected in 42% (86% asymptomatic). This data obtained through ECG monitoring reveals an arrhythmia that is a candidate to cause cerebrovascular events such as AF, even if patients were asymptomatic [22]. In a study investigating the frequency of atrial fibrillation in patients receiving long-term hemodialysis treatment, 183 patients with preserved left ventricular systolic functions and receiving long-term hemodialysis treatment were included. The atrial fibrillation rate was found to be 13.1%. However, in this study, the presence of atrial fibrillation was determined by electrocardiography [23]. In our study, patients with normal baseline ECG were included, and the presence of AF was revealed by a 24-hour Holter. In our

study, PAF was detected in 8.8% of the patients on 24-hour Holter ECGs.

Limitations

Because our study was single-center and retrospective, there were limitations, such as examining the laboratory and imaging tests of the patients from past records. In addition, there were no findings regarding the fluid electrolyte changes during the hemodialysis procedure, the amount of ultrafiltration applied to the patients, or the hemodynamic data during the procedure. Because Holter ECG recordings in our study are limited to 24 hours, more arrhythmia recordings can be detected with longer rhythm recordings.

Conclusion

Detecting arrhythmia in the interdialytic process in patients receiving hemodialysis due to CRF is important for the follow-up and treatment process of the patients. The arrhythmias that can be treated in this patient group is quite frequent. Holter ECG is an important guide in the follow-up of arrhythmias in hemodialysis patients with CRF.

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Effects of previous exposure to different medications on the clinical course of COVID-19 patients in Istanbul, Turkey

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Ethics Committee Approval
This study was approved by Clinical Research Ethics Committee of Marmara University Faculty of Medicine (May 8, 2020, protocol code: 09.2020.552). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Multiple studies have investigated the effects of drugs that alter ACE2 expression, such as renin-angiotensin system inhibitors, non-steroidal anti-inflammatory drugs, and thiazolidinediones, on the clinical course of coronavirus disease-2019 (COVID-19). But a consensus has not yet been reached, and it has been stated that they do not have any effect. There are publications in which metformin is associated with low mortality and insulin with high mortality. Data from different parts of the world are important given that the rate of spread of COVID-19 may be related to the expression status of ACE2 or TMPRSS2 receptors or some other unknown genetic factors. This study aims to examine the effects of medications used chronically in the last 6 months before contracting COVID-19 on the clinical course of COVID-19 in a sample of Istanbul, Turkey.

Methods: In this retrospective cohort study, which included 525 patients diagnosed with COVID-19 between March and November 2020 from four family health centers in Istanbul, the records of the patients were retrospectively analyzed. In addition to demographic information, all medications chronically used by the patients in the last 6 months before the diagnosis of COVID-19 were noted. The effects of demographic data and medications on the three main endpoints of the study, which were hospitalization, intensive care unit (ICU) admission, and mortality, were analyzed using logistic regression models.

Results: Of the 525 COVID-19 patients included in the study, 109 (20.8%) were hospitalized, 18 (3.4%) were treated in ICU, and 11 (2.1%) patients died. Increasing age is associated with hospitalization, ICU admission and mortality. Also, the presence of COVID-19 thoracic computed tomography (CT) findings and polypharmacy was associated with increased hospitalization. Living alone and the presence of COVID-19 thoracic CT findings was associated with increased ICU admission. When adjusted for age and comorbidity, logistic regression models revealed that medications for diabetes mellitus (DM) increased the probability of hospitalization (OR: 3.9, 95% CI 1.2-13.0), and calcium channel blockers (CCBs) increased the probability of ICU admission (OR: 15.8, 95% CI 2.1–120.2) and mortality (OR: 295.1, 95% CI 4.6–18946.6).

Conclusion: Previous use of DM medications and CCBs may negatively affect the clinical course of COVID-19.

Keywords: COVID-19, SARS-CoV-2, epidemiology, pharmacoepidemiology, hypoglycemic agents, calcium channel blockers

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Introduction

The pandemic caused by the coronavirus disease-2019 (COVID-19) has caused millions of people's death since December 2019 and continues to do so. Although an effective drug treatment has not yet been found, vaccines developed against COVID-19 have been applied worldwide since the last months of 2020. On the other hand, studies on which factors affect the severity of the disease are continuing. Studies indicate that age is the primary risk factor for COVID-19-related hospitalization and/or death. In addition, it has been revealed that the clinical course of COVID-19 is more severe in patients with chronic diseases, such as hypertension (HT), cardiovascular diseases (CVD), diabetes mellitus (DM), obesity, chronic kidney failure, and cancer [1-4].

The cellular structure and receptors of the severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) that causes COVID-19 were found in March 2020. It was determined that the virus entered the cell with the angiotensin-converting enzyme-2 (ACE2) receptor, and the transmembrane protease serine 2 (TMPRSS2) receptor facilitated the entry of the virus into the cell [5]. Since then, the use of drug groups, such as ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [6–8], ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs) [9,10], and thiazolidinediones [11], which may cause an increase or decrease in ACE2 expression, has been investigated in large-scale studies during the COVID-19 pandemic.

In general, it has been demonstrated that these drugs do not affect the severity or mortality of COVID-19. Besides, some studies have reported that metformin was associated with decreased mortality and insulin was associated with increased mortality [11–14]. Dipeptidyl peptidase-4 (DPP4) inhibitors have been reported to be associated with the good or poor clinical course of COVID-19 [11,15,16].

Considering that the rate of spread of COVID-19 may be related to the expression status of ACE2 or TMPRSS2 receptors [17,18] or to some other genetic factors that are not yet known, data in different parts of the world are important. With this study, we aimed to examine the effects of previous drug utilization in the last 6 months before contracting COVID-19 on the clinical course of COVID-19 by presenting data from Istanbul, Turkey.

Materials and methods

This retrospective cohort-type study started in May 2020 under the direction of the Marmara University Health Sciences Institute Medical Pharmacology Department and was carried out between May 2020 and October 2021. Patients registered at Istanbul Uskudar Zeynep Kamil Family Health Center (FHC), Sultanbeyli Jandarma Ustegmen Rahim Celik FHC, Beyoglu 6th FHC, and Eyup Islambey FHC were included in the study. Those diagnosed with COVID-19 between 11 March 2020 and 30 November 2020 constituted the study population.

Inclusion criteria were to be a patient enrolled in the FHCs mentioned above and to have a positive COVID-19 PCR test between 11 March 2020 and 30 November 2020 or positive COVID-19 thoracic CT findings despite a negative test. The exclusion criterion from the study was the inability to access the medical information of the included patients via *e-nabiz* (an application that Turkish citizens and health professionals can access health data collected from health institutions via the internet and mobile devices).

The records of the patients included in the study were scanned retrospectively. Data scanning was performed via family medicine information systems and *e-nabiz*. The patients' data were collected by the researcher working in the relevant FHC and participating in the study. The information obtained from the patient files were as follows: patient's age, gender, marital status, education level, employment status, occupation, smoking habit, date of the first diagnosis, first application complaint, COVID-19 PCR test result, presence of COVID-19 findings in thoracic CT, received COVID-19 pharmacological treatment, presence of comorbidity, and medications chronically used in the previous 6 months. Chronic drugs were prescribed to be taken daily for ≥ 30 days. Using five or more different drugs for more than 6 months was considered polypharmacy. The medications utilized in the previous 6 months were recorded according to the Anatomic Therapeutic Chemical (ATC) 5 classification. It was then further grouped according to ATC 3. These data were compared with the three main endpoints of the study, namely, the need for hospitalization, an intensive care unit (ICU), and mortality in comparative analyses.

We did not perform sample size calculation because all COVID-19 patients registered to the FHCs included in the study during the first wave of the COVID-19 pandemic were involved. Therefore, we avoided selection bias.

To obtain study data from family medicine information systems and *e-nabiz*, permission was obtained from the Turkish Republic Ministry of Health General Directorate of Health Services Scientific Research Platform on 29.04.2020. Before collecting the study data, an application was made for the approval of the Marmara University Faculty of Medicine Clinical Research Ethics Committee, and the ethics committee approval was obtained on 08.05.2020 with the protocol code 09.2020.552. The study was carried out following the principles in the Declaration of Helsinki.

Statistical analysis

SPSS 21.0 was used for statistical analysis. Frequency analysis was performed by specifying numbers and percentages for categorical variables. Normal distribution was tested using the Kolmogorov-Smirnov test. Mean and standard deviation were used for continuous variables, and median and range of values were used for non-parametric variables as measures of central tendency and dispersion, respectively. Logistic regression was used to compare the independent variables with the three dependent variables. Correlation analysis and the Pearson Chi-square test confirmed the direction of the comparisons. All logistic regression models were adjusted for age and comorbid conditions. Demographic data were also compared between outpatients, hospitalization, ICU admission, and mortality using the Pearson-chi square test and Fisher's exact test, when needed. For parameters with non-normal distribution, ranks were compared using the Kruskal-Wallis test. For normally distributed parameters, means were compared using a one-way analysis of

variance (ANOVA) test. In the presence of significant variables, Tukey's post hoc test was performed after the ANOVA test, the Dunn test was performed after the Kruskal-Wallis test, and Pearson chi-square or Fisher's exact test in pairs was performed after the Pearson chi-square or Fisher's exact test. *P*-values <0.05 were considered statistically significant.

Results

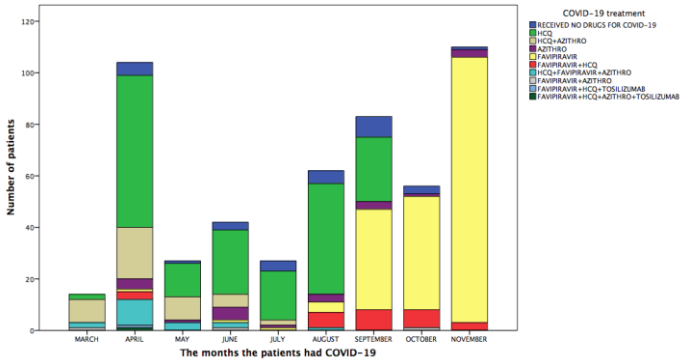
Between March 2020 and November 2020, a total of 525 patients with COVID-19 PCR positive (n=504; 96.0%) or PCR negative and CT positive (n=21; 4.0%) were included in the study from the previously determined FHCs. Demographic and baseline characteristics were compared between outpatient, hospitalized, ICU, and dead patients (Table 1). While the most common complaint in outpatients was fatigue, the most common complaint in patients admitted to the hospital or ICU or who died was cough. Cough, fever, and shortness of breath were more common in hospitalized patients in the ICU or who died than outpatients (*P*=0.008) (Table 1). Education level, employment status and occupation data were not included in the analyses because the relevant data were unavailable for the study population.

Table 1: Demographic and other characteristics of patients

	Total	Outpatient	Hospitalization	Admission to the ICU	Mortality	*P*-value
Gender, n (%)						0.30[F]
Female	260 (49.5)	210 (50.6)	49 (45.0)	8 (44.4)	7 (63.6)	
Male	265 (50.5)	205 (49.4)	60 (55.0)	10 (55.6)	4 (36.4)	
Age [a], median (min-max)	41 (0.5-94)	36 (0.5-80)	57 (11-90)	69.5 (38-88)	72 (42-94)	0.01[K]
Marital status [b], n (%)						0.02[F]
Married	333 (63.4)	253 (61.0)	80 (73.4)	10 (55.6)	5 (45.5)	
Alone	192 (36.6)	162 (39.0)	29 (26.6)	8 (44.4)	6 (54.5)	
Presence of complaints [c], n (%)						0.01[F]
Asymptomatic	143 (27.4)	133 (32.0)	10 (9.2)	1 (5.6)	1 (9.1)	
Symptomatic	382 (72.6)	282 (68.0)	99 (90.8)	17 (94.4)	10 (90.9)	
Weakness	141 (26.9)	108 (26.0)	33 (30.3)	4 (22.2)	1 (9.1)	0.32[A]
Cough [d]	129 (24.6)	79 (19.0)	50 (45.9)	10 (55.6)	7 (63.6)	0.01[A]
Fever [c]	96 (18.3)	56 (13.5)	40 (36.7)	5 (27.8)	2 (18.2)	0.01[A]
Headache	58 (11.0)	50 (12.0)	8 (7.3)	1 (5.6)	0	0.42[A]
Throat ache [e]	48 (9.1)	38 (9.2)	10 (9.2)	3 (16.7)	0	0.03[A]
Back pain	45 (8.6)	38 (9.2)	7 (6.4)	0	0	0.56[A]
Loss of taste and smell	37 (7.0)	35 (8.4)	2 (1.8)	0	0	0.12[A]
Shortness of breath [a]	33 (6.3)	8 (1.9)	24 (22.0)	7 (38.9)	5 (45.5)	0.01[A]
Rhinorrhea	8 (1.5)	8 (1.9)	0	0	0	0.54[A]
Diarrhea	4 (0.8)	4 (1.0)	7 (6.4)	0	0	0.79[A]
Sputum	3 (0.6)	3 (0.7)	0	0	0	0.85[A]
PCR positivity [a], n (%)						0.01[F]
PCR positive	504 (96.0)	410 (98.8)	93 (85.3)	13 (72.2)	9 (81.8)	
PCR negative, BT positive	21 (4.0)	5 (1.2)	16 (14.7)	5 (27.8)	2 (18.2)	
CT findings [a], n (%)						0.01[F]
Positive	165 (31.4)	69 (16.6)	95 (87.2)	17 (94.4)	10 (90.9)	
Negative	360 (68.6)	346 (83.4)	14 (12.8)	1 (5.6)	1 (9.1)	
Smoking, n (%)						0.12[K]
Smoker	77 (14.7)	64 (15.4)	13 (11.9)	0	0	
Quit	50 (9.5)	31 (7.5)	19 (17.4)	3 (16.7)	0	
Non-smoker	398 (75.8)	320 (77.1)	77 (70.6)	15 (83.3)	11 (100.0)	
Comorbidity [a], n (%)						0.01[F]
Not present	299 (57.0)	266 (64.1)	33 (30.3)	2 (11.1)	1 (9.1)	
Present	226 (43.0)	149 (35.9)	76 (69.7)	16 (88.9)	10 (90.9)	
HT [c]	125 (23.8)	73 (17.6)	52 (47.7)	8 (44.4)	5 (45.5)	0.01[A]
DM [c]	73 (13.9)	42 (10.1)	31 (28.4)	7 (38.9)	4 (36.4)	0.01[A]
HL [c]	49 (9.3)	27 (6.5)	21 (19.3)	4 (22.2)	3 (27.3)	0.01[A]
Asthma/COPD [d]	48 (9.1)	26 (6.3)	22 (20.2)	6 (33.3)	4 (36.4)	0.01[A]
CVD [c]	34 (6.5)	17 (4.1)	17 (15.6)	4 (22.2)	2 (18.2)	0.01[A]
Kidney diseases [f]	10 (1.9)	4 (1.0)	6 (5.5)	2 (11.1)	2 (18.2)	0.01[A]
CVO [a]	8 (1.5)	1 (0.2)	6 (5.5)	2 (11.1)	2 (18.2)	0.01[A]
Drug utilization [d], n (%)						0.01[F]
No	176 (33.5)	161 (38.8)	15 (13.8)	1 (5.6)	0	
Yes	349 (66.5)	254 (61.2)	94 (86.2)	17 (94.4)	11 (100.0)	
Medications (ATC codes)						
Drugs for acid rel. dis. [1] (A02)	110 (21.0)	72 (17.3)	38 (34.9)	6 (33.3)	2 (18.2)	
Drugs used in diabetes (A10)	64 (12.2)	34 (8.2)	30 (27.5)	7 (38.9)	4 (36.4)	
Antithrombotic agents (B01)	43 (8.2)	21 (5.1)	22 (20.2)	5 (27.8)	3 (27.3)	
Cardiac therapy (C01)	12 (2.3)	3 (0.7)	9 (8.3)	2 (11.1)	1 (9.1)	
Diuretics (C03)	10 (1.9)	6 (1.4)	4 (3.7)	1 (5.6)	1 (9.1)	
Beta blocking agents (C07)	42 (8.0)	22 (5.3)	20 (18.3)	4 (22.2)	1 (9.1)	
CCBs [2] (C08)	28 (5.3)	12 (2.9)	16 (14.7)	5 (27.8)	4 (36.4)	
Agents acting on RAS [3] (C09)	82 (15.6)	46 (11.1)	36 (33.0)	7 (38.9)	3 (27.3)	
Lipid modifying agents (C10)	31 (5.9)	13 (3.1)	18 (16.5)	4 (22.2)	2 (18.2)	
Endocrine drugs [4] (H)	27 (5.1)	19 (4.6)	8 (7.3)	0	0	
Nervous system (N)	150 (28.6)	104 (25.1)	46 (42.2)	7 (38.9)	3 (27.3)	
Drugs for obst. air. dis. [5] (R03)	50 (9.5)	32 (7.7)	18 (16.5)	5 (27.8)	3 (27.3)	
Antihistamines for systemic use (R06)	42 (8.0)	31 (7.5)	11 (10.1)	2 (11.1)	1 (9.1)	
Polypharmacy [a], n (%)						0.01[F]
No	465 (88.6)	390 (94.0)	74 (67.9)	12 (66.7)	8 (72.7)	
Yes	60 (11.4)	25 (6.0)	35 (32.1)	6 (33.3)	3 (27.3)	
Total, n (%)	525 (100.0)	415 (100.0)	109 (100.0)	18 (100.0)	11 (100.0)	

ATC: Anatomical Therapeutic Chemical Classification System, [a] The differences between outpatient and hospitalization, outpatient and ICU, outpatient and mortality are statistically significant. [b] The differences between outpatient and hospitalization, hospitalization and mortality are statistically significant. [c] The difference between outpatient and hospitalization is statistically significant. [d] The differences between outpatient and hospitalization, outpatient and mortality are statistically significant. [e] The differences between outpatient and ICU, hospitalization and ICU, mortality, and ICU are statistically significant. [f] The differences between mortality and outpatient, mortality and hospitalization, mortality, and ICU are statistically significant. [1] Drugs for acid-related disorders, [2] Calcium channel blockers, [3] Renin-angiotensin system, [4] Systemic hormonal preparations, excluding sex hormones and insulins, [5] Drugs for obstructive airway diseases, [F] Fisher's exact test, [K] Kruskal-Wallis test, [A] One-way analysis of variance (ANOVA)

Figure 1: Treatment change according to the months of COVID-19.



HCQ: hydroxychloroquine, AZITHRO: azithromycin

The COVID-19 treatment approach varied from March 2020 to November 2020 (Figure 1). While in April 2020, the predominant treatment was hydroxychloroquine, by November 2020, the predominant treatment was favipiravir according to guidelines of the Turkish Ministry of Health. Considering the mortality, ICU admission and hospitalization rates by month, the highest mortality rate was seen in June 2020 at 4.8%. The highest hospitalization and ICU admission rate was seen in March 2020, 92.9% and 14.3%, respectively (Table 2).

Table 2: Hospitalization, ICU admission, and survival rates by month.

	Hospitalization, n (%)		ICU admission, n (%)		Survival, n (%)	
	Yes	No	Yes	No	Exitus	Alive
March 2020	13 (92.9)	1 (7.1)	2 (14.3)	12 (85.7)	0	14 (100.0)
April 2020	36 (34.6)	68 (65.4)	3 (2.9)	101 (97.1)	1 (1.0)	103 (99.0)
May 2020	11 (40.7)	16 (59.3)	2 (7.4)	25 (92.6)	1 (3.7)	26 (96.3)
June 2020	15 (35.7)	27 (64.3)	3 (7.1)	39 (92.9)	2 (4.8)	40 (95.2)
July 2020	5 (18.5)	22 (81.5)	0	27 (100.0)	0	27 (100.0)
August 2020	7 (11.3)	55 (88.7)	2 (3.2)	60 (96.8)	1 (1.6)	61 (98.4)
September 2020	8 (9.6)	75 (90.4)	0	83 (100.0)	0	83 (100.0)
October 2020	6 (10.7)	50 (89.3)	2 (3.6)	54 (96.4)	2 (3.6)	54 (96.4)
November 2020	8 (7.3)	102 (92.7)	4 (3.6)	106 (96.4)	4 (3.6)	106 (96.4)
Total	109 (20.8)	416 (79.2)	18 (3.4)	507 (96.6)	11 (2.1)	514 (97.9)

Increasing age was associated with an increased probability of hospitalization, mortality (P=0.01), and ICU admission (P=0.04). In addition, the presence of thoracic CT findings increased the probability of hospitalization 21 times (P<0.001), and polypharmacy increased the probability of hospitalization by two times (P=0.03). Those with thoracic CT findings were 18 times more likely to be admitted to the ICU than those without (P=0.01). Being married was associated with a reduced probability of ICU admission (P=0.02) (Table 3).

Table 3: Effects of demographic and other characteristics of patients on hospitalization, ICU admission, and mortality.

	Hospitalization		ICU admission		Mortality	
	OR (%95 CI)	*P*-value*	OR (%95 CI)	*P*-value*	OR (%95 CI)	*P*-value*
Age	1.0 (1.0-1.1)	0.01	1.0 (1.0-1.1)	0.04	1.1 (1.0-1.2)	0.01
Gender (Male)	1.7 (0.9-3.1)	0.11	3.2 (0.9-11.7)	0.07	1.6 (0.3-8.8)	0.58
Marital status (Alone)	0.6 (0.3-1.2)	0.15	0.2 (0.1-0.8)	0.02	0.2 (0.0-1.3)	0.10
Smoking	0.7 (0.3-1.7)	0.46	NA	1.00	NA	1.00
Being symptomatic	2.0 (0.9-4.7)	0.10	1.4 (0.2-12.7)	0.76	0.6 (0.1-6.4)	0.66
Thorax CT finding positivity	21.4 (11.0-41.6)	<0.001	18.6 (2.2-158.0)	0.01	7.0 (0.8-64.3)	0.08
Presence of comorbidity	1.0 (0.5-2.2)	0.98	2.6 (0.3-21.3)	0.37	0.7 (0.1-9.2)	0.81
Drug use	1.4 (0.6-3.3)	0.39	1.6 (0.1-23.8)	0.75	NA	1.00
Polypharmacy	2.7 (1.1-6.3)	0.03	0.8 (0.2 – 2.7)	0.72	0.4 (0.1-2.0)	0.29

NA: not applicable, *Logistic regression

The number of patients with asthma/chronic obstructive pulmonary disease (COPD) was 48 (Table 1). In 62.5% of these patients, COVID-19 thoracic CT findings were positive. Asthma/COPD was associated with developing thoracic CT findings; $x^2(1)=23.667$; P=0.007.

There was no statistically significant difference in developing COVID-19 thoracic CT findings between never smoked/quit smoking and being a smoker (P=0.13). The same was true when non-smokers were compared with quitting/smoking (P=0.25). The effects of medications chronically used in the previous 6 months before contracting COVID-19 on hospitalization, ICU admission, and death were analyzed using the logistic regression models adjusted for age and comorbidity. DM medications increased the probability of hospitalization by three times (P=0.03) (Table 4), while CCBs increased the probability of admission to the ICU 15 times (P=0.01) (Table 5) and the probability of mortality 295 times (P=0.01) (Table 6). When DM drugs are subdivided into metformin, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists, DPP4 inhibitors, SGLT-2 inhibitors, and insulin, in the logistic regression model adjusted for age and comorbidity, there was no statistically significant difference between the subgroups of DM medications in terms of effects on hospitalization, ICU admission, or mortality (P>0.05).

Table 4: Effects of medications utilized in the last six months before contracting COVID-19 on hospitalization.

	Hospitalization			
	OR	%95 CI		*P*-value*
Medications (ATC codes) [1]				
Drugs for acid related disorders (A02)	1.0	0.5	1.8	0.96
Drugs used in diabetes (A10)	3.9	1.2	13.0	0.03
Antithrombotic agents (B01)	1.4	0.5	3.9	0.52
Cardiac therapy (C01)	3.0	0.5	18.3	0.24
Diuretics (C03)	0.9	0.1	5.3	0.89
Beta blocking agents (C07)	1.2	0.4	3.4	0.78
Calcium channel blockers (C08)	1.5	0.6	4.1	0.41
Agents acting on renin-angiotensin system (C09)	0.9	0.4	2.3	0.86
Lipid modifying agents (C10)	2.8	0.7	11.6	0.16
Endocrine system agents [2] (H)	0.5	0.2	1.4	0.19
Nervous system (N)	1.5	0.9	2.6	0.15
Drugs for obstructive airway diseases (R03)	0.6	0.2	1.6	0.33
Antihistamines for systemic use (R06)	1.0	0.4	2.5	0.96
Covariates				
Age	1.1	1.0	1.1	<0.001
Hypertension	0.9	0.3	2.2	0.77
Cardiovascular disease	0.7	0.2	2.5	0.56
Cerebrovascular disease	1.2	0.2	9.5	0.83
Asthma/COPD [3]	2.4	0.9	6.2	0.07
Chronic kidney disease	1.5	0.3	6.9	0.62
Hyperlipidemia	0.4	0.1	1.3	0.12
Diabetes	0.5	0.2	1.7	0.28

[1]Anatomical Therapeutic Chemical Classification System, [2]Systemic hormonal preparations, excluding sex hormones and insulins, [3]COPD: chronic obstructive pulmonary disease, *Logistic regression

Table 5: Effects of medications utilized in the last 6 months before contracting COVID-19 on ICU admission.

	ICU admission			
	OR	%95 CI		*P*-value*
Medications (ATC codes) [1]				
Drugs for acid related disorders (A02)	0.3	0.1	1.9	0.22
Drugs used in diabetes (A10)	5.8	0.4	87.9	0.21
Antithrombotic agents (B01)	1.6	0.2	14.4	0.67
Cardiac therapy (C01)	0.6	0.0	15.6	0.79
Diuretics (C03)	0.2	0.0	6.2	0.34
Beta blocking agents (C07)	1.2	0.1	21.2	0.91
Calcium channel blockers (C08)	15.8	2.1	120.2	0.01
Agents acting on renin-angiotensin system (C09)	2.2	0.2	21.5	0.49
Lipid modifying agents (C10)	3.8	0.1	131.1	0.46
Endocrine system agents [2] (H)	0.0	0.0	NA[4]	1.00
Nervous system (N)	1.0	0.3	3.7	0.94
Drugs for obstructive airway diseases (R03)	0.9	0.1	7.6	0.90
Antihistamines for systemic use (R06)	1.0	0.1	8.2	0.98
Covariates				
Age	1.1	1.0	1.1	<0.001
Hypertension	0.0	0.0	0.6	0.02
Cardiovascular disease	3.5	0.4	33.8	0.28
Cerebrovascular disease	2.2	0.1	59.2	0.63
Asthma/COPD [3]	6.8	0.8	56.0	0.08
Chronic kidney disease	2.4	0.2	28.5	0.49
Hyperlipidemia	0.1	0.0	4.0	0.23
Diabetes	0.6	0.0	9,2	0.71

[1] Anatomical Therapeutic Chemical Classification System, [2] Systemic hormonal preparations, excluding sex hormones and insulins, [3] COPD: chronic obstructive pulmonary disease, [4] NA: not applicable, * Logistic regression.

Table 6: Effects of medications utilized in the last 6 months before contracting COVID-19 on mortality.

	Mortality			
	OR	**%95 CI**		***P*-value***
Medications (ATC codes) [1]				
Drugs for acid related disorders (A02)	0.0	0.0	1.7	0.08
Drugs used in diabetes (A10)	14.8	0.1	3929.6	0.34
Antithrombotic agents (B01)	11.8	0.6	245.0	0.11
Cardiac therapy (C01)	8.5	0.0	11943.9	0.56
Diuretics (C03)	0.0	0.0	2.2	0.09
Beta blocking agents (C07)	0.0	0.0	NA[4]	1.00
Calcium channel blockers (C08)	295.1	4.6	18946.6	0.01
Agents acting on renin-angiotensin system (C09)	0.5	0.0	12.8	0.68
Lipid modifying agents (C10)	114.4	0.0	NA[4]	0.36
Endocrine system agents [2] (H)	0.0	0.0	NA[4]	1.00
Nervous system (N)	0.1	0.0	1.9	0.14
Drugs for obstructive airway diseases (R03)	1.3	0.0	46.5	0.90
Antihistamines for systemic use (R06)	0.5	0.0	33.9	0.73
Covariates				
Age	1.1	1.0	1.3	<0.001
Hypertension	0.0	0.0	1.4	0.08
Cardiovascular disease	73.9	2.1	2622.5	0.02
Cerebrovascular disease	NA[4]	0.0	NA[4]	1.00
Asthma/COPD [3]	13.4	0.4	426.4	0.14
Chronic kidney disease	9.5	0.1	867.2	0.33
Hyperlipidemia	0.0	0.0	22.5	0.17
Diabetes	0.7	0.0	158.5	0.91

[1] Anatomical Therapeutic Chemical Classification System, [2] Systemic hormonal preparations, excluding sex hormones and insulins, [3] COPD: chronic obstructive pulmonary disease, [4] NA: not applicable, * Logistic regression.

Regarding COVID-19 pharmacological treatments, according to the Chi-square analysis that included only hospitalized patients, different COVID-19 pharmacological treatments were not associated with ICU admission and mortality (P>0.05).

Discussion

In this study, carried out in the first wave of COVID-19, the effects of demographic data and drugs chronically utilized in the last 6 months before contracting COVID-19 on the probability of hospitalization, ICU admission, and mortality were examined in primary care. Increasing age was associated with all three main endpoints of the study. In addition, the presence of COVID-19 thoracic CT findings and polypharmacy were associated with an increased probability of hospitalization while being alone, and the presence of COVID-19 thoracic CT findings was associated with an increased probability of ICU admission. Regarding drugs, DM medications increased the probability of hospitalization, and CCBs increased the probability of ICU admission and mortality.

Increasing age and comorbidity are important risk factors for the severe clinical course of COVID-19 since the beginning of the COVID-19 pandemic [1,2,4]. We also obtained similar results in our study; HT, DM, hyperlipidemia, asthma/COPD, cardiovascular, kidney, and cerebrovascular diseases were associated with the clinical course of COVID-19. It was observed that HT increased the probability of ICU admission, while CVD increased the probability of mortality 73 times.

Since the beginning of the pandemic, numerous studies have shown that ACEI/ARBs are associated with COVID-19 in harmful or protective ways. According to data from most large-scale studies and meta-analyses, RAS blockers do not change the clinical course of COVID-19 [7,19,20]. Similar findings were obtained in our study; it was observed that ACEI and ARBs did not affect the clinical course of COVID-19.

In our study, it was also observed that DM medications increased the probability of hospitalization 3-fold. However, it did not affect ICU admission and mortality. In the logistic regression analysis, DM medications were divided into metformin, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 agonists, DPP4 inhibitors, SGLT-2 inhibitors, and insulin; no significant difference was observed between the drug groups in terms of their effects on hospitalization. However, a Chi-square analysis revealed that all DM drug subgroups were associated with hospitalization, and SGLT-2 inhibitors were associated with mortality and admission to the ICU. In the literature, it is stated that the use of metformin is generally associated with a decrease in mortality due to COVID-19, while the use of insulin is associated with an increase [11,12,21].

Regarding other DM drug groups, some publications show different results from each other. In a study involving 2.85 million patients with type 2 DM in the UK, statistical evidence was presented that patients receiving metformin, SGLT2 inhibitors, and sulfonylurea treatments had a lower risk of death than those who did not take these drugs. The same study determined that the risk of death was higher in those given insulin and DPP-4 inhibitors than in those who did not [11].

According to Yang et al.'s [12] meta-analysis, which included 17 studies and analyzed data from approximately 21,000 patients, metformin was associated with significantly reduced mortality in COVID-19 patients with DM. Regarding insulin therapy, in Yu et al.'s study, in addition to matching other medical characteristics, propensity score matching was applied to HbA1c levels, and insulin therapy was associated with increased mortality. It has been stated that insulin therapy at a more advanced stage in type 2 DM may be a residual confounding factor, although pairings have been made [21]. Unfortunately, we could not make a match based on the clinical level of DM in the case of DM drugs. In our study, which included 525 COVID-19 patients, 64 were diagnosed with DM and 64 received DM medication. When DM medications were divided into subgroups, there was no difference in their effects on the three main endpoints of this study, which may be due to the small patient groups. Regarding DPP4 inhibitors, a meta-analysis stated that they were associated with higher mortality in COVID-19 patients [11], whereas another stated the opposite [15]. In Hariyanto et al.'s [16] study, DPP-4 inhibitors did not change the severity of COVID-19.

In our study, CCBs are closely related to ICU admission and increased mortality. Studies were showing parallel findings [22,23]. In Mendez et al.'s [22] study, including 245 HT patients hospitalized due to COVID-19, 75 patients using CCBs and 175 patients not using CCBs were compared. CCB group had a significantly increased risk of intubation or death. In Jackson et al.'s [23] study, the need for mechanical ventilation and mortality were investigated in 297 hospitalized COVID-19 patients; prior ARB or CCB use was found to double the probability of mortality. According to a population case-control study, the risk of developing COVID-19 symptoms in people with HT who received CCBs was significantly increased, and disease risk was significantly lower in ARB and diuretic users [24].

On the other hand, studies indicating that CCBs reduce the mortality of COVID-19 or the possibility of serious illness

have also been published [25,26]. A study by Chouchana et al. [26], which included 3686 patients with HT hospitalized for COVID-19, demonstrated that CCBs reduced the probability of mortality [25]. In a meta-analysis, there was a significant reduction in all-cause mortality and disease severity in CCB users.

Considering why CCBs may worsen the COVID-19 clinic, as in our study, CCBs can inhibit type II pneumocyte secretion, leading to alveolar collapse [27]. In addition, precapillary vasodilation due to CCBs may cause alveolar edema [28–31]. Another reason may be that CCBs may cause hypoxic pulmonary vasoconstriction in patients with pulmonary disease, leading to profound hypoxemia [22,32–35]. On the other hand, the reason why CCBs may improve the clinical course of COVID-19 is that calcium is necessary for the virus's life cycle, so CCBs cause depletion in intracellular calcium, interfering negatively with the life cycle process [36,37]. *In vitro* studies suggest that CCBs can be used in therapy by reducing intracellular calcium levels, which provide the environment for virus entry [38]. Additionally, some studies have demonstrated the anti-inflammatory and anticoagulant effects of CCBs [37,39].

When we examined the effect of marital status on the clinical course of COVID-19, we found that being married reduced the possibility of ICU admission. In the literature, we could not find any other study examining the effect of marital status on the clinical course of COVID-19. In addition, publications are investigating the relationship between being married or living alone with the frequency of anxiety and depression during the COVID-19 pandemic; in these studies, it was stated that the frequency of depression was higher in the COVID-19 pandemic in those who were single [40,41]. This may lead to suppression of the immune system and be associated with a worse clinical course of COVID-19. It needs to be confirmed by larger studies.

Strengths and limitations

This study is the first study in Turkey investigating the relationship between drug utilization in chronic diseases and COVID-19 clinical course using primary care data. In the study by Senkal et al. [42], 611 hospitalized COVID-19 patients were included in the study, and they aimed to reveal the possibility of severe COVID-19 clinics in patients under ACEI or ARB treatment. It was concluded that chronic ACEI exposure was associated with a reduced likelihood of serious disease. Since our study presented primary care data, we had the opportunity to compare the effects of chronically used drugs on the clinical course of COVID-19 between outpatients diagnosed with COVID-19 and patients admitted to the hospital, ICU, or death. It is known that some genetic and ethnic factors under investigation, especially ACE2 and TMPRSS2 expression, may predispose to COVID-19. Accordingly, it has been reported that some patients might experience the disease more severely or mildly [17,18]. In this context, studies conducted in different countries that reveal the factors affecting the clinical course of COVID-19 gain importance.

One of the limitations of our study is that it was impossible to exclude all confounders since this study was retrospective. For example, since the anthropometrics of the patients were not known, the presence of overweight status was unknown if the obesity diagnosis was not stated in the patient records. Other than that, when the study population of 525 was subdivided, there was a small number of patients for comparison. Regarding CCBs, although the established logistic regression models have been adjusted for age and comorbidity, it should be considered that they are mostly used in the elderly hypertensive population.

Conclusion

We have demonstrated that increasing age, HT, and CVD are associated with the severe clinical course of COVID-19; being married reduces the probability of ICU admission due to COVID-19. Concerning drugs, DM medications increased the probability of hospitalization 3-fold, while CCBs increased the probability of ICU admission 155-fold and mortality 295-fold. On the other hand, it was observed that RAS blockers (ACEIs and ARBs) did not affect the clinical course of COVID-19. Larger cohort studies and meta-analyses, as with ACEI and ARBs, are needed for CCBs and DM medications.

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The relationship between renal resistive index and hypertensive end-organ damage: A cross-sectional study

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Ethics Committee Approval
The study was approved by Health Sciences University Samsun Research and Training Hospital ethics committee (date: 1 June 2021, decision number: GOKA/2021/11/5). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The prevalence of hypertension increases with age and one out of every three adults over the age of 40 has hypertension. Hypertensive end-organ damage is an important predictive factor for patient morbidity and mortality. This study aimed to investigate the role of the renal resistive index (RI) in predicting retinopathy and nephropathy in hypertensive patients.
Methods: This study was cross-sectional in design. Sixty hypertensive patients who were followed in Samsun Research and Training Hospital Internal Medicine outpatient clinic were included in the study. In all patients, a routine ophthalmological examination, including visual acuity, anterior segment examination, and dilated ocular fundus examination, was performed. Urinary albumin to creatinine ratio (mg/g) was measured in spot urine samples, and a level ≥30 mg/g was accepted as the presence of proteinuria. Renal Doppler ultrasonography was performed using Esaote mylab x 9 model sonography device vovex probe (C1-8) 3.5 MHz. RI values were measured using Xflow Doppler at the level of interlobular or arcuate arteries of both kidneys. First, the patients were divided into two groups (with or without retinopathy). The patients who had retinopathy were then divided into two groups according to their retinopathy degree. Hypertensive retinopathy was graded according to the Scheie classification. The patients were also divided into two groups according to their proteinuria status (with or without proteinuria).
Results: The mean of renal RI was 0.59 (0.04) in patients without retinopathy (n=15), 0.63 (0.05) in patients with grade 1 hypertensive retinopathy (n=29), and 0.66 (0.04) in patients with grade 2 hypertensive retinopathy (n=15). The difference between groups was statistically significant (overall P=0.001). It has been shown that proteinuria develops more frequently in cases in which the renal value is above 0.7, and these results were statistically significant (P=0.034).
Conclusion: This study indicates that renal RI increase is a valuable tool for estimating retinopathy and proteinuria in hypertensive patients.

Keywords: hypertensive end-organ damage, renal resistive index, retinopathy, nephropathy

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Introduction

The prevalence of hypertension varies in the adult population and increases with age. One out of every three adults over the age of 40 has hypertension. Hypertensive end-organ damage is an important problem that causes morbidity and mortality. For this reason, in the latest international hypertension guidelines, medical treatment is recommended in addition to lifestyle modifications for people whose end-organ damage risk is increased and whose blood pressure level is above 130/85 mmHg [1,2]. Hypertension-related end-organ damage is an important predictive factor for cardiovascular risk [3]. The length of time that a patient has been hypertensive and his/her arterial blood pressure are major determinants of hypertension-related organ damage. To investigate the effects of high blood pressure, a 24-h ambulatory blood pressure measurement was performed on 130 hypertensive patients, and it was found that myocardial wall thickness and peripheral vascular resistance were higher in patients with higher mean systolic blood pressure [4]. The European Society of Cardiology hypertension diagnosis and management guidelines strongly suggest using the Systematic COronary Risk Evaluation (SCORE) system during the treatment of hypertensive patients [1]. This scoring system aims to identify high-risk patients in the early period and to initiate medical treatment earlier for patients with high cardiovascular risk. Predicting cardiovascular risk, especially in young patients or newly diagnosed hypertensive patients, is possible using this scoring system.

Hypertensive retinopathy, hypertensive nephrosclerosis, hypertension-related cerebrovascular changes, and left ventricular hypertrophy are the major hypertension-related end-organ injuries. The risk of stroke in patients with retinopathy is a frequently studied topic because of the close relationship between retinal and cerebral vascularity. It has been previously shown in a study that the presence of hypertensive retinopathy is associated with an increased risk of stroke, and the risk of stroke increases as the retinopathy degree increases [5]. In another study, in which hypertensive retinopathy was divided into severe and mild, it was shown that the risk of hemorrhagic stroke correlated with the severity of retinopathy [6].

Considering studies examining the relationship between hypertensive retinopathy and coronary artery disease, Duncan et al.'s study concerning middle-aged male patients revealed that retinal microvascular changes led to an increase in the risk of coronary artery disease and related events that are 2.1 times in the high-risk versus the low-risk patient group [7].

The pathogenesis of hypertensive retinopathy is believed to consist of complex and intertwined phases rather than progressing via sequential steps. These phases are defined as the vasoconstrictive, exudative, sclerotic, and complicated sclerotic phases [8].

The presence of microalbuminuria in hypertensive patients at the time of diagnosis is a risk factor for the presence of left ventricular hypertrophy [9]. It has been shown that in patients with a diagnosis of essential hypertension, an elevation in the the renal resistive index (RI) occurs. The index is correlated with carotid intima–media thickness and microalbuminuria [10]. The RI is the ratio of peak systolic velocity to end-diastolic velocity in the flow pattern of vascular structure and is an indicator of vascular resistance.

This study aimed to investigate the role of the renal RI in predicting retinopathy and nephropathy in hypertensive patients.

Materials and methods

This study was cross-sectional in design. Sixty hypertensive patients who were monitored in the Samsun University, Samsun Research and Training Hospital Internal Medicine outpatient clinic were included in the study. The patients were divided into three groups according to their retinopathy development status: (1) those who did not develop retinopathy, (2) those who developed stage 1 retinopathy, and (3) those who developed stage 2 retinopathy. All patients were also divided into two groups according to their proteinuria status.

To determine the number of patients to be included in the study, a power calculation was done, and the minimum number of patients recommended for study inclusion was found to be 60 with 80% power and 95% confidence interval at a $P < 0.05$ significance level [11]. In all patients, a routine ophthalmological examination, including visual acuity, anterior segment examination, intraocular pressure measurement, and dilated ocular fundus examination, was performed. Fundus examination was done after instilling tropicamide 1% and cyclopentolate 1% eye drops, and retinal abnormalities were noted and graded according to Scheie classification (*): (1) Grade 0: No visible changes; (2) Grade 1: barely detectable arterial narrowing; (3) Grade 2: obvious arterial narrowing with focal irregularities; (4) Grade 3: grade 2 plus retinal hemorrhage, exudates, cotton wool spots, or retinal edema; and (5) Grade 4: grade 3 plus papilloedema [12].

Venous blood samples following 12 h of fasting were collected to measure blood glucose, creatinine, and glycosylated hemoglobin levels. Urinary albumin to creatinine ratio (mg/g) was also measured and calculated in spot urine samples. Conditions that could cause false positive measurements in urinary albumin excretion were evaluated and the measurement was repeated after that. Albumin to creatinine ratio ≥30 mg/g was accepted as the presence of albuminuria [13].

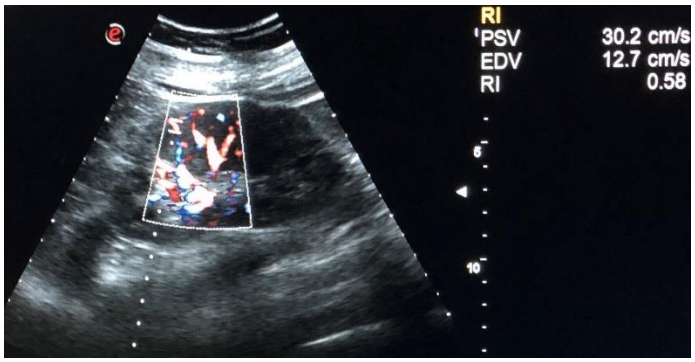
Renal doppler ultrasonography was performed using Esaote mylab x9 model sonography device vovex probe (C1-8) 3.5 MHz. The patients were examined under supine and bilateral decubitus positions. Bilateral renal parenchymal thickness and length were measured in the long axis plane with B-mode. RI values were measured at the level of interlobular or arcuate arteries from the upper, middle, and lower parenchyma of the kidney with Xflow Doppler, and measurements were taken at least three times after which average values were obtained (as shown in Figure 1).

The duration of hypertension and patients' demographic characteristics were recorded to evaluate the risk factors affecting retinopathy. Patients with a diagnosis of secondary hypertension, those with known chronic kidney disease, those with a diagnosis of diabetes mellitus, and/or those under the age of 18 were excluded from the study.

The ethical evaluation of our study was performed by Samsun University Samsun Research and Training Hospital

ethics committee, and it was approved on 1.6.2021 with the decision number GOKA/2021/11/5.

Figure 1: X-Doppler image of resistive index (RI) measurement at the level of the interlobular and arcuate arteries



Statistical analysis

The statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) Program Version 22.0. Normally distributed continuous variables were expressed as mean (standard deviation), while non-normally distributed continuous variables were expressed as median (lowest–highest). Categorical variables were expressed as n (%). A chi-squared test was used to compare the variables between groups. One-way analysis of variance (ANOVA) and post hoc Tukey honestly significant difference (HSD) tests were used to compare continuous variables between the groups. A receiver operating characteristic (ROC) curve analysis was done to determine the RI cut-off value. A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 60 hypertensive patients, including 38 women, and 22 men, were included in the study. The mean age was 52.6 (11.8) years. The median duration of hypertension in the patients was 4 years (0–40 years). According to the calculated urinary albumin excretion (UAE), the number of patients with a UAE of 30 mg/g and above was 22 (36.7%) while the number of patients without proteinuria was found to be 38 (63.3%).

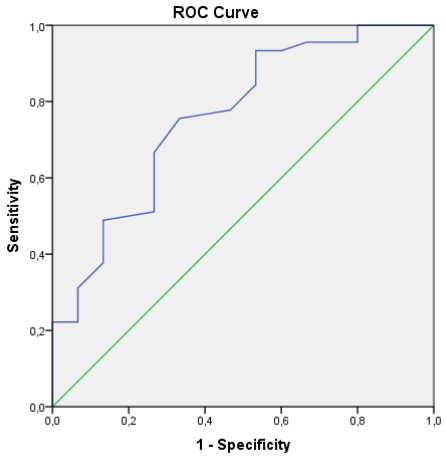
The number of patients without retinopathy was 15 (25%), the number with grade 1 retinopathy was 29 (48.3%), and the number with grade 2 retinopathy was 16 (26.7%).

RI measurements were obtained from all 60 patients, and 18 (30%) patients with a mean renal RI value below 0.61 and 42 (70%) patients with RI value above 0.61 were noted.

According to the ROC curve analysis, the RI cut-off value to determine retinopathy was determined as 0.61 with a sensitivity of 76% and specificity of 67%. The area under the curve (AUC) was 0.761 with 95% confidence interval (CI) values for AUC ranging from 0.619 to 0.903. The ROC curve is shown in Figure 2. It was shown that in patients with a greater RI level, hypertensive retinopathy frequency significantly increased (Table 1).

The mean of renal RI values was 0.59 (0.04) in patients without retinopathy (n=15), 0.63 (0.05) in patients with grade 1 hypertensive retinopathy (n=29), and 0.66 (0.04) in patients with grade 2 hypertensive retinopathy (n=15). The difference between groups was statistically significant (overall *P*=0.001). In the post hoc analysis, it was determined that this difference was due to the difference between those without retinopathy and those with grade 1 retinopathy (*P*=0.047) and those without retinopathy and those with grade 2 retinopathy (*P*=0.001). No statistically significant difference between the grade 1 and the grade 2 retinopathy groups was found (*P*=0.11).

Figure 2: Receiver operating characteristic (ROC) curve to determine retinopathy



Diagonal segments are produced by ties.

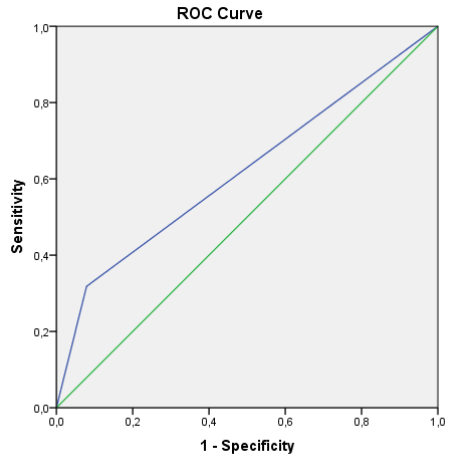
Table 1: The effect of the renal resistive index (RI) on retinopathy

	Retinopathy (-) n (%)	Retinopathy (+) n (%)	*P*-value*
Renal resistive index			
<0.61	8 (44.4)	10 (55.6)	0.023
≥0.61	7 (16.7)	35 (83.3)	
Renal resistive index	**Grade 0-1 retinopathy n (%)**	**Grade 2 retinopathy n (%)**	
<0.61	17 (94.4)	1 (5.6)	0.015
≥0.61	27 (64.3)	15 (35.7)	

*Pearson Chi-Squared Test

According to the ROC curve analysis, RI cut-off value to determine proteinuria was determined as 0.63 with a sensitivity of 64% and specificity of 5%. The AUC was 0.620 with a 95% CI range for the AUC ranging from 0.465 to 0.774 The ROC curve is shown in Figure 3.. A significant relationship between RI increase and proteinuria status could not be shown (Table 2). Moreover, Spearman's test showed that renal RI levels did not correlate with the level of proteinuria (r=0.226; *P*=0.09).

Figure 3: ROC curve according to determine microalbuminuria



Diagonal segments are produced by ties.

Table 2: The effect of the renal resistive index on proteinuria

	UAE <30 mg/g n (%)	UAE ≥30 mg/g n (%)	*P*-value*
Renal resistive index			
<0.63	22 (73.3)	8 (26.7)	0.108
≥0.63	16 (53.3)	14 (46.7)	

UAE: urinary albumin excretion

Discussion

Hypertension-related end-organ damage is an important marker of cardiovascular risk. Retinal, glomerular, and cerebral vascular damage due to hypertension constitute the trivet of microvascular complications. Mild hypertensive retinopathy (grades 1 and 2) is associated with an increase in cardiovascular and stroke risks [14].

The risk of stroke in patients with retinopathy is a frequently studied topic because of the close relationship between retinal and cerebral vascularity [5]. Duncan et al.'s study on middle-aged male patients revealed that retinal microvascular changes lead to an increase in the risk of coronary artery disease and related events that is 2.1 times more in the high-risk patient group versus normal subjects [7].

In a study conducted on hypertensive individuals over the age of 65, it was shown that the risk of hypertensive retinopathy increases as the UAE level increases [15]. In another study on renal resistive index and hypertension, it was shown that as RI increases, the incidence of proteinuria and carotid intima–media thickness increases in hypertensive individuals [10]. However, not enough studies examining the role of RI in predicting hypertensive retinopathy have been published..

Diabetic patients were not included in our study due to the increased incidence of retinopathy in diabetic patients and the fact that it is not always possible to reveal the underlying cause of retinopathy and nephropathy development in the presence of hypertension in this patient group. To exclude diabetic patients, the patients were questioned in terms of their past medical history, and venous plasma glucose and glycosylated hemoglobin values were measured in all patients after 12 h of fasting. If the patients were diagnosed with diabetes mellitus according to the new measurements, they were excluded from the study.

Previous studies demonstrated that the renal RI increases in the presence of diabetic retinopathy compared to the healthy population [16]. We think that exclusion of diabetic patients in our study is valuable for measuring the relationship between the renal RI and hypertensive end-organ damage. It was shown in a previous study that ambulatory arterial stiffness index increase was correlated with hypertensive end-organ damage. In that study, the effect of ambulatory arterial stiffness index on hypertensive end-organ damage did not differ between those patients who were on antihypertensive medications and those who were not [17].

It is also known that renal RI values increase due to glomerulosclerosis development in the presence of chronic renal failure [18]. For this reason, the glomerular filtration rate (GFR) was calculated by measuring the creatinine level of all patients included in the study.

As a result of the analysis of 60 patients who met these criteria, it was observed that the frequency of retinopathy was higher if the RI value was 0.61 and above. Renal RI values greater than 0.61 may predict hypertensive retinopathy with 77.8% sensitivity and 83.4% positive predictive value. For this reason, we think that RI can be used to indicate end-organ damage in hypertensive patients; thus, cardiovascular risk factors should be reviewed more carefully in patients with high RI levels.

Proteinuria and ultimately nephrosclerosis are important end-organ damage events in patients with hypertension. Ozmen et al. [19] reported that renal RI values increase in patients with diabetic nephropathy, and the levels of proteinuria were found to correlate well with intrarenal RI.. Our results show that proteinuria is slightly increased in patients with higher renal RI levels. It was shown in our study that proteinuria develops more frequently in cases in which the renal RI value is above 0.7, and these results were statistically significant. Our result is compatible with some other studies in the literature in which the risk of proteinuria increases above an RI cut-off value of 0.7 [20,21].

However, some investigators mention that RI cut-off levels should be determined according to the patient group and for this reason, we performed an ROC curve analysis to determine the best cut-off level [22,23]. Unfortunately, when we re-evaluated the results according to the measured cut-off level ROC curve analysis, no significant difference between the patients with and without microalbuminuria was found.

Limitations

In our study, no patient with advanced stage (grade 3/4) retinopathy participated in the study. We would like to point out this situation as the most important limitation of our study. To generalize the results of the study, we think that prospective studies are needed by including more patients with all four stages of hypertensive retinopathy.

Conclusion

This study shows that renal RI levels increase in hypertensive nondiabetic patients who have retinopathy. Renal RI starts to increase earlier than the glomerular filtration decline in hypertensive patients who have retinopathy. This increase is an important point for identifying patients at high risk for hypertensive end-organ damage.

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Plateletcrit as a prognostic marker in Hodgkin lymphoma: A pilot study

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Ethics Committee Approval
The study was approved by the Ethics Committee of Suleyman Demirel University Faculty of Medicine (dated 11.03.2021 and numbered 137). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Hodgkin lymphoma (HL) is a lymphoproliferative malignancy associated with inflammation. Plateletcrit (PCT) is a mean platelet volume (MPV) and platelet count-derived marker that is useful for evaluating malignancies and inflammatory diseases. International Prognostic Score (IPS-7) and more recently, IPS-3, are two indices indicating the prognosis of patients; however, widespread and easy to interpret prognostic markers are still needed for HL evaluation. Very few studies evaluating the prognostic significance of platelet indices in HL have been published, so we aimed to show the relationship between PCT and other adverse prognostic factors in HL and evaluate whether PCT can be used as a prognostic marker in HL.

Methods: After excluding patients with insufficient data, 75 patients diagnosed with HL and 150 healthy controls were retrospectively analyzed in this case-control study. Evaluation of relationship of PCT and adverse HL prognostic factors, such as age, gender, hemoglobin, leukocytes, lymphocytes (absolute value and percentage), albumin, Ann Arbor stage and B symptoms, IPS-3 and-7 prognostic scores and post-treatment relapse, and progression-free survival of the patients were studied.

Results: Mean MPV values were significantly lower, mean platelet values were significantly higher inpatient group (all $P<0.001$). Patients with high sedimentation had significantly higher mean PCT than those without ($P=0.031$) and a moderately positive correlation between PCT and sedimentation were found ($r=0.33$, $P<0.01$). Mean PCT values after treatment significantly decreased compared to baseline levels ($P<0.001$).

Conclusion: PCT may be useful as a prognostic marker in HL. Further studies were needed to evaluate the relationship between PCT and other prognostic factors, such as IPS-3 and -7.

Keywords: plateletcrit, Hodgkin lymphoma, prognosis

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Introduction

Hodgkin Lymphoma (HL) is a rare lymphoproliferative disease with an incidence of 2 to 3/100000 and a peak incidence of twenty to thirty years [1]. Epstein-Barr virus seems to play a major, although not essential, part in pathogenesis, and viral DNA can be found in substantial proportion of lymph node specimens [2]. The Reed–Sternberg cell, hallmark of the disease, has substantial portions of inflammatory regions compared to malignant ones [3]. These cells are surrounded by large number mature lymphocytes and pro-inflammatory cells showing the inflammatory nature of HL. The disease can be sub-grouped as classic and nodular lymphocyte predominant HL, and 95% of patients are diagnosed as classic HL [4]. Positron emission computed tomography/computed tomography (PET/CT) is generally used for staging and guiding treatment strategies, such as chemotherapy and radiotherapy. Approximately 80% of patients can be cured with a combined modality approach, but only 50% of relapsed patients can achieve long-term success with autologous stem cell transplantation; therefore, research to find different solutions for these patients is ongoing [5]. Programmed death protein 1 (PD-1), a transmembrane protein responsible for T-cell exhaustion and inactivation in peripheral tissues, and cytotoxic T-lymphocyte-associated antigen 4, a T-cell inhibitor found on T cells located in lymph nodes, has attracted much attention since Reed–Sternberg cells also use these pathways to evade immune response [6]. Due to immune mechanisms responsible in the origin and pathogenesis of HL, immune checkpoint inhibitors, such as nivolumab and pembrolizumab, are increasingly used in general practice [7].

Platelets originate from megakaryocytes in the bone marrow and are primarily responsible for the primer stage of hemostasis. In recent years, their role in the immune system has been highlighted asthey release pro-inflammatory cytokines, are responsible for phagocytosis of microbes, mediate leukocyte migration and netosis [8]. Mean platelet volume (MPV) represents the area of platelets in circulation and is associated with platelet activation. Plateletcrit (PCT) is a MPV-bound platelet index and usually associated with inflammatory diseases and cancer [9,10]. Given the inflammatory pathways responsible for HL, the association of platelet indices and HL poses an unanswered question that remains to be determined. Very few studies regarding this issue are available, so in this study, we evaluated whether any relationship between HL, its therapy, and other prognostic factors and PCT exist.

Materials and methods

Two hundred patients diagnosed with HL and treated in our hospital from 2010 to 2020 and 150 healthy controls were retrospectively included in the study. After excluding patients with insufficient data, 75 patients diagnosed with HL and 150 healthy individuals (control group) were retrospectively analyzed. The control group consisted of healthy blood donors who had a complete blood count evaluation before donation. Those who had a diagnosis of chronic inflammatory disease, chronic infection, and/or malignancy in the control group were excluded from the study. In the patient group, the complete blood count at diagnosis and after therapy was recorded, and PCT was calculated. First, whether MPV and PCT differed significantly in patient group was checked after which the evaluation of the relationship between PCT and age, gender, hemoglobin, leukocytes, lymphocytes (absolute value and percentage), albumin, Ann Arbor stage and B symptoms, IPS-3 and -7 prognostic scores, post-treatment relapse, and progression-free survival of the patients was determined. Progression-free and overall survival results were recorded as months.

Statistics analysis

Statistics analyses were performed using a package program. Descriptive statistics were represented as number, percentage, mean, and standard deviation. Conformity of continuous variables to normal distribution was examined. Student's t-Test was used for the comparison of normally distributed variables in two independent groups, and the Mann_Whitney U Test was used for non-normally distributed variables. A Kruskal–Wallis multiple comparison test was used to compare more than two independent groups that did not fit normal distribution. The difference in frequency between the groups was compared using the chi-squared test. Dependent group Student's t-Test was used for comparisons of measurements with pairwise times. The relationship between the variables was determined by Pearson's correlation analysis. In multivariate analyses, the independent effects of possible factors (variables associated with univariate analysis and close to the type 1 error level [cut-off value P=0.25]) on PCT were examined using a linear regression model. The variance inflation factor (VIF) values were examined for the multicollinearity problem among the independent variables. Those above VIF 3 were not included in the model. The "enter" method was used for linear regression analysis. The model fit was examined using the required residual and fit statistics.

The approval of the Ethics Committee of Suleyman Demirel University Faculty of Medicine dated 11.03.2021 and numbered 137 were obtained for the study. Informed consent was obtained from all the participants, and all study steps were performed in accordance with Declaration of Helsinki.

Results

The mean age of Hodgkin patients at diagnosis was 51.1 (17.8; min 20–max 86), while the mean age of the control group was 48.3 (10.3; min 20–max 66). In the first phase of the study, patients and those in the control group were compared, and the results are presented in Table 1. No differences between the HL group and the controls in terms of age and gender were found (P=0.214 and P=0.100, respectively). Compared to the control group, mean MPV values were found to be significantly lower and PLT mean values were found to be significantly higher in the HL group (P<0.001and P=0.001, respectively). Although the mean PCT values in the HL group were higher than the control group, this difference was not statistically significant (P=0.107, Table 1).

PCT values of patients at diagnosis and the factors affecting this value were examined in univariate and multivariate analyses (Table 2). No significant differences were found with PCT according to age, gender, presence of B symptoms, Ann-Arbor stage, relapse status, IPS-3 and -7 scores, subtypes, presence of bulky lesions, chemotherapy, and total and

progression-free survival of patients. It was found that patients with sedimentation counts higher than 50 mm/h had significantly higher mean PCT than those without (P=0.031). In the linear regression model, each unit increase in sedimentation count caused a significant increase in the PCT value by 0.001 units (P=0.003, Table 2).

Table 1: Differences between Hodgkin lymphoma and control group

Characteristics	HL	Control group	*P*-value
Age*	51.1 (17.8)	48.3 (10.3)	0.214
Gender**			
Women n (%)	28 (37.3%)	40 (26.7%)	0.100
Men n (%)	47 (62.7%)	110 (73.3%)	
PCT*	0.217 (0.08)	0.202 (0.03)	0.107
MPV*	7.8 (1.0)	8.4 (0.8)	<0.001
PLT*	293.2 (120.9)	242.9 (47.4)	0.001

* independent groups T-test, ** Chi-square test, PCT: Plateletcrit, MPV: Mean Platelet Volume, PLT: Platelet, HL: Hodgkin Lymphoma

Table 2: Factors Associated with plateletcrit counts in patients with HL

Characteristic		n	Single analysis		Multiple analysis ¥	
			Mean (SD)	*P*-value	B (95% CL)	*P*-value
Age µ	50≤	37	0.205(0.07)	0.172	0.001(0.000-0.001)	0.233
	50>	38	0.230(0.09)			
Gender µµ	Woman	28	0.209(0.08)	0.472		
	Man	47	0.223(0.08)			
B Symptom µ	Available	30	0.214(0.09)	0.755		
	None	45	0.220(0.07)			
Ann-arbor*	1	3	0.246(0.06)	0.284		
	2	31	0.218(0.06)			
	3	29	0.230(0.08)			
	4	12	0.179(0.11)			
Relapse µµ	Available	13	0.211(0.10)	0.955		
	None	62	0.219(0.08)			
Ips3 *	0	23	0.221(0.06)	0.192	-0.02(-0.044-0.004)	0.094
	1	34	0.217(0.08)			
	2	11	0.249(0.10)			
	3	7	0.158(0.10)			
Ips7 *	0	8	0.230(0.05)	0.091		
	1	18	0.202(0.07)			
	2	18	0.213(0.05)			
	3	15	0.216(0.09)			
	4	12	0.233(0.11)			
	5	2	0.377(0.07)			
	6	2	0.112(0.02)			
Subtype*	Classical HL	16	0.217(0.10)	0.300		
	Lymphocyte Predominant	6	0.216(0.06)			
	Mix cellular	25	0.226(0.07)			
	Nodular sclerosan	22	0.225(0.08)			
	Lymphocyte rich	5	0.169(0.04)			
	Lymphocyte depleted	1	0.098(0.00)			
Bulky lesion µµ	Available	5	0.206(0.10)	0.705		
	None	70	0.219(0.08)			
Sedim µµ	50≤	44	0.203(0.06)	0.031	0.001(0.00–0.001)	0.003
	50>	31	0.238(0.10)			
PFS *	50≤	39	0.209(0.09)	0.544		
	51-100	16	0.221(0.07)			
	101-150	14	0.224(0.09)			
	150>	6	0.252(0.04)			
OS *	50≤	31	0.209(0.08)	0.210	0.00(0.000–0.001)	0.231
	51-100	20	0.211(0.09)			
	101-150	16	0.220(0.08)			
	150>	8	0.263(0.04)			
CT *	ABVD	65	0.212(0.08)	0.794		
	BEACOOP	8	0.221(0.11)			
	DHAP	2	0.218(0.18)			
Total		75	0.218(0.08)			

Data were presented as mean (standard deviation). µ independent groups T test, µµ Mann–Whitney U test, *Kruskal–Wallis test, ¥ model fit values for multiple regression analysis. (R=0.422; R Square=0.178; Adjusted R Square=0.131; Durbin–Watson=1.910). PFS: Progression free survival, OS: Overall survival, CT: Chemotherapy, Sedim: Sedimentation, ABVD: Adriamycin–Bleomycin–Vinblastine–Dacarbazine, BEACOPP: Bleomycin–Etoposide–Adriamycin–Cyclophosphamide–Oncovin–Procarbazine–Prednisone, DHAP: Dexamethasone, high dose Cytarabine–Cisplatin, PCT: plateletcrit: IPS: International Prognostic Score

Correlations between the mean PCT value of patients and their variables were examined. A moderately negative correlation (r=–0.38) between PCT and MPV values of patients was found, and a moderately positive correlation between PCT and sedimentation was also found (r=0.33; P<0.01, Table 3).

The mean PCT value of male patients was 0.223 (0.08) at diagnosis and PCT significantly decreased to 0.172 (0.06; P<0.001) after chemotherapy. An insignificant decrease was found in female patients after treatment (P=0.226). When all patients were evaluated together, mean PCT values at diagnosis and after chemotherapy were 0.218 (0.08) and 0.177 (0.07), respectively, and this decrease was also significant (P<0.001).

Table 3: Correlation of PCT Counts and Other Variables in HL Patients

Characteristic	PCT (r)
Age (r)	0.07
MPV (r)	-0.38**
PFS (r)	0.21
OS (r)	0.22
SEDIM (r)	0.33**

**P<0.01, r: Pearson correlation coefficient, PCT: Plateletcrit, MPV: Mean Platelet Volume, PFS: Progression free survival, OS: Overall survival, SEDIM: Sedimentation

Discussion

IPS-3 and -7 are new scoring systems for evaluating the prognosis of HL. The IPS-7 score incorporates age, gender, albumin count, hemoglobin, white blood cell count and lymphopenia and highlights prognosis at diagnosis. Recently, it was shown that the IPS-3 score (age, hemoglobin >10.5 g/dl, and stage) defined comparable results to those defined in IPS-7 [11]. It is necessary to evaluate new and easily available prognostic factors, such as IPS-3. In our study, mean platelet count was significantly higher and mean MPV value was significantly lower in HL patients. Increased platelet counts could be attributable to malignancy, which is an etiological factor that is associated with secondary thrombocytosis. Karagoz et al. [12] has shown an increase in platelet counts compared to controls in colon malignancy occurs. Decreased MPV can be seen in a variety of diseases, such as inflammatory bowel diseases, systemic lupus erythematosus, and neoplasm [13]. Decreased MPV values were found in lung and cervical cancer in which a pre-operative low MPV count was considered an adverse prognostic factor [14,15]. Only one study evaluating the prognostic status of MPV in HL has been published. While MPV was not used as a prognostic marker in this study, mean MPV was significantly lower in patients with venous thromboembolism compared to those without [16].

Platelet counts were also elevated significantly in the patient group compared to controls. Platelets were found to be elevated in a variety of cancers and high platelet count was associated with metastatic disease and poor prognosis [17]. Thrombocytosis was found to be a common finding in lymphomas [18]. We also found significantly higher mean platelet values in HL patients in agreement with studies in the literature.

High PCT was found to be an adverse prognostic factor in non-small cell lung cancer [10]. Also, high PCT levels were significantly associated with tumor stage, size, and vascular invasion in colorectal carcinoma [19]. We found that mean PCT was higher in patients compared to control group even though the difference was insignificant. This finding could be attributed to two reasons. First, mean platelet count was higher and mean MPV was lower in the HL group. PCT is associated with both variables, so this association could be the reason for insignificant high PCT value. Second, our study group has a low number of

patients compared to other studies. With a much larger study group, PCT might also be significantly affected.

In this study, whether PCT could be a prognostic factor for HL was evaluated, and it was shown that only high sedimentation rate (> 50 mm/h) was associated with significantly elevated PCT. Elevated erythrocyte sedimentation rate has been shown to be an adverse prognostic factor for HL, and our results were consistent with those in the literature [20]. A significant positive correlation with each unit of sedimentation elevation and PCT was found. Also, when all study groups were analyzed, PCT levels declined significantly after chemotherapy. Besides the relationship with elevated sedimentation rate, we could not find any relationship between PCT and other adverse prognostic factors.

Only a few studies evaluating the prognostic status of platelet-derived factors in HL have been published. Tao et al. reported that low platelet/platelet distribution width and high platelet/lymphocyte ratio were adverse prognostic factors in patients with newly diagnosed advanced stage HL [21]. In early stages, pre-treatment neutrophil/lymphocyte and platelet/lymphocyte ratios were found to be significant factors related to progression in HL [22]. Rupa-Matysek et al. [16] evaluated the prognostic significance of MPV in HL and found high platelet and low MPV levels in HL compared to the control group, and while MPV could not be used as a prognostic marker, it could a useful tool for predicting thrombosis in HL. We also found low MPV and high platelet counts in patients with HL.

Limitations

Some drawbacks in this study should be mentioned. The number of patients in our study group was small compared to other studies evaluating the prognostic status platelet indices; in addition, the study was not a prospective one. These two drawbacks could be major factors affecting our research results. With much larger study groups as in literature, we might reach more robust conclusions about other adverse prognostic factors and PCT. However,, to our best knowledge, our study is the first in its field to evaluate the prognostic status of PCT in HL, so it should add some useful and new information to the literature.

Conclusion

For the first time in the literature, this study showed that high PCT values are associated with high sedimentation rate, and treatment leads to a significant reduction PCT counts, so PCT could be used as a prognostic marker in HL. Studies with much larger patient groups should be arranged to evaluate the prognostic significance of PCT with other adverse prognostic factors, such as IPS-3 and -7 in HL.

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Evaluation of quality of life in the elderly who have fallen

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The study was approved by the Çankırı Karatekin University Ethics Committee (Meeting No. 18, Date: 05.01.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Approximately 30% of older adults fall at least once per year; consequently, falls are a significant public health concern in the elderly. The most common outcomes are fractures, immobility, high morbidity, and mortality rates. In recent years, quality of life (QoL) is used as a criterion to guide social policies for the elderly. The high prevalence of falls can have serious consequences on the QoL of older people, resulting in prolonged hospitalization, institutionalization, need for care, social isolation, anxiety, and depression. Therefore, it is essential to understand the effect of falls on QoL and influencing factors. In light of this study's results, it is intended to provide recommendations for social policy that will protect the elderly from falls and maintain their high QoL. This study aimed to determine the QoL and the factors affecting the elderly who have fallen.

Methods: The research was a cross-sectional study. The study sample consisted of 90 elderly individuals who applied to the hospital due to falls. The inclusion criteria were being 65 years of age or older, applying to the hospital's emergency department, orthopedic or orthopedic surgery clinic due to a fall, not having passed 6 months from the date of discharge, and agreeing to participate in the study voluntarily. Data were collected through face-to-face interviews in January–June 2021 using the purposive sampling method. The Elderly Introduction Form was used to obtain sociodemographic data of the participants, as well as data on falls and their experiences after falls. The Quality of Life Scale for the Elderly was used to determine QoL. The student's t-test was used to compare two categorical variables. ANOVA was used for more than two variables, and logistic regression analysis was also applied.

Results: QoL levels were classified as poor, fair, and good, and 58.9% of the participants were found to have a fair QoL. In addition, according to the scale's total score average of 3.17 (0.473), the general quality of life was found to be fair for all participants. According to the t-test and ANOVA results, the QoL was higher for those with higher education levels and those living with their spouses ($P<0.05$). The QoL was low in those who had fractures, had surgery, were hospitalized for more than 4 days, and had chronic diseases ($P<0.05$). In the regression analysis model, age, economic status, and the number of drugs used were effective on QoL.

Conclusion: The quality of life was poor in the elderly who experienced fractures and were hospitalized. Balance-enhancing exercises in the elderly can prevent falls and associated complications. Low education level, chronic illness, and drug use reduced the quality of life. For education, literacy courses and lifelong learning programs can be applied to the elderly. For diseases, healthy aging policies can be implemented.

Keywords: aged, quality of life, falls, social policy

Introduction

A fall is the unintentional tipping to the ground or a lower level without secondary cause or external forces [1]. Approximately 30% of older adults fall at least once per year, making falls in the elderly a significant public health concern [2]. When examining previous research on older adults living in the community, it was determined that 27.6% of older adults had fallen in the previous year in a study conducted in Brazil with a very large sample size [3]. Even among the elderly without any balance disorder, the rate of falls was 29.8% in a separate field study [4] that screened the elderly for fall risk. In addition, it was reported that the rate of falls was 32% among those aged 65–74 and 51% among those aged 85 and older [5].

Falls, which are extremely common among the elderly, can impair functional capacity and lead to loss of autonomy. The most common outcomes are fractures, immobility, activity restrictions, nursing home confinement, deteriorating health, and mortality risk. In addition, psychological issues include fear of falling again, increased health care costs, family issues, and limited participation in social life [6]. In old age, increased bone mineral loss and a decrease in muscle mass and strength, known as sarcopenia, increase both the risk of falls and the risk of fracture after a fall. Consequently, hospitalization, morbidity, and mortality rates rise [1].

Quality of life (QoL) is the state of being well and satisfied with life within the environmental conditions and opportunities in which people live. People's level of functionality, health, and psychological conditions affect their QoL [7]. Old age is a period of physical decline, an increase in chronic diseases, and a decrease in participation in social activities. For this reason, the concept of QoL is much more important in old age. In developed countries, all public policies are focused on the QoL of the elderly by actively participating in society [8]. Because aging rates are higher in developing countries, QoL is used as a criterion to guide social policies [9].

When the relationship between falls and QoL in the elderly is examined, it has been reported that due to the acute consequences of falls, such as fractures and fear of falling, the physical, psycho-social, and functional abilities of those who fall deteriorate in the longer term, which has a significant impact on their perceived health and QoL [10]. Therefore, the high prevalence of falls can have serious consequences on the QoL of older people, resulting in prolonged hospitalization, institutionalization, restriction of activity and mobility, changes in balance and postural control, social isolation, anxiety, and depression. Therefore, it is essential to understand the strengthening and protective factors for falls, take precautions against falls, and avoid reducing the QoL of the elderly [5].

This study aimed to examine the effects of falls, one of the most prevalent and significant geriatric syndromes, on the QoL of the elderly. How is the life quality of the elderly affected by a fall? What are the factors affecting this process? How do fractures, the treatment process, having to undergo an operation, the length of hospitalization, permanent disability, and rehabilitation services impact the QoL of the elderly following a fall? How do the sociodemographic and economic characteristics of the elderly affect their QoL after a fall? In light of the answers to all of these questions, this study intended to provide recommendations for social policy that will protect the elderly from falls and maintain their high QoL.

Materials and methods

Subjects

The research was descriptive and cross-sectional. The study employed a method of purposeful sampling. The study sample consisted of ninety elderly individuals admitted for falls to the Ramadi Training and Research Hospital in Al-Anbar, Iraq. The study universe was determined from hospital records based on the number of elderly patients admitted to the hospital in October 2020 due to falls within one month. Within a month, 30 elderly patients were admitted due to falls. In a period of three months, this number would reach 90, and the study universe was estimated to be 90. Because the number of participants included in the study within three months based on the inclusion criteria was less than anticipated, data collection continued until the target universe size was reached. The number of participants reached 90 in June 2021, at which point the study was terminated. As a result, data collection occurred over the course of six months until the sample size and universe size were equal.

The inclusion criteria were being 65 years of age or older, applying to the hospital's emergency department, orthopedic or orthopedic surgery clinic due to a fall, not having passed 6 months from the date of discharge, and agreeing to participate in the study voluntarily. Exclusion criteria included being younger than 65 years old, having a mental disorder or hearing impairment that made it difficult to comprehend the questionnaire questions, or refusing to participate in the study.

Evaluation parameters

Two forms, the Elderly Introduction Form and Quality of Life Scale, were used in the study.

The Elderly Introduction Form was a questionnaire designed by the researchers. With this questionnaire, sociodemographic data of the participants, as well as data on falls and the process they experienced after falls, were obtained. Did the elderly experience a fracture or other disability after the fall, did they receive outpatient treatment or hospitalization, and what was the duration of hospitalization and discharge time? In addition, did they receive any rehabilitation services after discharge? Intercalarily, data such as body mass index, economic status, and the presence of other chronic diseases were obtained with this form.

The Quality of Life Scale for the Elderly comprised six sub-dimensions: general life, physical health, emotional and psychological, social relations, environment, and spiritual. The validity and reliability studies of the scale were conducted, and it was reported to be valid for the Iraqi elderly and reliable, with a Cronbach's alpha of 0.88 [11]. It is a five-point Likert-type scale. The scoring system is based on averages. Those with a mean score between 1.00–1.80 are considered to have a very poor QoL. Those with a mean score between 1.81–2.60 are considered to have a poor QoL, 2.61–3.40 fair, 3.41–4.20 good, and 4.21–5.00 very good QoL [11]. Written permission was obtained from the relevant author to use the scale. In addition, after the study was completed, Cronbach's alpha of this scale was calculated for our current study sample and found to be 0.91.

Face-to-face interviews were conducted with the participants. In accordance with the inclusion criteria, patients who had been admitted to the emergency department, surgery, or orthopedics clinic in the previous six months due to falls and received treatment services were visited in their homes. Those who voluntarily agreed to participate in the study were informed about the study and provided informed consent. The research was conducted in accordance with the Helsinki Declaration. The Çankırı Karatekin University Ethics Committee (Meeting No. 18, Date: 05.01.2021) and the Al Anbar Ministry of Health Scientific Research Committee approved the study (No: 2, Date: 11.01.2021).

Statistical analysis

The SPSS for Windows version 24.0 software package was used for data evaluation. Descriptive statistics (mean, standard deviation, number, and percentile) were given for categorical and continuous variables. For the causal relationships between categorical variables, firstly, the compatibility of the scale scores with normal distribution was checked by the Kolmogorov-Smirnov test. Because the scale scores were normally distributed, the student's t-test was used to compare two categorical variables, and ANOVA was used for more than two variables. Logistic regression analysis was also applied. $P<0.05$ and was considered statistically significant.

The dependent variable of the study was the QoL scale score. The independent variables were sociodemographic data and all other questions related to falls in the Elderly Introduction Form section of the questionnaire.

Results

When the QoL levels of the participants were evaluated based on the average scale scores, it was determined that 58.9% of the participants had a moderate QoL (Table 1). When the QoL levels of the participants were evaluated with the sub-dimensions of the scale, it was determined that the QoL was at a good level in the social relations and spirituality sub-dimensions and at a moderate level in all other sub-dimensions. According to the total mean scale score of 3.17 (0.473), the overall QoL level was found to be moderate for all participants of the study (Table 2).

Table 1: Number and percentage values of the participants according to the mean scores of quality of life

Level of the Quality of Life	n	%
Very Poor [1.00–1.80]	0	0.0
Poor [1.81–2.60]	12	13.3
Fair [2.61–3.40]	53	58.9
Good [3.41–4.20]	25	27.8
Very Good [4.21–5.00]	0	0.0
Total	90	100

Table 2: Evaluation of quality of life sub-dimensions in the elderly after falls

Sub-Domains of the Quality of Life	Mean	SD	Evaluation
General life	3.30	0.736	Fair
Physical health	2.62	0.362	Fair
Emotional and psychological	3.20	0.619	Fair
Social relations	3.45	0.698	Good
Environment	2.66	0.619	Fair
Spiritual	3.80	0.674	Good
Total	3.17	0.473	Fair

The effect of the sociodemographic data of the participants on their QoL was significant in the variables of age, educational status, and cohabitation. The QoL of the elderly in the younger age group (65–74 years) was higher than that of the elderly in the older age group ($P<0.001$). QoL was higher in university and high school graduates compared to illiterate elderly participants ($P<0.001$). QoL was higher in the elderly living with a spouse or living with both spouse and children than in the elderly living without a spouse and living only with children ($P=0.052$). When the effect of the economic data of the elderly on their QoL was analyzed, the QoL of the elderly who received pensions was higher than the elderly who had no income ($P=0.001$). The QoL of the elderly whose income met their needs was higher than the elderly whose income did not meet their needs ($P=0.011$) (Table 3).

Table 3: The effect of sociodemographic and economic data on quality of life in elderly people who had a fall

	Categories	n	%	Mean	SD	F / t	*P*-value
Age	65–74 years	51	56.7	3.34	**0**.485	9.314	<0.001*
	75–84 years	29	32.2	3.02	**0**.364		
	≥ 85	10	11.1	2.79	**0**.330		
Gender	Male	42	46.7	3.09	0.454	1.517	0.133
	Female	48	53.3	3.24	0.484		
Marital Status	Married	67	74.4	3.09	0.454	2.679	0.052
	Widowed	15	16.7	3.24	0.484		
	Divorced	5	5.6	3.25	**0**.477		
	Single	3	3.3	2.91	**0**.346		
Education	Illiterate	28	31.1	2.97	**0**.390	5.376	<0.001*
	Literate	23	25.6	3.18	**0**.531		
	Primary School	15	16.7	3.01	**0**.375		
	Middle School	5	5.6	3.27	**0**.439		
	High School	10	11.1	3.42	**0**.309		
	University	9	10.0	3.72	**0**.387		
Body mass index [BMI]	Underweight (<18.5)	4	4.4	3.14	**0**.345	1.328	0.270
	Normal weight (18.5–24.9)	35	38.9	3.28	**0**.494		
	Overweight (25–29.9)	17	18.9	3.19	**0**.527		
	Obesity (≥ 30])	34	37.8	3.06	**0**.425		
Live at home	Alone	1	1.1	3.00	**0.0**	3.096	0.020*
	Wife/Husband	9	10.0	3.38	**0**.736		
	Wife/Husband and children	59	65.6	3.24	**0**.437		
	Children	19	21.1	2.86	**0**.333		
	Other	2	2.2	3.21	**0**.152		
Economic situation	No income	37	41.1	3.07	**0**.394	4.408	0.001*
	Elderly pension	3	3.3	3.19	**0**.408		
	Disabled pension	3	3.3	2.34	**0**.240		
	Salary from spouse	3	3.3	3.08	**0**.396		
	Pension	43	47.8	3.34	**0**.474		
	Other	1	1.1	2.45	**0.0**		
Do you have any other income?	No	52	57.8	3.19	**0**.487	1.379	0.312
	Rent	34	37.8	3.18	**0**.464		
	Assistance	4	4.4	2.82	**0**.260		
Is your income sufficient for your needs?	Yes	35	38.9	3.32	**0**.466	4.752	0.011*
	Sometimes	24	26.7	3.22	**0**.372		
	Not Enough	31	34.4	2.98	**0**.497		

F: ANOVA, t: t-test, SD: Standard deviation, *P*: significance ($P<0.05$)*

In the elderly after a fall, the QoL of participants who experienced a fracture was lower than those who did not experience a fracture ($P<0.001$). Participants who were hospitalized had lower QoL than those who were treated as outpatients ($P<0.001$). Participants who were hospitalized for 3 days or less had a higher QoL than those who were hospitalized for 4 days or more ($P<0.001$). Participants who had to undergo surgery for a fall had a lower QoL than participants who did not undergo surgery ($P<0.001$). Participants with a discharge time of fewer than 3 months had a higher QoL than participants with a discharge time between 3 and 6 months ($P=0.008$). Participants who received physical therapy and rehabilitation services after the treatment process had a lower QoL than those who did not ($P=0.012$). Participants with at least one chronic disease had a lower QoL than those with no chronic disease ($P<0.001$). Participants who regularly used 3 or more medications on a daily basis had a lower QoL than participants who used less than 3 or no medications ($P<0.001$) (Table 4).

The model by which the effect of demographic characteristics on the QoL was examined is statistically significant (F=2.79 [$P<0.001$]). Independent variables affect 50.1% of QoL in a statistically significant way. The effect of the constant on the QoL of 3.194 units in the model was statistically significant; these are age, economic situation, and the number of medications used regularly (Table 5). However, according to the regression model,

except for these three independent variables, no other independent variables were statistically significant.

Table 4: The effect of treatment recovery process, and general health status on quality of life in the elderly after falls

Variables	Categories	n	%	Mean	SD	F / t	*P*-value
What kind of problem/injury did you experience due to falling?	Fracture	35	38.9	2.85[a]	**0**.341	10.239	<0.001*
	Dislocation	8	8.9	3.43[b]	**0**.289		
	Sprain	19	21.1	3.32[b]	**0**.488		
	Swelling	20	22.2	3.35[b]	**0**.442		
	Tendon damage	8	8.9	3.56[b]	**0**.366		
Have you been to the hospital?	Yes	41	45.6	2.92	0.355	5.369	<0.001*
	No	49	54.4	3.39	0.456		
Duration of hospitalization	None	49	54.4	3.39[b]	0.456	8.901	<0.001*
	1–3days	16	17.8	3.04[b]	0.380		
	4–6 days	6	6.7	2.76[a]	0.371		
	8–10 days or more	19	21.1	2.84[a]	0.375		
Have you had an operation?	Yes	40	44.4	2.88	0.342	6.399	<0.001*
	No	50	55.6	3.41	0.430		
When were you discharged?	None	3	3.3	3.78[b]	0.257	3.397	0.008*
	One week	14	15.6	3.30[b]	0.585		
	Fifteen days	19	21.1	3.35[b]	0.419		
	One month	14	15.6	3.10[b]	0.518		
	Three months	25	27.8	3.10[b]	0.403		
	Six months	15	16.7	2.89[a]	0.323		
Have you received rehabilitation services?	Yes	19	21.1	2.93	0.443	6.556	0.012*
	No	71	78.9	3.24	0.463		
Do you have a chronic disease?	Yes	59	65.6	3.04	0.475	3.981	<0.001*
	No	31	34.4	3.43	0.358		
How many drugs do you use in a day regularly?	None	31	34.5	3.43[b]	0.358	7.497	<0.001*
	One	4	4.4	3.40[b]	0.351		
	Two	26	28.9	3.16[b]	0.499		
	Three or more	29	32.2	2.83[a]	0.339		

F: ANOVA, t: t-test, SD: Standard deviation, [a, b] Statistical significance exists between the categorical variables with the letters a and b (P<0.05)*.

Table 5: Impact of age, economy and number of used medications variables (independent variables) on quality of life (dependent variable) according to regression analysis

Dependent variable	**B unstandardized**	**T-test**	***P*-value**	**Model**		**ANOVA**		
Independent variable						**Df**	**F**	***P*-value**
Intercept	3.194	3973.0	<0.001					
Age	-0.190	1.870	0.065	R	0.712	65	2.79	<0.001*
Economic	0.017	0.446	0.657	R^2	0.508			
Drugs number	-0.121	-0.967	0.337	R^{-2}	0.498			

R: Sample regression, Df: Degree of Freedom, Sig: Significant*, F: F- Test, R^2: Regression Square, R^{-2}: Adjusted Regression Square

Discussion

The results of this study, in which the QoL levels of the elderly after falls were measured and the factors affecting their QoL were identified, were discussed in light of previously published national and international research. In a study involving a total of 1,792 elderly individuals, the QoL among those who had fallen in the previous year was found to be moderate despite being lower than among those who had not fallen in the previous year. The median QoL score of the elderly who had fallen was identical to the median score of the entire sample [12]. In a study conducted in Thailand among elderly people of various ethnic backgrounds and revealing the relationship between falls and QoL, the negative impact of falls on the QoL was revealed, and 68.6% of the elderly were reported to have a moderate QoL [13]. In a study involving 4,260 elderly women treated for falls in Korea, 44.7% of participants reported a high quality of life, 55.3% reported a low QoL, and the sample as a whole was considered to have a moderate QoL [14]. In the present study, the QoL of the participants was found to be moderate, with a mean score of 3.17 (0.473), and the present study was consistent with the literature. In another study using the same scale that we used in the current study, the QoL of the elderly was found to be good, with a mean score of 3.91 (0.436), independent of falls. The reason for the good QoL in this study was that the elderly were engaged in physical activity. In the same study, QoL was low in the elderly who did not engage in physical activity [11].

When sociodemographic data were analyzed in a study examining the relationship between falls and QoL, the QoL of the elderly over 75 years of age was lower than the elderly aged 65–74 years [15]. In another study involving older people who experienced falls, older people had lower QoL scores than younger elderly [14]. In another study, age, gender, and marital status were reported to affect the QoL in older people [16]. In another study, older men were reported to have a higher QoL than older women [17]. Contrary to all these study results, there were also studies reporting that age and gender had no effect on the QoL of the elderly [18]. In our current study, the QoL of the elderly in the younger age group (65–74 years) was found to be higher than the elderly in the older age group. The reason for this is that as age increases, mineral loss from the bones of the elderly increases, and the bones become weaker. The current study sample consists of elderly people who have fallen. The older elderly have a higher risk of injury after a fall and a lower rate of recovery during the treatment process. Accordingly, lower QoL was an expected result. In the present study, gender had no effect on the QoL. The reason for this was that the treatment opportunities after a fall were the same for both genders, and there was no effect of gender in equal environmental conditions.

When the educational status was analyzed, in most of the published studies, educational level was beneficial to the life quality of the elderly [19]. Consistent with previous research, participants with a high level of education had a high QoL in the current study. This was expected, as activities such as Internet use, book reading, and self-care during the recovery process were associated with education level.

One study found that the post-fall QoL for elderly people living with their spouses was high [14]. The present study was consistent with previous research. Because the definition of QoL is a person's satisfaction with life, it was expected that the elderly living with their spouses would have higher scores than those who had lost their spouses.

In previous research, the QoL of seniors with a higher socioeconomic status was higher than that of seniors with a lower socioeconomic status [13,20–21]. The present study was consistent with previous research. Although factors affecting the QoL vary across countries and cultures, it is indisputable that the economy was the most significant constant factor.

In a systematic review of 49 published studies that examined the variable of experiencing fractures, the QoL of the elderly who experienced fractures was lower than that of the elderly who did not experience fractures [22]. The present study was consistent with previous research. The treatment process, pain, and recovery-related anxiety were sufficient to diminish life quality.

In a study involving elderly patients who were hospitalized for fractures and underwent surgery, it was found that the participants' QoL scores decreased significantly between the time they were admitted to the hospital and one month after discharge and that their average length of hospital stay was 5 days

[23]. In the current study, those who were hospitalized had a lower QoL than those who were not hospitalized, those who underwent surgery had a lower QoL than those who did not, and those who stayed in the hospital for 4 days or more had a lower QoL than those who stayed in the hospital for 3 days or less. In terms of discharge time, the present study was distinct from previous research. In the present study, the reason for the lower QoL of those whose hospital stay lasted between three and six months was interpreted as a decrease in life satisfaction as time passed due to the participant's inability to fully regain their former health.

According to studies, physical therapy and rehabilitation applications for orthopedic disorders improve the elderly's QoL [24]. The present study found the opposite to be true. In the current study, participants who received physical therapy and rehabilitation services following a fall had a low QoL. This was attributed to the fact that participants with mild injuries, sprains, and strains following a fall did not require rehabilitation services. It was believed that the elderly applicants for rehabilitation services included individuals who had fractures and undergone surgery.

It was reported that elderly people with chronic diseases had a lower QoL following a fall than elderly people without chronic diseases [13,14]. The present study was consistent with previous research. According to previous research, the QoL of the elderly declines as the number of medications they take on a daily basis rises [25]. The present study was consistent with previous research. The reason for this is that polypharmacy, drug interactions, and side effects increase the risk of falls in the elderly by causing balance disorders; consequently, a decline in QoL is inevitable.

Strengths and limitations

One of the researchers worked in the hospital where the study was conducted. The researcher contacted the participants while they were lying in the ward and obtained their consent. The researcher visited the participants at home and completed the questionnaires within a maximum of 6 months after the participants were discharged. Face-to-face interviews were conducted, an environment of trust was established, and data were collected accurately and hygienically.

Due to COVID-19, some elderly people did not accept health personnel into their homes. In order to prevent this situation from negatively affecting the study, the data collection period was extended, and an adequate sample size was reached.

Conclusion

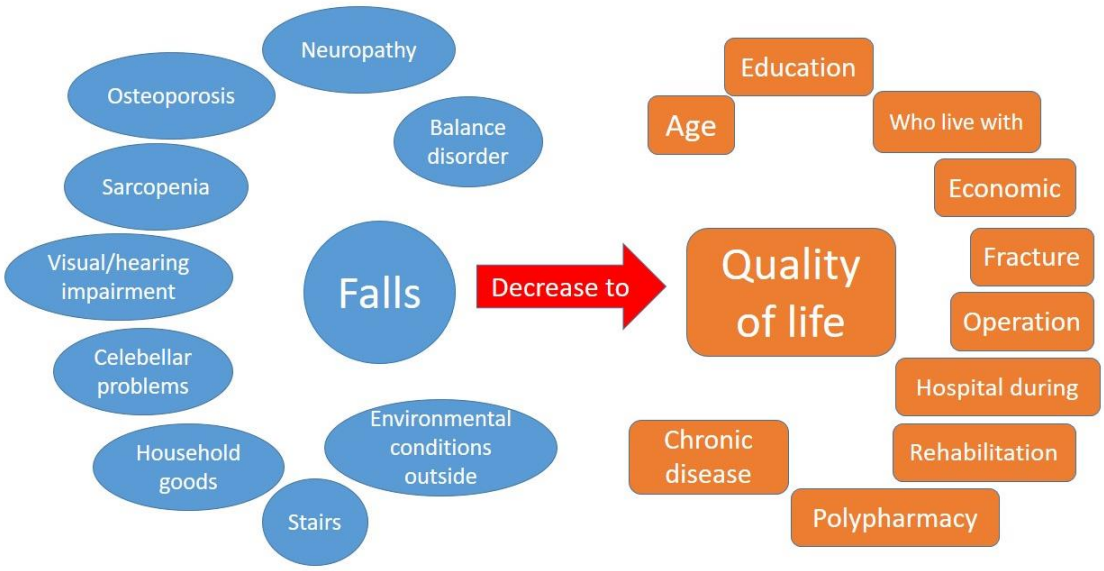
In light of the results of the study, protective and preventive health policies for the elderly were developed. These policy recommendations, developed to protect the elderly from falls and to improve their quality of life, were presented as a figure (Figure 1).

Social and health policy suggestions

To enhance the QoL of the elderly, falls should be prevented. Balance disorders should be prevented in the elderly to avoid falls. The elderly should be encouraged to walk and engage in physical activity. Public services for the elderly should be expanded, particularly those provided by local governments. The elderly should be provided with physical activity in the presence of physiotherapists and sports instructors at elderly living centers. Physical activity safeguards the elderly by delaying the onset of muscle atrophy [sarcopenia] and osteoporosis, which are the leading causes of falls. To raise the elderly's awareness, it is necessary to create public service announcements and posters. For the elderly, useful television programming should be developed (Figure 1).

Everyone should have a gerontologist or social worker registered with them in government family health centers, just as everyone has a family doctor. These professionals should monitor the elderly and refer them to social services that safeguard their health. In addition to assisting the elderly with home modifications, these professionals should take measures to prevent them from tripping and falling at home, such as removing carpets with curled edges, high door thresholds, and stairs without handrails. Vision, hearing, and neurologic examinations should be performed routinely on the elderly. There should be measures taken to facilitate the outdoor lives of the elderly. The elderly should be able to ride urban public transportation vehicles in comfort and safety, and city sidewalks and landscaping should be designed with the elderly in mind (Figure 1).

Figure 1: Risk factors for falls, quality of life, and factors affecting the quality of life



In addition to enhancing the QoL of the elderly by protecting them from falls, it is necessary to address factors that have a direct impact on QoL; courses in literacy should be made available to elderly illiterates. Opportunities for lifelong learning should be provided. Education on healthy living and conscious drug use should be organized. Activities such as sudoku should be organized to protect their cognitive skills and projects should be created to protect their fine motor skills. To prevent elderly poverty, employment policies should be implemented for the elderly. The quality of health services in hospitals should be enhanced, geriatrics clinics should be expanded, and post-discharge rehabilitation services should be increased (Figure 1).

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Congruence of radiological scoring systems used in COVID-19 pneumonia and effect of comorbid diseases on radiological features

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Ethics Committee Approval
The study was approved by the Ethics Committee of Binali Yildirim University (decree no: 27/10/2022-/04/6).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Several scoring systems have been developed to standardize radiological findings in patients with COVID-19 pneumonia. The most commonly used scoring systems in the radiological examination of COVID-19 are those of the North American Radiology Association (RSNA), British Thoracic Society (BTS), and COVID-19 Reporting and Data System (CO-RADS). However, the compatibility between these radiological scoring systems has not been evaluated before. Therefore, this study evaluated the radiological features of COVID-19 pneumonia and congruence between radiological scoring systems and determined the effect of comorbidities and demographic characteristics on radiological features and thoracic computed tomography (TCT) findings in the context of COVID-19.
Methods: A retrospective cohort study was performed on patients attending our unit with a suspicion of COVID-19 who also had a positive real-time transcriptase-polymerase chain reaction (RT-PCR) test. All TCT images were subjected to the RSNA, BTS, and CO-RADS scoring systems. Demographic data such as age and gender, and comorbid conditions were recorded.
Results: TCT showed peripheral, posterior, and bilateral involvement in 97.7%, 97.7%, and 87.6% of the patients, respectively. The most common TCT finding was ground glass appearance, which was found in 95.5% of the patients. The Charlson Comorbidity Index (CCI) score was found to have an impact on RSNA and BTS criteria (P=0.011 and P=0.014), while age, gender, and the presence of comorbidities such as cardiovascular disease (CVD), diabetes mellitus (DM), and chronic pulmonary disease (CPD) did not have such an effect (P>0.05 for all). On the other hand, CCI scores and the presence of CPD had an association with CO-RADS, but there was no effect of age, gender, DM, and CVD (P=0.915 and P=0.730).
Conclusion: TCT plays an important role in early management, isolation, and follow-up of patients with COVID-19 pneumonia. The radiological scoring systems were found to exhibit good compatibility, but comorbid conditions could have an impact on the assessment. Therefore, we conclude that these radiological assessment criteria are useful in the management and monitoring of such patients.

Keywords: COVID-19, pneumonia, radiological appearance, scoring systems, comorbid diseases

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Introduction

Coronaviruses are important pathogens in both humans and animals. Toward the end of the year 2019, a clustering of pneumonia cases caused by a novel type of coronavirus was observed in the city of Wuhan in Hubei Province, China, which rapidly spread to other parts of the world. In February 2020, the disease was declared a pandemic and termed as coronavirus disease 2019 (COVID-19) [1]. Lungs represent the most important site of involvement in COVID-19 [2]. Therefore, radiological documentation of lung involvement is of the utmost importance.

Although real-time transcriptase-polymerase chain reaction (RT-PCR) is the gold standard diagnostic modality, radiological findings have also been commonly used for diagnosis due to inadequate access to PCR testing in some parts of the world, as well as false-negative results early in the course of the disease [3,4]. The reported sensitivity of chest X-rays is between 30% and 60% [5]. Therefore, it should be borne in mind that a normal chest X-ray does not rule out a diagnosis of COVID-19, and clinically suspicious cases should be assessed with thoracic computed tomography (TCT).

In a previous report, the observed sensitivities of TCT and RT-PCR in establishing a diagnosis of COVID-19 were 98% and 71%, respectively [6,7]. Thus, even in the absence of a positive RT-PCR result, the presence of positive TCT findings in patients with suspected COVID-19 pneumonia allows early diagnosis [6-8]. However, TCT should always be interpreted in light of clinical manifestations.

The North American Radiology Association (RSNA) criteria have been proposed as a means to reduce variability and achieve standardization in patient reporting, as well as to reach a terminological consensus while assessing a possible diagnosis of COVID-19 pneumonia [9]. A similar attempt to standardize TCT findings in COVID-19 pneumonia was made by the British Thoracic Society (BTS) [10]. The COVID-19 Reporting and Data System (CO-RADS) is another categorical assessment scheme to estimate the presence of COVID-19 in patients with moderate to severe symptoms and to document pulmonary involvement of COVID-19 [11]. COVID-19 pneumonia has also been classified clinically into four groups [12] to achieve clinical and radiological standardization among patients, which may facilitate the use of similar terminology for diagnosis and management of patients as well as the creation of algorithms for clinicians. In this study, our objective was to assess the congruence between RSNA, BTS, and CO-RADS scoring systems for radiological classification of pulmonary involvement in patients with COVID-19. Also, we aimed to determine factors that impact the scores. Another objective was to evaluate the frequency of the most common sites of pulmonary involvement (central, peripheral, posterior, anterior, or bilateral etc.), total area of pulmonary involvement (number of lobes), and frequent radiological features (e.g. ground glass appearance, air bronchogram, subpleural lines, halo, reverse-halo sign, air bubbles, vascular enlargement, bronchial widening etc.). We also determined the effect of age, gender, and comorbidities on radiological features of COVID-19.

Materials and methods

We retrospectively evaluated consecutive patients with COVID-19 and a positive RT-PCR result who had TCT findings consistent with COVID-19 pneumonia between May 1, 2021, and November 31, 2021. Data from digital hospital records were used to record demographic information and comorbid conditions (cardiovascular disease [CVD], diabetes mellitus [DM], chronic pulmonary disease [CPD], etc.). The CCI score was calculated for each patient. TCT images were obtained in a supine position without contrast media using a 256-slice CT device for all patients (Aquillon, Toshiba Medical Systems, Tokyo, Japan). TCT images were assessed by a team of experienced medical specialists consisting of one radiologist (18 years of expertise) and three pulmonologists (20, 20, and 10 years of expertise, respectively) at workstations (Syngo Via Console, Software v. 2.0; Siemens Medical Solutions, Erlangen, Germany).

Each image was evaluated with regard to lung parenchyma, bronchial pathology, pleural effusion, concurrent pericardial effusion, and mediastinal lymphadenopathy (LAP). Recorded lung parenchymal pathologies included the number of lobes involved, the presence of ground-glass appearance, air bubbles, subpleural bands, reticular densities, and fibrosis. Air bronchograms and bronchial wall injuries were assessed when evaluating bronchial pathologies.

RSNA, BTS, and CO-RADS scores were recorded. The RSNA chest CT classification system includes four categories: negative for pneumonia, atypical, indeterminate, and typical [9]. The BTS classifies COVID-19 radiology as classic COVID-19 (100% compatible), probable COVID-19 (71-99% compatible), uncertain (<70% compatible), and “COVID-19 excluded” (<70% compatible with another diagnosis) [10]. CO-RADS was developed by the Dutch Association for Radiology with grades ranging from 1 to 5 to suggest ascending disease probability according to the CT chest findings [11].

The exclusion criteria were the absence of a PCR test result, poor image quality, and a history of lung fibrosis or emphysema. The study procedures were carried out after ethical approval by the local ethics committee of Erzincan Binali Yıldırım University (decree no: 27/10/2022-/04/6). The study was performed according to the ethical standards specified in the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

Analysis of the data was done with IBM SPSS 19 (IBM Corp. Released 2010. Armonk, NY). Categorical variables were reported as n (%), and descriptive statistics for continuous variables were reported as the mean (standard deviation) or median (minimum-maximum) value according to the distribution type. A chi-squared test was used in the analysis of categorical variables. Whether continuous variables had a normal distribution was evaluated by the Kolmogorov-Smirnov test. The Mann-Whitney U test was used when comparing the numbers of lobes in groups in cases where assumptions were not provided, and a student's t test was used in the cases provided. In all statistical analyses, $P<0.05$ was considered significant.

Results

A total of 396 patients were included, of which 56.1% (n=222) were male and 43.9% (n=174) were female. The mean age of the patients was 56.18 (18-94). TCT showed peripheral, posterior, and bilateral involvement in 97.7% (n=387), 97.7% (n=387), and 87.6% (n=347) of the patients, respectively. The most common TCT finding was ground glass appearance in 95.5% of the patients (n=378; Table 1, Figure 1). The most common comorbid conditions included CVD in 34.3% (n=136), chronic pulmonary disease (CPD) in 24.2% (n=96), diabetes mellitus (DM) in 21.7% (n=86), allergic conditions in 14.4% (n=57), and cancer in 2.8% (n=11).

Figure 1: A: ground glass view in the middle lobe of the right lung and in the lower lobe superior segment and air bubbles in the lower lobe superior segment to the right lung. B: Peripheral halo with ground glass densities in the left lung lower lobe air bubble view. C: Paving stone view and several air bubbles in the lower lobe superior segment of the left lung D: Peripheral ground glass view.

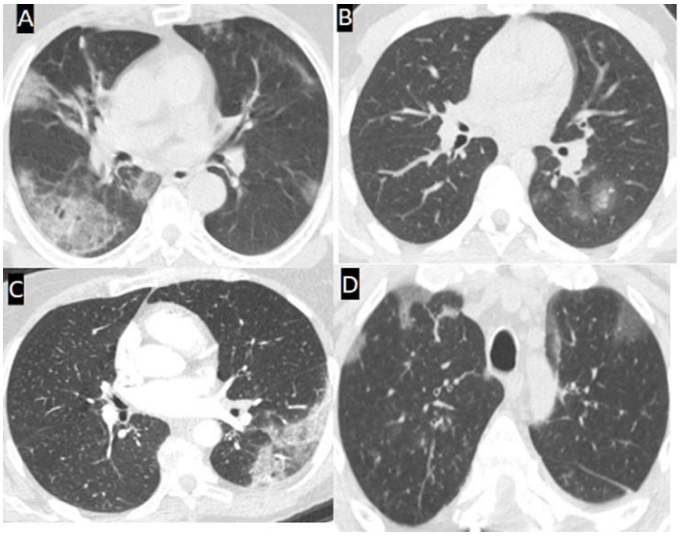


Table 1: Radiological findings of patients with COVID-19 pneumonia on thorax CT are observed

		n	%
Peripheral	No	9	2.3
	Yes	387	97.7
Posterior	No	9	2.3
	Yes	387	97.7
Bilateral	No	49	12.4
	Yes	347	87.6
Ground glass	No	18	4.5
	Yes	378	95.5
Consolidation	No	240	60.6
	Yes	156	39.4
Air bronchogram	No	383	96.7
	Yes	13	3.3
Vascular enlargement	No	284	71.7
	Yes	112	28.3
Bronchial dilatation	No	362	91.4
	Yes	34	8.6
Halo	No	391	98.7
	Yes	5	1.3
Reverse halo	No	393	99.2
	Yes	3	0.8
Nodule	No	390	98.5
	Yes	6	1.5
Air bubble	No	366	92.4
	Yes	30	7.6
Subpleural band	No	283	71.5
	Yes	113	28.5
Reticular density	No	344	86.9
	Yes	52	13.1
Pleural thickening	No	394	99.5
	Yes	2	0.5
Pleurisy	No	388	98.0
	Yes	8	2.0
Pericardial effusion	No	395	99.7
	Yes	1	0.3
Paving stone	No	345	87.1
	Yes	51	12.9

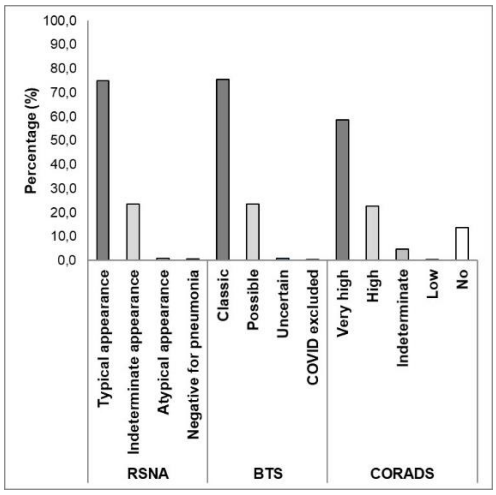
Table 2 shows the results of RSNA, BTS, and CO-RADS classification in COVID-19 patients. Score assessments based on RSNA and BTS criteria were found to be congruent Also, CO-RADS scores were in agreement with RSNA and BTS scores (Figure 2). Increasing patient age was associated with an increased number of bilateral involvement, consolidation, subpleural bands, reticular density, and disease stage at presentation, while no association was found between age and dominant site of involvement (i.e., posterior, peripheral, etc.) (P<0.001, P=0.026, P<0.001, P=0.001, P=0.002, P=0.069, and P=0.627, respectively). Also, age was not associated with an increased incidence of ground glass appearance, vascular enlargement, number of lobes involved (P=0.692, P=0.637, and P=0.167, respectively), RSNA, BTS, and CO-RADS scores (P=0.086, P=0.084, and P=0.059, respectively) (Figure 3).

Table 2: RSNA, BTS and CO-RADS scores of our patients diagnosed with COVID-19 pneumonia

		n	%
RSNA	Typical appearance	297	75.0
	Uncertain appearance	93	23,5
	Atypical appearance	4	1.0
	No pneumonia	2	0.5
BTS	Classical	299	75.5
	Possible	93	23.5
	Uncertain	3	0.8
	No COVID	1	0.3
CO-RADS	1	54	13.6
	2	1	0.3
	3	19	4.8
	4	90	22.7
	5	232	58.6

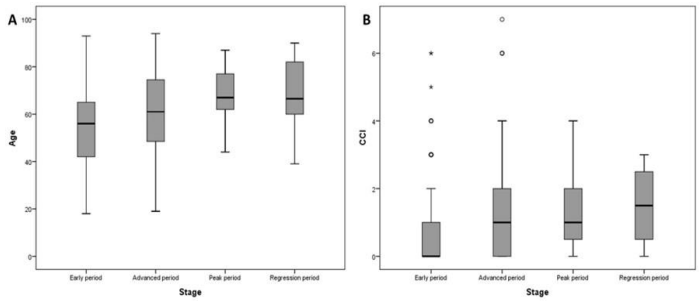
RSNA: North American Radiology Association, BTS: British Thoracic Imaging Society, CO-RADS: Coronavirus disease 2019 (COVID-19) Reporting and Data System

Figure 2: Compatibility of RSNA, BTS and CO-RADS indices in thorax CT classification of patients with COVID-19 Pneumonia



RSNA: North American Radiology Association BTS: British Thoracic Imaging Society CO-RADS: Coronavirus disease 2019 (COVID-19) Reporting and Data System

Figure 3: The effect of age (A) and CCI score (B) of patients with COVID-19 pneumonia on disease stage,



CCI: Charlson Comorbidity Index

Our findings showed that gender had no effect on bilateral, posterior, or peripheral involvement in patients with COVID-19 pneumonia (P=0.278, P=0.975, and P=0.184,

respectively). Also, gender had no effect on the occurrence of ground glass appearance, consolidation, vascular enlargement, subpleural bands, and reticular densities (P=0.054, P=0.0551, P=0.163, P=0.175 and P=0.519, respectively) or on the disease stage at presentation, number of lobes involved, and RSNA, BTS, and CO-RADS scores (P=0.234, P=0.530, P=0.764, P=0.625, and P=0.109, respectively). CCI scores were associated with bilateral involvement, reticular densities, advanced disease stage at presentation, and the indeterminate appearance category in RSNA, BTS, and CO-RADS (P=0.002, P=0.02, P=0.048, P=0.011, P=0.014, and P=0.046, respectively). On the other hand, there was no association between CCI scores and dominant posterior or peripheral involvement, ground glass appearance, consolidation, vascular enlargement, subpleural bands, and number of lobes involved (P=0.870, P=0.337, P=0.260, P=0.112, P=0.148, P=0.30, and P=0.096, respectively) (Figure 3).

COVID-19 pneumonia patients with CVD were more likely to have bilateral involvement, reticular densities, subpleural bands, and higher disease stage at presentation (P=0.012, P<0.001, P=0.017, and P=0.009, respectively). However, there were no associations between CVD and posterior or peripheral involvement, ground glass appearance, consolidation, and vascular enlargement (P=0.439, P=0.439, P=0.926, P=0.680, and P=0.777, respectively). Also, the presence of CVD had no effect on the number of lobes involved and on RSNA, BTS, and CO-RADS scores (P=0.253, P=0.609, P=0.622, and P=0.730, respectively) (Figure 4A). The presence of DM in patients with COVID-19 pneumonia was found to increase the likelihood of ground glass appearance, reticular density, vascular enlargement, and number of lobes involved (P=0.017, P=0.039, P=0.019, and P=0.043, respectively). However, it did not have an effect on the incidence of bilateral involvement as well as posterior and peripheral involvement (P=0.178, P=0.435, and P=0.110). Also, the presence of DM had no effect on the occurrence of consolidation, subpleural band, disease stage at presentation, and RSNA, BTS, and CO-RADS scores (P=0.639, P=0.141, P=0.113, P=0.057, P=0.491, and P=0.915, respectively) (Figure 4B). In patients with COVID-19 pneumonia, the presence of CPD was found to affect CO-RADS scores (P=0.015), while it had no effect on bilateral involvement, posterior or peripheral involvement, ground glass appearance, consolidation, vascular enlargement, subpleural bands, reticular density, disease stage at presentation, number of lobes involved, and RSNA and BTS scores (P>0.05 for all).

Discussion

COVID-19 pneumonia is a readily transmittable viral pneumonia of the lower airways caused by the novel coronavirus SARS-CoV-2. Numerous studies have been carried out to evaluate the TCT findings in COVID-19 patients, particularly with respect to the role of TCT in early diagnosis of pneumonia. Establishment of diagnostic radiological standards may facilitate the use of common diagnostic and therapeutic terminology and development of clinical algorithms. Our results show that scoring systems used for reporting TCT images are in good agreement, but comorbid conditions could have an impact on the scores obtained in these systems.

Many studies have established that ground glass densities represent the most common pathological imaging finding in COVID-19 and are thought to arise from pulmonary edema and hyaline membrane formation [13]. These areas are identified in 88% to 98% of the patients, they are frequently bilateral, and they mostly involve lower lobes and peripheral sites [14-17]. Similarly, all of our patients had ground glass appearance (mostly bilaterally and peripherally).

In patients with ground glass appearance, the most common accompanying sign is consolidation, which a post-mortem study has shown to be caused by cellular accumulation of fibro-myxoid exudate in the alveoli [18]. Several reports suggest that consolidation may be a predictor of disease progression [19]. Previous reports suggest that 5 to 36% of COVID-19 patients may have consolidation, which was the second most common radiological finding in our patients.

Vascular enlargement is thought to arise from capillary wall injury and was observed in 56.5% of the study population in a study involving 919 patients [20]. In our study, 28.3% of the patients had this finding. More common occurrence of vascular enlargement in patients with DM may be a sign of worse prognosis and increased likelihood of thrombotic complications.

In a previous study from China, patients who required intensive care unit (ICU) admission were older and had at least one comorbidity [21]. In a retrospective study, elderly patients with COVID-19 were more likely to be admitted to the ICU and had higher mortality than younger patients [22]. Aging causes anatomical alterations, muscular atrophy, reduced lung reserve, and reduced airway clearance in the lungs [22]. Such factors may explain the increased morbidity and mortality among elderly COVID-19 patients.

In our study, increasing age was associated with more advanced disease stage, increased consolidation, subpleural bands, reticular density, and bilateral involvement but not with vascular enlargement, ground-glass appearance, or the number of lobes. TCT reporting scores did not change with age. More advanced disease at presentation may be an indicator of more severe clinical features in the elderly, while increased incidence of subpleural bands and reticular densities may be predictors of fibrosis following COVID-19.

Women are less likely to be affected by bacterial and viral infections compared to men, presumably due to factors involving the innate and adaptive immune responses [23]. Accordingly, the risk of ICU admission among COVID-19 patients was found to be 1.55-times higher in males than in female patients [24]. In a study involving 1813 patients, patients admitted to the ICU were more likely to be male and elderly [24]. However, in our study, gender did not have an effect on the stage of the disease, the number of lobes involved, bilateral posterior involvement, peripheral involvement, pathological imaging findings, and TCT scoring systems.

In a previous study, certain comorbid conditions have been associated with elevated ACE-2 receptor expression [25]. In a review of 29,096 COVID-19 patients, 8.3%, 8.03%, 6.19%, and 4.83% of the patients were found to have comorbid DM, CVD, CPD, and HT, respectively [26]. In our study, the most common comorbidity was CVD. Also, COVID-19 patients with higher CCI scores were more likely to present with a more

advanced disease stage. CCI scores were found to affect RSNA, BTS, and CO-RADS and were associated with an increased likelihood of bilateral reticular involvement. Our results suggest that patients with higher CCI scores present with more advanced disease stage, despite having more widespread involvement.

DM is associated with elevated ACE-2 expression, impaired T cell function, and increased interleukin-6 (IL-6) [27,28]. DM patients may also have impairment in innate immunity, increased susceptibility to infections due to impaired phagocytic functions [29], and excessive pro-inflammatory cytokine release [30]. Similarly, another study found higher morbidity and mortality in diabetic COVID-19 patients [31]. In our study, 21.7% (n=86) of the patients had DM, which did not have an impact on disease stage at presentation or RSNA, BTS, and CO-RADS scores. On the other hand, DM was associated with an increased number of lobes involved, vascular expansion, ground glass appearance, and increased reticular density. Increased occurrence of lung involvement, vascular enlargement, and reticular density may present predictors of ICU admission and mortality in these subjects.

Asthmatic COVID-19 patients have an increased risk of asthma episodes, pneumonia, and ARDS [32]. Elevated ACE-2 expression may facilitate the entry of the virus into cells and may worsen the disease course [26]. In our study, the presence of CPD in COVID-19 patients was not associated with more advanced disease at admission, reticular density, subpleural band, bilateral involvement, posterior, peripheral dominance, increased ground glass appearance, increased consolidation, or increased lobe count. On the other hand, while CPD in these patients did not affect RSNA and BTS scores, it was found to affect CO-RADS scores.

Since most HT patients receive treatment with ACE inhibitors, ACE-2 receptors are upregulated, possibly increasing the susceptibility of these subjects to COVID-19 infection [33]. HT patients may also have impaired CD8 T cell function and cytokine dysregulation. Increased ACE-2 expiration in the cardiovascular may lead to fatal outcomes including myocarditis [26]. However, it was observed that having CVD did not affect posterior or peripheral involvement, the prevalence of ground glass appearance density, increased consolidation, increased vascular involvement, number of involved lobes, and RSNA, BTS, and CO-RADS scores. In our study, COVID-19 patients with CVD had more peaks and an increased number of hospital admissions. These observations suggest that COVID-19 patients with CVD may have a worse prognosis with increased risk of fibrosis following infection.

Our literature search did not reveal any studies comparing different radiological reporting systems in patients with COVID-19 pneumonia. Our findings showed good agreement between RSNA, BTS, and CO-RADS systems, suggesting that these TCT reporting systems may facilitate the standardization of radiological reporting of TCT imaging. In our study, CCI scores had an impact on RSNA and BTS scores, while age, gender, CVD, DM, and CPD had no such effect. CCI scores and the presence of CPD had an effect on CO-RADS scores, while age, gender, DM, and CVD did not affect them. Therefore, CCI scores and CPD should probably be taken into consideration when using radiological reporting systems for COVID-19.

Limitations

The limitations of our study include its retrospective nature and acquisition of study data from the hospital database.

Conclusion

In conclusion, TCT imaging plays an important role in the early diagnosis of COVID-19 patients. Radiological scoring systems for COVID-19 pneumonia exhibit a good level of agreement, which supports their usefulness in the diagnosis and treatment of these patients. Comorbid conditions in these patients may have an impact on these scoring systems when utilized for classification of the lung involvement. Further studies examining pathological correlations are warranted to determine the prognostic factors of this disease.

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Conversion arthroplasty after failed extracapsular hip fracture fixation is associated with high complication rates

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Ethics Committee Approval
The study was approved by Cukurova University ethics committee approval was obtained (Date:12.02.2021, Number: 108/20).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: There is no standard treatment of choice that addresses all extracapsular fractures, which account for approximately half of the elderly hip fractures. Arthroplasty is mostly favored secondary to unsuccessful fixation or unstable primary fractures. However, conversion arthroplasty complication rates are high in the literature. This study compares arthroplasty performed after unsuccessful fixation and primary arthroplasty for unstable extracapsular hip fractures.

Methods: In this retrospective study, we compared the first-year results of the groups that underwent conversion arthroplasty (cHA) and the primary arthroplasties (pHA) for extracapsular hip fractures. In the cHA group, patients were indicated for operation if there was a failure of fixation after extracapsular hip fractures (n=44). In the pHA group, patients were for unstable extracapsular hip fractures (n=44). In the cHA group, failure of fixation causes were cut-out of lag screws (54.5%), cut-through of lag screws (9.1%), non-union of fractures (27.3%), and osteonecrosis of femoral heads (9.1%). While total hip replacement was applied to all patients in the cHA group, total hip replacement was applied to ten patients in the pHA group and hemiarthroplasty to 34 patients. In comparing groups, duration of operation, amount of bleeding, intraoperative complications, post-operative complications, mobilization capacities, functional status, and mortality rates were used.

Results: There were 44 patients in both groups. The surgical time (134.3 [34.5)] vs. 66 [16], [P<0.001]), the amount of bleeding (1000 ml [400] vs. 300ml [200], [P<0.001]), the need for red blood cell transfusion in the operations (80% vs. 32%, [P<0.001]), and the frequency of intraoperative femur fracture (30% vs. 0%, [P<0.001]) were larger or longer in the cHA group compared to pHA group (P<0.001). While 14 complications requiring surgical intervention were observed in 12 of 44 patients in the CHA group in the post-operative 1st year, four complications were observed in four of 44 patients in the pHA group. There was no difference in mortality rates (3 vs. 3, [P=1]), mobilization capacities (5.9 [2.1] vs. 5.7 [2.0], [P=0.597]), and functional status (12.5 [3.3] vs. 13.0 [2.7], [P=0.434]) between the groups.

Conclusion: Arthroplasty performed as conversion surgery after unsuccessful fixation has a higher risk of intraoperative and post-operative complications than primary arthroplasty performed after extracapsular hip fractures. We believe the cases prone to implant failure, non-union, or restricted mobilization because of the patient and fracture-type reasons should be treated with primary arthroplasty.

Keywords: conversion arthroplasty, unstable hip fracture, hip arthroplasty

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Introduction

Hip fractures are one of the major causes of morbidity and mortality in the elderly and create more burden on health systems with the aging of society. In Turkey, approximately 42,000 hip fractures were seen in 2019 among those over 50 years of age. It is estimated that this amount will increase by 12% at the end of 2024 [1]. In the first 6 months after injury, mortality can reach up to 50%, although it varies according to the patient's age, comorbid diseases, the treatment method performed and the mobilization time after treatment [2-4].

Intracapsular proximal femoral fractures in the elderly tend to be treated with arthroplasty rather than fixation methods due to the poor healing potential and high reoperation rates [5]. However, this consensus does not come true for extracapsular fractures, which account for about half of all hip fractures [6]. While fixation is a successful treatment option for stable fractures [7-9], the success rate is low, and complication rates are high in unstable fractures [7,8,10,11]. Some complications, such as loss of fixation, cut-out, and non-union, sometimes lead to irreparable situations to perform internal fixation [10,12,13]. In such cases, arthroplasty is the treatment of choice as a salvage procedure [14,15]. However, when arthroplasty is performed after failed fixation, a more challenging procedure is waiting for the surgeon with high complication rates [15-16]. For this reason, arthroplasty can be preferred as the primary treatment method in unstable fractures of the elderly where the chance of success is low fixation only [2,17].

Our study aims to determine whether arthroplasty is more successful as the first treatment in unstable trochanteric fractures by comparing our cases of conversion arthroplasties and primary arthroplasty cases after failed fixation.

Materials and methods

Çukurova University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (Date: 12.02.2021, Number: 108/20) approval was obtained before the study. Between January 2015 and December 2019 at our hospital, 44 hips of 44 patients (27 female, 17 male) over the age of 60 underwent conversion hip arthroplasty (cHA) due to fixation failure of proximal extracapsular hip fractures, excluding the diagnosis of infection. In 29 of 44 hips (65.9%), intramedullary devices (short or long) were used for fracture fixation in the first operation, while plate-screw constructs were used in 15 hips (34.1%). The mean time between the fixation and conversion procedure was 10.45 months. The indication for cHA was a cut-out of the lag screw in 24 (54.5%) patients, cut-through in four (9.1%), and non-union more than 12 months after fixation in 12 (27.3%). In four (9.1%) patients, hip arthroplasty was done due to osteonecrosis in the femoral head.

The cases who underwent conversion hip arthroplasty after the failure of fixation (cHA group) were matched with a control group consisting of 44 patients who were admitted with the diagnosis of unstable extracapsular proximal femur fractures and underwent primary hip arthroplasty (total/partial) (pHA) by the same team during the same period (pHA group). Written informed consent was obtained from all participants. Patients were matched one to one according to age, sex, body mass index (BMI), and the American Society of Anesthesiologists (ASA) rating.

Patient medical records, operative notes, and radiographs were retrospectively reviewed. All operations were performed by the same team using a posterolateral approach and cementless implants. We routinely performed hematologic tests to rule out infection in the cHA group, including complete blood cell count, erythrocyte sedimentation rate, and C-reactive protein (CRP) before operation. In suspected cases, preoperative joint aspiration and microbial cultures are routinely performed. In addition, samples were taken from all patients from the implant periphery and hip joint for microbiological examination during the operation. In our hospital, red blood cell transfusions were standardized according to a protocol based on the guidelines for perioperative transfusion by the National Institutes of Health Consensus Conference [18].

In cHA cases, the length of the femoral stems was at least 30 mm distal to the last screw of the previous implant (Figure 1). Short femoral stems were preferred if a long intramedullary nail was used in the previous operation. The pHA group preferred fully porous coated stems with distal fit or grit-blasted titanium niobium alloy stems (Figure 2). The acetabular component was selected according to the adequacy of the abductor mechanism and the presence of any neurological disease leading to instability. Constrained components were preferred when the abductor mechanism was severely impaired or in the presence of neurological disease. In the pHA group, bipolar cups were used in patients with short life expectancy and without hip degeneration, while total hip arthroplasty was performed in patients with hip degeneration and long life expectancy.

The patients in both groups were allowed to walk with full weight bearing with an assistive device the day after the operation, as they tolerated. The same antibacterial and thromboembolic prophylaxis was applied in both groups. All patients were followed routinely at the 6th week, 3rd month, 6th month, and 12th month postoperatively. In the follow-up, the observation was mainly aimed at the capacity and the quality of mobilization and the need to use the assistive device in addition to the routine hip examination.

We compared the length of the operation, intra-operative blood loss, the requirement of transfusion, intraoperative complications, and hospital stay between the two groups. The comparison continued on post-operative complications, reoperation for any reason, ambulation status (preinjury and 12th month follow-up), and post-operative mortality rate until the first year follow-up. With the information obtained from the patient or family members, the ambulatory capacity before the fracture and at the 12th month after the operation was classified with a Parker score [19]. The functional status of the patients was evaluated with the Postel Merle d'Aubigné score [20].

Figure 1: (A-B) Anteroposterior and lateral hip radiographs of the patient who developed a cut-out at the post-operative 3rd month after extracapsular hip fracture fixation. (C-D) Post-operative anteroposterior hip radiographs of the patient who underwent conversion arthroplasty. The femoral stem was at least 30 mm distal to the last distal screw (black arrow).

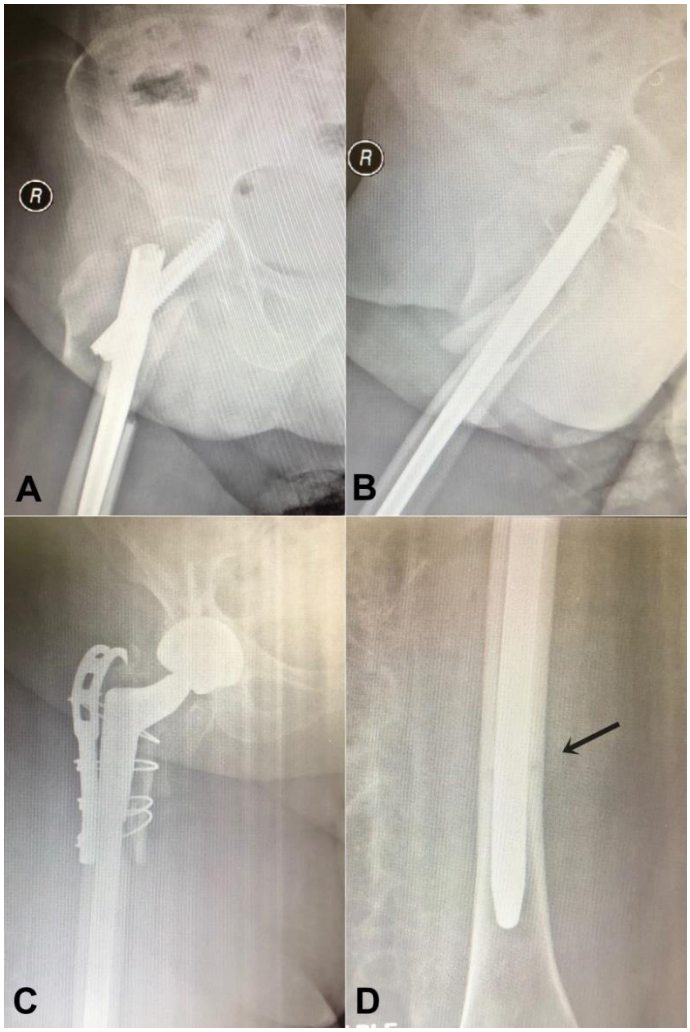
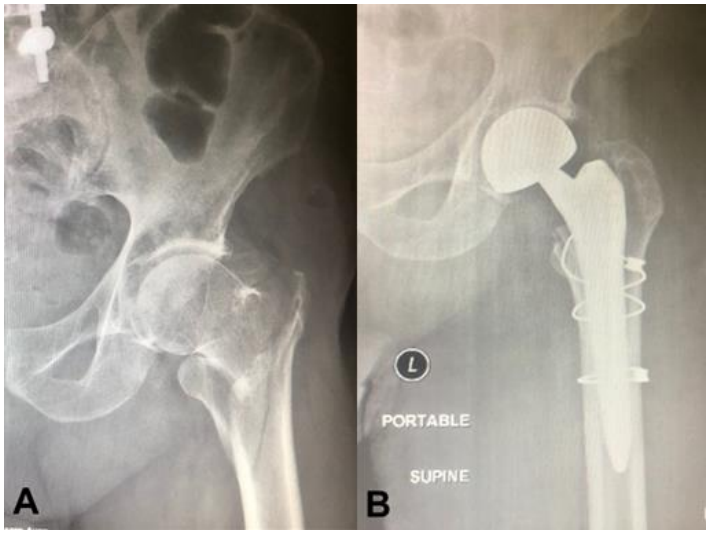


Figure 2: (A) Preoperative and (B) post-operative radiographs of a patient with an unstable extracapsular hip fracture treated with primer hip arthroplasty.



Statistical analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean, standard deviation, and median and IQR where appropriate. The chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test. For the comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. For comparison of preoperative-postoperative Parker measurements, paired samples t-test was used. For comparing hospitalization duration between ASA scores, the Kruskal Wallis test was used, and Bonferroni adjusted Mann Whitney U test was used for multiple comparisons of groups. For univariate analysis, event-free survival was calculated by the Kaplan-Meier method, and the log-rank test was performed to compare OS between study groups. All analyses were performed using IBM SPSS Statistics Version 20.0 (IBM SPSS Statistics for Windows, IBM Corp. Released 2011, Armonk, NY: IBM Corp) statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

There was no difference in gender, ASA score, and BMI between the groups, but the mean age of the pHA group was higher (P=0.011). The patients' demographic data are given in Table 1. The surgical time (134.3 [34.5] vs. 66 [16], [P<0.001]), the amount of bleeding (1000 ml [400] vs. 300ml [200], [P<0.001]), the need for red blood cell transfusion (80% vs. 32%, [P<0.001]), and the frequency of intraoperative femur fracture (30% vs. 0%, [P<0.001]) were larger or longer in the cHA group compared to pHA group (Table 2).

Table 1: Patients' characteristics

	Groups		*P*-value
	cHA	**pHA**	
Age, Mean, (SD)	71.2 (9.5)	75.6 (6.1)	0.011
Gender, n (%)			
Male	17 (%39)	11 (%25)	0.170
Female	27 (%61)	33 (%75)	
BMI, Mean (SD)	29.8 (4.2)	29.4 (5.2)	0.750
ASA Score, n (%)			
1	5 (%11)	3 (%7)	0.814
2	25 (%57)	26 (%59)	
3	14 (%32)	15 (%34)	
Side, n (%)			
R	16 (%36)	21 (%48)	0.280
L	28 (%64)	23 (%52)	
Preoperative hemoglobin level g/dL, Mean (SD)	12.4 (2.4)	12.1 (1.5)	0.591
Preoperative hematocrit level %, Mean (SD)	38.0 (5.2)	36.4 (4.2)	0.107
Preoperative INR, Mean,(SD)	0.99 (0.15)	1.02 (0.13)	0.541

BMI: Body Mass Index, ASA Score: American Society of Anesthesiologists Score, INR: International Normalized Ratio

Table 2. Intraoperative characteristics

	Groups		*P*-value
	cHA	**pHA**	
Surgical time (Minutes), Mean (SD)	134.3 (34.5)	66.0 (16.0)	<0.001
Intraoperative bleeding amount (ml), median (IQR)	1000 (400)	300 (200)	<0.001
Intraoperative red blood cell transfusions, median (IQR)	1.5 (1)	0 (1)	<0.001
Intraoperative red blood cell transfusions, n(%)			
0	9 (20%)	30 (68%)	<0.001
1	13 (30%)	10 (23%)	
2	12 (27%)	3 (7%)	
3	8 (18%)	1 (2%)	
4	1 (2%)	0 (0%)	
6	1 (2%)	0 (%0)	
Intraoperative fractures, n(%)			
No	31 (70%)	44 (100%)	<0.001
Yes	13 (30%)	0 (0%)	

cHA: conversion hip arthroplasty, pHA: primary hip arthroplasty, IQR: interquartile range, SD: standard deviation

Total hip arthroplasty was performed in all 44 patients in the cHA group. Revision femoral stem was used in 32 (72.7%) of these patients, while primary stem was used in 12 (27.3%) patients. Hemiarthroplasty was performed in 34 patients (77.3%) in the pHA group, while total hip arthroplasty in 10 (22.7%). Constrained cups were used in three patients in the cHA group

for abductor arm defect and/or neurological imbalance, while no constrained systems were used in any patients in the pHA group.

No significant difference was observed between the groups in terms of hospitalization time and transfusion during the post-operative follow-up period in the hospital. When the total amount of transfusions were compared, it was observed that more patients and more transfusions were performed in the cHA group than in the pHA group (P<0.001) (Table 3).

Table 3: Postoperative characteristics

	Groups		*P*-value
	cHA	pHA	
Length of hospitalization, days, median(IQR)	5 (2)	4 (1	0.084
Post-operative red blood cell transfusion, Median (IQR)	0 (2)	0 (1)	0.456
Post-operative red blood cell transfusion, n (%)			
0	22 (51%)	23 (52%)	0.198
1	7 (16%)	14 (32%)	
2	11 (26%)	5 (11%)	
3	3 (7%)	2 (5%)	
Total red blood cell transfusion, median (IQR)	2 (1)	1 (2)	<0.001
Total red blood cell transfusion, n (%)			
0	5 (12%)	16 (36%)	<0.001
1	5 (12%)	16 (36%)	
2	16 (37%)	6 (14%)	
3	10 (23%)	6 (14%)	
4	3 (7%)	0 (0%)	
5	3 (7%)	0 (0%)	
6	1 (2%)	0 (0%)	

IQR: interquartile range

Twelve of 44 patients in the cHA group have shown 14 complications requiring surgical intervention in the first year follow-up. Of these 14 surgical interventions, nine were surgical debridement due to wound problems, two were open reduction for dislocation, one was an acetabular revision due to recurrent dislocation, one was a two-stage total revision due to infection, and one was femoral revision due to the subsidence of the femoral stem. In the pHA group, four complications were observed in four of 44 patients during the same period. Two were wound problems requiring surgical debridement, and two were dislocations treated with closed reduction. In the first year, three deaths occurred in both groups. The main causes of death in the pHA group were myocardial infarction in one patient, ischemic stroke in one, and lung disease in one. In the cHA group, two patients died from ischemic stroke and one from myocardial infarction (Table 4).

Table 4: 1st year complications, mortality and functional status

	Groups		*P*-value
	cHA	pHA	
1st year complications, patients (%)			
No	32 (73%)	40 (91%)	0.027
Yes	12 (27%)	4 (9%)	
1st year mortality, patients(%)			
No	41 (93.2%)	41 (93.2%)	1
Yes	3 (6.8%)	3 (6.8%)	
Parker Score at 1st, (SD)	5.9 (2.1)	5.7 (2.0)	0.322
The Merle d'Aubgine Postel Score at 1st year, mean (SD)	12.5 (3.3)	13.0 (2.7)	0.434

At the 12th month of the operation, the walking capacity of all patients decreased compared to pre-injury. While the mean Parker score was 7.9 (1.6) before injury in the cHA group, it was 5.9 (2.1) at the 12th-month follow-up (P<0.001). These values were 7.5 (1.2) and 5.7 (2.0) in the pHA group, respectively (P<0.001). No difference was observed when the functional levels of the groups were compared in the 12th month. The mean Merle d'Aubgine Postel score in the 12th month was 12.5 (3.3) in the cHA group and 13.0 (2.7) in the pHA group (P=0.434).

Discussion

Hip fractures significantly burden health systems with the aging of society [1]. Mortality in hip fractures in the first 6 months can reach up to 50% even with modern treatment methods [3,17,21]. Surgical treatment methods have lower mortality rates than conservative methods because the patient can be re-mobilized quickly [3]. Factors that increase mortality are advanced age, high ASA grade, delayed surgery, low mobilization capacity before fracture, and delayed mobilization with full weight bearing [2,4,21–26]. Among these mortality factors, we can only change the time delay of surgery and early mobilization with full weight bearing. Ottesen et al. [4] stated that early mobilization and full weight-bearing after hip fracture surgery reduce complications and mortality, so the chosen surgical method should be a method that will allow early full weight-bearing.

Similarly, many publications state that mobilization with early full weight bearing decreases mortality and complications [23-25]. Patients admitted to our clinic with a hip fracture are targeted to undergo surgery within the first 24 h unless they have significant contraindications. Thirty-six (82%) of 44 patients in the pHA group in our study were operated on within the first 48 h (28 within the first 24 h). The most common reasons in patients with a delay of more than 48 h were antiaggregant usage and unstable cardiac condition. The mortality rate of these 44 patients within 12 months was 6.8%. In the literature, 12-month mortality rates of various surgical methods vary between 14.5% and 30% [2,9,11,17,27]. We believe that this success rate and decreased mortality in our series is due to early surgery, which allows full weight bearing with an assistive device in the early post-operative period.

Fixation is the primary treatment method for stable extracapsular hip fractures [7-9]. However, this consensus does not exist for unstable fractures. In unstable fractures, the success of fixation methods decreases and complication rates increases [7,8,10–11]. Loss of fixation and position of the fracture, cut-out, non-union, and infection are common complications [10,12,13]. The reason for the continuous evolution of the hip screws is because of these unwanted but expected problems of these instruments. These complications sometimes cause irreparable problems, and arthroplasty is used as a conversion procedure [14,15]. However, arthroplasty procedures after failed fixation are more challenging and have high complication rates [15-16]. Due to the necessity of implant removal, deranged anatomy, and the requirement for revision frequently stems, conversion arthroplasty is a longer and more complicated procedure, with more bleeding [15,27–30]. The incidence of intraoperative fracture, which is one of the most important complications of conversion arthroplasty performed on the ground of extracapsular fracture, is up to 47% [28,30-32]. In our series, in the cHA group, the operation time was longer (134.3 [34.5] min vs. 66.0 [16.0] min), and the bleeding volume was higher (1000 ml [400] vs. 300 ml [200]) compared to the pHA group. In addition, while no intraoperative fractures were observed in the pHA group, 13 (30%) of 44 patients in the cHA group developed fractures. The reasons for more common intraoperative fractures in cHA are decreased bone density due to prolonged immobilization after fracture, defects in the bone during removal

of old implants, and increased need for revision stems. Therefore, Archibeck recommended placing prophylactic cables in the area of old screw holes [15].

Our study had some limitations. Our study, which was designed retrospectively, lacked randomization. Although ASA grade, gender, and age were taken into account when choosing the pHA group, the mean age of patients in the pHA group was higher than that of the cHA group. Our study compared only the first-year follow-up after the operation. Different results can be obtained with a longer follow-up time. Arthroplasty and fixation in extracapsular hip fractures should be compared with large patient groups over longer periods.

Conclusion

In conclusion, arthroplasty performed as conversion surgery after unsuccessful fixation has a higher risk of intraoperative and post-operative complications than arthroplasty performed after a fracture. We believe that cases prone to implant failure, non-union, or prolonged immobilization due to unreliable fixation should be treated with primary arthroplasty to avoid undesired complications.

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The effect of thromboelastogram-guided transfusion on postoperative complications and transfusion requirement in the post-reperfusion period in liver transplantation surgery

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Ethics Committee Approval
The study was approved by the Non-Pharmaceutical and Non-Medical Device Research Ethics Committee of Necmettin Erbakan University, Date: 06/01/2023, Number: 2023-4101.
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Conflict of Interest
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Abstract

Background/Aim: Liver transplantation surgery is one of the most common abdominal surgeries requiring blood transfusion. Coagulation parameters vary during the perioperative period because of the patient profile. Blood transfusion management should be carefully controlled to avoid causing dysfunction in the newly transplanted organ. Various laboratory parameters are used to achieve this. This study aimed to investigate the effect of transfusion managed by conventional coagulation tests or thromboelastogram (TEG) on blood product consumption and postoperative outcomes in the post-reperfusion period.

Methods: The records of 90 recipients who underwent transplantation between January 1, 2012, and November 30, 2022, were retrospectively analyzed. Twenty patients who were administered blood transfusion under TEG guidance in the post-reperfusion period constituted the case group, while 20 patients non-consecutive randomly selected among other patients who were administered blood transfusion with conventional coagulation tests constituted the control group. In conclusion, 40 patients were included in this retrospective case-control study. We retrospectively analyzed demographic data, surgical data, perioperative laboratory parameters, intraoperative total and post-reperfusion blood and blood product transfusions, TEG parameters, and postoperative complications.

Results: No difference was found between the groups regarding demographic data, etiological factors, surgical data, and preoperative laboratory parameters ($P>0.05$). There was a significant decrease in the amount of fresh frozen plasma (FFP) transfused in the case group compared to the control group in the intraoperative total and post-reperfusion period ($P=0.011$, $P=0.003$). There was no difference between the groups regarding other blood product transfusions and postoperative complications ($P>0.05$). Regarding the effects of intraoperative total and post-reperfusion blood and blood products on ventilator stay, intensive care unit stay, length of stay (LOS), hepatic artery thrombosis, graft rejection, postoperative kidney damage, and first 28-day mortality, only a weak negative correlation was found between intraoperative total and postreperfusion fibrinogen use and LOS (r=-0.325/$P=0.041$, r=-0.354/$P=0.025$).

Conclusion: TEG-guided transfusion in the post-reperfusion period reduced total blood product consumption. Besides, the increase in the use of fibrin has led to a decrease in LOS. However, using TEG has no significant effect on postoperative mortality and morbidity. TEG and an objective assessment of patient clinical status may be an ideal guide for transfusion strategy.

Keywords: liver, transplantation, thromboelastography, blood transfusion

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Introduction

Thanks to the advancements in surgical techniques, anesthesia management, and graft preservation in liver transplantation, transplantation can be terminated with a minimal requirement for transfusions [1]. However, transfusion requirements in transplant surgery remain highly variable, and there is no universal consensus regarding transfusion thresholds [2]. Different factors determine the need for blood transfusions, such as perioperative anemia, coagulation disorders, decreased platelet counts, and surgical complications. Besides, the procoagulant and anticoagulant components of the coagulation cascade are affected to varying degrees in patients with liver failure. For this reason, bedside, rapid-result, and comprehensive viscoelastic tests should be used in liver transplantation surgery rather than conventional coagulation tests, which provide information about certain steps of the coagulation cascade [3]. Although it is generally believed that viscoelastic tests will reduce the amount of transfusion and thus the risk of postoperative complications, the dynamic and multifactorial process in liver transplant patients makes it mandatory to manage transfusion not only with laboratory tests but also with the clinical status of the patient.

The most significant changes in the coagulation cascade in liver transplantation occur between the end of the anhepatic phase and the post-reperfusion period when the new organ anastomosis is performed [4]. In our clinic, thromboelastogram (TEG) is routinely studied in all patients, particularly post-reperfusion. In patients for whom TEG cannot be studied for various reasons, transfusion is administered under the guidance of conventional coagulation tests. The clinical evaluation of clot formation is one of the most important parameters in making a transfusion decision, along with laboratory parameters. In this context, we retrospectively analyzed the prospectively collected data of liver transplantation patients received in our clinic in the last decade and conducted a case-control study. In this way, we planned to compare the effect of transfusion guided by TEG or conventional coagulation tests on postoperative complications and transfusion volume. It is hypothesized that TEG-guided transfusion will reduce the amount of transfusion and thus the postoperative mortality and morbidity.

Materials and methods

The study was designed as a retrospective case-control study in a university hospital in line with the principles stated in the Declaration of Helsinki, with the decision of Necmettin Erbakan University Non-Pharmaceutical and Non-Medical Device Research Ethics Committee (Decision No: 2023/4101). File records of recipients who underwent liver transplantation between January 1, 2012, and November 30, 2022, were retrospectively reviewed. Recipients under 18 years old who had liver transplants again within 30 days after the first transplantation, who had combined liver and kidney transplantation, who died intraoperatively, and whose file records were insufficient were excluded from the study. Twenty recipients whose blood transfusion was administered under TEG guidance after the reperfusion period of the surgery constituted the case group. Among the recipients whose transfusion was managed with conventional coagulation tests, 20 recipients selected by non-consecutive random method constituted the control group.

In our faculty, liver transplantation is performed under a special procedure with the same surgical and anesthesia team. All recipients are monitored by electrocardiogram, pulse oximetry, invasive and noninvasive arterial pressure measurement, neuromuscular monitoring, and bispectral index measurement. Anesthesia induction is achieved by administering propofol (1–2 mg/kg), fentanyl (1 mcg/kg), and rocuronium (0.5 mg/kg). After endotracheal intubation, anesthesia was maintained with desflurane inhalation and remifentanil infusion (0.05–0.4 mcg/kg/min) in a 50% air-50% O_2 mixture with a bispectral index between 40 and 60%. Lung ventilation is provided with a tidal volume of 5–6 mL/kg and a respiratory rate of 10–14/min, keeping the end-tidal CO_2 value in the 35–45 mmHg range. Positive end-expiratory pressure was maintained at 5 mmHg.

Ultimately, recipients are anesthetized, and internal jugular vein catheterization is performed under ultrasonography guidance. During the surgery, the recipients are warmed with a warming blanket, and their body temperature is monitored. The target mean arterial pressure during transplantation is 65 mmHg and above. Hemodynamic disorders are treated with fluid therapy and vasoactive drugs (norepinephrine 0.01–0.05 mcg/kg/min). Crystalloids, colloids, and albumin infusions are used in fluid therapy. Patients receive erythrocyte suspension (ES) transfusions to maintain hemoglobin (Hb) between 8 and 9 g/dL and to maintain O_2 supply.

Preoperative hemogram, biochemistry, international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen values were studied for all recipients. In surgery, TEG or conventional coagulation tests are routinely performed in the first hour after reperfusion, depending on the suitability of the conditions (availability of consumables). TEG or conventional coagulation tests can be performed in case of severe bleeding at other stages of transplantation. In patients undergoing TEG, 2 units of fresh frozen plasma (FFP) are administered when the R time ≥11 min, while 1 unit of apheresis platelet suspension (PS) is administered when the MA <30 mm, and 2 g of fibrinogen concentrate or 4 units of cryoprecipitate when the alpha angle <55. In patients undergoing conventional coagulation tests, 2 units of FFP are transfused when INR >2 or aPTT >30, 2 g of fibrinogen concentrate or 4 units of cryoprecipitate when fibrinogen <120 g/dL, and 1 unit of apheresis PS when platelets <30,000 × 10^3/µL. If microvascular leakage occurs, tranexamic acid (10–15 mg/kg) is administered despite transfusions in the post-reperfusion period. Clinical signs of surgical bleeding are not ignored when transfusing blood products, and the process is managed in correlation with the surgical team. After surgery, patients are transferred to the reanimation unit for postoperative care.

Thrombelastography analysis was conducted using TEG_5000, version 4.2 (Haemoscope Corporation, Niles, IL, USA). One milliliter of complete blood was taken from the citrated tube and transferred to a kaolin tube. The complete blood was gently mixed for full contact with the kaolin. An automatic pipette transferred 340 µl of the mixture to the test bath. To

antagonize citrate, 20 µl calcium chloride is added to the test bath with an automatic pipette, and the test is started.

In accordance with this protocol, the data scanned from the files of liver transplant recipients included gender, age, body mass index (BMI), model for end-stage liver disease (MELD) score, cause of liver failure, previous abdominal surgery, hypertension, diabetes, preoperative kidney injury, encephalopathy, upper gastrointestinal (GI) bleeding, portal vein thrombosis (PVT), portopulmonary hypertension, presence of ascites, preoperative creatinine, Na, K, albumin, bilirubin, Hb, INR, aPTT, platelet, fibrinogen values, post reperfusion Hb, platelet, fibrinogen, INR, aPTT values, intraoperative total fluid loss, amount of diuresis, amount of administered crystalloid, colloid and albumin, amount of ES, PS, fibrinogen, FFP, cryoprecipitate transfused intraoperatively and after reperfusion, surgical duration-related data, presence of reperfusion syndrome, whether the donor is alive or cadaver, presence of postoperative complications (kidney damage, hepatic artery thrombosis, graft rejection, mortality in the first 28 days), LOS, and TEG parameters.

The primary outcome measure was the difference in intraoperative transfused blood and blood products, and the secondary outcome measure was the difference in the development of postoperative complications.

Statistical analysis

The data obtained in this study were analyzed using the SPSS 23.0 package program. Descriptive statistical values of all measurements are presented. Shapiro-Wilk's test was conducted when analyzing the normality of the scores between the groups since n<30. Because of the normality test, it was determined that the values between the groups did not show normal distribution at $P<0.05$. Hence, the Mann-Whitney U test was used to analyze the groups' differences. The chi-square test was used to examine intergroup dependence in categorical data. When analyzing the difference and dependency between the groups, $P<0.05$ was considered the significance level, and it was considered that there was a significant difference between the groups when $P<0.05$ and there was no significant difference between the groups when $P>0.05$.

Results

The records of 90 recipients who underwent transplantation between January 1, 2012, and November 30, 2022, were retrospectively analyzed within the scope of the study. As a result of the final cohort formed by inclusion and exclusion criteria, 40 recipients were included in the study. The flow diagram of the study is given in Figure 1.

When the causes of liver failure were analyzed, the etiologic factors of the recipients were: cryptogenic in ten (25%), autoimmune in eight (20%), primary sclerosing cholangitis in five (12.5%), hepatocellular carcinoma in 14 (35%), and intoxication in three (7.5%). The preoperative characteristics are given in Table 1.

When the preoperative laboratory parameters of the recipients were analyzed, no significant difference was found between the two groups (Table 2).

The mean duration of surgery was 494 min, and the mean anhepatic phase duration was 77.17 min. It was determined that reperfusion syndrome developed in four (20%) patients in the case group and six (30%) patients in the control group. The distribution of intraoperative and surgical data between the groups is presented in Table 3.

Figure 1: Flow diagram of the study.

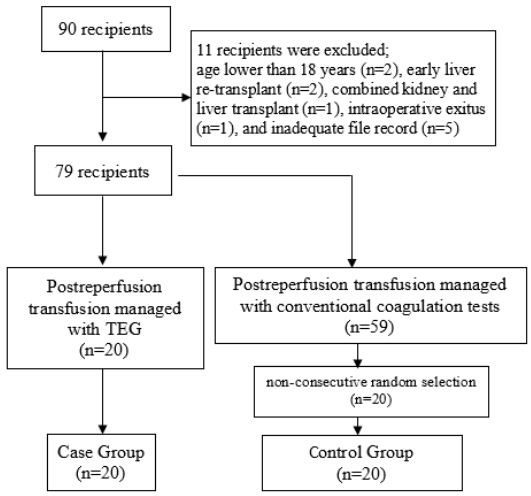

Table 1: Preoperative recipient characteristics (mean[SD], n [%]).

	Case group (n=20)	Control group (n=20)	*P*-value
Age (year)	43.10(14.05)	45.35(12.89)	0.583
Gender (M/F)	12 (60%) / 8 (40%)	9 (45%) / 11 (55%)	0.342
BMI (kg/m ^{2})	26.01(2.76)	26.35(3.61)	0.718
MELD Score	21.90(8.52)	17.55(8.57)	0.086
Previous abdominal surgery	0 (0%)	2 (10%)	0.487
Preoperative kidney injury	5 (25%)	4 (20%)	1.000
Preoperative hypertension	4 (20%)	4 (20%)	1.000
Preoperative diabetes mellitus	4 (20%)	2 (10%)	0.661
Preoperative encephalopathy	10 (50%)	7 (35%)	0.337
Preoperative upper GIS bleeding	3 (15%)	3 (15%)	1.000
Preoperative PVT	2 (10%)	0 (0%)	0.487
Preoperative pulmonary Hypertension	2 (10%)	1 (5%)	1.000
Presence of preoperative ascites	1 (%5)	3 (%15)	0.605

SD: standard deviation, M: Male, F: Female, BMI: Body mass index, MELD: Model for end-stage liver disease, GIS: Gastrointestinal system, PVT: Portal vein thrombosis

Table 2: Preoperative recipient laboratory parameters (mean[SD]).

	Case group (n=20)	Control group (n=20)	*P*-value
Creatinine (mg/dL)	0.85(0.47)	0.74(0.37)	0.398
Na (mmol/L)	135.30(5.38)	137.55(6.60)	0.142
K (mmol/L)	4.06(0.50)	4.28(0.80)	0.718
Albumin (g/dL)	2.98(0.62)	3.32(0.66)	0.114
Bilirubin (mg/dL)	6.50(7.68)	7.19(6.77)	0.698
Hemoglobin (g/dL)	10.53(1.60)	10.32(2.80)	0.547
Platelet (x10 ^{3}/uL)	95.15(29.88)	100.85(56.50)	0.678
Fibrinogen (mg/dL)	152.15(35.14)	158.30(31.46)	0.692
INR	1.97(0.83)	2.21(1.47)	0.968
aPTT (seconds)	40.76(9.51)	40.37(10.75)	0.602

SD: standard deviation, Na: Sodium, K: Potassium, INR: International normalized ratio, aPTT: Active partial thromboplastin time

Table 3: Intraoperative and surgical data (mean[SD], n [%]).

	Case group (n=20)	Control group (n=20)	*P*-value
Dissection time (min)	174.85(69.95)	213.75(108.31)	0.277
Anhepatic phase duration (min)	82.10(18.83)	72.25(17.88)	0.149
Warm ischemia time (min)	82.60(18.58)	84.50(18.13)	0.543
Total surgery time (min)	463.25(108.91)	524.75(166.42)	0.253
Reperfusion syndrome (n(%))	4 (20%)	6 (30%)	0.465
Intraoperative total fluid loss (ml)	2445.00(1127.409	2652.50(2061.84)	0.678
Intraoperative total diuresis (ml)	474.00(158.73)	707.75(402.40)	0.060
Intraoperatively administered crystalloid (ml)	5160.00(1595.19)	5500.00(1577.14)	0.698
Intraoperatively administered colloid (ml)	1140.00(839.42)	1350.00(650.91)	0.068

SD: standard deviation

When TEG values were analyzed in the first hour after reperfusion in the case group, it was determined that the mean R time was 11.50 min, K time was 8.67 min, MA value was 41.49 mm, G value was 4.07 dyne/cm^2, LY 30 was 0.31%, and alpha angle was 41.24 degrees. When intraoperative total and

postreperfusion blood and blood product transfusions were analyzed, it was found that there was no significant difference in ES, PS, fibrinogen concentrate, and cryoprecipitate transfusions, whereas FFP concentration transfusion was significantly lower in the case group (P=0.011, P=0.003). Intraoperative total and post-reperfusion blood and blood product transfusion rates are shown in Table 4 and Table 5.

Table 4: Intraoperative total blood and blood product transfusion (mean[SD]).

	Case group (n=20)	Control group (n=20)	*P*-value
Erythrocyte suspension (unit)	2.30(1.72)	2.05(2.44)	0.314
Fresh frozen plasma (unit)	1.20(1.64)	2.75(1.94)	0.011*
Platelet suspension (unit)	0.25(0.44)	0.05(0.22)	0.289
Fibrinogen concentrate (gr)	1.10(1.21)	0.40(0.82)	0.096
Cryoprecipitate (unit)	0.80(1.64)	1.40(2.35)	0.565
Albumin (mL)	200.00(107.61)	170.00(103.11)	0.265

SD: standard deviation, *P<0.05

Table 5: Post-reperfusion laboratory parameters and blood and blood product transfusions (mean[SD]).

	Case group (n=20)	Control group (n=20)	*P*-value
Hemoglobin (g/dL)	8.62(1.20)	9.11(1.82)	0.495
Platelet (x10 ^{3} /uL)	95.85(47.78)	81.45(32.59)	0.301
Fibrinogen (mg/dL)	117.30(49.69)	114.85(25.99)	0.947
INR	3.17(1.33)	3.54(1.38)	0.314
aPTT (seconds)	54.56(13.31)	72.49(32.04)	0.127
ES (unit)	0.90(0.72)	0.60(0.88)	0.157
FFP (unit)	0.60(0.94)	1.65(0.75)	0.003*
TS (unit)	0.25(0.44)	0.00(0.00)	0.183
Fibrinogen Concentrate (gr)	0.90(1.02)	0.40(0.82)	0.183
Cryoprecipitate (unit)	1.00(1.78)	1.20(1.88)	0.799

SD: standard deviation, INR: International normalized ratio, aPTT: Active partial thromboplastin time, ES: Erythrocyte suspension, FDP: Fresh frozen plasma, PS: Platelet suspension, *P<0.05

It was determined that 26 (65%) transplanted livers were obtained from cadavers and 14 (35%) from living donors. No significant difference was found between the groups regarding cadaver and living donor ratios (P>0.05). Similarly, there was no significant difference in postoperative outcomes of transplantations performed from cadavers or living donors (P>0.05). Besides, there was no difference between the groups in the postoperative complications that developed in the recipients (Table 6).

Table 6: Postoperative complication development (mean[SD], n[%]).

	Case group (n=20)	Control group (n=20)	*P*-value
Postoperative kidney injury	10(50%)	8(40%)	0.525
Hepatic artery thrombosis	5(25%)	3(15%)	0.695
Graft rejection	8(40%)	7(35%)	0.744
Length of stay on the ventilator (days)	1.90(3.54)	2.75(4.55)	0.547
Duration of icu stay (days)	5.60(4.51)	6.10(6.61)	0.678
Length of hospital stay (days)	15.65(11.44)	15.95(6.79)	0.620
First 28 days of mortality	8(40%)	7(35%)	0.744

SD: standard deviation

Regarding the effects of intraoperative total and post-reperfusion blood and blood products on ventilator stay, intensive care unit stay, LOS, hepatic artery thrombosis, graft rejection, postoperative kidney damage, and first 28-day mortality, only a weak negative correlation was found between intraoperative total and postreperfusion fibrinogen use and LOS (r=-0.325/P=0.041, r=-0.354/P=0.025).

Discussion

In this retrospective case-control study, we investigated the effect of TEG or conventional coagulation tests on the number of transfused blood products and postoperative complications in the post-reperfusion period of liver transplantation. According to the results of the study, it was found that the amount of transfused FFP decreased when TEG was used. However, there was no change in the number of other blood products. There was no difference between the two groups regarding the development of postoperative complications, but the LOS decreased with increasing fibrinogen use.

Simultaneous changes in the procoagulant, anticoagulant, and fibrinolytic system in end-stage liver failure cause a process in which the coagulation system is rebalanced globally. This new balance may cause bleeding in patients and increase the tendency to hepatic artery thrombosis and portal vein thrombosis [5]. In addition to changes in the coagulation system, the presence of systemic infection, portal hypertension, and renal dysfunction also increase the risk of bleeding [6]. Apart from these changes that make it difficult to manage the coagulation system, each stage of the liver transplant operation also causes variations in coagulation and poses serious challenges to patient blood management. Hypercoagulability often occurs at the onset of surgery, whereas progressive fibrinolysis is seen in the anhepatic phase. Coagulation gradually improves in 1 h after reperfusion of the liver allograft [7]. However, due to increased demand for a limited donor supply, the use of high-risk donors has increased recently, including advanced-age donors, significant steatosis, post-mortem donations, and infections. This leads to delayed allograft function and the risk of severe perioperative bleeding in critically ill recipients [8]. Therefore, in these patients, coagulation should be closely monitored, and any bleeding episodes should be accurately recognized.

Conventional coagulation tests are insufficient to predict bleeding in patients with liver failure [9]. TEG and rotational thromboelastometry are increasingly used to guide transfusions in liver transplant patients [10]. Current evidence on the use of TEG in liver transplantation suggests that using TEG rather than conventional coagulation tests results in fewer blood product transfusions without increased mortality or complications. TEG was first used in liver transplantation by Kang et al. [7], and a 33% reduction in transfusion volume was achieved. Wang et al. [11] compared two different TEG protocols in their study. While fewer FFP transfusions were performed in the strict protocol group (R time>15 min or MA of <40 mm), there was no difference in mortality. De Pietri et al. [12] randomized 60 liver transplant patients to a TEG-based transfusion protocol and significantly reduced the transfusion. De Pietri also found that TEG use had no adverse effect on 30-day and 6-months survival [13]. Perioperative TEG values also have potential value in predicting outcomes of liver transplantations. Zahr Eldeen et al. [14] reported that preoperative TEG values could predict early hepatic artery thrombosis. Contrary to common literature, Gaspari et al. [15] reported that TEG use did not reduce blood product consumption. The most important difference of this study from the other studies is that since they used kaolin TEG, they kept the threshold values considerably lower than the literature, specifically for MA and alpha angle. We also use kaolin TEG in the clinic and apply thresholds similar to this study. However, the most important difference of this study from our study is that they methodologically developed a scoring method and formed their cohort according to this scoring rather than randomly. Although there was no statistical difference in our study regarding demographic and surgical data, this difference in methodology may have caused

the difference in study results. Our study found that using TEG decreased blood product transfusion, in line with the general literature. We found that 91 blood and blood product units were used in the case group and 180 units in the control group. There was a significant difference in terms of TDP use, with significantly less TDP use in the case group. Meanwhile, we detected no significant difference between the groups regarding mortality and morbidity.

Perioperative transfusions are associated with worse postoperative outcomes [16]. Significant differences are observed in transfusion practices among anesthesiologists due to the transplantation process. Depending on coagulopathy and portal hypertension, blood product transfusion may be required during the dissection phase [17]. Deepening of coagulopathy in the anhepatic phase, particularly delayed graft function or worsening graft failure shortly after reperfusion, may also increase the need for transfusion. Similar to other recommendations, The Liver Intensive Care Group of Europe (LICAGE) recommends avoiding blood transfusion in the absence of clinically significant bleeding associated with coagulopathy [18]. Although the use of viscoelastic tests for targeted treatment of coagulopathy in liver transplantation is included in the European Society of Anesthesia (ESA) guidelines, a consensus is needed for cut-off values to guide optimal transfusion in practice [19]. The success of conservative transfusion policies in transplant recipients who tolerate very low platelet counts in the absence of active bleeding is remarkable [20]. Platelet transfusion was found to be an independent risk factor for worse outcomes in liver transplantation [21]. Hence, platelet transfusion is recommended in the presence of clinically significant bleeding supported by viscoelastic tests. Similarly, we used MA values of <30 in the case group and<30,000 in the control group as threshold values, although much higher values have been determined in the literature. We did not encounter any problems in bleeding control, and no correlation between platelet transfusion with postoperative complications was detected.

Due to the dynamic process of transplantation surgery, the correlation of viscoelastic tests with conventional coagulation tests in different phases of surgery is also different. Coagulopathy, which deepens gradually in other phases, improves with the onset of allograft function, typically by the end of the first hour [7]. Yoon et al. [22] compared conventional laboratory tests with TEG values at various stages of liver transplantation and found that TEG and conventional coagulation tests showed a good correlation in the dissection and post-reperfusion phases, whereas TEG was more advantageous in the anhepatic phase. In our clinic, we perform blood product transfusion after reperfusion by supporting clinical indicators with laboratory parameters, especially because it also shows the function of the allograft and may affect postoperative graft function. We found that the amount of FFP was significantly lower in the TEG-guided case group, but there was no difference in the transfusion of other blood products. Although not statistically significant, this may be due to higher fibrinogen use in the case group. Besides, although we did not observe any correlation between conventional test values and TEG values, we can state that there is less correlation between INR and aPTT values and R time compared to other parameters. Another factor in these results may be that our MELD scores were lower than 25 in both groups, and the patients did not have an increased transfusion risk.

Increased infection rates and hepatic artery thrombosis after liver transplantation have been associated with ES transfusion [23]. While still provider- and institution-dependent, some guidelines suggest that morbidity and mortality will be reduced when more liberal transfusion strategies are applied to patients with cardiac comorbidities, targeting a hemoglobin of ≥9 g/dL. Likewise, the World Health Organization also recommends restrictive transfusion strategies in critically ill patients that have been shown to have no detrimental effect on outcomes [24]. Many studies have argued for a threshold Hb concentration of 7 g/dL for transfusion and a Hb threshold value between 8–9 g/dL in those with a higher risk of side effects of anemia [25]. Optimizing cardiac output, ventilation, and oxygenation helps improve tolerance to lower Hb concentrations. In our clinic, we optimized all factors affecting oxygen delivery in transplantation and determined the Hb threshold value for ES transfusion as 8–9 g/dL. In the study, we transfused an average of 2 units of ES in both case and control groups. We believe that these values are quite low for transplantation surgery. Moreover, intraoperative total and post-reperfusion transfused ES were not correlated with postoperative complications. We consider strategies such as restrictive fluid therapy in the dissection phase, low Hb threshold values we determined for ES transfusion, avoiding prophylactic treatment for all blood products, and transfusing only in the case of clinically active bleeding supported by laboratory values that affect these results.

Most fibrinogen is synthesized in the liver, and its half-life is shortened in chronic liver failure [26]. When hemodilution or massive bleeding occurs, fibrinogen is the first factor to reach critical levels [27]. A fibrinogen concentration below 150 mg/dL increases hemorrhagic tendency; therefore, signs of fibrinogen deficiency on viscoelastic tests should suggest that fibrinogen transfusion may be necessary [19]. In their observational study, noval-Padillo et al. [28] found that ES, FFP, and PS transfusion decreased by 50%, and transfusion-free transplantation rates increased from 3.5% to 20% in patients receiving fibrinogen. A study on fibrinogen and FFP in surgical and trauma patients concluded that fibrinogen levels were generally associated with improved outcome measures, whereas FFP caused serious side effects [29]. In our study, it was found that fibrinogen values decreased in both groups in the post-reperfusion period. Although the amount of fibrinogen given intraoperatively (total and after reperfusion) was higher in the case group than in the control group, the difference was insignificant. Regarding the effect on postoperative complications, there was a negative correlation between fibrinogen use and LOS.

Limitations

Our study had some limitations. First, the data set was obtained retrospectively. This may lead to biases in the objectivity of the results. The second is that the number of cases was small, and we randomly selected the control group by non-consecutive sampling. Our results could have been much more objective if we had used a scoring method in which different factors were standardized when selecting the control group.

Furthermore, the small number of cases decreased the power of statistical analyses. Although TEG is a real-time test, it is also a test that gives instant results. Thus, the coagulation cascade should be evaluated more frequently in a dynamic process such as liver transplantation. If repeated sequential TEG measurements had been studied in each phase of surgery, the effect on transfusion rates might have been much different. Similarly, if TEG studies could be continued in the postoperative period, the effect of the strategy applied, particularly in the post-reperfusion period, on postoperative complications could be evaluated more accurately.

Conclusion

In conclusion, TEG-guided transfusion decreased total blood product consumption in the post-reperfusion period. Besides, the increase in the use of fibrin has led to a decrease in LOS. The use of TEG has no significant effect on mortality and morbidity. Although there is still a need to establish thresholds for transfusion, using TEG combined with an objective assessment of patient clinical status may be an ideal guide for transfusion strategy.

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Evaluation of pediatric renal transplant recipients admitted to the intensive care unit: A retrospective cohort study

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Ethics Committee Approval
The study was approved by the Başkent University Institutional Review Board (project No. KA 22/113).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The best course of treatment for children with end-stage kidney disease (ESKD) is renal transplantation (RT), but some pediatric RT recipients are admitted to an intensive care unit (ICU) post-transplant. In the early and late post-operative phases, clinical data about pediatric RT recipients who are admitted to ICU are available. In this study, we aimed to evaluate demographic features, main reasons, and outcomes of pediatric RT patients admitted to the ICU during the early and late post-operative phases.
Methods: This study was a cohort study. We analyzed the medical records of pediatric RT recipients (<18 years of age) who were admitted to the ICU between May 30, 2011, and October 16, 2021, at our center, retrospectively. Patients ≥18 years of age and those without available data were excluded. We obtained the following data from ICU follow-up records and hospital medical records. The median (minimum-maximum) for continuous variables, frequencies, and percentages for categorical variables were used. The Chi-square test was used to compare categorical variables. We created graphs using percentages and frequencies to summarize the results.
Results: Nineteen (16.5%) of the 115 pediatric patients who underwent RT were admitted to the ICU during the study period. Thirteen patients (68.4%) were male, and the mean age was 10.2 (4.9) years. Hypertension (21.2%) was the most common comorbidity. Eighteen (94.7%) received transplants from living donors. Cystic-hereditary-congenital disorders (42.1%, n=8) and congenital anomalies of the kidney and urinary tract (26.3%, n=5) were among the etiologies of ESKD. Ten patients (52.6%) were admitted to the ICU >6 months after transplantation. Epileptic seizure (n=6, 31.6%), respiratory failure (n=4, 21.1%), and cardiac diseases (n=2, 10.5%) were among the main reasons for ICU admission. During ICU follow-up, invasive mechanical ventilation was needed for five patients (26.3%), and renal replacement treatment was needed for four patients (21.1%). The mean length of ICU was 12.4 (28.5), and the mean hospital stay was 25.8 (29.4) days. The ICU and hospital survival rates were 78.9% and 97%, respectively, while 3.5% was the hospital mortality rate. Hemorrhagic cerebrovascular disease, acute hepatic failure, and cardiogenic shock secondary to pericardiocentesis were the causes of death in the ICU.
Conclusion: Patients mostly had ICU admissions because of epileptic seizures and acute respiratory failure. A multidisciplinary approach involving pediatric nephrologists, transplant surgeons, and an intensive care team successfully manages pediatric RT recipients admitted to the intensive care unit.

Keywords: end-stage kidney disease, renal transplantation, renal transplant recipient, intensive care unit, pediatric

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Introduction

The best course of treatment for children with end-stage kidney disease (ESKD) is renal transplantation (RT) [1]. In Turkey, living-related RT procedures have been in place since 1975 [2]. The most common causes of ESKD among pediatric patients are congenital, cystic, and hereditary disorders and primary glomerular diseases [3]. A successful RT aims to improve quality of life and increase life expectancy. Short-term graft survival has improved recently, but long-term results have only slightly improved. Graft rejection and poor graft survival rates remain because of the adverse effects of immunosuppressive regimens, underlying diseases, and more intense pediatric immunoreactivity [4,5]. As a result, pediatric RT recipients may have complications related to transplantation or their underlying diseases that adversely affect patient and graft survival [6].

The need for intensive care unit (ICU) follow-up may be seen in pediatric recipients with certain medical or perioperative complications after RT [5,6]. Although most pediatric RT recipients do not require ICU admission in the immediate posttransplant period, some centers may routinely admit them [7-9]. However, in the early and late post-operative phases, there are available clinical data about pediatric RT recipients who are admitted to ICU. Approximately 10% of adult RT recipients are admitted to the ICU, most commonly 6 months after RT [10]. Clinical features, etiologies, and complications differ in pediatric RT recipients from adults. The outcomes, reasons for admission, and time after RT can differ among pediatric RT recipients who require ICU [10-13].

There is a lack of information about pediatric RT patients admitted to the ICU in early and late post-operative periods. So, in the present study, we aimed to identify the demographic characteristics, comorbidities, main reasons for ICU admission, the need for management of respiratory complications and mechanical ventilation, the lengths of ICU and hospital stay, and outcomes of pediatric RT recipients who were admitted to the ICU during the early and late post-operative periods.

Materials and methods

We retrospectively analyzed the medical records of pediatric RT recipients (<18 years of age) who were admitted to the ICU between May 30, 2011, and October 16, 2021. Patients ≥18 years of age and those without available data were excluded. Pediatric RT recipients under 18 whose data were available for ICU admission were included in the study. Our center's pediatric RT recipients are not routinely admitted to the ICU in the immediate post-operative period. All RT pediatric patients had been sent to pediatric ICU immediately after surgery in some centers [9].

The study's primary outcome was to determine the incidence and causes of ICU admission and reasons for mortality in the ICU or hospital among pediatric RT recipients. The secondary outcome was identifying ICU supportive treatments (the need for renal replacement therapy [RRT], mechanical ventilation/tracheotomy) and length of ICU and hospital stay.

We obtained the following data from ICU follow-up records and hospital medical records: age, sex, weight, height, body mass index (BMI), comorbidity, immunosuppression regimen, etiologies of ESKD, time of ICU admission, Acute Physiology and Chronic Health Evaluation System (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Scale (GCS) score, vital signs of ICU admission, the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (Pao_2/Fio_2 ratio), type of respiratory support, need for mechanical ventilation and tracheotomy, presence of acute kidney injury (AKI), AKI stage, and need for RRT, presence and type of shock, type of vasopressor and inotropic therapy, presence of infections, laboratory values, length of ICU and hospital stays, and ICU and hospital mortality rates.

AKI was identified based on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines [14]. Sepsis and septic shock were defined according to international guidelines for managing sepsis and septic shock [15].

This study was approved by the Başkent University Institutional Review Board (project No. KA 22/113).

Statistical analysis

SPSS software (SPSS: An IBM Company, version 25.0, IBM Corporation) was used for statistical analysis. The median (minimum-maximum) for continuous variables, frequencies, and percentages for categorical variables were used. The non-parametric continuous variables were compared by the independent samples t-test, the Mann-Whitney test for quantitative data analysis, and the Chi-square test, and Fisher's exact test was used for qualitative data analysis. We created graphs using percentages and frequencies to summarize the results. *P*-value <0.05 was considered statistically significant.

Results

During the study period, 1343 solid-organ transplant procedures (1134 adult and 209 pediatric patients) were performed at Başkent University (Ankara, Turkey). In the Ankara Hospital of Başkent University, 652 renal (537 adults, 115 pediatric), 261 liver (93 adults, 168 pediatric), and 81 heart (51 adults, 30 pediatric) transplant procedures were performed. Nineteen (16.5%) of the 115 pediatric patients who underwent RT during the study were admitted to the ICU. The mean age was 10.2 (4.9) years (range, 1–17 years). Thirteen patients were male (68.4%), and six were female (31.6%) (Figure 1). The mean height, body weight, and body mass index were 127 (27.1) cm, 31 (17.2 kg), and 17.7 (4.4) kg/m^2, respectively. Fourteen recipients were underweight, four were normal, and one was obese according to BMI status. Eighteen (94.7%) received transplants from living donors, and one was from a deceased donor (5.3%). Hypertension (21.2%) was the most common comorbidity. Cystic-hereditary-congenital diseases (42.1%, n=8), congenital anomalies of the kidney and urinary tract (CAKUT) (26.3%, n=5), primary glomerular diseases (21.1%, n=4), and large vessel diseases (10.5%, n=2, 10.5) were among the etiologies of ESKD. (Table 1).

The combination of mycophenolate mofetil, tacrolimus, and prednisolone (57.9%) was the most common immunosuppression regimen. RRT was required for 78.9% of the

pediatric RT recipients (seven with hemodialysis, eight with peritoneal dialysis) before transplant. Four patients (21.1%) had preemptive RT.

Figure 1: Flowchart of pediatric renal transplant (RT) recipients, showing admission to the intensive care unit (ICU).

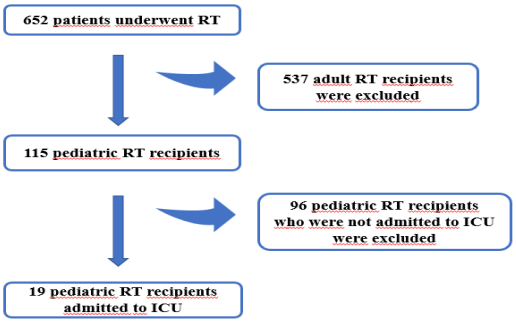

Table 1: Demographic and clinical features of pediatric renal transplant recipients.

	mean (SD)
Age, years	10.2 (4.9) (range, 1-17)
Weight, kg	31 (17.2)
Height, cm	127 (27.1)
Body mass index, kg/m^2	17.7 (4.4)
Mean duration from RT to ICU admission, days	294.6 (365.1)
	n (%)
Female	6 (31.6)
Male	13 (68.4)
Living donor	18 (94.7)
Comorbidity	
Hypertension	4 (21.1)
Cardiovascular disease	3 (15.8)
Liver disease	2 (10.5)
RRT before transplantation	
Hemodialysis	7 (36.8)
Peritoneal dialysis	8 (42.2)
Etiology for RT	
Cystic-hereditary-congenital diseases	8 (42.1)
Congenital anomalies of the kidney and urinary tract	5 (26.3)
Primary glomerular diseases	4 (21.1)
Large vessel diseases	2 (10.5)

Results are presented as mean (SD) or number of patients (%). ICU: intensive care unit, RRT: renal replacement therapy, RT: renal transplantation, SD: standard deviation.

The mean duration from RT to ICU admission was 294.6 (365.1) days. Ten patients (52.6%) were admitted to the ICU >6 months after transplantation. Only four pediatric RT recipients (3.5%) were admitted to the ICU within the first 24 hours postoperatively (Table 2). Nine patients (47.4%) were admitted from other wards within our hospital. Sixteen patients (84.2%) had medical reasons, and three (15.8%) had surgical reasons for ICU admission. Epileptic seizure (n=6, 31.6%), respiratory failure (n=4, 21.1%), and cardiac diseases (n=2, 10.5%) were among the main reasons for ICU admission (Table 2).

The mean APACHE II score was 15.0 (5.0), the mean GCS score was 14.1 (1.7), and the mean SOFA score was 2.8 (2.6) at ICU admission. At ICU admission, the mean arterial pressure was 93.8 (22.1) mmHg, heart rate was 117.8 (29.4) beats/min, body temperature was 36.6 (0.9) °C, and peripheral oxygen saturation was 97.7 (2.5) % (Table 2).

The Pao_2/Fio_2 ratio was below 300 in five patients (26.3%). Two patients received high-flow oxygen therapy (10.5%). Five patients (26.3%) were intubated, and two patients (10.5%) required a tracheotomy. Five patients (26.3%) required invasive mechanical ventilation (26.3%), and three patients (15.8%) were treated with noninvasive mechanical ventilation (Table 3).

Table 2: Characteristics of pediatric renal transplant recipients admitted to the ICU.

Characteristic	mean (SD)
Time from RT to ICU admission, days	294.6 (365.1)
Time to ICU admission after RT	**n (%)**
First 24 hours	4 (21.1)
First month	2 (10.5)
1 to 6 months	3 (15.8)
>6 months	10 (52.6)
Cause of ICU admission	
Epileptic seizure	6 (31.6)
Acute respiratory failure	4 (21.1)
Cardiac diseases	2 (10.5)
Early post-operative complication	2 (10.5)
Intracranial hemorrhage	1 (5.3)
Acute kidney injury	1 (5.3)
Acute liver failure	1 (5.3)
Post-operative follow-up (nontransplant-related)	1 (5.3)
Infection-sepsis	1 (5.3)
Severity scores at ICU admission	**mean (SD)**
APACHE II	15.0 (5.0)
GCS	14.1 (1.7)
SOFA	2.9 (2.6)
Vital signs at ICU admission	
MAP, mmHg	93.8 (22.1)
Heart rate, beats/min	117.8 (29.4)
Fever, °C	36.6 (0.9)
SpO_2, %	97.7 (2.5)

Results are presented as mean (SD) or number of patients (%). APACHE II: Acute Physiology and Chronic Health Evaluation System, GCS: Glasgow Coma Score, ICU: intensive care unit, MAP: mean arterial pressure, SD: standard deviation, SOFA: Sequential Organ Failure Assessment, SpO_2: peripheral oxygen saturation.

Table 3: Respiratory system features of patients.

	n	%
Pao_2/Fio_2 ratio		
>400	8	42.1
300-400	6	31.6
200-300	3	15.8
100-200	2	10.5
<100	0	0
Type of respiratory support		
HFOT	2	10.5
NIMV	3	15.8
IMV	5	26.3
Tracheotomy	2	10.5

HFOT: high-flow oxygen therapy, IMV: invasive mechanical ventilation, NIMV: noninvasive mechanical ventilation, Pao_2/Fio_2: ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

Three patients (15.8%) had sepsis, two patients (10.5%) had septic shock, two patients (10.5%) had hypovolemic shock, and one patient (5.3%) had cardiogenic shock. The incidence of sepsis and septic shock among all pediatric RT recipients (n=115) was 4.3%. Because of shock, vasopressor and inotropic therapies were administered to three patients each (15.8%) (Table 4).

Table 4: Complications and treatment of pediatric renal transplant recipients admitted to the intensive care unit.

	n	%
Cardiogenic shock	1	5.3
Hypovolemic shock	2	10.5
Septic shock	2	10.5
Sepsis	3	15.8
Vasopressor therapy	3	15.8
Inotropic therapy	3	15.8
AKI	4	21.1
Stage I	2	10.5
Stage II	0	0
Stage III	2	10.5
RRT	4	21.1
CRRT	1	5.3
IHD	3	15.8

AKI: acute kidney injury, CRRT: continuous renal replacement therapy, IHD: intermittent hemodialysis, RRT: renal replacement therapy.

Six patients (31.6%) had a bloodstream infection, four patients (21.1%) had a urinary tract infection (UTI), and two patients (10.5%) had a cytomegalovirus infection. There were wound infections in three patients (15.8%), drain infections in two patients (10.5%), fungal pneumonia in one patient (5.3%), and candidemia in one patient (5.3%). No peritonitis was observed.

During ICU follow-up, four patients (21.1%) had AKI; two patients were classified as stage 1, two patients as stage 3, and four different patients (21.1%) required RRT, of which three required intermittent hemodialysis and one required continuous RRT (Table 4).

At ICU admission, the mean levels of blood urea nitrogen, creatinine, potassium, hemoglobin, white blood cells, C-reactive protein, and lactate were 37.2 (42.8) mg/dL, 2.3 (3.1) mg/dL, 3.9 (0.7) mg/dL, 9.8 (1.9) mg/dL, 11.5 (9.0) 10^3/μL, 40.8 (42.7) mg/dL, and 3.0 (3.1) mmol/L, respectively (Table 5).

Table 5: Laboratory parameters of pediatric renal transplant recipients at intensive care unit admission.

Laboratory measurement	mean (SD)
Hemoglobin, mg/dL	9.8 (1.9)
White blood cells, 10^3/μL	11.5 (9.0)
Platelets, 10^3/μL	207.7 (124.1)
Blood urea nitrogen, mg/dL	37.2 (42.8)
Creatinine, mg/dL	2.3 (3.1)
Sodium, mg/dL	134.2 (7.1)
Potassium, mg/dL	3.9 (0.7)
Phosphate, mg/dL	4.0 (1.8)
Calcium, mg/dL	1.8 (1.9
Albumin, g/dL	3.3 (0.8)
CRP, mg/dL	40.8 (42.7)
INR, %	1.3 (1.1)
Lactate, mmol/L	3.0 (3.1)

CRP: C- reactive protein, INR: International Normalized Ratio, SD: standard deviation.

The mean length of ICU was 12.4 (28.5), and the mean hospital stay was 25.8 (29.4) days. The mean length of ICU and hospital stay in the group with preemptive RT (1.5 [0.6] and 12.0 [8.3] days) were shorter than the length of stays in the group without preemptive RT (15.6 [31.8] days [*P*=0.29] and 29.8 [32.6] days [*P*=0.27]). The ICU mortality rate was 21.1%, and the hospital mortality rate was 3.5%. The ICU mortality was similar to the expected mortality rate of 21%, as calculated from the mean APACHE II score. One pediatric RT recipient (0.9%) died within the first 24 h. The cause of death was intracranial hemorrhage. Our pediatric RT patients had ICU and hospital survival rates of 78.9% and 97%, respectively. Hemorrhagic cerebrovascular disease, acute hepatic failure, and cardiogenic shock secondary to pericardiocentesis were the main causes of death in the ICU.

Discussion

In our retrospective single-center study, the overall incidence of ICU admission among pediatric RT recipients was 16.5% during the posttransplant period. In our study, the most common causes of ESKD among children were cystic-hereditary-congenital diseases, CAKUT, and focal segmental glomerular sclerosis. Most of our patients admitted to the ICU were in the period > 6 months after transplantation. Epileptic seizures and acute respiratory failure were the most common reasons for ICU admission. The ICU and hospital survival rates were 78.9% and 97% among our pediatric RT recipients, respectively.

Previous studies have reported incidences of immediate ICU admission in pediatric RT recipients of 77.7% to 100% [7-9]. Both our overall incidence (16.5%) and immediate incidence (3.5%) were lower than published studies among pediatric RT recipients admitted to the ICU [7,8]. RT is performed safely and successfully in pediatric patients in our center. Our center does not routinely admit pediatric RT recipients to the ICU in the immediate post-operative period.

In our pediatric RT recipients admitted to the ICU, the most common causes of ESKD were focal segmental glomerular sclerosis, vesicoureteral reflux, and nephrotic syndrome, similar to that presented in other clinical trials [5,16]. In contrast to adults, the main causes of ESKD in pediatric patients are focal segmental glomerulosclerosis, obstructive uropathy, and reflux nephropathy [3,13]. Similar to our study, the most common causes of ESKD are focal segmental glomerulosclerosis and reflux nephropathy [5,17,18]. Our center's pediatric RTs are performed for indications similar to other centers and guidelines [13,19].

Most of our study's patients admitted to ICU were more than 6 months after transplantation. Like pediatric RT recipients, most adult RT recipients are also admitted to the ICU > 6 months after RT [10,12,20-22]. This situation can be associated with the effectiveness of the current preventive practices (vaccination, prophylaxis, preemptive therapies) applied before RT and during the first 6 months posttransplant.

Reasons for admission to the hospital in the early or late periods after RT are mainly surgical reasons not related to RT and medical reasons [23,24]. In our pediatric RT recipients, ICU admissions were mostly because of epileptic seizures and acute respiratory failure. Since some of our patients were admitted more than 6 months after RT, the side effects of immunosuppressive therapies were also frequent reasons for ICU admission. Children need prolonged immunosuppressive therapy after RT, and these drugs' short- and long-term side effects are challenging for patients and clinicians.

Acute respiratory failure and sepsis are the main causes of ICU admission in adult RT recipients [10,12,20-22,25]. There are multiple reasons for acute respiratory failure in adult RT recipients [10,12]. Among our pediatric RT recipients admitted to the ICU, respiratory failure due to pneumonia, acute pulmonary thromboembolism, and post-operative residual muscle relaxants was observed. Therefore, managing RT recipients requires a multidisciplinary approach (transplant history, perioperative and post-operative follow-up, immunosuppressive regimens, and determination of underlying chronic disorders) [10,22].

Preemptive transplantation is defined as a transplant before the initiation of dialysis. It avoids many of the associated long-term complications of ESKD and dialysis. Also, preemptive transplants may be more cost-effective [13,26]. The duration time for patients on dialysis can be shortened or not performed at all. Thus, it can significantly affect the cost of care for children with ESKD. In our study, we did not analyze cost-effectiveness. However, the ICU or hospital stays for patients with preemptive transplants were shorter than those without preemptive transplants. Therefore, we suggest that the ICU and hospital care costs may have been indirectly reduced.

UTI was the most common infection in pediatric RT recipients. The highest risk for UTI is within the first 6 months posttransplant [27-29]. Similar to previous studies, the prevalence of posttransplant UTI was 21.1% in our pediatric RT recipients to ICU admission [11,28]. Septic shock due to UTI was observed in only one patient.

In our pediatric RT recipients, although our study period covered both early and late posttransplant periods, the incidence

of sepsis and septic shock (4.3%) was lower than reported in the study from Faizal et al. [8]. This can be explained by the success and effective preoperative, intraoperative, and post-operative care of RT recipients.

The North American Pediatric Renal Transplant Cooperative Study, which included data from 1987 to 2010, reported that the 5-year survival rate for living donor transplant was 96.1% and the 5-year survival rate for deceased donor transplant was 93.3% in recipients under 18 years of age [30]. The survival rates for ICU patients and total patients were 78.9% and 97% among our pediatric RT recipients admitted to ICU. Our ICU survival rates were lower than other studies [8,9]. Although we included pediatric RT recipients admitted to the ICU in early and late periods after transplant, our overall survival rate was similar to other published studies [5,26].

The ICU and hospital mortality rates were 21.1% and 3.5% in our pediatric RT recipients admitted to the ICU. The ICU mortality rate was similar to the expected mortality rate, as calculated from the mean APACHE II score. Our 24-hour mortality rate among all pediatric RT recipients was 0.9%, and the cause of mortality was not associated with RT. Faizal et al. [8] reported that neither graft loss nor deaths occurred among pediatric RT recipients admitted to ICU in the immediate post-operative period. Pape et al. showed that one patient (1%) died during ICU stay among their patient group [9]. One reason for the different mortality rates in our study was that we included both early and late posttransplant periods. Mortality rates may vary due to patient differences, the criteria for ICU admission, the time from RT to ICU admission, and immunosuppressive agents. Mortality among our patients was for extrarenal reasons not associated with surgical causes during the perioperative period.

Limitations

This study was a retrospective study with data obtained from medical records, and it was conducted at a single center, which limits the generalizability of the results.

Conclusion

The most common causes were epileptic seizure, and acute respiratory failure in our cohort of pediatric RT recipients admitted to the ICU. We admitted our patients to ICU more than 6 months after RT. The ICU and hospital survival rates were 78.9% and 97% among our pediatric RT recipients, respectively. The ICU mortality rate was similar to the expected mortality rate based on the APACHE II score. Therefore, a multidisciplinary approach involving pediatric nephrologists, transplant surgeons, and an intensive care team successfully manages pediatric RT recipients who are admitted to ICU.

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Serum C-NLR score, a new inflammatory marker, predicts tumor histopathology and oncological outcomes of localized clear cell renal carcinoma after nephrectomy: A single center retrospective analysis

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Ethics Committee Approval
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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Several blood and serum-based parameters have been described as prognostic markers of clear cell renal cell carcinoma (ccRCC). But most of these markers have inconsistent results and are not used in routine clinical practice. Therefore, novel potential predictor biomarkers are needed for the management of ccRCC patients in clinical practice. Here, we investigate the predictive value of a novel marker, serum C-NLR score, for pathological characteristics and oncological outcomes of ccRCC.
Methods: A total of 162 RCC patients who underwent radical or partial nephrectomy between January 2015 and January 2021 were evaluated in a retrospective cohort study setting. The serum C-NLR score was compared according to the tumor histopathology-associated parameters. The predictive role of those parameters and C-NLR score on the oncological outcomes of ccRCC was also investigated.
Results: The median serum C-NLR scores exhibited statistically significant increases in ccRCC patients with pathological necrosis, lymphovascular invasion, and variant differentiation. Among histopathological characteristics, only tumor necrosis and variant differentiation were associated with overall survival (OS) and tumor grade with metastasis-free survival (MFS) (no metastasis detected in grade 1–2 tumors) in Kaplan Meier analyses. Serum C-NLR score was also associated with OS but not MFS. In the univariate analyses, tumor necrosis, variant differentiation, and C-NLR score were associated with OS of localized RCC patients who underwent nephrectomy (HR: 0.29; 95% CI: 0.08–1.01; *P*=0.04, HR: 6.01; 95% CI: 1.66–21.82; *P*=0.006 and, HR: 1.21; 95% CI: 0.20–5.16; *P*=0.04). However, in the multivariate analysis, only variant differentiation and C-NLR score were associated with OS (HR: 1.43; 95% CI: 0.82–2.98; *P*=0.03 and HR: 1.21; 95% CI: 0.20–5.16; *P*=0.04). Tumor grade was directly associated with MFS because grade 1–2 tumors did not exhibit any metastasis.
Conclusion: Serum C-NLR score was higher in worse histopathological entities. Moreover, it predicts the OS for patients with ccRCC as an independent factor.

Keywords: clear cell renal cell carcinoma, c-reactive protein, neutrophils, lymphocytes, survival analysis

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Introduction

Renal cell carcinoma (RCC) raised from the renal tubular epithelium is a heterogeneous group of cancers. It represents 1% to 3% of adult malignancies in humans worldwide [1,2]. Among the urological cancers, RCC is the most lethal, and approximately 40% of patients with RCC die because of the disease progression [2]. Clear cell renal cell carcinoma (ccRCC) is the most common subtype and accounts for the majority of kidney cancer deaths [1,3]. Localized ccRCC can be treated with partial or radical nephrectomy, ablation treatment, or active surveillance. The removal of kidney cancer tissue with nephrectomy is a curative approach; however, up to 30% of patients with ccRCC with localized disease eventually develop metastases [1]. Because ccRCC has higher clinical and pathological heterogeneity, it is difficult to predict the survival outcomes of patients in clinical practice [3].

The well-known disease predictors for ccRCC are tumor grade and stage. Other important prognostic factors in ccRCC are lymphovascular invasion (LVI), variant differentiation (VD), and fat invasion. Their prognostic roles have been studied, with the authors reporting that they correlated with survival rates [4]. Alternative prognostic parameters (e.g., molecular prognostic factors) have also been proposed. However, their major limitations are higher costs and lower availability in routine clinical practice [5]. Therefore, several blood and serum-based parameters have been discussed as possible prognostic markers of ccRCC [5-8]. However, most such studies provide inconsistent results, and their prognostic value in ccRCC patients must be confirmed [8].

In our opinion, novel potential predictor biomarkers must be emphasized and used for clinical studies and, then, routine clinical settings. In the present study, we primarily aimed to investigate the predictive value of serum C-NLR score for pathological characteristics and oncological outcomes of ccRCC.

Materials and methods

After the approval of the study by the Review Board of Bagcilar Training and Research Hospital (Approval ID: 2022/11/14/035, Approval Date: 16/11/2022), we conducted a retrospective review of our institutional data, including radiology, laboratory, and pathology data. A total of 162 renal cell carcinoma (RCC) patients who underwent radical or partial nephrectomy between January 2015 and January 2021 were evaluated. Inclusion criteria were having a clear cell subtype of RCC with no history of previous or concomitant malignancy other than kidney cancer. Patients who had metastatic disease and N+ status at the diagnosis and cases with the final diagnosis of benign pathology and papillary and chromophobe subtypes after the surgery were not included. Additionally, patients with the N+ stage at final pathology and patients with incomplete follow-up and/or missing data were also excluded. The history of any anemia, active inflammatory diseases, and acute infection were other exclusion criteria.

Characteristics of the kidney masses, including size, side, polarity, localization, and egzofitic or endofitic nature, were assessed by cross-sectional imaging studies. Preoperative serum levels of the neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio (NLR), and C-reactive protein (CRP) were extracted from our institutional data. CRP and NLR levels were classified as normal or elevated based on the cutoff points accepted as 10 mg/L and 2.26, respectively. The cutoff points for the parameters, CRP and NLR, were adapted from the associated previous studies [9,10]. The combined score of CRP and NLR levels was established as the C-NLR score, as reported by Zhu et al. [11]. It is classified as C-NLR score 2; with elevated serum CRP and NLR levels, C-NLR score 1; with elevated serum level in one of them, and C-NLR score 0; with normal serum CRP and NLR levels. Pathological findings were also extracted from our institutional data. All pathological investigations were performed by a single experienced neuropathologist. Tumor stage was determined based on the 2010 TNM classification of malignant tumors staging system, and tumor grade was defined according to the Fuhrman and WHO/ISUP grading systems.

The follow-up schedule was determined as physical examination, blood biochemistry, and radiologic imaging with a contrast-enhanced computerized abdominal tomography every 3–6 months for 2 years and 6–12 months in years 2–5 according to the individual patient and tumor characteristics. The last survival follow-up date was June 01, 2021. Overall survival (OS) and metastasis-free survival (MFS) were calculated as times from surgery to death or last follow-up and from surgery to metastasis or the last follow-up in localized ccRCC patients.

Statistical analysis

Statistical analysis was performed with SPSS Version 22.0 statistic software package (IBM SPSS Inc., Chicago, IL). Data distributions and tests of normality were evaluated with the Shapiro-Wilk test. Descriptive statistic methods, including mean (standard deviation), median (interquartile range) and percentages, were used to evaluate data. Two groups' comparisons were performed using the independent t-test, Mann-Whitney U test, or Chi-square test. Differences were considered significant at two-sided $P<0.05$ and 95% confidence interval. The serum C-NLR score was compared in patients with PT1 and PT2-T4 ccRCC, in patients with grade 1–2 and grade 3–4 tumors, in patients with and without tumor necrosis in pathology, in patients with and without LVI, and in patients with and without VD. Survival analysis and curves for serum C-NLR score and histopathological tumor characteristics were performed according to the Kaplan-Meier method and compared by the log-rank test.

Results

Out of 162 patients, 18 with incomplete follow-up and 26 with missing data were excluded. Additionally, seven patients with the pathological diagnosis of oncocytoma and seven and nine patients with the pathological diagnosis of chromophobe and papillary RCC, respectively, were also excluded. Fifteen pathological N+ patients were not included in the study. Ultimately, a total of 80 localized ccRCC patients were investigated.

The mean age and mean tumor volume were 56.76 (11.33) years and 54.35 (28.89) mm, respectively. The mean serum levels of NLR and CRP were 2.35 (1.15) and 21.82 (11.35) g/dL, respectively. The mean operative time was 180.187 (66.43) min. The mean age, tumor volume, ischemia time (in

partial cases), and operative time for partial and radical nephrectomy cases are shown in Table 1. The median ASA score and Clavien-Dindo complication score were 2 (2) and 1 (1), respectively. The median hospital stay was 4 (3) days. On the pathological reports, the median pT stage and Fuhrman/WHO-ISUP grade were 1 (2) and 2 (2), respectively. The median postoperative follow-up period was 48.00 (22.00) months with 4 to 50 months intervals. Out of 80 patients, 35 (43.75%) were female, and 55 (56.25%) were male. Forty-seven (58.3%) patients had comorbidities, and 17 (21.3%) of them had multiple comorbid disorders. Detailed information about frequencies of the comorbid diseases, anatomical tumor characteristics with solid-cystic discrimination, applied surgical methods for nephrectomy, characteristics of surgical complications, and pathological tumor characteristics are provided in Table 2.

Table 1: The mean age, tumor volume, ischemia time (in partial cases) and operative time for partial and radical nephrectomy cases.

	Partial nephrectomy cases	Radical nephrectomy cases	*P*-value
Age (Years), Mean(SD)	53.63 (10.94)	58.64 (11.26)	0.06*
Tumor diameter (mm), Mean(SD)	33.40 (11.21)	66.80 (4.10)	<0.001*
Ischemia time (min.), Mean(SD)	17.53 (9.02)	-	
Operative time (min.), Mean(SD)	187.50 (55.25)	165.80 (72.50)	0.44*

SD: Standard deviation, * Independent t test.

Table 2: Frequencies of the comorbid diseases, anatomical tumor characteristics with solid-cystic discrimination, applied surgical methods for nephrectomy, characteristics of surgical complications, and pathological tumor characteristics.

	n	%
Comorbidity		
DM	26	32.5
HT	35	43.8
CAD	26	32.5
CRF	8	10
HF	1	1.3
Tumor laterality		
Left	37	46.2
Right	43	53.8
Polar tumor localization		
Superior	25	31.2
Middle	34	42.5
Lower	17	21.2
Whole kidney	3	3.8
Anterior-posterior tumor localization		
Anterior	30	37.5
Posterior	30	37.5
Medial	20	25
Exophytic mass	64	80
Tumor nature		
Solid	53	66.3
Cystic	9	11.3
Mixed	18	22.4
Nephrectomy		
Partial	30	37.5
Radical	50	62.5
Nephrectomy		
Open	33	41.3
Laparoscopic	47	58.7
Complications	13	16.3
Clavien-Dindo		
1	0	0
2	8	61.5
3	4	30.8
4	0	0
5	1	7.7
Positive surgical margin	5	16.7
Tumor necrosis	21	26.3
Lymphovascular invasion	21	26.3
Variant differentiation	10	12.5
pT stage		
T1	48	60
T2	13	16.2
T3	17	21.3
T4	2	2.5
Tumor grade		
1	5	6.3
2	38	38
3	27	27
4	10	10

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery diseases, CRF: Chronic renal failure, HF: Heart failure.

One patient died on the third postoperative day due to a massive pulmonary embolus. During the 50 months follow-up, ten patients died. OS was estimated as 64.5%. The mean OS time was 44.78 (1.52) months (95% CI: 41.78–47.77). Seven patients exhibited metastatic progression during the follow-up. Two of them were in regional lymph nodes, and five were in the lungs. The mean time of metastasis was determined as 13.57 (3.74) months (95% CI: 6.22–20.96), and the mean MFS time was 46.08 (1.41) months (95% CI: 43.31–48.84).

The serum C-NLR score exhibited significant differences in the ccRCCs with pathological necrosis, lymphovascular invasion, and variant differentiation in comparison to the ccRCC's without them. On the other hand, it was also significantly different according to the pT stage and tumor grade (Table 3). Among histopathological characteristics, only tumor necrosis and variant differentiation were associated with OS and tumor grade with MFS (no metastasis detected in grade 1–2 tumors) in Kaplan Meier analyses (Table 4, Figures 1 and 2). OS was 46.49 (1.45) months (95% CI: 43.63-45.35) vs. 37.87 (3.89) months (95% CI: 30.24–45.50) for tumor necrosis - and + cases, respectively (P=0.03). They were 45.24 (1.70) months (95% CI: 42.68–47.80) vs. 29.87 (7.10) months (95% CI: 15.95–43.79) for variant differentiation - and + cases, respectively (P=0.002). On the other hand, serum C-NLR score was also associated with overall survival but not MFS (Table 5, Figure 2). In the univariate analyses, tumor necrosis, variant differentiation, and C-NLR score were associated with OS of localized RCC patients who underwent nephrectomy (HR: 0.29; 95% CI: 0.08–1.01; P=0.04, HR: 6.01; 95% CI: 1.66–21.82; P=0.006 and, HR: 1.21; 95% CI: 0.20–5.16; P=0.04, respectively). However, in the multivariate analysis, only variant differentiation and C-NLR score were associated with the OS of the patients (HR: 1.43; 95% CI: 0.82–2.98; P=0.03 and HR: 1.21; 95% CI: 0.20–5.16; P=0.04, respectively). Tumor grade was directly associated with MFS because grade 1–2 tumors did not exhibit any metastasis.

Figure 1: Overall survival Kaplan Meier graphs according to the parameters, tumor necrosis and variant differentiations, and metastasis free survival according to the tumor grade.

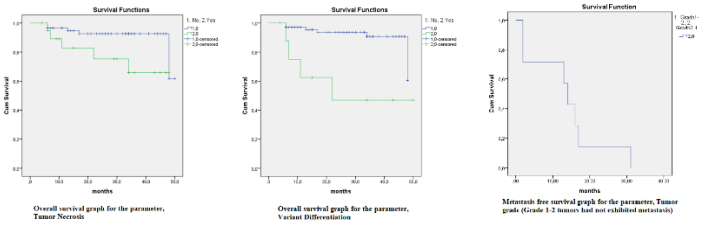

Figure 2: Overall survival Kaplan Meier graph according to the C-NLR scores.

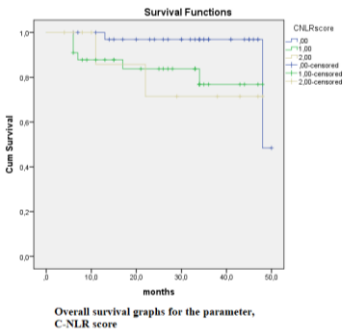

Table 3: Serum C-NLR scores according to the tumor histopathology and patient outcomes

	pT1	**pT2-T4**	***P*-value**
C-NLR Score, Median(IQR)	0.5 (1)	0.5 (1)	0.02*
	Grade 1-2	**Grade 3-4**	***P*-value**
C-NLR Score, Median(IQR)	0 (1)	1 (1.5)	0.03*
	Tumor Necrosis -	**Tumor Necrosis +**	***P*-value**
C-NLR Score, Median(IQR)	0 (1)	1 (1)	0.001*
	LVI -	**LVI+**	***P*-value**
C-NLR Score, Median(IQR)	0 (1)	1 (1.5)	0.005*
	VD -	**VD+**	***P*-value**
C-NLR Score, Median(IQR)	1 (1)	1 (1.5)	0.01*
	Survivors	**Dead**	***P*-value**
C-NLR Score, Median(IQR)	1 (1)	1 (0)	0.09*
	Metastasis -	**Metastasis +**	***P*-value**
C-NLR Score, Median(IQR)	1 (1)	1 (1.5)	0.02*

NLR: Neutrophil to lymphocyte ratio, IQR: Interquartile range, LVI: Lymphovascular infiltration, VDI: Variant differentiation, * Mann Whitney U test.

Table 4: OS and MFS according to tumor histopathology.

	pT1	**pT2-T4**	***P*-value**
OS, Mean(SD)	45.51 (1.86) months (95% CI: 40.86-48.16)	43.64 (1.52) months (95% CI: 38.45-48.83)	0.51
	Grade 1-2	**Grade 3-4**	***P*-value**
OS, Mean(SD)	44.05 (2.16) months (95% CI: 39.80-48.29)	44.02 (1.91) months (95% CI: 40.26-47.78)	0.62
	Tumor Necrosis -	**Tumor Necrosis +**	***P*-value**
OS, Mean(SD)	46.49 (1.45) months (95% CI: 43.63-45.35)	37.87 (3.89) months (95% CI: 30.24-45.50)	0.03
	LVI -	**LVI+**	***P*-value**
OS, Mean(SD)	45.77 (1.60) months (95% CI: 43.63-48.91)	39.47 (3.72) months (95% CI: 32.17-46.78)	0.18
	VD -	**VD+**	***P*-value**
OS, Mean(SD)	45.24 (1.70) months (95% CI: 42.68-47.80)	29.87 (7.10) months (95% CI: 15.95-43.79)	0.002
	pT1	**pT2-T4**	***P*-value**
MFS, Mean(SD)	13.00 (0.00) months (95% CI: 13.00-13.00)	13.66 (4.43) months (95% CI: 4.98-22.35)	0.39
	Grade 1-2	**Grade 3-4**	***P*-value**
MFS, Mean(SD)	- -	13.57 (3.74) months (95% CI: 6.22-22.91)	-
	Tumor Necrosis -	**Tumor Necrosis +**	***P*-value**
MFS, Mean(SD)	14.50 (1.50) months (95% CI: 11.56-17.44)	13.20 (5.39) months (95% CI: 2.62-23.78)	0.15
	LVI -	**LVI+**	***P*-value**
MFS, Mean(SD)	13.00 (0.00) months (95% CI: 13.00-13.00)	13.66 (4.43) months (95% CI: 4.98-22.35)	0.39
	VD -	**VD+**	***P*-value**
MFS, Mean(SD)	10.33 (4.25) months (95% CI: 1.99-18.67)	16.00 (5.95) months (95% CI: 4.32-27.67)	0.26

OS: Overall survival, MFS: Metastasis free survival, SD: Standard deviation, LVI: Lymphovascular infiltration, VDI: Variant differentiation.

Table 5: OS and MFS according to the serum C-NLR scores.

	CNL Score 0	**CNLR Score 1**	**CNLR Score 2**	***P*-value**
OS Mean(SD)	47.87 (1.30) months (95% CI: 45.32-50.42)	40.68 (2.69) months (95% CI: 35.39-45.97)	39.00 (5.49) months (95% CI: 28.23-49.76)	0.04
	CNL Score 0	**CNLR Score 1**	**CNLR Score 2**	***P*-value**
MFS Mean(SD)	16.00 (0.00) months (95% CI: 16.00-16.00)	10.66 (4.48) months (95% CI: 1.87-19.45)	15.66 (8.41) months (95% CI: 0.00-32.15)	0.76

OS: Overall survival, MFS: Metastasis free survival, SD: Standard deviation.

In brief, the C-NLR score is associated with worse tumor histopathology, and it can predict OS as an independent factor.

Discussion

The TNM stage, reflecting tumor invasion, lymph node metastasis and distant metastasis, and tumor grade, is the most widely used system for predicting RCC prognosis [12,13]. The current RCC staging system is an updated version of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification [14]. On the other hand, the Fuhrman and WHO/ISUP grading systems have been used to examine the pathological tumor grade [15]. Although TNM and grading systems are useful prognostic parameters, they are not perfect. The major component of the T staging is tumor diameter. However, tumor diameter could not be fully representative of tumor volume. Other well-known prognostic parameters about tumor histopathology, such as tumor necrosis, lymphovascular infiltration, and sarcomatoid and rhabdoid differentiations, are used in clinical practice. However, several studies reported that they were deficient [13]. Moreover, RCC is a heterogeneous group of tumors with some unusual clinical and pathological characteristics that make it difficult to predict outcomes [14].

In this regard, the conflicting knowledge about present prognostic factors has resulted in consideration of new factors in the literature [13].

Today, it is well known that inflammation is involved in the initiation and progression of various cancers, including RCC. Some hematologic parameters, including lymphocytes and neutrophil counts, neutrophil-to-lymphocyte ratio (NLR), and CRP, are simple and cheap laboratory data reflecting inflammation and have been extensively studied in cancers [12,16]. A large number of studies have reported their prognostic value for various cancers and RCC. However, all these parameters indicate only one aspect of inflammation, and the combination of those factors in an index could more accurately predict prognosis than a single index [12]. For RCC, it has been shown that most of these measurements are statistically significant prognostic factors for localized and metastatic RCC [16-18]. The immunological status and inflammatory response in individual patients are thought to influence tumor growth and disease progression, and several studies have suggested that systemic inflammation measured by NLR and CRP also plays a key role in RCC. Moreover, systemic inflammation-related biomarkers CRP and NLR may provide additional prognostic information [8,19].

In the late 2010s, the combination of CRP and NLR was discussed, and several types of research investigated its role in predicting the outcomes of some cancers and diseases [11,20-23]. To our knowledge, no study has addressed the combination of CRP and NLR for patients with RCC. In this regard, in the present study, we investigated the role of the recently developed C-NLR score, a novel inflammatory marker, in predicting the histopathological and survival outcomes of localized ccRCC cases. The serum C-NLR score exhibited significant differences with worse histopathological entities such as pathological necrosis, lymphovascular invasion, and variant differentiation. On the other hand, it was also significantly higher in the advanced pT stage and tumor grade. We determined the prognostic significance of the C-NLR score for OS and found that the C-NLR score provides significant OS information. In univariate Cox regression, the C-NLR score was associated with OS and remained independently associated with survival in multivariate analysis. Our findings are consistent with the literature. In 2012, Tomita et al. [23] showed that the combined use of preoperative NLR and CRP was an independent prognostic determinant for non-small cell lung cancer (NSCLC). Later on, similarly, Oh et al. [21] investigated its role in hepatocellular carcinoma (HCC). These authors found that CRP and NLR were utilized as prognostic indicators of HCC that appeared to be more evident when used in combination. They concluded that this is probably due to the significant synergistic effect of the two inflammatory markers. The predictive role of the combination of both parameters in soft tissue cancer was also reported by Nakamura et al. [20]. Recently, Zhu et al. [11] investigated the combination of both parameters in asthma. These authors concluded that since both NLR and CRP are

elevated in asthmatic patients, it is necessary to develop a novel marker – the combined score of CRP level and NLR (C-NLR score) – that can take full advantage of meanings of both NLR and CRP in asthmatic patients. The authors generated a C-NLR scoring system and found C-NLR, a novel inflammatory marker, is a promising marker to distinguish children with exacerbated asthma from healthy children. Similarly, Liu et al. [22] investigated the combined use of CRP and NLR in a newly generated nomogram for patients with COVID-19 and found that NLR and CRP are potential and reliable predictors of COVID-19 prognosis and can triage patients at the time of admission.

Limitations

Our study has some limitations. A major limitation is the retrospective nature of the study protocol, which limits the efforts to address potential sources of bias and establish the sample size. Another is the small sample size. Therefore, we aimed to plan optimal inclusion and exclusion criteria. Because of the small sample size, our numbers of metastatic patients and deaths were relatively small. Therefore, the analysis of survival outcomes might have been affected adversely. However, we specifically intended to investigate the role of C-NLR score in patients with localized ccRCC subtype. The major strength of the current study is that it is the first study investigating the C-NLR score in predicting RCC outcomes. This work can path the way for further large-scale studies.

Conclusion

Serum C-NLR score was higher in worse histopathological entities that are associated with mortality and morbidity, such as pathological necrosis, lymphovascular invasion, and variant differentiation. Moreover, it predicts the OS for patients with localized ccRCC as an independent factor. In our opinion, this is a promising finding for the management of ccRCC. With future confirmatory results, the C-NLR score may be used in routine clinical practice and become a practical guide for urologists in the management of the localized ccRCC.

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Evaluation of left renal vein and IVC variations in MDCT examinations performed in patients with a preliminary diagnosis of renal calculi

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Ethics Committee Approval
The study was approved by the Ethical Committee of Haseki Research and Training Hospital, 14.12.2022, 208-2022.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Left renal vein (LRV) and inferior vena cava (IVC) variations are not rare, an observation that is extremely important to understanding the presence of these structures before performing surgery. This study aimed to evaluate the type and frequency of IVC and LRV variations with multi-detector computer tomography (MDCT) in patients admitted with a preliminary diagnosis of renal calculi and to evaluate the relationship of these variations with renal calculi, renal cysts, and horseshoe kidneys.

Methods: We retrospectively analyzed 1640 patients who underwent abdominal CT for suspicious renal calculi between January 2018 and December 2019. This retrospective cohort study consisted of 1604 patients after the exclusion criteria. Renal surgery and/or renal agenesis examinations without enough diagnostic quality due to motion artifacts were considered the exclusion criteria. Age, gender, presence and types of IVC and renal variations, and presence of renal calculi, renal cysts, and horseshoe kidney were recorded. The relationship between variation types and presence of renal calculi, renal cysts, and horseshoe kidneys was evaluated.

Results: IVC and LRV variations were detected in 107 patients (6.7%). The prevalence of circumaortic LRV (CLRV) and retroaortic LRV (RLRV), left IVC, and double IVC in 65 patients was 4.1%, 2.4%, 0.1%, and 0.1%, respectively. Male gender predominance in both total and RLRV were found in the variations (P=0.033 and P=0.033, respectively). Urinary calculi were found in 1016 (63.3%) of the patients, kidney cysts in 247 (15.4%), and horseshoe kidneys in 10 (0.6%). No correlation between the presence of renal calculi, kidney cysts, and horseshoe kidney and the presence of variations in patients with LRV was found (P=0.433, P=0.215, and P=0.500, respectively).

Conclusions: LRV and IVC variations are not uncommon. It is necessary to be informed about these variations before performing retroperitoneal surgery to prevent possible complications. LRV and IVC variations can be easily recognized in pre-diagnosed renal calculi on MDCT without the use of an intravenous contrast agent.

Keywords: inferior vena cava, left renal vein, renal stone disease, computed tomography, retroaortic, circumaortic

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Introduction

Embryonic development of the bilateral renal vein (RV) and inferior vena cava (IVC) occurs between the fourth and eight weeks of the intrauterine period, and development of each structure is closely related [1]. Variations in the anastomoses of the supracardinal, subcardinal, and cardinal veins during embryonic development cause RV and IVC variations [2]. The most common left RV (LRV) variations are circumaortic LRV (CLRV) and retroaortic LRV (RLRV), and their incidence is reported as 10.2% in the literature. The most common IVC variations are IVC duplication and left-sided IVC with a rate of 0.5% as reported in the literature [3,4].

Prior to performing retroperitoneal surgery, interventional vascular procedures, and donor nephrectomies for transplantation, it is vital to identify RV and IVC variations. Moreover, this situation becomes even more critical in laparoscopic surgeries in which vascular repair is more challenging compared to open surgeries [3,5,6]. Therefore, the surgeon performing the laparoscopy should be aware of possible vascular variations in this region to avoid unnecessary blood loss or transition to conventional surgery [7,8]. RV variations are usually asymptomatic and are detected incidentally during radiological examinations, retroperitoneal surgery, or interventional procedures [5]. Multi-detector computed tomography (MDCT) evaluation of the RV and its variations is a fast, easy-to-apply, and preferred imaging method.

This study aimed to evaluate the type and frequency of LRV and IVC variations with MDCT in patients who received a preliminary diagnosis of renal calculi and to investigate the possible relationship of these variations with gender differences and other accompanying kidney pathologies and variations (renal calculi, renal cyst, horseshoe kidney). As far as we know, our study is the first in the literature to evaluate the frequency of renal variations in all patients presenting with a preliminary diagnosis of renal calculi.

Materials and methods

Study population and study design

All patients admitted for renal calculi in our hospital's Radiology Department between January 2018 and December 2019 and referred for non-contrast abdominal CT were included in this study. The study was conducted based on the ethical standards stated in the Declaration of Helsinki, and the study was approved by the ethics committee of Haseki Training and Training hospital (Decision Number: 208-2022). Informed consent was waived from the participants due to the retrospective design of the study.

A total of 1640 patients were included in the study. Exclusion criteria were a history of renal operation (right n=12, left n=8), renal agenesis (left n=1, right n=1), examinations without enough diagnostic quality due to motion artifacts (n=14). The final study population consisted of 1604 patients.

Computed tomography imaging protocol

Abdominal CT examination was performed using a 128-detector CT device in standard calculi protocol (PHILIPS Ingenuity). Oral and intravenous (IV) contrast material was not used since the examination was performed with a preliminary diagnosis of renal calculi and based on the calculi protocol. Specific scanning parameters were used: (1) tube voltage was 100 Kv, (2) tube current 150 mAs, (3) pitch was 1.441, and (4) gantry rotation time was 0.4 sec. The evaluation was based on axial images or sagittal and coronal multi-planar reformat (MPR) images from axial images in necessary cases. Images were analyzed by two radiologists with 16 years of CT experience.

Image analysis

The LRV crosses the aorta anteriorly and extends to the IVC and was evaluated as a normal preaortic LRV. The LRV passing behind the aorta and draining into the IVC was defined as RLRV and CLRV when the LRV drained into the IVC by forming a loop both behind and in front of the aorta. The placement of the IVC on the right side of the aorta in the axial images was considered to be structurally normal. If the IVC had one branch on each side of the aorta, it was defined as a double IVC. The demographic characteristics of the patients, the presence of renal, ureteral, and bladder calculi, renal cysts, and horseshoe kidneys were noted.

Statistical analysis

The SPSS 15.0 for Windows (SSPS Inc. Chicago, İlinois, USA) program was used for statistical analysis. Descriptive statistics were presented as numbers and percentages for the categorical variables and as mean, standard deviation, and minimum and maximum values for numerical variables. The rates in the groups were compared with the chi-squared test. The alpha significance level was set at 0.05.

Results

A total of 1604 patients with 595 females (37.1%) and 1009 males (62.9%) were included in the study. The ages of the patients ranged from 0 to 89 years (mean age [SD], 44.7 [15.5]) as shown in Table 1.

IVC and LRV variations were detected in 107 patients (6.7%) and RLRV in 65 patients (4.1%) as shown in Figure 1, CLRV in 38 patients (2.4%) as shown in Figure 2a and b), left IVC in two patients (0.1%) as shown in Figure 3a and b, and double IVC in two patients (0.1%) as shown in Figure 4a and b. The presence of total variations in the male gender was significantly higher than in the female gender (27 females [4.5%] versus 80 males [7.9%]; *P*=0.033). When subgroups were evaluated, RLRV was higher in men than in women (16 females versus 49 males; *P*=0.033). All four IVC variations in the study were observed in males (Table 2).

Table 1: Distribution of patients by gender

		Gender		
	n	**Female**	**Male**	***P*-value**
n (%)	1604	595 (37.1)	1009 (62.9)	
Age; Mean (SD) (Min-Max)	44.7 (15.5) (0-89)	45.7 (15.5) (12-88)	44.1 (15.4) (0-89)	0.045

Table 2: Renal vein anomalies distribution of the gender

n=1604		**Gender**		
	Total	**Female**	**Male**	***P*-value**
LRV variation n (%)				
Retroaortic LRV	65 (4.1%)	16 (2.7%)	49 (4.9%)	0.033
Circumaortic LRV	38 (2.4%)	11 (1.8%)	27 (2.7%)	0.293
IVC variation n (%)				
Left IVC	2 (0.1%)	0 (0.0%)	2 (0.2%)	0.533
Double IVC	2 (0.1%)	0 (0.0%)	2 (0.2%)	0.533
Total variation n (%)	107 (6.7%)	27 (4.5%)	80 (7.9%)	0.009

IVC: inferior vena cava, LRV: Left renal vein

Figure 1: 55-year-old female patient, axial multi-detector computed tomography (MDCT) image reveals the retroaortic left renal vein (RLRV) traveling posterior to the aorta (arrows).

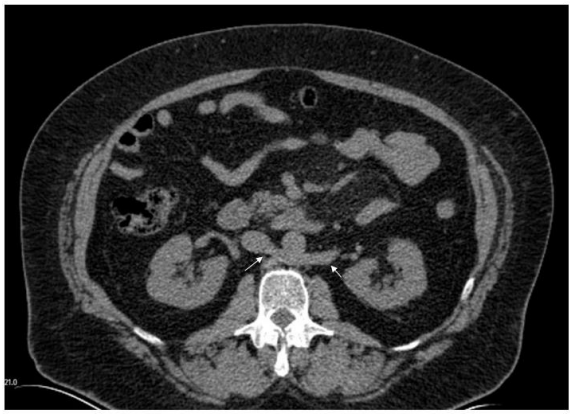


Figure 2: Sixty-one -year-old male patient, axial MDCT images reveal the preaortic and retroaortic segments of the circumaortic left renal (CLRV) (arrows). The right kidney is atrophic, and a calculi image is revealed in the left renal pelvis.

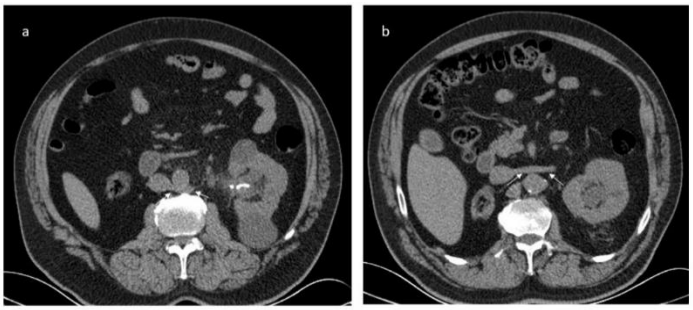


Figure 3: Sixty-seven-year-old male patient, right and left inferior vena cava (IVC) are revealed on a) coronal multi-planar reformat (MPR) b) axial MDCT images (arrows).

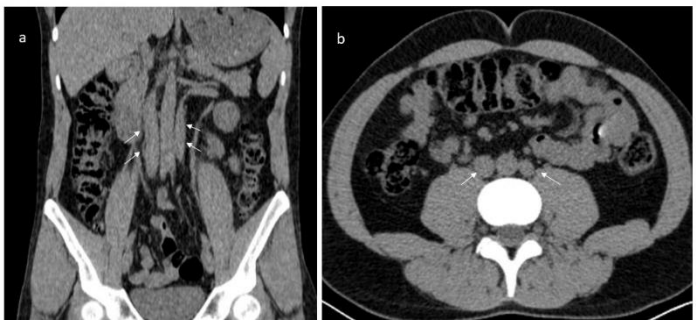
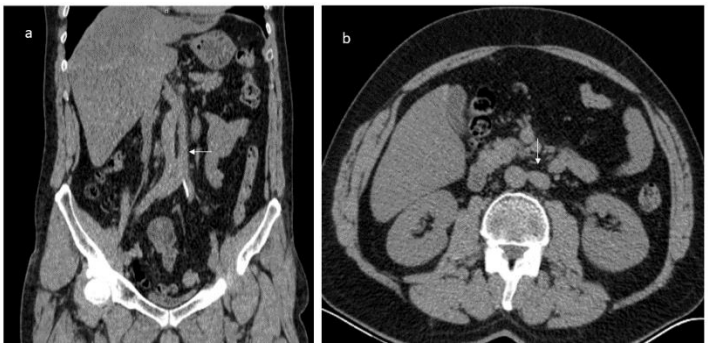


Figure 4: Forty-nine--year-old female patient with left transpositioned IVC (arrows) on a) coronal and b) axial MPR MDCT images.



Calculi were detected in the urinary system in 1016 (63.3%) patients. Of these, 839 (52.3%) had kidney calculi, 415 (25.9%) had ureteral calculi, and 51 (3.2%) had bladder calculi. Renal cysts were detected in 247 (15.4%) patients and horseshoe kidneys in 10 patients (0.6%). The incidence of calculi and cysts in males was significantly higher than in females (P<0.001 and P=0.017, respectively) as shown in Table 3.

No correlation was found between the presence of renal calculi, kidney cysts, and horseshoe kidneys with the presence of variation in patients with left renal variation (P=0.433, P=0.215, and P=0.500, respectively) as shown in Table 4. When the left RV variations were evaluated according to subgroup classifications as RLRV and CLRV, no significant correlation was found between the presence of kidney calculi and the presence of variation (P=0.179 and P=0.345, respectively) as shown in Table 5.

Table 3: Renal stone disease, cyst, and horseshoe kidney distribution of the gender

n=1604		Gender		
	Total	Female	Male	*P*-value
Calculi n (%)	1016 (63.3%)	329 (55.3%)	687 (68.1%)	<0.001
Kidney	839 (52.3%)	284 (47.7%)	555 (55.0%)	
Ureter	415 (25.9%)	108 (18.2%)	307 (30.4%)	
Bladder	51 (3.2%)	7 (1.2%)	44 (4.4%)	
Cyst n (%)	247 (15.4%)	75 (12.6%)	172 (17.0%)	0.017
Horseshoe kidney n (%)	10 (0.6%)	3 (0.5%)	7 (0.7%)	0.753

Table 4: Relationship between renal veins variations and calculi, horseshoe kidney, and renal cysts

	Renal vein variation		
	No	Yes	
	n (%)	n (%)	*P*-value
Calculi	952 (63.6%)	64 (59.8%)	0.433
Kidney	785 (52.4%)	54 (50.5%)	
Ureter	396 (26.5%)	19 (17.8%)	
Bladder	48 (3.2%)	3 (2.8%)	
Horseshoe kidney	9 (0.6%)	1 (0.9%)	0.500
Cyst	235 (15.7%)	12 (11.2%)	0.215

Table 5: Relationship between retroaortic LRV and circumaortic LRV with calculi

	Renal vein variation				
	Retroaortic LRV	Circumaortic LRV	No		
	n (%)	n (%)	n (%)	*P*1	*P*2
Calculi	36 (55.4%)	27 (71.1%)	952 (63.6%)	0.179	0.345
Kidney	31 (47.7%)	22 (57.9%)	785 (52.4%)	0.453	0.506
Ureter	9 (13.8%)	10 (26.3%)	396 (26.5%)	0.023	0.985
Bladder	2 (3.1%)	1 (2.6%)	48 (3.2%)	1.000	1.000

*P*1: retroaortic LRV versus control, *P*2: circumaortic LRV versus control

Discussion

In our patient group consisting of 1604 patients, all had a pre-diagnosis of renal calculi, and we detected 107 RV and IVC variations in total with as RVLV in 65 patients (4.1%), CLRV in 38 patients (2.4%), double IVC in two patients (0.1%), and left IVC in two patients (0.1%). Male gender predominance in both total and RLRV in the variations was noted. We did not determine a significant relationship when the relationship between IVC and LRV variations with renal calculi, cysts, and horseshoe kidneys were evaluated.

IVC and the LRV are formed as a result of anastomoses and regressions of three pairs of precursor veins, namely the subcardinal, supracardinal, and posterior cardinal veins, that occurs between the fourth and eighth weeks of intrauterine life [9]. The anastomoses of the supracardinal and subcardinal veins form the RVs. The left part of the circumaortic venous ring has a ventral and a dorsal arm, and the dorsal arm atrophies during normal development. The development of the ventral arm forms the normal preaortic vein. If the ventral arm regresses, the dorsal arm continues to develop, RVLV occurs, and if both fail to regress, CVLV occurs. Dysfunction in left supracardinal vein regression results in double IVC formation, and right supracardinal vein regression dysfunction causes left IVC formation [1,7,10]. A wide range of LRV and IVC variations have been demonstrated in the literature. Dilli et al. [11] determined the rates of RLRV and CRLV as 2.68% and 1.66%, respectively, in their study involving 1204 patients. The computed tomography/magnetic resonance imaging (CT/MRI) study in which Şahin et al. [12] evaluated 2189 patients reported RLRV at a rate of 2% and CLRV at 0.3%. Özgül et al. [7] revealed the frequency of RLRV and CLRV to be 1.1% and 0.3%, respectively, in their study, which examined 8517 patients.

Ayaz et al. reported these rates as RLRV 5.85% and CLRV 3.15% in their positron emission tomography/computed tomography (PET/CT) study in which they evaluated 222 patients [13]. Arslan et al. examined 10,124 patients, and they determined these rates to be 3.9% and 1.9%, respectively [5]. In the general population, left IVC has been defined as 0.2% to 0.5% and double IVC as 0.2% to 3% [2]. Almost all of the aforementioned studies were performed using CT or MRI with contrast administration. Although all patients in our study presented with a specific preliminary diagnosis, such as renal colic, the percentages of IVC and RV variations in our study were close to other studies in the literature.

While studies reporting no relationship between left RV variations and gender have been published, Dilli et al. [3,11] found RLRV more frequently in women than in men [7,14]. In our study, however, the total variation and amount of RLRV were statistically higher in males than females, a result that is different from the literature in this sense. This condition may be related to characteristics of our patient population.

Variations in IVC and LRV rarely present clinically. They are mainly detected incidentally during imaging, surgery, and/or autopsy [7]. Although such variations are mostly asymptomatic, their detection before retroperitoneal surgery is vital. Missing it prior to surgery may lead to nephrectomy, bleeding, and even death during retroperitoneal surgery [7,8]. Since the length of the LRV is longer than the right, this type of variation is preferred in left kidney transplantation. Therefore, the course of the LRV should be known precisely in such an operation [12]. Besides, differential diagnosis of RV variations from retroperitoneal tumors or possible retroperitoneal lymph nodes in patients with renal and testicular tumors is critical [15].

IVC and RV variations can be evaluated using an invasive method, such as venography, in addition to non-invasive methods, such as ultrasonography (US), color Doppler US (CDUS), MRI, and/or CT [16]. US and CDUS are preferred since they are easily accessible and cheaper than other methods, but they may be insufficient in obese patients. Today, multi-detector computed tomography (MDCT) is a non-invasive, reliable method for evaluating abdominal organs and vascular structures [2]. We used non-contrast CT scans in our study because the was performed in patients with a preliminary diagnosis of renal calculi.

Studies in the literature evaluating the relationship between variations and malignancy and renal tumors are available [5,7,8]. However, apart from our study, we could not find any studies evaluating the relationship between variations and renal cysts in the literature. The present study calculated the prevalence of renal cysts as 15.4%. However, we did not find a significant relationship between the described variations and the presence of such cysts.

Our study is the first study in the literature to evaluate the frequency of renal variation in all patients presenting with a preliminary diagnosis of renal calculi. In our study, the total calculi prevalence was calculated as 63.3%. However, when we evaluated patients with variations in both total and subgroups classified as RLRV and CLRV, no significant relationship between variations and the presence of calculi was found. Our study is the second study that investigated the relationship between variations and calculi in the literature. The study of Arslan et al. [5] determined the calculi rate to be 16.4% in a patient population who underwent CT for different indications. While no relationship was observed between renal variations and renal calculi in their study, they demonstrated a significant relationship between left renal calculi and LRV variations in the evaluation while considering subgroups. We think that the reason for the difference between our study and theirs may be related to the fact that we classified subgroups as RLRV and CLRV instead of dividing patient subgroups into right and left kidneys. However our calculi rate is quite high compared to the other study, and our study included 3.2% bladder stones, which we could not attribute to specific kidney issues of the patients.

The horseshoe kidney is the most common type of renal fusion anomaly, and its prevalence has been reported as between 0.1% and 0.3% in the literature [17,18]. In our study, 10 patients in total presented with with horseshoe kidneys, and the prevalence was determined as 0.6%, which is close to the rate stated in the literature. Very few studies evaluating the relationship between horseshoe kidneys, RV, and IVC variation in the literature can be found. Ichikawa et al. detected IVC anomalies more frequently in patients with horseshoe kidneys compared to the normal population [19]. Ichikawa et al. [20] revealed in an another study that the total venous anomaly rate was 28.6% in patients with horseshoe kidneys and evaluated it as higher than the normal population. Leblebisatan et al. [18] reported that the variation rate was 5.18 times higher in patients with horseshoe kidneys of RLRV than those without. In our study, a total of four patients had IVC variation, but these patients did not have a horseshoe kidney. Only one of the patients with horseshoe kidney had a CLRV anomaly. In our study, we did not find a significant relationship between horseshoe kidney and LRV variations unlike results reported in the literature. We thought that this difference might be related to our patient population.

Limitations

Our study has some limitations. First of all, our study is single-centered; thus, it is not community based and may not represent the general population. The retrospective nature is another limitation of the study.

Conclusion

The radiologist needs to be aware of renal and IVC variations to prevent catastrophic complications that may develop in aortic, renal, and retroperitoneal surgeries. The data indicate that the rate of renal and IVC variation in patients with a pre-diagnosis of renal calculi is close to the studies in the literature involving patient groups with miscellaneous complaints.

LRV and IVC variations can be easily recognized in patients with pre-diagnosed renal calculi using MDCT without an IV contrast agent.

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