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Original Investigations

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Can Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio be Used as Inflammatory Markers to Predict Length of Hospital Stay After Total Laparoscopic Hysterectomy for Benign Indications?

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ABSTRACT

Objective: To investigate the possible effects of inflammatory parameters obtained from complete blood count in the postoperative first day of total laparoscopic hysterectomy on the length of hospital stay in patients without any complications.

Methods: Linear regression analysis was performed to find associations between hospital stay and the associated variables. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values of postoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP) for long hospital stay (>3 days).

Results: Postoperative values of NLR (r=0.332, p<0.001), PLR (r=0.325, p<0.001), and CRP (r=0.404, p<0.001) were moderately associated with the duration of hospital stay. In ROC analysis, the post-op cut-off value of 25 mg/L for CRP predicted long hospital stay with a sensitivity of 65% and specificity of 63% [area under the curve (AUC): 0.657, p=0.002, confidence interval (CI) 0.563-0.752], the post-op cut-off value of 159 for PLR with a sensitivity of 60% and specificity of 58% (AUC: 0.688, p<0.001, CI 0.600-0.776) and the post-op cut-off value of 4.96 for NLR with a sensitivity of 60% and specificity of 58% (AUC: 0.618 p=0.017, CI 0.520-0.717).

Conclusion: We observed a direct correlation between postoperative first-day values of NLR, PLR, and CRP with the length of hospital stay. NLR, PLR, and CRP values may be helpful to predict the length of hospital stay and can be used instead of each other.

Keywords: Benign gynecologic surgery, hospital stay, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, total laparoscopic hysterectomy

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INTRODUCTION

Inflammatory response after surgery is an ordinary outcome which ends up with tissue repair. The increase in neutrophil levels accompanied with a decrease in lymphocyte levels are characteristics for the inflammatory response. Therefore, neutrophil-to-lymphocyte ratio (NLR) comes out as a simple index of inflammation (1). In the literature, NLR was shown to be associated with surgical complications and the length of hospital stay in certain surgeries (2,3). Another inflammatory marker calculated from hemogram is the platelet-to-lymphocyte ratio (PLR). As a result of endothelial tissue damage, platelets (PLTs) are gathered in the affected area. Therefore, an increase in the number of PLTs is inevitable for inflammation. Hence, PLR appears to be another simple inflammation index due to increase in PLT count and decrease in lymphocyte count (Lym#) (4,5). PLR has also been shown to be associated with the length of hospital stay in various surgeries (6). NLR and PLR are both newly recommended inflammatory markers to estimate the prognosis of surgical treatment in clinics. Investigations regarding NLR and PLR concerning prognosis of patients after surgeries including gynecological cancer, cardiac surgeries, and emergency surgeries are available in prior literature (7). Women need surgical intervention due to benign uterine lesions, which is mainly a hysterectomy. Hysterectomy is the second leading cause of total surgeries after cesarean section (8). With medical advancements and available laparoscopic equipment, open surgery is becoming less preferred where minimally invasive techniques have been replaced with classical methods. Due to short hospital stay, rapid return to work, less pain and good cosmetic results, laparoscopic hysterectomy (LH) has substantially increased the era of hysterectomy procedures especially for the last two decades (9). The main reason for this is probably that LH leads to fewer inflammatory responses when compared to open abdominal hysterectomy (10). Although the inflammatory response is supposed to be lower with total laparoscopic hysterectomy (TLH), unpredictable inflammatory response as a result of the operation has been still unenlightened and it can be associated with hospital stay. On the other hand, there is no data to date on the relationship between the length of hospital stay and hemogram inflammatory parameters in patients who have undergone TLH for benign indications. The purpose of this study is to investigate the possible effect of inflammatory parameters that can be easily obtained from complete blood count on the postoperative first day of TLH on the length of hospital stay in patients without any complications for the first time.

METHODS

Patients who underwent TLH without any postoperative complications and biochemical abnormality between January 2014 and November 2018 in a training and research hospital were enrolled in this retrospective cohort study. Informed consent was obtained from each patient before surgery to allow the use of medical data related to their operation for research at our clinic. Ethical approval was obtained from the University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee and the study was planned in accordance with the declaration of Helsinki (decision no: 90, date: 28.05.2020). The patients with endometriosis, endometrial cancer, cervical cancer, a new diagnosis of chronic lymphocytic leukemia, Behçet's disease, biochemical abnormality, the patients who used anti-inflammatory medications, and the patients who had severe intraabdominal adhesions were excluded. In addition, the patients with ureter injury, bladder injury, bowel injury, superficial inferior mesenteric artery injury, vaginal cuff hematoma and vaginal cuff dehiscence were also excluded from the study. Patients who underwent TLH without any postoperative surgical complications such as severe hemorrhage, high fewer, ureteral, colon or vascular injuries were enrolled in the study. Patients with a uterus greater than 16 weeks of gestation and patients with gynecologic cancer were excluded from the study due to possible long operation time triggering more inflammation (Figure 1). Indications for the operations were as follows: myoma uteri, endometrial hyperplasia, abnormal uterine bleeding, adenomyosis, ovarian cysts, cervical dysplasia, and endometrial polyps. All patients were examined with ultrasound at least two times, in which the first examination was performed in outpatient clinic and the second one was performed one day before the operation by a gynecologist. Endometrial sampling was performed in patients with abnormal uterine bleeding prior to surgery. Final pathology of benign uterine disorders was confirmed from the paraffin blocks of hysterectomy material of all patients. The physical condition classification of the American Society of Anesthesiologists (ASA) was similar (ASA1-ASA2) in both groups. Standard antibiotic prophylaxis with cefazolin 2 g was applied just before the operation. All the operations were performed under general anesthesia with endotracheal tube intubation. TLH was performed conventionally with all intraabdominal steps with four ports, including the vaginal closure, and the specimen was taken out through the vaginal way. Oophorectomy was optional, although salpingectomy was performed in all patients. Hemostasis in the operations was performed with the use of bipolar dissection. Medical data such as age, body mass index (BMI), parity, operation time, intraoperative bleeding, duration of hospital stay, history of cesarean section, and smoking were obtained from the medical records. BMI was calculated by dividing weight (kg) by square of height (meters). Operation time was determined as the duration from starting the skin incision to merging incision sides. The amount of bleeding during the operation was calculated by subtracting the irrigation fluid from the total amount of suction fluid. Only suction material was considered in patients in whom no irrigation was used. Duration of hospital stay was determined as the time from the first day of operation until discharge of the patient. Patients were discharged from the hospital when their vital signs became normal, bowel activity returned, and ambulation of the patient was achieved with no further need for analgesics. A complete blood count was recorded on the last

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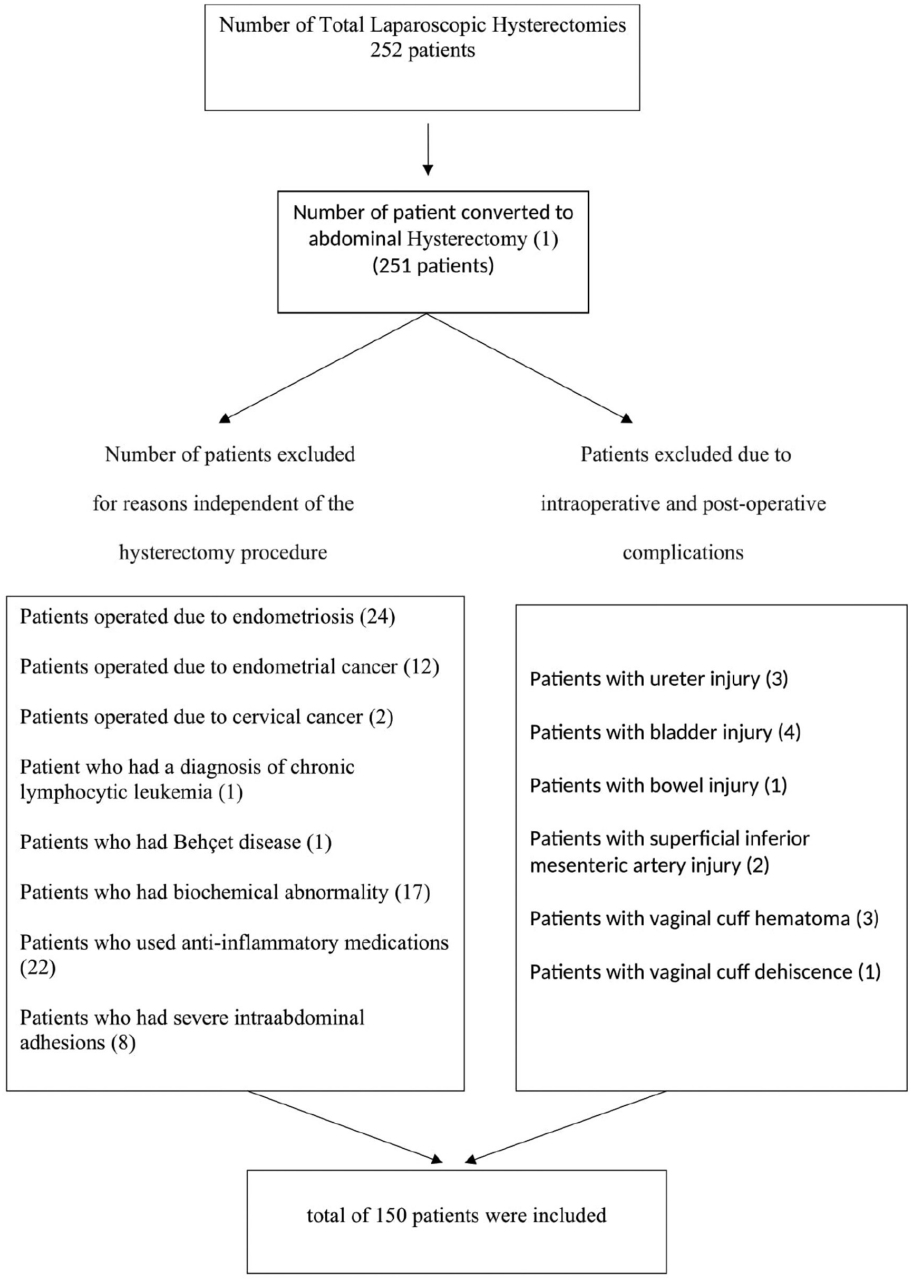

Figure 1. Flow chart of the patient selection

preoperative day and the first day after the operation. Levels of C-reactive protein (CRP) are routinely seen on the first day of operation in our clinic. Intramuscular dexketoprofen is applied twice and low molecular weight heparin is used in all patients postoperatively. Any of the patients received perioperative or postoperative blood transfusion. Analysis of the hemogram was performed using Variant II Hemoglobin Testing System (Dubai Biotechnology and Research Park, Dubai, United Arab Emirates). Analysis of CRP levels were performed by using Uni Cell Dxl 800 chemistry system (Beckman Coulter, Fullerton, Calif., USA). Inflammatory indicators in hemogram that we recorded were: neutrophil count (Neu#) of 2 to 8 10^3/μL; Lym# of 1 to 5 10^3/μL and PLT count of 150 to 400 10^3/μL. NLR and PLR were calculated by dividing the absolute number of neutrophil and absolute number of PLTs to the absolute number of lymphocytes, respectively. These two indices of inflammation were compared between patients who were hospitalized for more than 3 days and equal to or less than 3 days. Choosing day 3 as a threshold was because the mean length of hospital stay after LH was shown as up to a maximum of 3 days in literature (11).

Statistical Analysis

The SPSS version 22 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. The variables were expressed as mean ± standard deviation or median (minimum-maximum) or number (%). The normality distribution of variables was evaluated using

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Kolmogorov-Smirnov test. Comparisons of continuous variables between two groups were performed with Student's t-test or Mann-Whitney U test. Chi-squared test was used to compare nominal variables. Linear regression analysis was performed to find possible associations between hospital stay and the associated variables. Correlation analysis of hospital stay with variables was performed with Pearson correlation test. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut off values of NLR, PLR, and CRP for long hospital stay (>3 days). P<0.05 was considered to be statistically significant and all p-values were two-sided.

RESULTS

A total of 150 patients with sufficient medical data were involved in this retrospective cross-sectional study. Demographic and clinical properties are included in Table 1. The mean age of this population was 48.7±7.26 (30-76) with mean BMI of 30.43±4.62 (18.1-45). One third percent of the patients were smokers. The mean value of preoperative hemoglobin was 1.9±1.61 g/dL. An intraoperative bleeding volume of 421±226 cc was observed in operations lasting within a mean value of 110.8±36 minutes. The mean hospital stay was 3.23±1.41 days. The mean preoperative NLR and PLR values were 2.29±0.91 and 146.2±49.5, respectively. When looking through the postoperative values for the same ratios, the mean value for NLR was 6.18±4.5 and the mean value of PLR was 172.2±77.8. Pre- and postoperative values of mean PLT volume were found as 9.1±1.0 and 9.0±1.3, respectively. Postoperative mean value of CRP was 29.6±21.8 mg/L. The most common indication for TLH was myoma uteri followed by abnormal uterine bleeding (Figure 2). Endometrial hyperplasia was the third most common indication of operation. The patients were further divided into two groups to evaluate the duration of hospital stay and its related factors. The two groups were identified by 52 patients who were hospitalized for three days or less and 98 patients hospitalized for more than three days. There was no statistical difference (Table 2) regarding age, BMI, parity status, history of cesarean section, smoking, operation time, intraoperative bleeding volume, preoperative NLR, and preoperative PLR. On the other hand, there were statistically significant differences between the groups in terms of postoperative NLR, PLR, and CRP values with p-values of 0.009, <0.001, and 0.002, respectively.

Table 1. Demographic and clinical properties of the patients

Patients (n=150)	
	n (%)
Multiparity	137 (91.3)
Cesarean section history	35 (33.3)
Smokers	50 (33.3)
	Mean ± SD (range) min-max
Age (years)	48.7±7.26 (30-76)
BMI (kg/m^2)	30.43±4.62 (18.1-45)
Preoperative hemoglobin (g/dL)	11.9±1.61 (6.4-15.1)
Intraoperative bleeding (cc)	421±226 (50-1100)
Operation time (minute)	110.8±36 (45-200)
Hospital stay (days)	3.23±1.41 (1-8)
Preoperative NLR	2.29±0.91 (0.71-8.25)
Preoperative PLR	146.2±49.5 (19.5-354)
Postoperative NLR	6.18±4.5 (0.51-28.8)
Postoperative PLR	172.2±77.8 (46-428)
Preoperative MPV	9.1±1.0 (7.1-13.5)
Postoperative MPV	9.0±1.3 (0.3-11.6)
Postoperative CRP (mg/L)	29.6±21.8 (3-120)

Data are given as mean ± standard deviation (minimum-maximum) or number, percent.
BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume, SD: standard deviation, CRP: C-reactive protein, min: minimum, max: maximum

The correlation between the duration of hospital stay with age, BMI, operation time, intraoperative bleeding, preoperative NLR, postoperative NLR, preoperative PLR, postoperative PLR, and postoperative CRP were demonstrated in Table 3. Correlation of duration of hospital stay was found with postoperative NLR (p<0.001), postoperative PLR (p<0.001), and postoperative CRP (p<0.001) values. There was no correlation between age, BMI, operation time, intraoperative bleeding, preoperative NLR, preoperative PLR, and hospital stay.

Regression analysis was performed to find the possible variables associated with the length of hospital stay. Postoperative CRP, NLR, and PLR values were found to be associated with long hospital stay (p<0.001). ROC analysis showed postoperative CRP, NLR, and PLR values to be significant predictors of long hospital stay. A postoperative CRP value of 25 was found to be able to estimate a long hospital stay with a sensitivity of 65% and specificity of 63% [area under the curve (AUC): 0.657, p=0.002, confidence interval (CI) (0.563-0.752)]. Similarly, a postoperative PLR value of 159 was

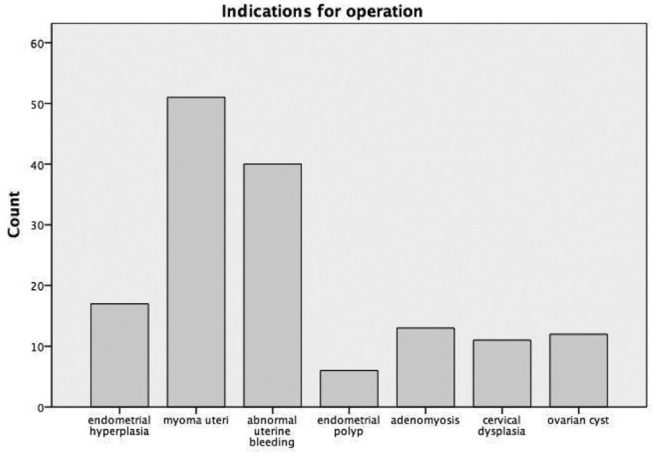

Figure 2. Distribution of indications for total laparoscopic hysterectomy

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Table 2. Comparison of the patients with hospital stay ≤3 days and >3 days

Hospital stay, n	≤3 days (98 patients)	>3 days (52 patients)	p-value
Age (y)	49.0±6.8	48.2±8.0	0.533**
BMI (kg/m²)	30.6±4.5	30.0±4.9	0.515**
CS history n (%)	26 (28)	9 (18)	0.168
Preoperative hb	12.0±1.7	11.7±1.5	0.217**
Smoker, n (%)	30 (31)	20 (39)	0.332
Operation time (days)	107±35.3	118±36.6	0.104*
Intraoperative bleeding (cc)	405±210.4	451±253	0.351*
Preoperative NLR	2.3±0.8	2.3±0.9	0.648*
Preoperative PLR	144.6±49.9	149.2±49.3	0.707*
Postoperative NLR	5.2±3.4	7.8±5.7	0.009*
Postoperative PLR	153.5±66.3	207.7±86.0	<0.001*
Preoperative MPV (fL)	9.2±0.9	9.1±1.0	0.676**
Postoperative MPV (fL)	9.2±0.9	8.8±1.9	0.230**
Postoperative CRP (mg/L)	25.0±17.0	38.3±27.0	0.002*

The results are given as mean ± standard deviation or number, percent (%). BMI: body mass index, CS history: cesarean history, hb: hemoglobin, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume, CRP: C-reactive protein
*Mann-Whitney U test was used for statistical analysis
**Independent t-test was used

Table 3. Correlation of the length of hospital stay with associated variables

	r	p-value
Age	0.033	0.686
BMI	0.072	0.381
Operation time	0.080	0.331
Intraoperative bleeding	0.056	0.493
Preoperative NLR	0.056	0.497
Preoperative PLR	0.055	0.501
Postoperative NLR‡	0.332	<0.001
Postoperative PLR‡	0.325	<0.001
Postoperative CRP (mg/L)	0.404	<0.001

BMI: body mass index, NLR: neutrophil-to-leucocyte ratio, PLR: platelet-to-lymphocyte ratio, CRP: C-reactive protein

found to have a sensitivity of 60% and specificity of 58% (AUC: 0.688, p<0.001, CI 0.600-0.776) and postoperative NLR value of 4.96 was found to have a sensitivity of 60% and specificity of 58% (AUC: 0.618, p=0.017, CI 0.520-0.717) (Figure 3).

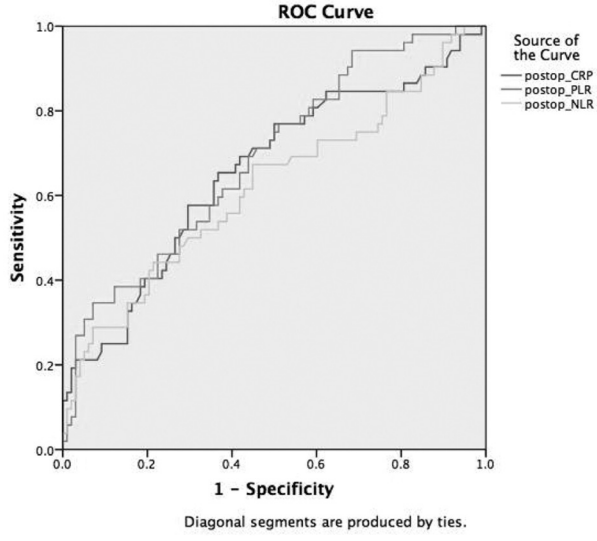

Figure 3. Receiver operating characteristic curves for neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein for the prediction of long hospital stay

CRP: C-reactive protein, NLR: neutrophil-to-leucocyte ratio, PLR: platelet-to-lymphocyte ratio, ROC: receiver operating characteristic

DISCUSSION

The associations of NLR, PLR, and CRP values with length of hospital stay in patients who underwent TLH without any postoperative complication was investigated in this study. Postoperative values of NLR, PLR, and CRP were found to be associated with the length of hospital stay. A 4.96 cut-off value of postoperative NLR and 159 cut-off value of postoperative PLR were found to have sensitivity of 60%, specificity of 58% and sensitivity of 60%, specificity of 58%, respectively, to predict the duration of hospital stay more than 3 days. These findings were similar to the sensitivity and specificity of CRP to predict a long hospital stay. Since 1989, annually performed laparoscopic hysterectomies have gradually increased in clinical practice. The main reasons for the preference of the laparoscopic approach are shorter hospital stay, faster return to normal life, and not being appropriate for vaginal hysterectomy (12). The length of hospitalization, even after an optimum laparoscopic surgery, can

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still result in differences among the patients, lasting up to 8 days (13). Inflammatory response or autoimmune characteristics of the patients can differ due to different phenotypes with a complex mechanism that is not fully elicited yet (14). Although laparoscopic surgeries lead to fewer inflammatory responses compared to open surgeries, the difference between patients may be due to the underestimated individual inflammatory response determined by multiple underlying factors. There are few studies investigating the association between the length of hospital stay and NLR for benign surgical interventions. Sengul et al. (15) demonstrated that preoperative NLR could add approximately one more day to the length of hospital stay in patients with complicated and uncomplicated appendicitis. Erdolu et al. (16) evaluated preoperative NLR in patients who underwent coronary artery by-pass surgery and showed that high NLR indicated not only a long hospital stay but also a long stay in the intensive care unit. A retrospective study conducted by Asada et al. (17) revealed that prolonged hospitalization was associated with high preoperative NLR. Paliogiannis et al. (18) investigated the indicators determining the hospital stay in open elective thoracic surgery and demonstrated weak correlation between preoperative NLR and hospital stay. In our study, the preoperative value of NLR was not found to be associated with long hospital stay because there was no ongoing preoperative inflammatory process and all of them were elective surgeries. Hence, the mean value of preoperative NLR did not differ between the groups. Postoperative NLR is also discussed in some studies of benign indications for predicting hospital stay. Zheng et al. (19) showed that postoperative NLR was lower in patients who underwent minimally invasive distal pancreatectomy when compared to patients who underwent open access and that the patients who underwent open access stayed in hospital more than 4 to 5 days. Da Silva et al. (2) studied the utility of NLR for predicting outcomes of bariatric surgery and showed that a NLR value of greater than 10 at the postoperative first day of surgery was associated with a prolonged hospital stay, corresponding to 3.7 times more than the patients having NLR less than 10. Bath et al. (20) discovered that not only the preoperative NLR but also the postoperative NLR were associated with long hospital stay stressing that especially postoperative NLR values tended to be higher in patients who underwent open surgery. In our study postoperative NLR was correlated with long hospital stay (>3 days) ($p<0.001$). Furthermore, in regression analysis, NLR was found to be a variable that was associated with long hospital stay. In ROC analysis, a cut off value of 4.96 for postoperative NLR with a sensitivity of 60% and specificity of 58% (AUC: 0.618, $p=0.017$, CI 0.520-0.717) predicted long hospital stay, which was similar to CRP [cut off the value of postoperative CRP was 25 with a sensitivity of 65% and specificity of 63% AUC: 0.657, $p=0.002$, CI (0.563-0.752)]. We assumed that the difference in the postoperative NLR values in such a standardized group was associated with the individual inflammatory response characteristics of each patient. As per the range of pre-op hemoglobin levels, some patients had anemia of varying severity. That is in itself a cause of increased infection rate. But still, our results are significant in predicting who will be infected more, even if they are anemic. Furthermore, NLR is a ratio and should not be affected from global decrease of complete blood count parameters. The structure of neutrophils and lymphocytes don't include iron therefore the amount of these again shouldn't be affected from anemia as they are inflammatory markers. Our findings were compatible with the literature in terms of predicting long hospital stay by using postoperative NLR values.

The PLR is another simple index that can be easily obtained from a complete blood count. This ratio is associated with surgical outcomes in the literature, one of which is the length of hospital stay but in a limited number. A retrospective study conducted by Xu et al. (21) found that the preoperative NLR and PLR with cut-off values of 2.9 and 129.5, respectively in ROC analysis were significantly higher in patients who underwent percutaneous nephrolithotomy. Therefore, the length of hospital stay was longer in that group (21). Another study, conducted by Pehlivanlı and Aydin (22), demonstrated that preoperative PLR together with NLR were increased in patients with perforated appendicitis compared to acute appendicitis or normal appendix. Consequently, prolonged hospitalization was an inevitable result for patients with perforated appendicitis (22). In our study, preoperative PLR was not associated with long hospital stay. We believe that non-inflammatory, elective gynecological indications cannot trigger the inflammatory process formerly; therefore, the preoperative ratios will be in normal range. To date, postoperative PLR has not been found to be associated with the length of hospital stay for any kind of benign surgical intervention in any known literature. In our study, elevated postoperative PLR was correlated with a long hospital stay. In addition, it was found to be associated with long hospital stay in regression analysis. In ROC analysis, a cut-off value of 159 for postoperative PLR with a sensitivity of 60% and specificity of 58% (AUC: 0.688, $p<0.001$, CI 0.600-0.776) predicted long hospital stay. This was similar to both CRP and NLR [cut off value of postoperative CRP was 25 with a sensitivity of 65% and specificity of 63% (AUC: 0.657, $p=0.002$, CI 0.563-0.752), cut-off value of postoperative NLR was 4.96 with a sensitivity of 60% and specificity of 58% (AUC: 0.618, $p=0.017$, CI 0.520-0.717)].

Study Limitations

In this study, we have some limitations. Although all biochemical indicators of the patients, both pre- and post- operatively were normal, tests were not performed for diabetes mellitus or insulin resistance. Diabetes mellitus, which is an important metabolic disease affecting wound healing, can be an indicator associated with inflammatory response. Secondly, ovarian status in surgery can be another variable. We did not mention whether an oophorectomy was performed or not under the assumption that hormonal status would not be affected within one month postoperatively. However, this could be an indicator interfering with the inflammatory response due to extra vessel sealing. Furthermore, we did not discuss the peritoneal drainage, and this

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could also affect serum biomarkers.

CONCLUSION

Postoperative NLR, PLR, and CRP were found to be associated with length of hospital stay in our population with benign gynecologic indications in whom the surgical intervention type was TLH without any surgical complication. The NLR value together with CRP and PLR, at the postoperative first day of TLH could be suggestive for predicting the length of hospital stay and could be used instead of each other independently because all predictive values of these 3 indexes in ROC curve were similar. Moreover, CRP is not a routine test used in daily practice after non-complicated benign gynecological surgeries. So, calculating NLR and PLR from complete blood count is cheap and easy for clinicians to assess the individual and unpredictable inflammatory response. In patients exceeding the described cut-off values, new anti-inflammatory treatments targeting the various steps of inflammation may be tried to shorten the length of hospital stay or antibiotics can be used in these patients to slow down the inflammatory response. It may be that preventing the aggregation of PLTs with medications may also contribute positively to slow down the inflammation. In future studies, NLR and PLR can be studied for detection of urinary, bowel or vessel injury. Randomized controlled trials with enlarged sample size are needed to enhance strategies in achieving shorter length of hospital stay and predicting possible complications after TLH or any other surgical interventions.

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Informed Consent: Informed consent was obtained from each patient before surgery to allow the use of medical data related to their operation for research at our clinic.

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The Relationship Between Early Diffusion Weighted Imagining Lesion Patterns and Stroke Mechanisms at Atherosclerotic Diseases of Medial Cerebral Artery

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ABSTRACT

Objective: The underlying etiological reason in the process of stroke is the most important factor that determines the prognosis. In this study in atherosclerotic middle cerebral artery (MCA) disease and internal carotic artey (ICA) disease or cardioembolic (CE), research the stroke mechanism and compare to the described study findings in the literature making use of early diffusion-weighted imaging (DWI) (with in 48 hours) in acute stroke cases.

Methods: In this study, DWI lesion patterns taken with in the first 48 hours in 51 patients who due to acute stroke have been compared to stroke subtypes identified within the first week depending on magnetic ressonance angiography (MRA) results in order to determine the differences between lesion patterns. The DWI lesions have been identified as multiple or single lesions depending on the pattern in the literature. Single lesion have been identified as perforating artery infarcts (PAI), pial artery infarcts (PI), and border-zone infacts (BZI). Multiple lesions have been identified double or triple combinations of single lesions. Upon assesment with MRA, stroke subtypes have been identified as MCA dissease, ICA dissease and CE.

Results: Among 51 patients, 11 have been found to be in MCA disease group (21.6%), 25 in ICA disease group (49.1%), and 15 in CE group (29.4%). In the MCA disease group PAI (18.2%), PI (27.3%) and BZI (9.1%) have been detected. The rate of multiple lesions is 45%. Multiple lesion pattern has been detected as high in all three stroke groups (ICA 44%, CE 53%). No lesion pattern have been detected as significantly high in the MCA dissease group (p=0.753).

Conclusion: It is important that the stroke mechanism can be predicted in the early period for the treatment. This study concluded that the stroke mechanism cannot be predicted in the early satge relying on the lesion pattern characteristic at DWI.

Keywords: Middle cerebral artery ischemia, internal carotis artery disease, cardioembolism, diffusion-weighted magnetic resonance imaging, stroke etiology

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INTRODUCTION

Atherosclerotic occlusive disease of the middle cerebral artery (MCA) is an important cause of stroke. New studies and developments with magnetic resonance imaging (MRI) for lesion localization are being added day by day (1,2). Topographic distribution of lesion patterns in intracranial ischemia may provide an early clue in determining the etiology (3,4). Possible mechanisms of cerebral ischemia in MCA infarcts may be thrombosis resulting in complete occlusion, artery-to-artery embolism, hemodynamic insufficiency, local branch occlusion, and a combination of these factors (5). Diffusion-weighted imaging (DWI) is the most sensitive diagnostic method for detecting acute ischemic lesion (6). DWI has been used in many studies investigating the pathogenesis of ischemic stroke in patients with atherosclerotic MCA disease (5-7). Studies have shown that echoplanar imaging measurements with DWI are much more sensitive than conventional MRI (6). Studies examining the relationship between stroke mechanisms and lesion patterns are diverse (5,7-9). However, there are several limitations in these studies, such as the study being limited to a single lesion pattern, not allowing comparison with different stroke etiologies, or the time elapsed between the appearance of stroke findings and DWI application varies from study to study.

In a study conducted to reveal the differences between lesion patterns in atherosclerotic MCA disease and lesion patterns in internal carotid artery (ICA) disease or cardioembolic (CE) and to define the mechanism of stroke, perforating artery infarcts (PAI) were found as single lesions or lesions in association with pial artery and border-zone infarcts (BZI). It was determined that this was a specific lesion pattern for MCA disease, and distal embolization associated with local branch occlusion was a common stroke mechanism in MCA disease (10).

The aim of our study was to determine whether the lesion patterns seen on early DWI (within 48 hours) differed in atherosclerotic MCA disease, ICA disease or CE, which was determined according to the findings detected in magnetic resonance angiography (MRA) in patients with acute stroke and to investigate whether the DWI patterns gave an idea to predict the etiology and mechanism of acute, and to compare the findings with the literature.

METHODS

Patient Selection

This was a single-center, retrospective, observational study. Between January 2010 and June 2012, retrospective analyzes of 51 patients, 34 male and 17 female, out of 1200 patients who were admitted to the Neurology Clinic of University of Health Sciences Turkey, Taksim Training and Research Hospital with acute stroke and met the study criteria. Approval for this study was obtained from the Ethics Committee of Taksim Training and Research Hospital (decision no: 6, date: 03.04.2013).

Patients who underwent DWI within 48 hours of the onset of symptoms which confirmed the diagnosis of acute infarction, who had ischemic lesions in the unilateral MCA territory or border-zone and whose ischemic lesion was compatible with MCA disease, ICA disease, or CE were included in the study. Patients with multiple infarcts in areas outside of a single MCA territory (with MCA infarction or bilateral hemispheric lesions in other territories), stroke type other than MCA disease, ICA disease and CE (metastatic occlusion, etc.) and with concomitant ICA and MCA disease were excluded from the study (Figure 1).

Clinical data were obtained by examining patient files. The findings of the patients were clinically grouped into two classes

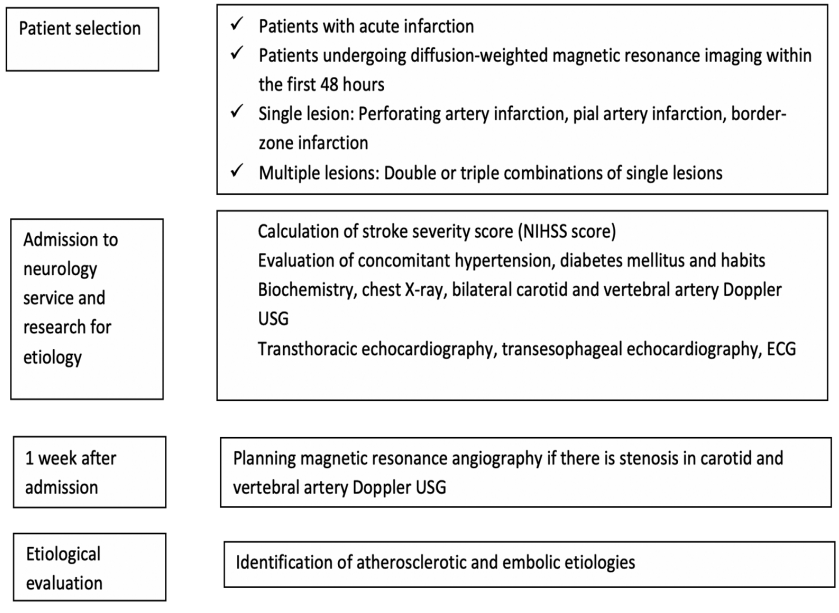

Figure 1. Flow-chart of the study
NIHSS: National Institutes of Health Stroke scale, ECG: electrocardiografi, USG: ultrasonography

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as lacunar syndromes (pure motor hemiparesis, pure sensorial stroke, sensory-motor hemiparesis, ataxic hemiparesis, dysarthria syndrome, dysarthria- clumsy hand syndrome) and non-lacunar syndromes (presence of cortical findings such as aphasia, neglect, gaze deviation, and changes in consciousness). The National Institutes of Health Stroke scale (NIHSS) was used for the numerical expression of stroke severity. In addition to MRI evaluation, patients' complaints at admission, clinical features, existing and accompanying diseases in their history, complete blood count, erythrocyte sedimentation rate, whole blood biochemistry, coagulation tests, electrocardiography (ECG), chest X-ray and urine test results were examined. Carotid and vertebral artery Doppler ultrasonography, transthoracic echocardiography, transesophageal echocardiography and 24-hour ECG follow-up were performed to investigate the etiology. As a result of these examinations, the risk factors, and etiologies of the patients in terms of stroke development were determined.

MRI was performed with a 1.5 tesla imaging device (Simens Avanto, Medical Systems) with echoplanar feature. 3800 ms repetition time (TR), 102 ms echo time (TE), matrix number 192-192, 5 mm slice thickness, 1.5 mm slice spacing, 21 axial slices, 240 mm image field, 0 and 1000 for DWIs. It was applied with a b value of 2 in s/mm^2. Those who showed an acute infarct pattern on DWI were transfered to the service for follow-up, examination, and treatment. Carotid-vertebral Doppler ultrasonography was performed in all patients. MRA examination was performed in the first week after admission to the service in patients with plaques that caused significant hemodynamic impairment in carotid-vertebral Doppler ultrasonography. Intracranial MRA with 3-dimensional TOF sequence was applied with 24 ms TR and ms TE 7 and 3-dimensional extracranial MRA with 20° flip angle, 159-159 matrix number and 240 mm field of view.

The topography of the ischemic lesion patterns on DWI of the patients was determined according to the vascular mapping published by Tatu et al. (11) in 1998. Vascular territories were determined as perforating, pial and border-zone. As PAI, striato-capsular infarcts and infarcts of perforating vessels of MCA were included. As pial infarcts (PI), infarcts in the territories of the superior and inferior cortical branches of the MCA were included. BZI were determined as infarcts in the anterior and posterior cortical border-zones and internal border-zone. Multiple DWI lesions were defined as hyperintense lesions observed in more than one vascular territory with no border neighborhood. According to Tatu's criteria, DWI lesions were small PAI (<2 cm in diameter), large PAI (>2 cm in diameter), PI, large region infarction, or BZI and multiple lesions (PAI and PI, PAI, PI and BZI, PAI and BZI, PI and PI, PI and BZI, and multiple BZI). PAIs smaller than 2 cm in diameter and PAIs larger than 2 cm in diameter were included in the PAI group. PI and BZI, which were seen as a single lesion, were divided into groups under the names of PI and BZI. The remaining combined patterns consisting of multiple lesions were included in a group called "combined multiple lesions" as the combination of single lesion patterns. Large MCA lesions, considered as a single lesion in the pattern literature, were also included in this last group as a combination of three single lesion patterns. The MRA findings of patients with MCA disease were considered in 3 grades: moderate stenosis (signal reduction greater than 50%), severe stenosis (image distal to MCA, but focal loss of signal) and complete occlusion.

Patients with 50% or more ipsilateral MCA stenosis or occlusion in MRA and no cause of CE or proximal to distal arterial embolism were defined as MCA disease. Patients with a stenosis or obstruction of 50% or more in the ipsilateral ICA and no evidence of MCA disease or a CE were included in the ICA disease group. Patients who had no atherosclerotic finding in cerebral vessels in MRA and who had embolic heart disease according to TOAST criteria were included in the CE group (11).

Statistical Analysis

The NCSS (Number Cruncher Statistical System) (Kaysville, Utah, USA) program was used for statistical analysis. Study data were presented using descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum). The conformity of the quantitative data to the normal distribution was tested with the Kolmogorov-Smirnov, Shapiro-Wilk test and graphical evaluations. Student's t-test was used for two-group comparisons of normally distributed quantitative data, and the Mann-Whitney U test was used for two-group comparisons of non-normally distributed quantitative data. Pearson chi-square test was used to compare qualitative data. The one-way analysis of variance and post-hoc Tukey test were used to reveal the difference between the groups. The significance level was accepted as $p<0.05$.

RESULTS

A total of 51 patients, 34 males (66.7%) and 17 females (33.3%), who were aged between 34 and 82 years, were included in the study. The mean age of men was 63.9±14.15 (range 34-80), and the mean age of women was 72.2±12.78 (range 38-82). MCA disease was found in 11 (21.6%) patients, ICA disease was found in 25 (49.0%), and CE was found in 15 (29.4%) patients. According to the presentation symptoms of the patients, clinical syndrome patterns were lacunar syndrome in 34 (66.7%) and non-lacunar syndrome in 17 (33.3%). In those with lacunar syndrome, the etiology was MCA disease in 9 (26.5%), ICA disease in 15 (44.1%), and CE in 10 (29.4%). Of the patients with MCA disease, 81% (9 patients) had lacunar syndrome. There were 15 (60%) patients who developed lacunar syndrome due to ICA disease. The rate of developing lacunar syndrome among patients with CE was 66.7%. In patients with non-lacunar syndrome, etiology was MCA disease in 2 (11.8%), ICA disease in 10 (58.8%), and CE in 5 (29.4%) patients. The rate of developing non-lacunar syndrome

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among patients with MCA disease was found to be 3.9%, while it was 19.6% in patients with ICA disease and 9.8% in patients with CE. The difference in the rates of developing lacunar syndrome or non-lacunar syndrome in different stroke types was evaluated with the chi-square test and no significant difference was found (p=0.441).

The mean NIHSS score calculated from the neurological findings of the patients at admission was 5.06±3.61 in patients with lacunar syndrome and 7.64±5.27 in those with non-lacunar syndrome and the difference was significant (p=0.045). The mean NIHSS score was 7.59±4.83 in patients with multiple lesions (22 patients), and 4.65±3.55 in patients with single lesion (29 patients), and the difference between the two groups was significant (p=0.016). The mean NIHSS score was 8.64±5.30 in patients with MCA disease, 4.60±3.18 in patients with ICA disease, and 6.13±4.66 in patients with CE. There was a significant difference between them [$F_{(20,50)}$=3.64, p=0.034]. With the post-hoc Tukey test, it was found that this difference stemmed from the difference between those with MCA disease and those with ICA disease.

Examples of lesion patterns by stroke subtype are shown in Figures 2, 3, 4, 5. No statistically significant difference was found between OSA disease, ICA disease and CE groups (p=0.753) (Table 1). Since the number of our patients was limited, PAI lesions smaller than 2 cm and PAI lesions larger than 2 cm were grouped under PAI lesion pattern, and lesion patterns consisting of various combinations of single lesions were grouped under multiple lesion patterns so that the groups could be compared (Table 1). There was no statistically significant difference in terms of lesion pattern between the different stroke subtypes (p=0.753).

Small or large PAI, PI or BZI single lesion patterns were detected in 29 (66.7%) patients. In 22 (33.3%) patients, it was observed that these lesion patterns formed multiple lesion patterns consisting of various combinations. There was no significant difference between different stroke subtypes in terms of developing a single or multiple lesion pattern (p=0.555) (Table 2) (The rates of multiple lesion pattern were 45.5% in the MCA disease group, 44.0% in the ICA group and 53.3% in the CE group). In the MCA disease group, the combination of PAI, PI and BZI (18.1%) and the combination of PAI and BZI (18.1%) were the most common multiple lesion patterns.

Diabetes mellitus (DM), one of the risk factors for stroke, was present in 1 (9.1%) of patients with MCA disease, 11 (44.0%) of patients with ICA disease, and 5 (29.9%) of patients with CE. There was no statistically significant difference between the types of stroke and DM coexistence (p=0.123). Hypertension (HT) was present in 5 (45.5%) of patients with MCA disease, 22 (88.0%) of patients with ICA disease and 9 (60.0%) of patients with CE. Association of HT was found to be significantly higher in the ICA disease group than in the other groups (p=0.020). There was a history of previous cerebrovascular disease (CVD) in 2 (18.2%) of patients with MCA disease, 4 (16.0%) of patients with ICA disease and 2 (13.3%) of patients with CE. There was no difference between stroke subtypes in terms of previous CVD history (p=0.943). Seventeen (33.3%) of the patients were smokers, and 4 (23.5%) of them were in the MCA disease group, 8 (47.1%) in the ICA disease group, and 5 (29.4%) in the CE group. There was no statistically significant difference between smoking and stroke subtypes (p=0.968).

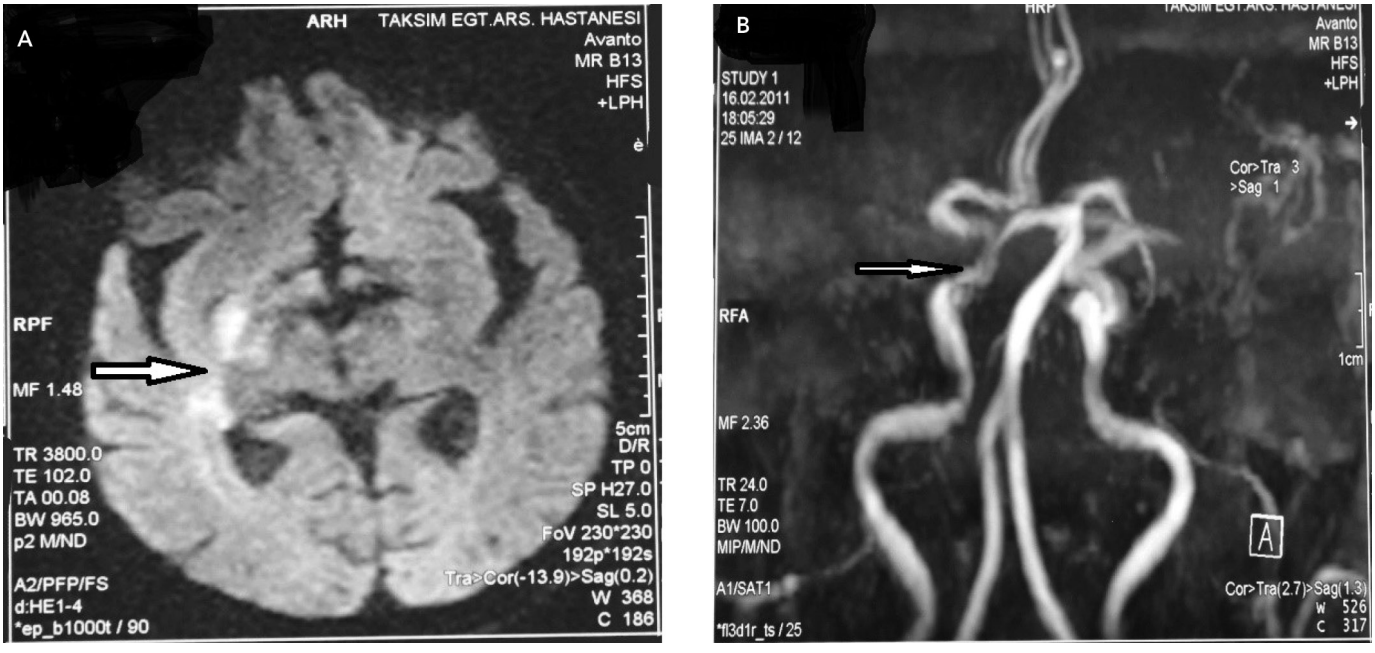

Figure 2. A) The lesion pattern of right perforating artery infarct in an 81-year-old patient with left hemiparesis and dysarthric speech. B) Magnetic resonance angiography image showing occlusion in the right middle cerebral artery

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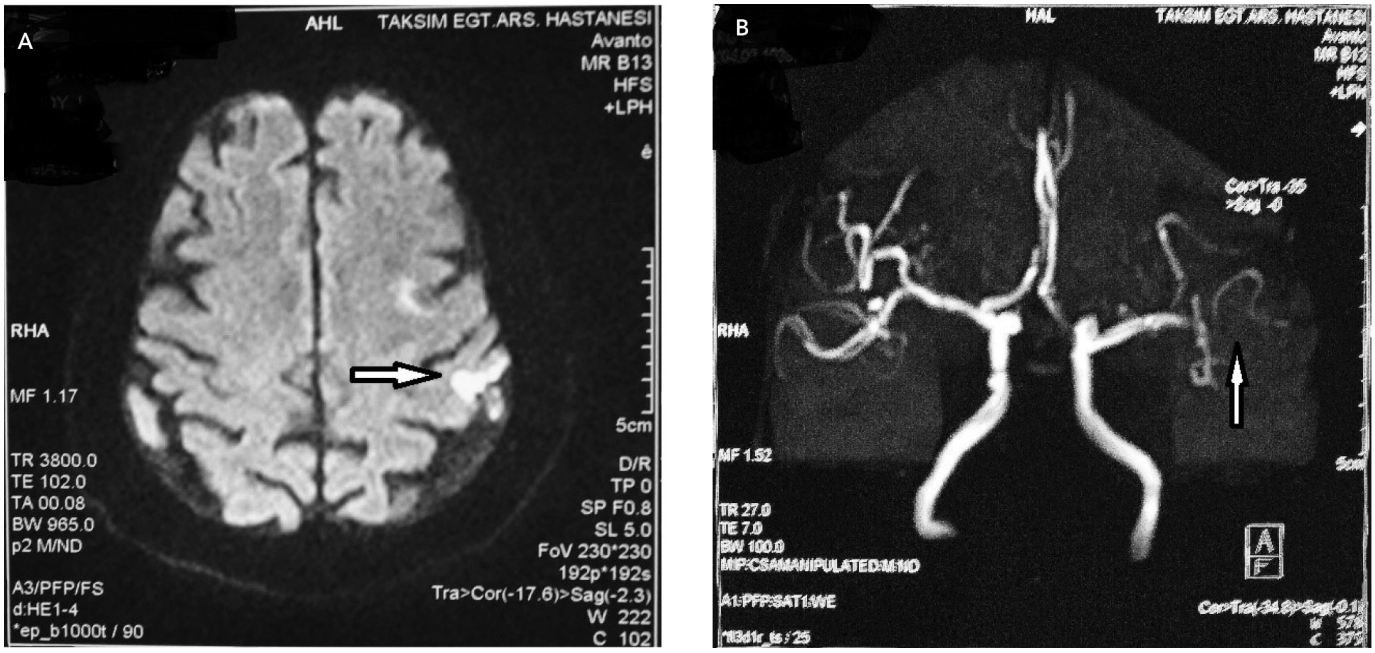

Figure 3. A) The lesion pattern of left pial infarct on diffusion weighted images of a 72-year-old patient with right hemiparesis. B) Cortical branch occlusion of the left middle cerebral artery on magnetic resonance angiography of the same patient

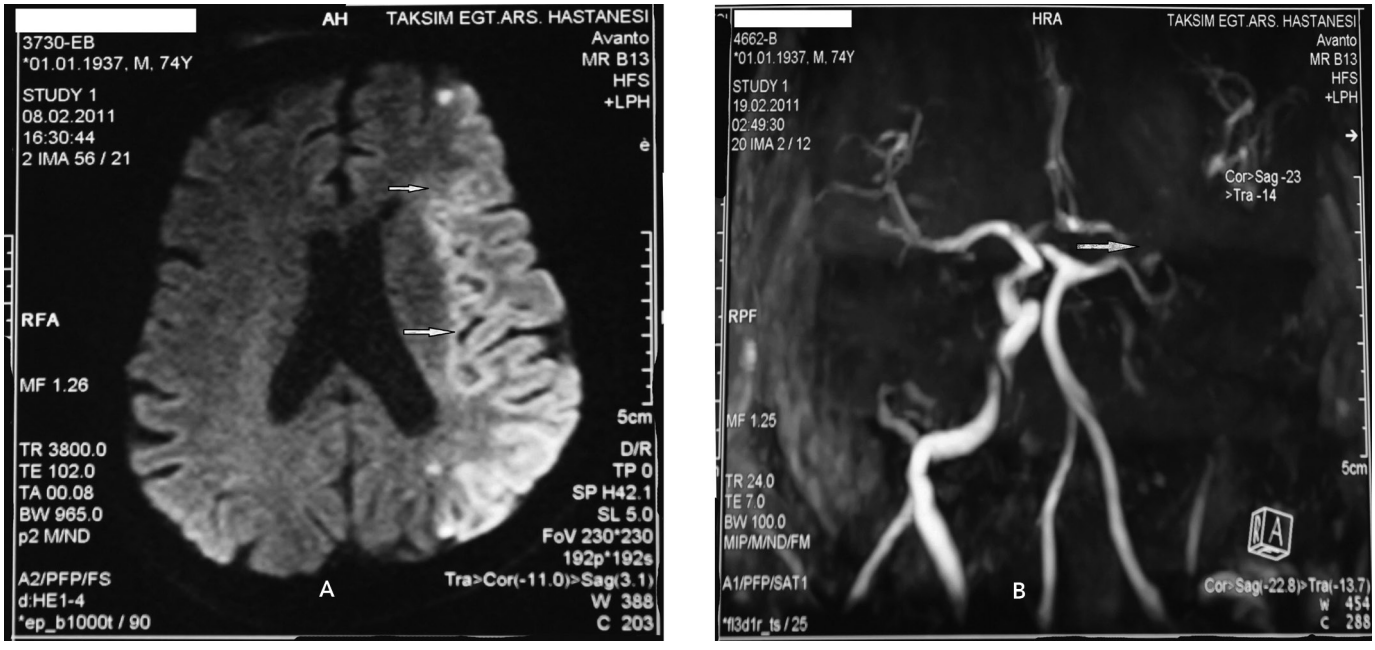

Figure 4. A) A 74-year-old patient presenting with motor aphasia and right hemiplegia has diffuse left middle cerebral artery infarction (a combination of perforating artery infarction, pial artery infarction, border-zone infarction patterns) on diffusion-weighted magnetic resonance imaging. B) There is a 70% stenosis in the left middle cerebral artery on magnetic resonance angiography of the same patient

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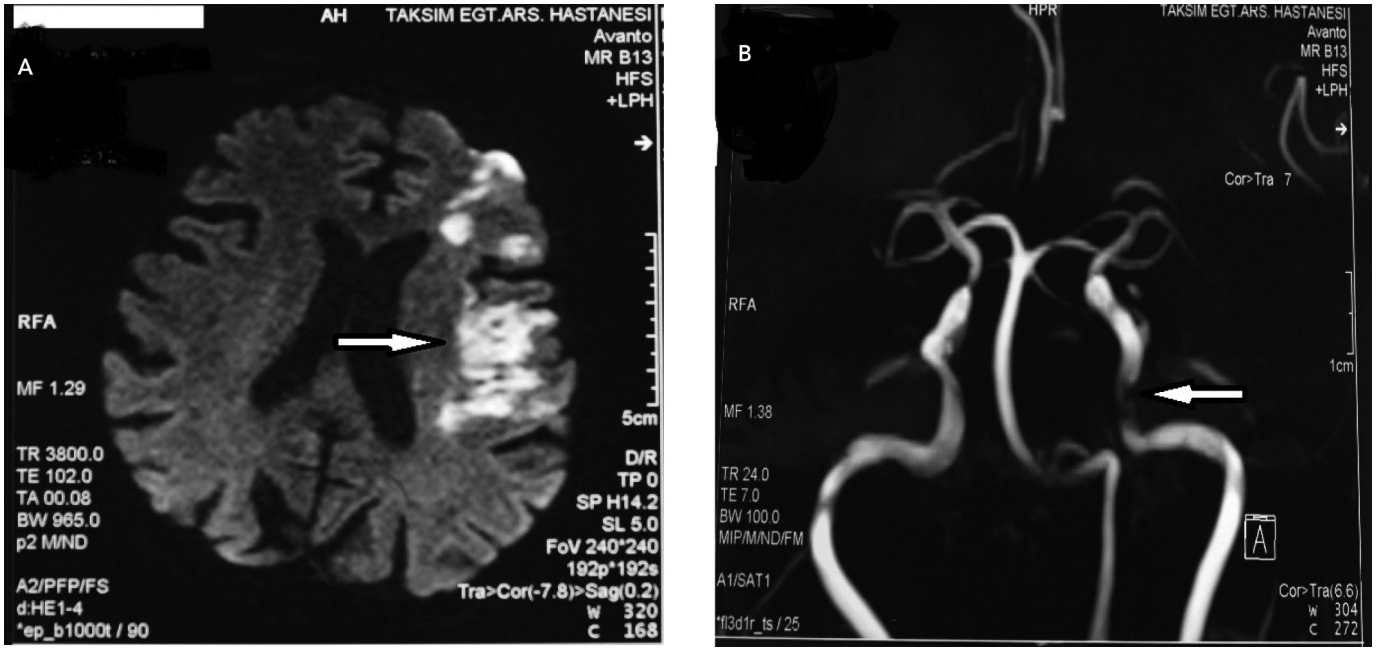

Figure 5. A) Combination of left perforating artery infarction, pial infarct and border-zone infarct lesion patterns in an 82-year-old patient with total aphasia and right hemiparesis. B) There is 50-60% stenosis in the left internal carotid artery in magnetic resonance angiography.

Table 1. Distribution of lesion patterns by stroke subtypes

Lesion pattern	Stroke type		
	MCA disease [n (%)]	ICA disease [n (%)]	CE [n (%)]
PAI	2 (18.2)	3 (12.0)	4 (26.7)
PI	3 (27.3)	9 (36.0)	3 (20.0)
BZI	1 (9.1)	2 (8.0)	0
Combined-multiple	5 (45.5)	11 (44.0)	8 (53.3)

MCA: middle cerebral artery, ICA: internal carotid artery, CE: cardioembolism, PAI: perforating artery infarct, PI: pial artery infarct, BZI: border-zone infarct

Table 2. Distribution of single or multiple lesions in different stroke subtypes

Number of lesions	Stroke type		
	MCA disease [n (%)]	ICA disease [n (%)]	CE [n (%)]
Single lesion	6 (54.5)	16 (64.0)	7 (46.7)
Multiple lesions	5 (45.5)	9 (36.0)	8 (53.3)

MCA: middle cerebral artery, ICA: internal carotid artery, CE: cardioembolism

DISCUSSION

In our study, the characteristics of the lesion patterns in atherosclerotic occlusive diseases of MCA were determined and compared with the findings in the literature. We did not detect a significant difference in the probability of developing multiple lesions in different stroke subtypes. Similarly, when stroke subtype and lesion pattern were compared, no difference was found between stroke subgroups. In a study involving 30 patients with acute MCA infarcts, the characteristics of the lesion (single or multiple lesion) and its pattern (whether the lesion was cortical or in the border-zone or in the territory of perforating artery) were defined using transcranial Doppler, DWI, and MRI. They found that the most common mechanism in MCA stenosis was a single penetrating artery infarction that caused a lacuna-like lesion, and that artery-to-artery embolization caused multiple small infarcts, especially in border-zone areas (5). However, in that study, the research was limited to a single lesion pattern, MCA ischemia

was evaluated and no comparison with other stroke etiologies was made. In our study, different etiologies, embolic and atherosclerotic, were also evaluated. In a study comparing lesion patterns in DWI and MRA lesions, vessel stenosis was classified as moderate (50-70%) and severe (70-90%) narrowing (10). After determining the stroke subtypes as MCA disease, ICA disease and CE, these subtypes were compared with the lesion patterns. In that study, they found that the combination of PAI and PI, and PAI, PI and BZI were specific lesion patterns for the MCA disease group, and they claimed that the PI lesion pattern originating from MCA could be a marker for embolism (10). They pointed out that the high frequency of the combination of PAI, PI and BZI in MCA disease might suggest an interaction between hypoperfusion and embolism as a stroke mechanism in this group. PAI lesion pattern smaller than 2 cm was found in the second frequency in patients with MCA disease. They attributed this to MCA-induced atheroma occlusion of the perforating artery inlet or isolated lipohyalinosis of the penetrating artery. This pattern was not accompanied by cortical field infarcts and the occlusions were mostly moderate, which distracted from the idea of embolization. However, despite this support, the authors evaluated the stroke mechanism that created the PAI lesion pattern as not clarified (10).

Multiple lesion pattern was the most detected lesion pattern in all three subgroups of our patients. High rate of combination of PAI, PI, BZI was similar to the findings of the study of Lee et al. (10). However, this was not a high rate specific to the MCA disease group. Although the high rate of PI lesion pattern in our patients with ICA disease was remarkable (36%) and its relationship with embolization was considered, no statistically significant difference was found.

Various studies have investigated the relationship between lesion patterns and occlusion mechanisms, using DWI to investigate the pathogenesis of ischemic stroke in atherosclerotic MCA disease (7,8). In 920 patients, stenosis was examined using MRA, and the difference between lesion patterns in extracranial occlusions and lesion patterns in intracranial occlusions was determined. While deep perforating and internal BZI were mostly detected in MCA infarcts, superficial perforating and territorial infarcts were detected in ICA disease (8). The same group of researchers evaluated 850 patients with transient ischemic attack and stroke clinically and neuroradiologically and found that the MCA group developed more lacunar syndrome patterns than the ICA group. They reported that the occlusions in the ICA group mainly caused total anterior circulation infarcts, and they found that the mean NIHSS score of this group was higher when compared to the mean NIHSS score of the MCA group (9). In lacunar syndromes, when multiple lacunae in which single lesions were observed, it was emphasized that other etiologies should be investigated in addition. Occlusion of more than one vessel was associated with embolism, while multiple scattered lesions in one vascular area were associated with large vessel disease (12). In our study group, there was no difference in terms of developing lacunar and non-lacunar syndromes according to etiology, and NIHSS score was found to be higher in those in the MCA disease group.

The difference in the time elapsed between the appearance of stroke symptoms and performing DWI creates difficulties in comparing these studies. This period varies between 5-6 days and 2 weeks (5,7-9). The time elapsed between the appearance of stroke symptoms and performing DWI is important. In this regard, 99 patients with acute ischemic stroke were examined with DWI within 6 hours after the onset of symptoms, the examination was repeated within 1 week, the lesion patterns were compared. They stated that it was possible to detect recurrences with DWI and that the time of performing DWI would affect the lesion pattern (12). In the study in which patients with recurrent ischemic stroke were evaluated in the same year, it was revealed that the lesion pattern in DWI performed in the early period (less than 24 hours from the onset of stroke) was associated with the stroke subtypes in the classification determined according to TOAST criteria (12,13).

In our study, no significant difference was found in terms of lesion patterns in different stroke subtypes. There were also studies that found a significant relationship between DWI and stroke subtypes (14). In a study reported from Turkey, while specific DWI patterns were found to be associated with small vessel disease, no significant distinguishing DWI patterns were found for large artery atherosclerosis and CE. It has been emphasized that classical diagnostic methods such as echocardiography and doppler USG maintain their importance (3). Rapid planning of all examinations remains important in determining the etiology of stroke, and imaging alone cannot replace these examinations.

When different stroke subgroups were evaluated in terms of risk factors in our study, history of HT in the ICA disease group was found to be significantly higher than the other groups (88.8%). In the literature, the history of DM was found to be significantly higher in the ICA disease group compared to other groups (10). In our study, DM was seen as a risk factor for all stroke subgroups, and no difference was found between the groups in terms of DM. No significant difference was found between groups in terms of smoking rate. These results were found to be similar to the studies conducted in the Turkish population (3).

Study Limitations

Our study was conducted on 51 patients who met the inclusion criteria. Conducting it in a single center was effective in the small number of patients who met the inclusion criteria for the study. Being retrospective also caused unwanted data loss and limited patient recruitment. Another limitation of the study was that MRA examinations of the patients were not repeated. Demonstrating the functioning of the recanalization process in different types of strokes may be the subject of research in future studies. Since we did not perform repeat MRA, no interpretation could be made for recanalization during infarct development, and it was concluded that a prospective study would provide more information.

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CONCLUSION

Stroke is a condition of which prognosis is positively affected when it is intervened in the early period. Different stroke mechanisms require different treatment strategies. Therefore, it is important that the mechanism of stroke is predictable in the early period. Although this study concluded that the character of the lesion pattern and the mechanisms of stroke occurrence could not be predicted with DWI in the early period, it revealed the importance of repeating the same study with a larger number of patients in a multicenter manner in the light of the results of the studies in the literature.

Ethics Committee Approval: Approval for this study was obtained from the Ethics Committee of Taksim Training and Research Hospital (decision no: 6, date: 03.04.2013).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - K.U.; Concept - K.U., S.Ü.Ö., Ş.F.H.; Design - K.U., Ş.F.H.; Data Collection and/or Processing - K.U., S.Ü.Ö.; Analysis and/or Interpretation - K.U., Ş.F.H.; Literature Search - K.U., S.Ü.Ö.; Writing - K.U., S.Ü.Ö.

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

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Factors Associated with Clinical Outcomes in Spontaneous Subarachnoid Hemorrhage

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ABSTRACT

Objective: This study aims at evaluating the factors affecting prognosis in patients with aneurysmal subarachnoid hemorrhage (SAH).

Methods: The charts and 6th month outpatient clinic records of the patients who were treated with the diagnosis of SAH between 2016 and 2020 were retrospectively reviewed. Post-discharge clinical status, adaptation to life, and disability status of 44 patients with aneurysmal SAH who were treated with endovascular or microsurgical techniques in our clinic were evaluated with the Glasgow Outcome Scale Extended (GOSE). The relationship between the patient's age, gender, timing of treatment, the location of the aneurysm, the World Federation of Neurological Surgeons (WFNS) scale score, Hunt-Hess scale (HHS) score, Fisher scale score and preoperative evaluations that might affect the GOSE score after discharge were examined.

Results: Forty-four patients who met the criteria were included in the study. The mean age of the patients was 49.1±10.3 (minimum-maximum: 29-77). Of those, 54.5% were females while 45.5% were males. Comorbidity was present in 54.5% of the patients. The most common aneurysm was the middle cerebral artery aneurysm with the rate of 27.3%. Of the aneurysmal SAHs, 45.5% were treated with microsurgical clipping and 27.3% with endovascular treatment. A statistically significant correlation was found between GOSE score and timing of treatment days (p=0.014), WFNS (p=0.002) and HHS scores (p<0.001). No statistically significant correlation was found between GOSE score and patient's age (p=0.47) and Fisher scale score (p=0.465).

Conclusion: In our study, the effects of early surgery, WFNS, and HHS scores on clinical outcome in cerebral aneurysmatic SAH were shown.

Keywords: Spontaneous subarachnoid hematoma, prognosis, clinical outcomes

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INTRODUCTION

Cerebral aneurysms (CA) occur in 3-5% of the general population (1). Aneurysm rupture causes subarachroid hemorrhage (SAH) and is associated with high mortality and morbidity (2). Its formation and pathophysiology have not been fully defined (3). Current treatment options consist of endovascular treatment and microsurgical clipping. Despite advances in surgical and endovascular techniques, equipment diversity in devices, and the improvements in intensive care units, mortality and morbidity associated with aneurysm rupture remain high (4). Treating ruptured aneurysms is required. The type of treatment is decided according to the choice of patients, the size and site of aneurysm. However, at vascular centers with a high annual number of microsurgical clipping, there is a tendency to perform clipping rather than applying endovascular treatment (5). Although the results of the International Study of Unruptured Intracranial Aneurysms and International Subarachnoid Aneurysm studies point to "coil first" with endovascular surgical intervention, there are ongoing discussions regarding the superiority of endovascular treatment and microsurgical clipping treatment over each other and which one should be preferred (6,7).

The Glasgow outcome scale-extended (GOSE) is used in the treatment of SAH and in the short and long-term follow-ups and results of these treatments, as in other cranial pathologies with brain injury (8,9). Many studies in the literature evaluate clinical outcome with GOSE. Correlation of applied treatment parameters and neurological status with GOSE is examined (8,9). Recently, some studies claimed that early aneurysm treatment achieves better clinical outcomes (8,10). There are also studies showing poor clinical outcomes in patients with WFNS grade IV and V SAH (9). There are few studies comparing GOSE score with preoperative parameters in SAH. No study was found in which all the mentioned parameters were compared with GOSE score.

In this study, we planned to investigate the effects of preoperative parameters and treatments in spontaneous SAH on clinical outcome.

METHODS

The data of 44 patients who developed SAH due to CA rupture and were admitted to our clinic and were treated between 2016-2020 were analysed retrospectively. The patients with spontaneous SAH who were admitted to our hospital within 72 hours after bleeding were included in the study. The patients with non-spontaneous SAH and those with previous record of neurological diseases (cerebrovascular disease, neurodegenerative diseases, etc.) were excluded from the study. All data of the patients were collected from the hospital database. Data were collected in the following categories: patient age, gender, World Federation of Neurological Surgeons (WFNS) scale score (Table 1) (11), Hunt-Hess scale (HHS) score (Table 2) (12), Fisher scale score (Table 3) (12), the site of aneurysm, the type of treatment performed (microsurgical clipping/endovascular treatment) and the number of days between first bleeding and application of treatment. In addition, the patients' adaptation to life and disability status were evaluated with the (GOSE) score (Table 4) (13) at the 6th month after discharge. Cerebral computed tomography (CT), cerebral CT angiography and Digital Subtraction Angiography (DSA) were performed in all patients after admission to the hospital. Control DSA was also performed in the patients at the 6th month.

The patients were treated by a single surgeon experienced in vascular surgery. They were operated with micro-Doppler and neuromonitoring.

Single or multiple aneurysm clips (Sugita®, Mizuho, Tokyo, Japan) were used during surgery. Endovascular treatment was performed by experienced senior neuroradiologists. Diagnostic or therapeutic angiography was performed with a routine femoral approach using biplane angio-graphic system with a flat panel detector (Toshiba Infinix, Toshiba Medical, Nasu, Japan). Lesions were treated with coils (Boston Scientific Corp., Natick, MA, USA) and stent (Neuroform® Stent System, Boston Scientific Corp., Natick, MA, USA).

All procedures were carried out in accordance with the 1964 Helsinki declaration. Written informed consent for scientific

Table 1. World Federation of Neurological Surgeons scale

Grade	Glasgow coma scale score	Motor deficit
I	15	Absent
II	13-14	Absent
III	13-14	Present
IV	7-12	Present or absent
V	3-6	Present or absent

Table 2. Hunt-Hess scale

Grade	Criteria
I	Asymptomatic, or minimal headache, nuchal rigidity
II	Moderate to severe headache, no neurological deficit except for cranial nerve palsy
II	Drowsiness, confusion, mild focal deficit
IV	Stupor, moderate to severe hemiparesis, early decerebrate posturing
V	Deep coma, decerebrate posturing, moribund

Table 3. Fisher scale

Grade	CT scan
1	No blood visualized
2	A diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) less than 1 mm thick
3	Localized clots and/or vertical layers of blood 1 mm or greater in thickness
4	Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots

CT: computed tomography

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Table 4. Glasgow outcome scale-extended

Category	Name	Definition
1	Death	
2	Persistent vegetative state	Unresponsive and speechless
3	Sever disability Lower	Requires frequent help of someone to be around at home most of the time every day
4	Sever disability Upper	Can be left alone >8 h during the day, but unable to travel and/or go shopping without assistance
5	Moderate disability Lower	Unable to work or only in sheltered workshop
6	Moderate disability Upper	Reduced work capacity; resumes <50% of the pre-injury level of social and leisure activities
7	Good recovery Lower	Minor problems that affect daily life; resumes >50% of the pre-injury level of social and leisure activities
8	Good recovery Upper	No current problems related to the brain injury that affect daily life

Table 5. Description of study participants

	Characteristics	
Age	$\bar{x}\pm s$	49.1±10.3
Gender	Female, n (%)	24 (54.5)
	Male, n (%)	20 (45.5)
Co-morbidities	Yes, n (%)	24 (54.5)
	No, n (%)	20 (45.5)
Hypertension	Yes, n (%)	20 (45.5)
	No, n (%)	24 (54.5)
Asthma	Yes, n (%)	4 (9.1)
	No, n (%)	40 (90.9)
Other co-morbidities	Yes, n (%)	10 (22.7)
	No, n (%)	34 (77.3)

Table 6. WFNS scale, HHS and Fisher scale scores

	Score	n (%)
WFNS scale	1	18 (40.9)
	2	10 (22.7)
	3	8 (18.2)
	4	5 (11.4)
	5	3 (6.8)
Fisher scale	1	3 (6.8)
	2	8 (18.2)
	3	17 (38.6)
	4	16 (36.4)
HHS	1	18 (40.9)
	2	10 (22.7)
	3	8 (18.2)
	4	5 (11.4)
	5	3 (6.8)

WFNS: World Federation of Neurological Surgeons, HHS: Hunt-Hess scale

purposes and clinical data collection were obtained from patients according to institutional protocol. Ethical approval was obtained from the local ethics committee (approval no: 319, date: 22.09.2021).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) 25.0 was used for statistical analysis (SPSS Inc.; Chicago, IL, USA). The Kolmogorov-Smirnov test was used to examine the normal distribution. According to results of normality analyses, the data was not normally distributed. The descriptive statistical methods (frequency, percentage, mean, standard deviation) were used to evaluate the demographic data. Pearson's chi-square test was used to compare the qualitative data. The Spearman correlation analysis was used for analysing the association of the quantitative data. The results were evaluated at a confidence interval of 95% and a significance level of $p<0.05$.

RESULTS

The total number of patients who were admitted to the clinic with the diagnosis of CA and underwent treatment between 2016 and 2020 was 44. The characteristic features of the patients are given in Table 5. Their mean age was 49.1±10.3 (minimum-maximum: 29-77). Of them 54.5% were females while 45.5% were males. Comorbidity was present in 54.5% of the patients. The three most common comorbidities were hypertension (HT) (45.5%), asthma and chronic obstructive pulmonary disease. WFNS scale, HHS and Fisher scale scores of the patients are shown in Table 6. The most common values for each scale were as follows: For WFNS scale score "Grade 1" in18 (40.9%) patients, for HHS score "1" in 18 (40.9%) patients, and for Fisher score "3" in 17 (38.6%) patients.

The angiography results of the patients with SAH were as follows: Twelve (27.3%) had middle cerebral artery (MCA) aneurysm, 8 (18.2%) anterior communicating artery (AcoA) aneurysm, 4 (9.1%) internal carotid artery aneurysm, 3 (6.8%) posterior communicating artery aneurysm, 2 (4.5%) distal anterior cerebral artery aneurysm, 2 (4.5%) posterior inferior cerebellar artery aneurysm, 1 (2.3%)

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basilar artery type aneurysm (Figure 1). Twelve (27.3%) patients were angiography negative. Except for these 12 patients, 20 (45.5%) patients were treated with microsurgical clipping and 12 (27.3%) patients with endovascular treatment, making the total number of treated patients 32. The mean number of days between bleeding and application of microsurgical clipping or endovascular treatment after SAH was 1.2, with the first day and the fifth day of bleeding representing the minimum and maximum values, respectively.

The study found a statistically significant negative correlation between GOSE score and timing of treatment (p=0.014) and a moderate significant negative correlation between GOSE and WFNS scale (p=0.002) and HHS scores (p<0.001) (Table 7). The overall mortality rate of the patients at the 6-month follow-up was 11.3%.

DISCUSSION

Nearly half of the SAH cases are caused by CA (14). Studies on predicting the prognosis of patients after SAH and the risk factors that affect the treatment outcome are still pending (15). In our current study, a negative correlation was found between WFNS scale and HHS scores, which were the preoperative evaluation scales, the GOSE score, and the timing of treatment applied.

Table 7. Relationship of clinical parameters with GOSE

	GOSE	
	r	p-value*
Surgery day	-0.390	0.014
WFNS	-0.477	0.002
HHS	-0.566	<0.001
Age	0.119	0.47
Fisher scale	-0.120	0.465

*Spearman correlation, GOSE: Glasgow outcome scale-extended, WFNS: World Federation of Neurological Surgeons, HHS: Hunt-Hess scale

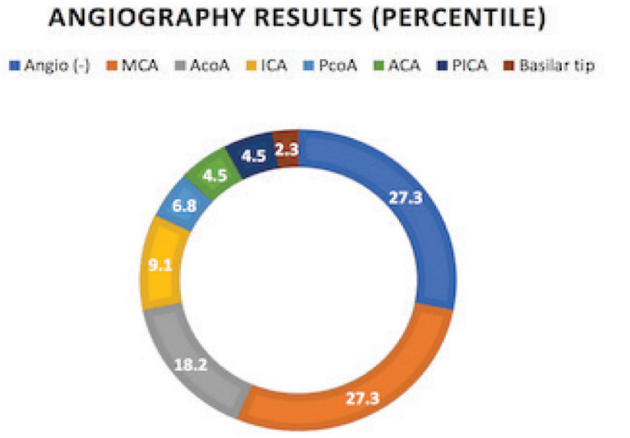

Figure 1. Angiography results (percentile)

MCA: middle cerebral artery, AcoA: anterior communicating artery, ICA: internal carotid artery, PcoA: posterior communicating artery, ACA: anterior cerebral artery, PICA: posterior inferior cerebellar artery

In this study, 27.3% of the 44 patients with SAH were found to have negative angiogram. When compared with the literature this rate is high. In the literature, angiogram negative SAHs constitute approximately 10-20% of spontaneous SAHs (16,17). It also has the same negative clinical outcomes as aneurysmal SAH (16,17). In line with the literature, GOSE scores of patients with angiogram negative SAH and aneurysmal SAH are similar. It is thought that the frequency of angiogram negative SAHs has increased, and this may be related to the widespread use of antiplatelet drugs (18).

Complications after SAH (vasospasm, ischemic neurological deficit, and brain infarction) are closely related to age and gender (19). While the incidence of complications is lower in elderly patients, they occur more commonly among the younger patients (20). It has been stated that 30-39 age group has higher risk whereas 60-69 age group has significantly lower risk (19). In addition, there are studies showing that the females are at higher risk of experiencing SAH and its complications (19,21). Our study, however, found no significant gender (p=0.395) or age (p=0.119) related difference among our patients in terms of risks. Although the studies in the literature generally state that age and gender are important risk factors, there are also articles with findings concurring that of our study (22).

HT is accepted as a risk factor for aneurysm formation and rupture (23). Laboratory studies have shown that a link exists between cerebral aneurysm and HT (24). Our study also found that HT was the most important morbidity accompanying SAH.

The most common site for aneurysm was MCA. In the literature, however, the most common site for aneurysm is ACoA which is the type of aneurysm with the highest rate of mortality and morbidity (3). The mortality rate we found in our study (11.7%) was unaffected by the site of aneurysm. We think that this differentiation may be related to the sample size of our study (n=44).

Discussions on the timing of surgery continue and varying views have been put forward about this issue thus far (25-27). However, in our study, we found a statistically significant relationship between the timing of surgery and GOSE score (p=0.014): The earlier the surgery was performed, the higher the patient's GOSE values and the lower the mortality and morbidity were.

A strongly negative correlation was found between the HHS and GOSE scores of the patients (p<0.001). As HHS score increased, survival rate decreased significantly. We think that it gives a very significant information about the prognosis. Past studies also support our findings (27-30). For example, studies conducted with 100 patients with SAH in 2001, with 3567 patients with SAH in 2007, with 720 patients with SAH in 2020, as well as some other studies conducted with many patients revealed the relationship between HHS score and prognosis (31-33). Like HHS score, WFNS scale score was also found to have a statistically significant relationship with GOSE score (p=0.002). As WFNS scale score increased, GOSE score decreased. A look at the literature shows that the findings about WFNS scale score and patient prognosis are compatible with our results (31-36).

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In the literature comparing clinical outcome and preoperative parameters, fewer parameters were examined than in our study. We determined that all parameters such as age, gender, day of surgery, HHS, WFNS Scale and Fisher scale scores, and aneurysm localization were not considered.

In our study, it was seen that the findings related to age and gender were not compatible with the literature. Findings on the day of surgery and WFNS scale score were consistent with the literature. Findings on HHS and Fisher scale scores supported the literature.

Study Limitations

The limitations of the study were that it was conducted in a single center, it was retrospective, and the number of patients was low. The low number of patients caused underpowered statistical analysis. Consequently, further comparative, long-term studies with larger patient groups are necessary to confirm these findings.

CONCLUSION

We suggest that WFNS scale and HHS scores of patients with aneurysmal SAH and timing of treatment provide important information about their GOSE scores and thereby the prognosis. Age, gender, comorbidities of the patients and the site of aneurysm did not make a significant contribution to the prognosis of the patients. Identifying and analysing the risk factors in studies with larger sample sizes will contribute to the literature. Conducting the study with a larger patient series will yield more reliable results.

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Results of Our Osteosynthesis Treatment with External Fixator in Risky Patients Aged 70 Years and Older with Intertrochanteric Femur Fracture and ASA III-IV

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ABSTRACT

Objective: We evaluated our union and functional results of osteosynthesis treatment with external fixator in high-risk patients aged 70 years or older with intertrochanteric femur fracture and American Society of Anesthesiology (ASA) III-IV.

Methods: Fractures were classified according to the Association for Osteosynthesis/Orthopedic Trauma Association (AO/OTA) classification. Preoperative waiting time, time to fracture union, limb length discrepancy, femoral neck-shaft angle, and level of activities of daily living were assessed. The union of the fractures was evaluated according to Foster's radiological evaluation criteria. Functional outcomes were evaluated according to the Barthel index of activities of daily living.

Results: The mean age of 38 patients was 80.35±7.27, 22 (57.9%) were females, 16 (42.1%) were males, and they were followed up for a mean of 15.9±4.1 months. The mean operation time of the patients was found to be 38±6.51 minutes. Thirty-one (81.5%) patients were operated under spinal anesthesia, and 7 (18.5%) patients were under general anesthesia and were discharged 4.3±4.71 days after the operation. Fracture groups according to AO/OTA classification were as follows: A1.1 in 3 (7.89%) patients, A1.2 in 14 (36.85%) patients, A1.3 in 4 (10.53%) patients, A2.1 in 8 (21.05%) patients, A2.2 in 4 (10.53%) patients, and A2.3 in 5 (13.15%) patients. The union of fractures were evaluated according to Foster's radiological scoring, and the mean time to union was found to be 123±11 days. A mean of 1.29±0.99 cm shortness was detected. The mean varus grade was 12.7°± 7.14°. According to Foster's scoring, successful results at the rate of 78.94% were obtained. Barthel index score was found to be 51.31±24.82 in the postoperative 6th month and 54.07±25.54 in the first postoperative year.

Conclusion: Osteosynthesis method with external fixator for intertrochanteric femur fractures of patients with ASA III-IV who were aged 70 years or over and had a high risk of surgery and anesthesia due to medical problems, might be preferred as an alternative treatment method since it was a closed surgery, it could be performed simply and quickly, and it reduced complications related to soft tissue injuries.

Keywords: Intertrochanteric fracture, external fixator, proximal femur, advanced age, ASA III-IV, osteosynthesis

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INTRODUCTION

Intertrochanteric femur fractures, which constitute 8-10% of all adult fractures, are serious injuries with high morbidity and mortality and an increasing incidence in osteoporotic patients. The complication rate of nonoperative treatment is high. Decubitus ulcers, urinary system infections, joint contractures, pneumonia, varus deformity and shortness, and mortality as a result of thromboembolism can be seen in elderly patients (1).

The aim of surgery is anatomical reduction of the fracture, stable fixation and early rehabilitation. Although the technical equipment is very advanced today, many patients with intertrochanteric fractures are considered risky in terms of anesthesia due to cardiological, pulmonary and hematological disorders in the elderly patient population (2). Osteosynthesis with external fixators can be a good alternative treatment as it is a minimally invasive method and can be performed in a short time.

In our study, we retrospectively evaluated the quality of life of the patients with intertrochanteric femur fracture and their fracture union status who had an American Society of Anesthesiologists (ASA) score of III-IV, were at risk in terms of anesthesia and surgery, and were over 70 years old.

METHODS

This retrospective cohort study was approved by the Taksim Training and Research Hospital Clinical Research Ethics Committee (decision no: 128, date: 04.09.2019) and informed consent was obtained from the patients.

Among 43 patients who were diagnosed as having intertrochanteric fracture of the femur, aged 70 years or over, had an ASA score of III-IV, and underwent osteosynthesis with external fixator, 38 patients with adequate follow-up were included in the study. The Association for Osteosynthesis (AO)/Orthopedic Trauma Association classification was used for the classification of fractures. Union of the fractures was evaluated according to Foster's radiological scoring. Thirty-eight patients were followed up for a mean of 15.9±4.1 months. The preoperative waiting time after the patients were admitted to the hospital, operation time, type of anesthesia, and mean time to discharge after the operation were examined. The Barthel index of activities of daily living (ADL) was used to measure ADL before the fracture, 6 months postoperatively, and 1 year postoperatively.

Pelvis and hip radiographs and complete blood count of the patients were performed in the controls. Varus deformity was investigated in anteroposterior pelvis radiographs in the control, and the distances between the medial malleolus and the spina iliaca anterior superior were measured clinically, and the length differences of the extremities were recorded. Removal of all external fixators was performed under local anesthesia. One day after the operation, the knee movements of the patients were controlled, and quadriceps exercises were started. On the second day, the patients were mobilized, and they started walking exercises with partial load.

Surgical technique: Closed reduction was performed under spinal or general anesthesia on a traction table, accompanied by fluoroscopy. The reduction was performed by bringing the lower extremity to 20 degrees of adduction and 10-15 degrees of internal rotation after traction. Then, under fluoroscopy control, a 2 mm Kirschner wire was sent to the head in accordance with the collodiaphyseal angle and the anteversion angle. Following the guide wire, at least 2, at most 4 transaxle nails were sent to the femoral head with a low-speed motor through a small incision. In order not to create cracks in the femoral cortex, the schanz screws that would be sent to the shaft were sent after they were drilled with a 3.2 mm drill. The second cortex was passed with the T handle in a controlled manner. All the schanz screws were fixed to the carbon AO type tubular external fixator with clamps (Figures 1, 2).

A first-generation cephalosporin was given to all patients prophylactically at a dose of 1 g parenterally 30-45 minutes (min) before the operation. Low molecular weight heparin (LMWH) was routinely started after the patients were admitted to the ward. There was no patient with additional pathology that prevented our application of LMWH. No blood transfusion was given to the patients during the operation. However, patients with low preoperative hemoglobin (Hgb) levels were provided with a preoperative Hgb value of >10 g/dL.

Statistical Analysis

The conformity of the variables to the normal distribution was examined by using histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation and interquartile range values were used while presenting descriptive analyzes. Changes in Barthel index values were examined with Repeated Measures and Paired Samples t-test. The limit of significance was accepted as $p<0.05$. Analyzes were performed using the software program SPSS (IBM SPSS Statistics for Macintosh, Version 28.0, Armonk, NY: IBM Corp, USA).

RESULTS

Of the 43 patients included in the study, 4 (9.3%) died within 1 month, and 1 (2.3%) within 3 months. The mean age of the remaining 38 patients was 80.35±7.27. Twenty-two (57.9%) patients were female and 16 (42.1%) were male.

Six of the male patients (15.79%) had right-sided and 10 (26.31%) had left-sided intertrochanteric femur fractures. Fourteen (36.85%) of the female patients had right-sided, and 8 (21.05%) had left-sided intertrochanteric femur fractures. The characteristics of the patients are summarized in Tables 1a and 1b, and complications are summarized in Table 2.

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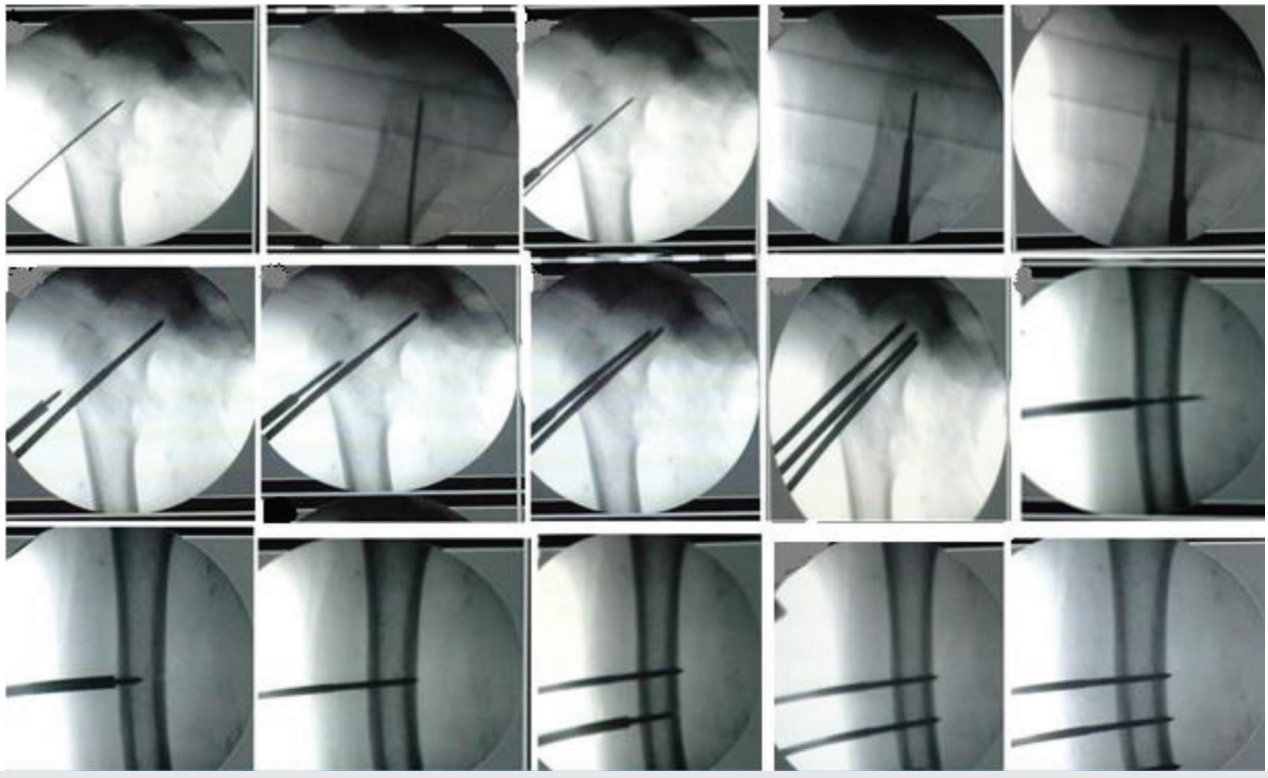

Figure 1. Surgical technique-scopy images

Figure 2. X-rays of our patient's in the preoperative period, postoperative period, control and after external fixator removal

The patients were followed for an average of 15.9±4.1 months. The patients were operated on an average of 6.8±4.16 days after admission to the hospital, and the mean hospital stay was 11.1±6.3 days. The mean operation time was 38±6.51 min. Thirty-one (81.5%) patients were operated under spinal anesthesia and 7 (18.5%) patients under general anesthesia. The patients were discharged after an average of 4.3 to 4.71 days after surgery. Transfusion was not needed due to intraoperative and postoperative blood loss.

According to Foster's radiological evaluation scoring, 8 patients were evaluated as Grade 1 (21.06%), 12 patients Grade 2 (31.57%), 6 patients Grade 3 (15.80%), and 12 patients Grade 4 (31.57%) (Table 3). Mean union time was 123±11 days, and shortness was detected at an average of 1.29±0.99 cm. The mean varus degree was measured as 12.7°±7.14°. According to Foster's radiological evaluation scoring, successful results were obtained at a rate of 78.94%. The Barthel index scores were found to be 58.68±28.53 preoperatively, 51.31±24.82 in the postoperative 6 months, and 54.07±25.54 in the 1st postoperative year (Table 4). As a result of the pairwise comparison, there was a significant decrease in the 6th month and 1st year values of Barthel index score compared to the pre-fracture value ($p<0.001$). There was a significant increase in Barthel index score in the 1st year compared to 6th month ($p=0.002$) (Table 5, Figure 3).

DISCUSSION

Of intertrochanteric femur fractures 90% occur in patients over 65 years of age, and the mortality rate in these fractures is 7-27% in the first 3 months after surgery (3) and around 20% in the first year (4). It has been associated with significant preoperative medical

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problems and postoperative complications (5). The time between admission to hospital and surgery is a factor affecting mortality in patients with intertrochanteric femoral fractures. It is known that elderly patients are at risk in terms of anesthesia due to significant preoperative medical problems. However, the prolongation of the preoperative preparation period for them to reach the optimum anesthetic state required for surgery paves the way for additional pathologies that increase mortality (6,7). In general, the consensus in the literature is that the comorbidities of patients with hip fracture should be evaluated rapidly within 12-24 hours before surgery and the operation should be performed within 2 days. When the literature was reviewed, the time to surgery was found as 7.7 days by Aksoy et al. (7) and as 5.76 days by Ozdemir et al. (8). The time from the date of admission to the operation in our patients was 6.8±4.16 days.

Table 1a. Patient characteristics

			n (%)
Gender	Female		22 (57.89)
	Male		16 (42.11)
Side	Right	Female	14 (36.8)
		Male	6 (15.8)
	Left	Female	8 (21.0)
		Male	10 (26.4)
ASA	ASA-III		23 (60.5)
	ASA-IV		15 (39.5)
Form of anesthesia	Spinal anesthesia		31 (81.5)
	General anesthesia		7 (18.5)
AO/OTA classification	A1.1		3 (7.89)
	A1.2		14 (36.85)
	A1.3		4 (10.53)
	A2.1		8 (21.05)
	A2.2		4 (10.53)
	A2.3		5 (13.15)

Table 1b. Patient characteristics

	$\bar{X} \pm s$
Age (years)	80.35±7.27
Length of hospital stay (days)	11.1± 6.3
Operation time (minutes)	38± 6.51
Follow-up time (months)	15.9±4.1
Waiting time before surgery (days)	6.8±4.16
Shortness (cm)	1.29±0.99
Varus degree	12.7±7.14
Healing time (days)	123±11
Barthel index score before fracture	58.68±24.57
Barthel index score-6th month	51.2±24.82
Barthel index score-1st year	54.08±24.1
Hemoglobin level-hospitalization (g/dL)	9.52±1.72
Hemoglobin level-1st month (g/dL)	10.09±1.33
Hemoglobin level-6th month (g/dL)	10.26±1.75
Hemoglobin level-1st year (g/dL)	11.24±1.07

Table 2. Complications in our patients

Complications	n (%)
Superficial pin site infection (DAHL 2)	7 (54)
Deep pin site infection (DAHL 4)	2 (15)
Deep vein thrombosis	1 (8)
Schanz screw migration	3 (23)
Total	13 (100)

Table 3. Clinical evaluation of the patients

Clinical evaluation of the patients		n (%)
Foster's radiological scoring	Grade 1	8 (21.06)
	Grade 2	12 (31.57)
	Grade 3	6 (15.80)
	Grade 4	12 (31.57)

Table 4. Barthel index score

Barthel index score	Before fracture	6th month after surgery	1st year after surgery
Mean ± SD	58.68±24.57	51.32±24.82	54.08±24.21
Median (IQR)	62.5 (45-75)	55 (30-65)	55 (40-70)

IQR: interquartile range, SD: standard deviation

Table 5. Comparison of Barthel index scores

Barthel index score	p-value
Before fracture-6th month-1st year	<0.001[1]
Before fracture-6th month	<0.001[2]
Before fracture-1st year	<0.001[2]
6th month-1st year	0.002[2]

[1]Repeated Measures, [2]Paired Samples t-test

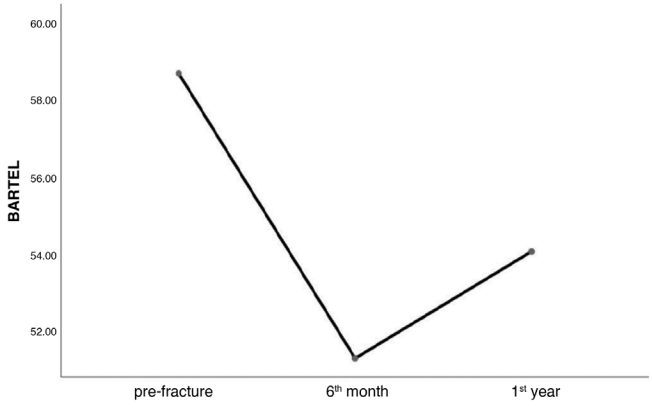

Figure 3. Change in the Barthel index score

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Figure 4. Clinical photographs of our patient

The operation time in external fixator surgeries is less than in other intertrochanteric fracture surgeries such as dynamic hip screw (DHS) and proximal femoral nail. In the study by Vossinakis and Badras (9), it was 21.2 min in the external fixator group, and it was 38.8 min in the DHS group, and in the study of Moroni et al. (10) it was 64±6 min in the DHS and it was 34±5 min in the external fixator group. Our average time of surgery with external fixator was 38±6.51 min.

The mean hospital stay times was found to be 8±4 days in the study by Aksoy et al. (7), 10.3±4 days in the study by Ozdemir et al. (8), 7±5 days in the study by Ozkaya et al. (11), 6±3 days in the study by Kazakos et al. (12), and it was found 7.3±1.1 days in the DHS group and 6.8±1.4 days in the external fixator group by Moroni et al. (13). In our study, we found the mean hospital stay of the patients to be 11.1±6.3 days. Patients were discharged on average 4.3±4.71 days after surgery.

An advantage of external fixators is that they can be removed without the need for a second operation. Performing a second surgical treatment in patients whose general condition is poor due to comorbidities carries a high risk in terms of anesthesia complications. The external fixators of all our patients were removed with local anesthesia. With closed surgery, periosteum and fracture hematoma are preserved, so union and healing are facilitated (14,15).

In our study, open reduction was not required in any of our patients. Approximately 1200 cc of bleeding can occur after hip fractures. This may cause dehydration and hemoconcentration in elderly patients. Vossinakis and Badras (16) emphasized in their study on patients treated with an external fixator that blood loss during surgery was negligible. Our patients did not need transfusion due to blood loss during or after the surgery.

Another problem in patients with external fixation may be stiffness of the knee joint and limitation of movement. It may be caused by the fixation of the vastus lateralis muscle and facia lata with the schanz screws, and this problem can be eliminated by placing the distal schanz screws as close to the proximal part of the femur as possible (16,17). In our study, we detected knee joint stiffness in one of our patients (Figure 4). We determined that the patient was hemiparetic and did not exercise. We did not encounter knee contracture in other patients in whom we started early mobilization.

Pin site infection is a common complication in external fixators and has been reported with a rate of 7-44% (16,18). However, these infections are superficial and rarely cause osteomyelitis. This rate increases in osteoporotic bones. Green (18) stated that two main factors led to pin site infection. One of them was nail base soft tissue necrosis and the other was excessive movement of nails and nail base soft tissues. Vossinakis and Badras (16) determined that mechanical and thermal damage predisposed to infection. He recommends paying attention to the soft tissues while applying the schanz screws, using a low-speed motor or hand perforator to avoid bone thermal necrosis, and supporting the circumference of the schanz screws with dressing materials to reduce skin movements. Moroni et al. (13) reported that there was no pin site infection with hydroxyapatite (HA) coated external fixator pins. Pizà et al. (19) was reported that there was no difference in terms of infection between HA coated and non-HA-coated pins, but HA coated pins adhered better to the bone and had less pin loosening.

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Seven (16%) of our patients had 2nd degree pin site infection and 2 (4.6%) had deep pin site infection. In these patients, infection was treated with antibiotics, and there was no need for washing or debridement.

External fixators can cause psychological problems due to their rough structure. Patients have to modify their clothes and lifestyle. Yildiz et al. (20) stated in their study that this situation mostly occured in the use of circular external fixator. In our patient population, the most common complaint was the limitation of lying position. Over time, we found that they easily adapted to this situation.

Thromboembolic diseases are one of the most common and dangerous complications after skeletal trauma. Fatal pulmonary embolism occurs in 7-10% of patients who develop deep venous thrombosis (DVT) (21). In our general practice, we start LMWH immediately after patients are admitted to the hospital. LMWH administration is usually discontinued 24 hours before surgery, and we continue to administer it 12 hours after surgery. We start early mobilization after the surgery and use elastic stockings. We continue to administer LMWH for 15 days after the patients are discharged. No clinically evident deep vein thrombosis was detected in our study.

Michel et al. (22) stated that ASA scoring could be used as a marker of mortality in the long term. Hamlet et al. (23) determined the three-year mortality rate as 23% in patients with ASA I and II, and 39% in patients with ASA III and IV, and stated that ASA classification was a good indicator of mortality. Richmond et al. (24) evaluated the mortality of hip fractures with ASA scoring in a series of 836 patients (patient group aged 64-84 years and patient group aged over 85 years). As a result, they found that mortality in hip fractures was not associated with ASA scoring in patients aged 85 years or over, but there was a relationship with ASA in the group aged 64-84 years. Especially in the younger patient group (64-84 years), they found a strong correlation between ASA III-IV and 2-year mortality (as ASA score increased, mortality increased). It is obvious that generalization cannot be made between ASA scoring and mortality in a very small series, but ASA scoring can provide a preliminary view on the mortality of patients with hip fracture, their postoperative state and returning to pre-fracture state.

The Barthel index was found to be 58.68±28.53 preoperatively, 51.31±24.82 in the postoperative 6th month, and 54.07±25.54 in the postoperative 1st year (Table 4). Compared to preoperative value, a decrease of 12.54% was detected in the Barthel index score in the postoperative 6th month and a decrease of 7.86% in the postoperative 1st year. As a result of the paired comparison, there was a significant decrease in the postoperative 6th month and 1st year values of the Barthel index compared to the preoperative value ($p<0.001$). There was a significant increase in the Barthel index score in the postoperative 1st year compared to the postoperative 6th month ($p=0.002$) (Table 5, Figure 3).

The fractures healed in 123±11 days in our study. 12.7°±7.14° varus and 1.29±0.99 shortness was detected. (Table 1b). Ozkaya et al. (11) found the mean time to union to be 4.1 months in all patients, the mean femoral neck-diaphyseal angle measured in the early postoperative period as 133°, and 132° at the final controls. Ozdemir et al. (8) found the mean time to union to be 12.3 weeks. They found varus (3°, 5°, 9°) in 3 patients (12%) and mean shortness of 1.33 cm in 3 patients (12%). Tomak et al. (25) removed the external fixator in an average of 12 weeks. They found varus in 2 (4.7%) patients and less than 2 cm shortness in 10 (23.8%) patients. They did not find implant loss, fracture, knee and hip joint stiffness.

Dhal et al. (17) achieved union in an average of 16 weeks in closed intertrochanteric femur fractures and in 28 weeks in open fractures in a series of 154 patients. They found a shortness of less than 2 cm in 74 (48%) of the patients and more than 2 cm in 9 (5.84%) patients. They reported that these shortnesses were caused by osteosynthesis in the varus during the first surgery or due to full weight bearing. Vossinakis and Badras (16) achieved union in an average of 11 weeks. They did not detect migration of the screw into the acetabulum by piercing the femoral head or screw slipping or screw breaking. They found an average of 1.8 cm shortness in 12 patients (27.27%).

Study Limitations

The limitations of our study were the absence of a control group, the relatively short follow-up period, and non-homogeneity of the additional pathologies of the patients (atrial fibrillation, diabetes mellitus, Alzheimer's disease, hypertension, chronic ischemic heart disease, chronic renal failure, myocardial infarction, chronic obstructive pulmonary disease, cerebrovascular disease, tuberculosis, Parkinson's disease). As the strong sides of our study, the patients were treated by the same surgical team and a single type of osteosynthesis technique was applied to all patients.

CONCLUSION

In patients with intertrochanteric femoral fractures who have additional medical problems and who are at high risk for surgery and anesthesia due to these problems; external fixator is an alternative treatment in the surgical treatment of intertrochanteric femur fractures because the operation time is very short, blood loss is less, the fracture hematoma is not evacuated due to close operation, the fracture heals in a short time, the postoperative hospital stay is short, patients regain mobility early, pressure ulcers and pulmonary complications are less, the rate of fixator-related complications is low, and removal of the fixator after union or re-arrangement of the fixator in case of mechanical failure does not require anesthesia.

Ethics Committee Approval: This retrospective cohort study was approved by the Taksim Training and Research Hospital Clinical Research Ethics Committee (decision no: 128, date: 04.09.2019).

Informed Consent: Informed consent was obtained from the patients.

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Pathogenetic and Prognostic Importance of Cyclin D1, Estrogen Receptor, and TAG72 in Cutaneous Vascular Tumors and Pericytic Tumors

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ABSTRACT

Objective: The present study aims to investigate the presence of pericyte loss in malignant vascular tumors and investigate the expression of cell cycle regulators, cyclin D1 and estrogen receptor (ER), and tumor-associated glycoprotein 72 (TAG72) in tumor cells and tumor microenvironment in benign/malignant vascular tumors and benign/malignant pericytic tumors.

Methods: Cyclin D1, ER, and TAG72 were examined by immunohistochemistry in 38 cases of tumors of vascular and pericytic origins. The data on metastasis and prognosis of malignant cases were retrieved from the hospital information system.

Results: The 38 patients included the following types of neoplasms: hemangioma (n=16), glomus tumor (n=9), epithelioid angiosarcoma (n=8), epithelioid hemangioendothelioma (n=3), infantile hemangiopericytoma (n=1), and malignant glomus tumor (n=1). No statistically significant difference was found in cyclin D1 expression between pericyte-derived tumors and malignant vascular tumors (p=0.508). When benign-malignant vascular and pericytic tumors were compared, no statistically significant difference was found in cyclin D1 expression between the 4 groups (p=0.465). No statistically significant difference was observed in staining between tumors of vascular and pericytic origin (p=0.104). ER expression was detected in only one case of malignant glomus tumor. TAG72 expression was not observed in any of the cases.

Conclusion: The present study supports the notion that cyclin D1 may be present as a driver mutation in this group of tumors. The findings of this study did not produce any data to support the hypothesis claiming that pericyte loss led to malignancy. We believe that our results on the comparison of cell cycle protein expressions in cutaneous vascular and pericytic tumors shed light for future studies to elucidate the pathogenesis of this group of rare tumors.

Keywords: Vascular tumor, pericyte, cyclin D1, estrogen receptor, TAG72

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INTRODUCTION

Vascular tumors are endothelium-derived neoplasms that are categorized as benign, intermediate, or malignant based on the World Health Organization classification of soft tissue tumors. The most common type of these tumors is hemangiomas, where total excision results in cure. However, recurrence may occur in patients in whom total excision cannot be performed, such as vertebral hemangiomas. The differential diagnosis of benign vascular tumors from malignant tumors is of critical importance and may sometimes be challenging, as is the case with anastomosing or epithelioid hemangiomas. The intermediate group involves retiform hemangioendothelioma, papillary intralymphatic angioendothelioma, composite hemangioendothelioma, Kaposi's sarcoma and pseudomyogenic hemangioendothelioma, which are locally aggressive tumors that rarely metastasize. Epithelioid hemangioendothelioma and angiosarcoma are malignant vascular tumors. Glomus tumor is the most common type of pericyte-derived tumors, and only a limited number of patients with malignant glomus tumor has been reported in the literature to date (1,2).

Accumulating observations show that not only genetic abnormalities in malignant cells but also tumor microenvironment play an effective role in the physiopathology of cancer. In addition to cancer-associated fibroblasts, immune cells, endothelial cells and pericytes are also the main cellular components of tumor microenvironment, and their various functions in tumor initiation and progression have been the subject of recent researches (3).

The first stage of tumor angiogenesis begins with pericyte-endothelial cell detachment. The detachment of pericytes, which are responsible for vascular stabilization, from the vascular wall allows endothelial cells to migrate to the surrounding matrix to form new blood vessels while increased vascular permeability leads to leakage of plasma proteins, which serve as a temporary matrix for the endothelium, as well as pericyte migration between integrins and plasma proteins (4,5). The facts that pericytes are the main cells that initiate tumor angiogenesis and that the way pericytic cell loss impairs vascular stabilization have led us to the question, "Do vascular tumors become malignant in the event of pericytic cell loss?"

The effects of estrogen and estrogen receptors (ER) on the G1 and G1-S phases of the cell cycle are well-established. Central to these cell cycle checkpoint mechanisms are the retinoblastoma susceptibility gene, pRB and the cyclin D1-CDK4 and cyclin E-CDK2 complexes that phosphorylate substrates, thereby allowing the initiation of DNA synthesis (6).

The present study aims to investigate the presence of pericyte loss in malignant vascular tumors and investigate the expression of cell cycle regulators, cyclin D1 and ER, and tumor-associated glycoprotein 72 (TAG72) in tumor cells and tumor microenvironment in benign/malignant vascular tumors and benign/malignant pericytic tumors in order to elucidate the pathogenesis of vascular and pericyte-derived tumors.

METHODS

Cutaneous vascular tumors and pericytic tumors diagnosed at pathology departments of two tertiary centers between 2016-2020 were included in the study. Data on the diagnosis, age, tumor location, metastasis and prognosis of the patients were retrieved from the hospital information system. This was a retrospective study of the archived materials of these patients.

Immunohistochemistry

Sections of 4-micron thickness were obtained from 38 paraffin-embedded archive tissues for immunohistochemistry (IHC) analysis, and then, these sections were deparaffinized and placed in a BenchMark XT device. Staining was performed after applying the antibodies, cyclin D1 (Ventana, RTU, clone SP4-R, USA), ER (Ventana, RTU, clone SP1, USA) and TAG72 (Cell Marque, RTU clone B72.3, USA). The preparations stained in an automated staining device were covered using an appropriate fluid-based covering material. Results were evaluated with an Olympus BX51 microscope.

Immunohistochemistry Evaluation

Scoring was performed simultaneously by two independent pathologists blinded for the clinical data. The intensity of cyclin D1 IHC staining was scored as +1, +2, and +3 for weak, moderate, and strong stains, respectively. The IHC score of cyclin D1 was reported as negative, low score (+1) and high score (+2 & +3) (7). ER expression was quantified in line with the scoring system proposed by Remmele and Stegner (8) for ER in breast cancer. Staining intensity was scored from 0 (no reaction) to 3 (strong reaction), and the percentage of stained nuclei was scored from 0 (no positive nuclei) to 4 (more than 80% positive nuclei). The scores of staining intensity and stained nuclei were then multiplied, yielding a total score of 0 to 12. Positive ER expression was defined as a score of 3 or more (9).

For the IHC evaluation of TAG72, we used the 12-point Remmele scoring system (score: 0-12). To calculate this score, a number out of 0, 1, 2, or 3 was chosen according to the intensity of staining, and a number out of 0, 1, 2, 3, or 4 was chosen according to the percentage of positive tumor cells. The final scores of staining intensity and stained nuclei were then multiplied, yielding a total score of 0 to 12(3×4). In this study, total scores below 3 were considered negative, and scores of 4-12 were considered positive (8,10).

Statistical Analysis

Patient demographics and data were analyzed using the SPSS 24 (IBM Corp., Armonk, NY, USA) software. The chi-square test was used to compare variables between the patients in groups, and the Kruskal-Wallis test was used for comparisons across the 4 groups. $P<0.05$ was considered statistically significant.

The study was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee (number: 102, date: 7 august 2020).

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RESULTS

Of the 38 patients, 26 had benign (16 hemangiomas, 9 glomus tumors, 1 infantile hemangiopericytoma) and 12 had malignant (8 epithelioid angiosarcomas, 3 epithelioid hemangioendotheliomas, 1 malignant glomus tumor) tumors. The tumors were in the extremities or the head and neck regions. The mean age of the 38 patients was 41.9 years (minimum: 1, maximum: 78).

The distribution of cyclin D1 and ER staining in tumor cells and ER staining in tumor microenvironment by diagnosis are shown in Table 1. There was no TAG72 staining in tumor cells and/or tumor microenvironment in any of the patients. No cyclin D1 staining was observed in tumor microenvironment in any of the patients.

Comparison of cyclin D1 expression between pericyte-derived tumors (9 glomus tumors, 1 infantile hemangiopericytoma, 1 malignant glomus tumor) and malignant vascular tumors (8 epithelioid angiosarcomas, 3 epithelioid hemangioendotheliomas) did not reveal a statistically significant difference (p=0.508). The cyclin D1, ER and TAG72 immunostainings in a malignant glomus tumor are presented in Figure 1.

Cyclin D1 and ER staining, follow-up duration, and metastasis status of malignant tumors are presented in Table 2.

When benign and malignant vascular and pericytic tumors were compared, no statistically significant difference was found in terms of cyclin D1 expression between the four groups (p=0.465). No statistically significant difference was observed in terms of cyclin D1 staining between vascular tumors and tumors of pericytic origin (p=0.104). Table 3 shows the cyclin D1 expression of the patients by diagnosis. Cyclin D1 immunostainings of the patients with hemangioma, hemangioendothelioma, and angiosarcoma are presented in Figure 2.

DISCUSSION

A better understanding of the variable expression of different pericyte markers in tumors would provide a better understanding of pericyte-mediated angiogenesis. Since there are only a limited number of studies in the literature, especially in tumors such as angiosarcoma, epithelioid hemangioendothelioma and malignant glomus tumor, which are rare and have poor prognosis, we believe that there is a need for studies aiming to elucidate the pathogenesis and shed light for further research on the treatment of these tumors. Although conducted with relatively small sample size, the present study is one of the few studies in the literature investigating the expression of cell cycle-regulatory proteins such as cyclin D1, ER, and TAG72 in tumors of vascular and pericytic origins to shed light on the pathogenesis of this group of tumors. We detected cyclin D1 expression in both benign and malignant tumors of vascular and pericytic origins, and we observed ER expression only in one case of malignant glomus tumor. We did not find a significant difference in these proteins between pericyte-derived tumors and vascular tumors. Our results suggest that especially cyclin D1 may be present as a driver mutation in this group of tumors; however, further comprehensive research is needed on this subject matter. Furthermore, we did not detect pericyte loss in malignant tumors. Findings of this study did not produce any data to support the hypothesis claiming that pericyte loss led to malignancy.

Overexpression of cyclin D1 may serve as a driver oncogene through the cell cycle-regulatory function of this protein. In the literature, amplification and/or overexpression of cyclin D1 has been shown in various human tumors, such as breast and parathyroid neoplasms (11). Moreover, there are studies supporting that this parameter indicates poor prognosis in tumors such as endometrial tumors (7). In our study, we found no significant difference in cyclin D1 expression between benign and malignant tumors. We detected low or high scores of cyclin D1 expression in 11 of our 12 malignant tumors. Despite the small sample size and limited follow-up period in our study, we believe that cyclin D1 expression may be a prognostic factor to predict metastasis and life expectancy in angiosarcoma cases provided that this is confirmed in larger future studies. Girard et al. (12) detected cyclin D1 expression in 12 of 16 benign glomus tumors located in the upper digestive tract and suggested that cyclin D1 overexpression might be involved in the pathogenesis of glomus tumors (12).

In the present study, comparison of cyclin D1 expression between 11 pericyte-derived tumors and 12 malignant vascular tumors did not reveal a statistically significant difference (p=0.508). Therefore,

Table 1. Distribution of cyclin D1 and ER staining in tumor cells and tumor microenvironment by diagnosis

Diagnosis	Cyclin D1			ER in tumor cells		ER in tumor microenvironment		Total number of cases
	Neg	Low score	High score	Negative	Positive	Negative	Positive	
Hemangioma	3	3	10	16	0	16	0	16
Glomus	1	2	6	9	0	9	0	9
Infantile hemangiopericytoma	0	1	0	1	0	1	0	1
Epithelioid hemangioendothelioma	1	1	1	3	0	3	0	3
Angiosarcoma	0	5	3	8	0	8	0	8
Malignant glomus	0	1	0	0	1	0	1	1

ER: estrogen receptor

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our findings did not produce any data to support the hypothesis in favor of pericyte loss in malignant vascular tumors. However, we believe that more robust results can be obtained with studies using IHC methods where staining is specific to pericytes.

There are studies in the literature demonstrating the effect of estrogen and ER in the pathogenesis of hemangiomas (13). Some studies have shown that estradiol modulates pericyte activity in the brain, thereby improving endothelial integrity (14). However, in our study, we did not detect ER expression in any of the benign and malignant tumors of vascular and pericytic origins, and we found ER expression only in one case of malignant glomus tumor. Estrogen may contribute to the malignant transformation of

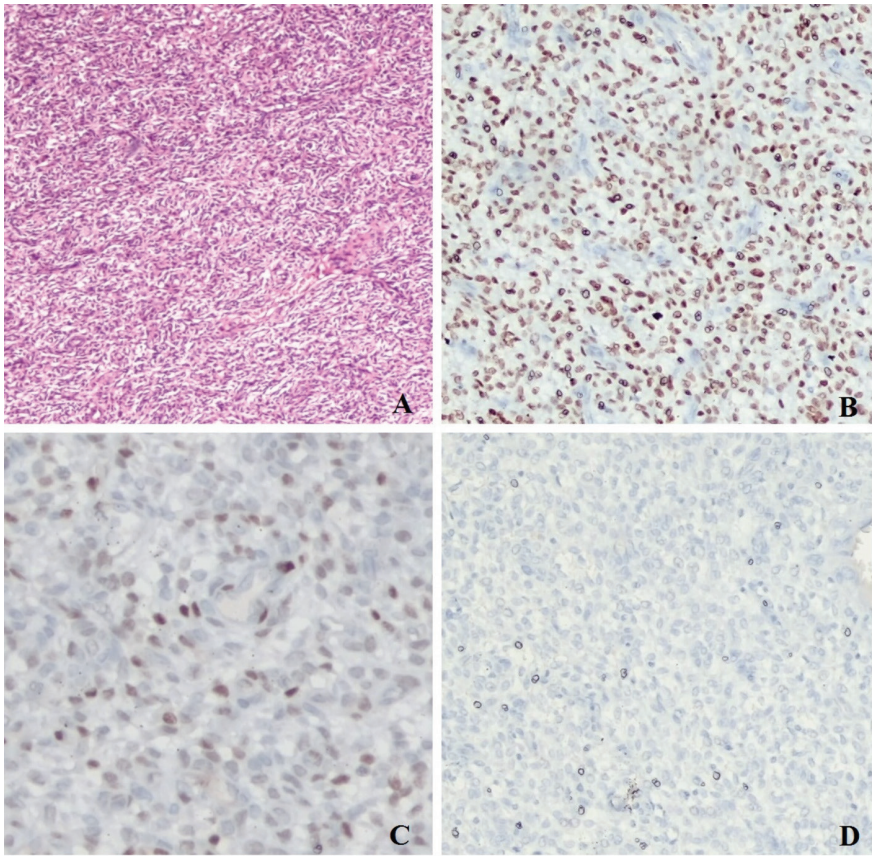

Figure 1. Malignant glomus tumor A: H&E x40, B: Estrogen receptor x100, C: cyclin D1 x100, D: TAG72 x100

Table 2. Cyclin D1 and ER staining, follow-up duration and metastasis status of malignant cases

Diagnosis	Number of cases	Cyclin D1	ER	Metastasis	Follow-up duration	Outcome
Angiosarcoma	1	Low score	Negative	Lung metastasis	12 months	
Angiosarcoma	2	High score	Negative	Null	13 months	
Angiosarcoma	3	High score	Negative	Lung metastasis	24 months	Exitus
Angiosarcoma	4	Low score	Negative	Lung metastasis	8 months	Exitus
Angiosarcoma	5	Low score	Negative	Null	14 months	Exitus
Angiosarcoma	6	Low score	Negative	Null	8 months	
Angiosarcoma	7	Low score	Negative	Null	6 months	Exitus
Angiosarcoma	8	High score	Negative	Null	12 months	Exitus
Malignant glomus	9	Low score	Positive	Null	7 months	
Hemangioendothelioma	10	Negative	Negative	Null	24 months	
Hemangioendothelioma	11	Low score	Negative	Null	24 months	
Hemangioendothelioma	12	High score	Negative	Null	21 months	

ER: estrogen receptor

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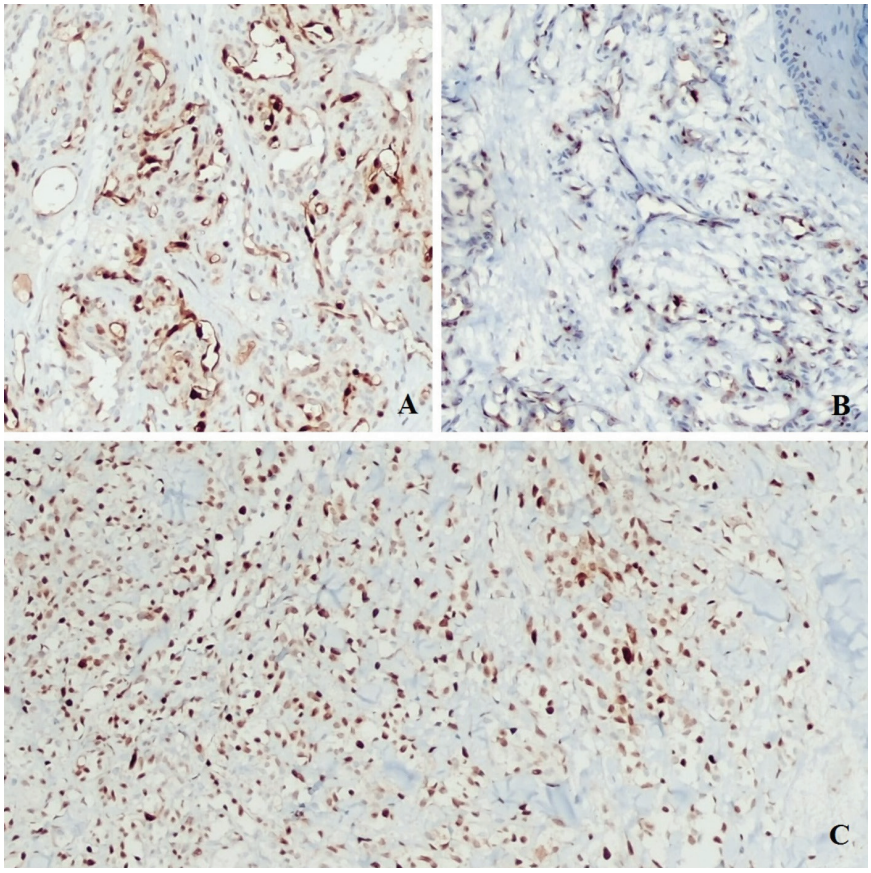

Figure 2. A: Hemangioma cyclin D1 high score x100, B: Hemangioendotelyoma, cyclin D1 low score x100, C: Angiosarcoma cyclin D1 high score x100

Table 3. Cyclin D1 expression in benign/malignant vascular and pericytic tumors

Diagnosis	Cyclin D1			Total (n)
	Negative (n)	Low score (n)	High score (n)	
Benign vascular tumors	3	4	10	17
Benign pericytic tumors	1	2	6	9
Malignant vascular tumors	1	6	4	11
Malignant pericytic tumors	0	1	0	1

pericytic tumors by affecting pericytic activity; however, we cannot draw a definitive conclusion in this regard since our study included only one malignant case of pericytic origin.

TAG72 is a high-molecular weight, tumor-associated glycoprotein known to be overexpressed in various carcinomas, including ovarian, breast, and colon tumors (15). The lack of TAG72 expression in normal adult tissues except secretory endometrial tissues has been proven (16). There are only a limited number of studies in the literature investigating TAG72 expression in angiosarcomas (17,18). These studies were conducted with a small sample size and the presence of TAG72 expression was shown in epithelioid angiosarcomas. However, we could not find any study investigating TAG72 expression in benign vascular tumors and pericytic tumors in the literature. Although staining was detected in the control tissue, we did not detect TAG72 expression in any of the benign or malignant tumors included in our study.

Study Limitations

The small sample size was the main limitation of our study. For this reason, statistical evaluation could not be made between subgroups. Further research is needed to evaluate the effect of estrogen on these tumors, especially by means of ER studies to be conducted in larger numbers of malignant glomus tumors, which are malignant pericytic tumors. Finally, we could not investigate pericytic cell loss using an IHC stain specific for pericytes in malignant tumors.

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CONCLUSION

We believe that our results on the comparison of cell cycle protein expressions in cutaneous vascular and pericytic tumors shed light for future studies to elucidate the pathogenesis of this group of tumors, which are rarely malignant.

Ethics Committee Approval: The study was approved by the Çukurova University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee (number: 102, date: 7 august 2020).

Informed Consent: Retrospective study.

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Tp-Te Interval and Tp-Te/QT Ratio Predict Coronary Artery Disease Severity in Non-ST Segment Elevation Acute Myocardial Infarction

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ABSTRACT

Objective: Novel electrocardiographic parameters such as Tp-Te interval and Tp-Te/QT ratio have been recently found to be associated with ischemia, and these markers' potential of predicting ventricular arrhythmias and mortality has been demonstrated in last decade. In this study, we aimed to investigate the relationship between the coronary artery disease severity and the Tp-Te interval, Tp-Te/QT, QT, and corrected QT interval in patients with non-ST segment elevation myocardial infarction (NSTEMI).

Methods: In this retrospective, single center cohort study we included 241 patients with NSTEMI. The recorded electrocardiograms (ECGs) and coronary angiograms were reviewed, and patients' demographics, laboratory values, ECG parameters, and the Syntax score (SS) were compared. The study population was divided into the following two groups: low SS (SS <22, n=158) and high SS (SS ≥22, n=83).

Results: The Tp-Te interval [79.2 (±12.2) ms vs. 111.6 (±11.5) ms, p<0.001], cTp-Te [87.7 (±14.5) ms vs. 116.6 (±15.8) ms, p<0.001], and Tp-Te/QT [0.210 (0.029) vs. 0.243 (0.028), p<0.001] were statistically significantly higher in the high SS group compared to the low SS group. In the multivariate regression analysis, the Tp-Te interval [odds ratio (OR): 1.464, confidence interval (CI): 1.118-1.918; p=0.006] and Tp-Te/QT ratio (OR: 0.210, CI: 0.215-0.562; p<0.001) were found to be the independent predictors of a high SS score. Tp-Te (rho =0.504, p<0.001) and Tp-Te/QT (rho =0.512, p<0.001) ratios were positively correlated with the SS.

Conclusion: This study demonstrates that prolonged Tp-Te interval and increased Tp-Te/QT ratio are independent predictors of high SS in patients with NSTEMI.

Keywords: Coronary artery disease severity, Tp-Te and Tp-Te/QT, novel ECG index, repolarisation parameters

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INTRODUCTION

Non-ST segment elevation myocardial infarction (NSTEMI) is an important cause of morbidity and mortality. Patients may present with transient chest pain as well as severe conditions such as malignant arrhythmia, syncope, and cardiac arrest. The severity of coronary artery disease (CAD), which has an important place in diffuse ischemia and necrosis, also plays a determinant role in the awareness of clinical progression (1). Diffuse and complex vessel involvement may be seen in daily clinical interventions for patients with NSTEMI. The Syntax score (SS), which has angiographic and clinical value, is currently used to make decisions about CAD severity and diffusiveness, possible complications, and long-term patient clinical outcome (2,3).

The Tp-Te interval is obtained from an electrocardiogram (ECG) by measuring the duration between the peak and termination of the T wave (4). QT and QTc reflect ventricular depolarization and repolarization, while Tp-Te has been proposed as a measure of transmural dispersion of repolarization (5). Recently, the Tp-Te interval has been identified as a reliable parameter to predict cardiac arrhythmias and sudden death (5). It has been shown that a prolonged Tp-Te interval and the Tp-Te/QT ratio, which are determined before revascularization during follow-up of patients experiencing ST-elevation myocardial infarction (STEMI), are associated with the incidence of cardiac events after discharge despite successful revascularization (6). Similarly, malignant arrhythmias such as ventricular tachycardia and fibrillation are more common in patients with a prolonged Tp-Te interval (7). In this study, we aimed to investigate if CAD severity could be estimated quickly and easily by measuring QT, cQT, Tp-Te, Tp-Te/QT in patients with NSTEMI.

METHODS

We retrospectively evaluated 277 patients who were hospitalized with the diagnosis of NSTEMI and underwent coronary angiography between October 2020 and February 2021. The diagnosis was based on the 2020 ESC NSTEMI-ACS guidelines (1). Patients with atrial fibrillation or atrial flutter or with an atrioventricular or intraventricular conduction defect; those with an implanted pacemaker, severe valvular disease, CAD, heart failure [ejection fraction (EF) <45%], renal failure, electrolyte disorders (hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia and hypermagnesemia) or hormone disorders (thyroid hormone disorder, adrenal hormone disorder); patients with a history of percutaneous intervention; or those receiving any anti-arrhythmic drug were excluded from the study. Thirty-six patients were excluded based on these criteria. Patients were treated according to the current guidelines. Patients were administered acetylsalicylic acid, clopidogrel, enoxaparin, beta-blockers, statins, and angiotensin-converting enzyme inhibitors unless they were contraindicated. This study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee (decision no: 87, date: May 26, 2021).

Study Parameters

Patients' age, smoking status, comorbidities (diabetes mellitus, hypertension), family history of CAD, anthropometrics (body mass index, kg/m^2), hip circumference, and waist circumference were recorded. Patients were considered as having diabetes mellitus if they were using blood glucose-lowering drugs or had a fasting plasma blood glucose level ≥126 mg/dL or postprandial blood glucose ≥200 mg/dL. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or taking any antihypertensive medication.

Coronary Angiography and Syntax Score

Coronary angiography images were evaluated by two experienced interventional cardiologists who were blinded to the study data. CAD severity was determined using SS. Scoring was determined for each vessel that was >1.5 mm in diameter and had >50% stenosis. SS was calculated as described on the website in detail. Parameters including age, creatinine clearance, peripheral artery disease, chronic obstructive pulmonary disease, left ventricular EF, left common CAD, gender, SS, procedure-related complications, and the patient's prognosis were recorded (8). Patients were grouped based on the SS values, as follows: SS ≤22 and SS ≥22.

Electrocardiography

Each patient underwent a 12-lead ECG using the same device (Phillips page writer TC30, USA) at admission. ECG images with 10-s recordings at a speed of 25 mm/s and standard voltage of 1.0 mV (10 mm) were analysed. The interval between the beginning of the QRS wave and the termination of the T wave was measured using the QT tangent DII method. The measurements were made at the V5-V6 derivation when the T wave could not be evaluated. The corrected QT interval was calculated using Bazett's formula. The Tp-Te interval was measured at the V5 superficial derivation from the peak to the T wave termination. The measurements were made at the V4 or V6 derivation if it could not be read at the V5 derivation due to artefacts or low voltage (<0.15 mV). If the downslope of the T wave was inconclusive, the T wave was extended by drawing a tangent to the steepest portion of the downslope until it crossed the isoelectric line. All measurements were made by a single cardiologist (E.I.) who was blinded to the patient's data and using semi-automated on-screen software (EP Calipers v1.13, EP Studios, Inc., USA).

Reproducibility

Intraclass correlation coefficients were calculated for the intraindividual and interobserver variation. ECGs from 10 randomly assigned patients were re-analysed by the same observer. For interobserver variability, the same patients and the same images were analysed by a second observer (E.S.). In case of disagreement, the ECGs were referred to a third observer. The

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intra-observer correlation coefficients for Tp-Te and QT were 0.907 and 0.950, and the inter-observer correlation coefficients were 0.880 and 0.936, respectively.

Statistical Analysis

The data were presented as mean (standard deviation) or median (interquartile range) for continuous variables and as the percentage (n) for categorical variables. The normality of distribution for continuous variables was determined using the Kolmogorov-Smirnov test. The participants were divided into two distinct groups according to the SS. The normally and non-normally distributed continuous variables were compared using a Student's t-test and the Mann-Whitney U test, respectively. The frequency of categorical variables in these groups was compared using the Pearson chi-square test. The parameters distinguishing the groups at a significant level (age, presence of diabetes, QTc, Tp-Te interval, and Tp-Te/QT) were included in binary and multiple regression analyses. Finally, the predictive performance of the serum Tp-Te interval and Tp-Te/QT ratio was determined using the receiver operating characteristics (ROC) analysis. We performed the Spearman analysis to determine the correlation between the SS and repolarization markers. A p-value of <0.05 was considered to be significant in all studies. The confidence interval (CI) was accepted as 95%. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was used for these assessments.

RESULTS

This study included 241 patients with a mean age of 62 (12) years. Patients were divided into groups based on the SS score as follows: low SS (SS <22; n=83) or high SS (SS ≥22; n=158). Baseline demographic and laboratory findings are shown in Table 1. No statistically significant difference was found between both groups in terms of gender (p=0.095), smoking (p=0.629), history of hypertension (p=0.625), dyslipidemia (p=0.755), and laboratory parameters (p>0.05). The high SS group was older, [57 (±10.43) vs. 70 (±8.87), p<0.001] and diabetes mellitus was more prevalent [75 (47%) vs. 54 (64%), p=0.014] compared to the low SS group.

In the ECG analysis, no statistically significant difference was observed in QT and corrected QT durations (p=0.272 and p=0.057, respectively) (Table 2). The Tp-Te interval [79.2 (±12.2) vs. 111.6 (±11.5), p<0.001], cTp-Te [87.7 (±14.5) vs. 116.6 (±15.8), p<0.001], and Tp-Te/QT [0.210 (0.029) vs. 0.243 (0.028), p<0.001] were statistically significantly higher in the high SS group compared to the low SS group (Figure 1).

Multivariate regression analysis was performed to determine the independent predictors. The Tp-Te interval [odds ratio (OR): 1.464, CI: 1.118-1.918; p=0.006] and Tp-Te/QT ratio (OR: 0.210, CI: 0.215-0.562; p<0.001) were found to be the independent predictors of a high SS score (Table 3). ROC analysis was performed to evaluate the predictive performance of Tp-Te and Tp-Te/QT levels to estimate a high SS. The ROC analyses showed that Tp-Te [area under the curve (AUC): 0.740, p<0.001] and Tp-Te/QT (AUC: 0.676, p<0.001) had a reasonable ability to predict severe CAD (Figure 2). The cut-off values for these parameters were 84.5 ms (with a sensitivity of 66.7% and specificity of 68.2%) and 0.219 (with a sensitivity of 72.01% and specificity of 65.2%), respectively. Spearman's analysis revealed that Tp-Te (rho =0.504, p<0.001) and Tp-Te/QT (rho =0.512, p<0.001) ratios were positively correlated with the SS (Figure 3).

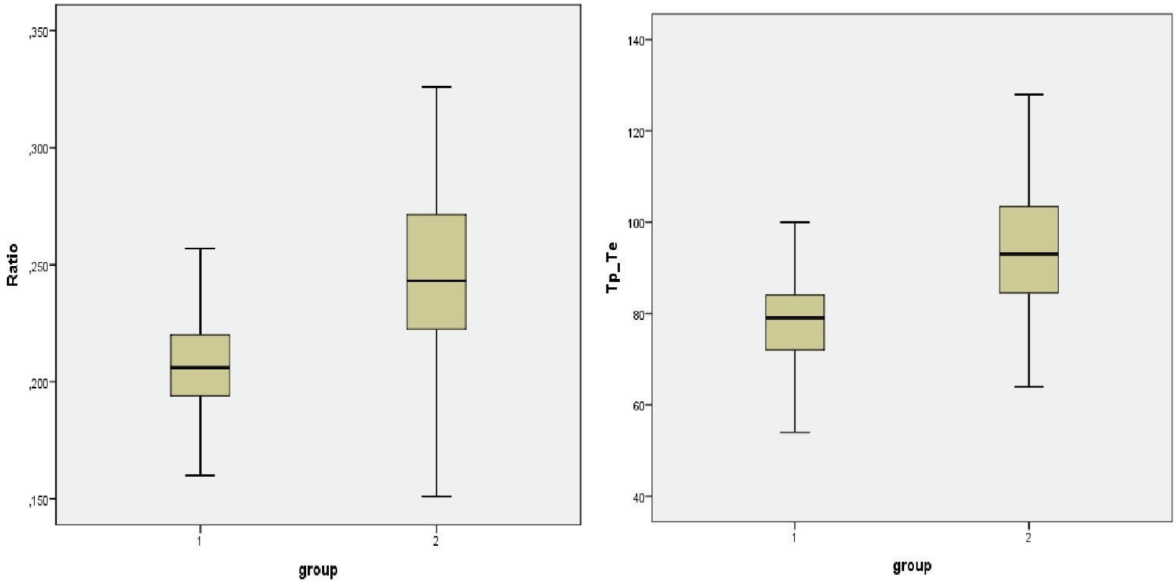

Figure 1. Comparison Tp-Te interval and Tp-Te/QT ratios between Syntax groups. Tp-Te interval and Tp-Te/QT ratio were significantly increased in the high Syntax score

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Table 1. Demographic and laboratory features of the study population

	Overall (n=241)	Low Syntax score (n=158)	High Syntax score (n=83)	p-value
Age; mean ± (SD)	62 (12)	57 (10.43)	70 (8.87)	<0.001
Women, n (%)	132 (54.7%)	84 (53.1%)	48 (58%)	0.095
Diabetes mellitus, n (%)	125 (51%)	75 (47%)	54 (64%)	0.014
Hypertension, n (%)	106 (43.9%)	67 (42.4%)	33 (42%)	0.351
Smoker, n (%)	141 (58.5%)	63 (57.3%)	51 (60.7%)	0.629
LVEF, %; Median [IQR]	65 [45-65]	65 [44-65]	60 [40-65]	0.216
WBC, 10^3/dL; Median [IQR]	9.3 [6.8-10.1]	9.5 [7.1-9.7]	9.3 [6.7-9.6]	0.786
Platelet, 10^3/dL; Median [IQR]	233 [197-283]	230 [200-276]	234 [205-280]	0.901
C-reactive protein, mg/dL; Median [IQR]	8.3 [3.5-8.9]	8.4 [3.3-8.9]	8.1 [3.1-8.7]	0.560
Creatinine, mg/dL; Median [IQR]	0.96 [0.75-1.2]	0.95 [0.73-1.1]	0.90 [0.65-1.4]	0.719
Sodium, mEq/dL; Median [IQR]	139.3 [132-143]	139 [133-144]	139.2 [130-144]	0.725
Potassium, mEq/dL; Median [IQR]	4.28 [4.0-4.4]	4.30 [4.1-4.46]	4.25 [4.05-4.5]	0.439
HDL-C, mg/dL; Median [IQR]	41.5 [35-45]	41 [37-44]	41.5 [37.5-44.6]	0.934
LDL-C, mg/dL; Median [IQR]	107.5 [95-117]	110 [97-115]	106[93-113]	0.313
Triglyceride, mg/dL; Median [IQR]	186 [145-225]	188 [150-230]	195 [166-268]	0.503
Total cholesterol, mg/dL; Median [IQR]	190.5 [167-255]	200 [173-278]	189 [166-251]	0.755
RCA dominance, n (%)	162 (67)	102 (64)	60 (72)	0.236
Three-vessel disease, n (%)	29 (12)	12 (7)	17 (20)	<0.001
LMCA disease, n (%)	15 (6.2)	3 (1.9)	12 (14)	<0.001
Heavy calcification, n (%)	44 (18)	15 (9)	29 (35)	0.006
Thrombus, n (%)	71 (29)	40 (25.3)	31 (25.3)	0.086
Lesion length >20 mm, n (%)	141 (58)	91(58)	50 (60)	0.092
Chronic total occlusion, n (%)	77 (32)	44 (27.8)	33 (39.7)	0.095
Severe tortuosity, n (%)	20 (8)	11 (7.5)	9 (10.8)	0.573

HDL-C: high-density lipoprotein-cholesterol, IQR: interquartile range, LDL-C: low-density lipoprotein-cholesterol, LMCA: left main coronary artery, LVEF: left ventricular ejection fraction, RCA: right coronary artery, WBC: white blood cell, SD: standard deviation

Table 2. Electrocardiographic measurements of the study population

	Low Syntax score (n=158)	High Syntax score (n=83)	p-value
QT duration, ms; Median [IQR]	382 [356-410]	387 [360-408]	0.272
Corrected QT duration, ms; Median [IQR]	413 [396-425]	425 [415-445]	0.057
Tp-Te interval, ms; Mean (SD)	79.2 (12.2)	111.6 (11.5)	<0.001
Corrected Tp-Te interval, ms; Mean (SD)	87.7 (14.5)	116.6 (15.8)	<0.001
Tp-Te/QT ratio; Mean (SD)	0.210 (0.029)	0.287 (0.028)	<0.001

IQR: interquartile range, SD: standard deviation

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Table 3. Multivariate predictors in high Syntax score

	Odds ratio	95% CI	p-value
Age	1.238	1.160-1.321	<0.001
Diabetes mellitus	0.610	0.277-1.343	0.219
Tp-Te interval	1.464	1.118-1.918	0.006
Corrected Tp-Te interval	0.978	0.907-1.054	0.557
Tp-Te/QT ratio	0.210	0.215-0.562	<0.001

CI: confidence interval

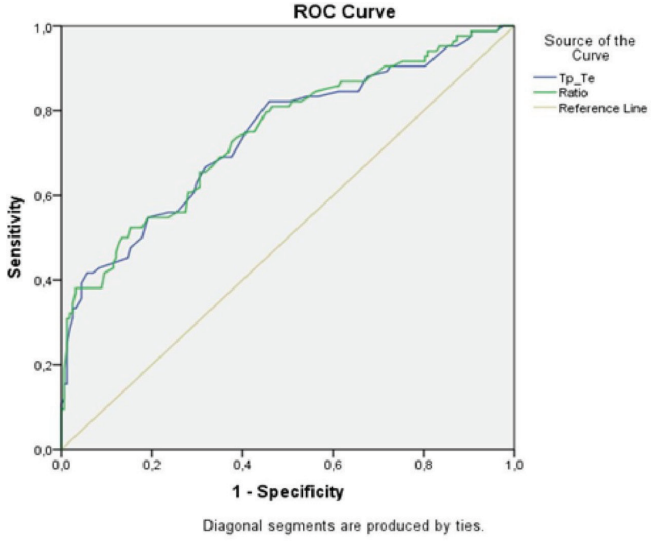

Figure 2. According to the ROC analyses, Tp-Te (AUC: 0.740, p<0.001), Tp-Te/QT (AUC: 0.676, p<0.001) had reasonable predictivity rates for severe coronary artery disease
ROC: receiver operating characteristics, AUC: area under the curve

DISCUSSION

In the present study, a strong correlation was found between the SS, which showed clinical and angiographic severity, and parameters that could be quickly studied using ECG results, such as the Tp-Te interval and Tp-Te/QT ratio.

The CAD severity is associated with the myocardial area that is at risk, increased plaque burden, degree of coronary stenosis, and multiple vessel disease. In addition, associated vasospasm affects perfusion disorder, and the ischemic area diffuseness (9).

The SS was calculated by combining previous anatomical and physiological scores. The SS helped determine the degree and localization of the stenosis in CAD as well as the size of the myocardial area that is supplied by the affected artery and perfusion disorder (10-12).

Perfusion disorder causes differences in the oxygen level and chemical and electrical changes between cells. The degree of exposure to ischemia varies from cell to cell. Metabolic and electromechanical differences between normal or less affected cells and cells with necrosis include alterations in the membrane potential and dispersion in ventricular repolarization (11,13,14).

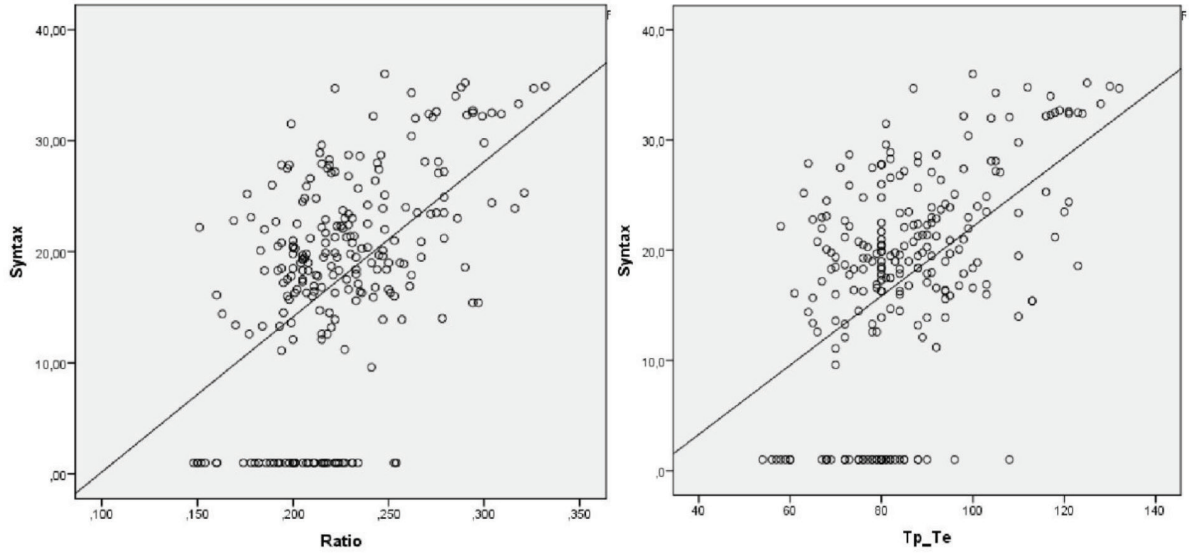

Figure 3. Correlation between the Syntax score and Tp-Te interval, Tp-Te/QT ratio. Tp-Te interval and Tp-Te/QT ratio were positively correlated with the Syntax scores

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This dispersion in the ventricular repolarization is shown on ECG as a prolongation of the Tp-Te interval.

Recent studies have revealed that changes in the Tp-Te interval and Tp-Te/QT ratio have a strong predictive value for estimating cardiac arrhythmias and cardiac events (15). Prolongation of the Tp-Te interval has been associated with sudden cardiac death and malignant arrhythmias in patients with ischemic and non-ischemic cardiomyopathies, congenital arrhythmia syndromes, and structural heart diseases (16). In a study in which patients were followed-up due to hypertrophic cardiomyopathy, the Tp-Te interval was reported to be a more specific marker than QT for predicting sudden cardiac death and ventricular fibrillation (17). In a study by Hetland et al. (18), a prolonged Tp-Te interval was found to be a predictor of ventricular arrhythmias, sudden cardiac death, and poor prognosis. Similarly, in a study by Özbek and Sökmen (19), an increased Tp-Te interval and Tp-Te/QT ratio measured before and after the intervention were associated with in-hospital and out-of-hospital mortality and the incidence of major cardiac events in patients with acute STEMI who were treated with percutaneous intervention or fibrinolytic therapy.

Besides ischemic conditions, Tp-Te and Tp-Te/QT parameters provide information about the disease severity and progression in patients with systemic inflammation (20). Current studies have proposed that the Tp-Te/QT ratio is a more accurate measurement for the distribution of ventricular repolarization compared to the QTd-cQTd duration (16-21). Although an elongation was found in the QT-cQT duration that showed general repolarization in cardiac ischemia, the parameters indicating dispersion in ventricular repolarization were more meaningful (22). Similarly, in our study, we found no significant difference in the QT-cQT duration.

In a recent study, the increase in the CAD spectrum from normal coronary arteries to acute coronary syndrome was found to be accompanied by a parallel prolongation in the Tp-e interval and increase in the Tp-e/QT and Tp-e/QTc ratios (23). Additionally, the same article stated that the CAD severity assessed using the SS was positively correlated with ventricular repolarization abnormalities in the Tp-e interval and the Tp-e/QT and Tp-e/QTc ratios, which was in agreement with our results. However, that article had only 121 patients with acute coronary syndrome (both STEMI and NSTEMI), and there was no grouping based on the SS. Our study adds value to the literature because it evaluates the relationship between ECG ventricular polarization parameters and CAD burden - assessed by the SS - in patients with NSTEMI.

Our hypothesis assumed that the increased CAD severity and diffuseness might lead to increases in ventricular repolarization duration and dispersion because it caused diffuse hypoxia and ischemia in the affected cardiac area and that this increase could be shown quickly and easily by measuring the following ECG parameters: QT, QTc, Tp-Te, and Tp-Te/QT. Results of our study showed that a high SS, which showed CAD severity and diffuseness were significantly correlated with Tp-Te and Tp-Te/QT, and the Tp-Te interval was an important predictor of a high SS.

Study Limitations

The retrospective and single-centre design of the study and the relatively small number of patients limited its strength. Previous studies focused on disease progression, and the patients were followed-up after revascularization. However, in the present study, the follow-up of the patients did not provide information about disease progression. Additionally, the semiautomatic nature of the ECG parameters rendered reaching standard values challenging. Although the sensitivity and specificity of the SS were high, intracoronary ultrasound, which offered information about coronary atherosclerosis, plaque burden, and thrombus burden, could not be used. Nevertheless, an extensive assessment of repolarization parameters may predict a more severe CAD burden in patients with NSTEMI.

CONCLUSION

This study indicates that calculating Tp-Te and Tp-Te/QT before an invasive procedure can provide information about CAD severity in hospitalized patients who are diagnosed as having NSTEMI. Prospective studies are needed to provide more information about the clinical outcomes in these risk-stratified patients according to the Tp-Te and Tp-Te/QT.

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee (no: KAEK/2021.05.87, date: May 26, 2021).

Informed Consent: Retrospective study.

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Is Pregabalin Addition to Infraclavicular Block, Effective in Distal Radius Surgery?

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ABSTRACT

Objective: Our study evaluated the effects of pregabalin (PR) on wrist function and chronic post-surgical pain (CPSP) following infraclavicular brachial plexus block for surgical repair of distal radius fractures.

Methods: Adult patients who underwent ultrasound-guided infraclavicular blockade (IB) plus surgical repair of a distal radius fracture between 2012 and 2017 were evaluated from hospital medical records retrospectively. Two different treatment protocols were used for postoperative analgesia. Group IB received standard analgesia protocol as 15 mg/kg IV paracetamol 4 times a day ±2 mg/kg IV tramadol and group PR received oral PR plus the standard protocol. The frequency of Tramadol use during hospital stay (TCHS) was also evaluated. The disability of the arm shoulder and hand (DASH) score and Mayo wrist score (MWS) were used to assess wrist function and a visual analog scale (VAS) was used for subjective pain severity assessment. CPSP and its neuropathic component were evaluated using the douleur neuropathique 4 (DN4) and Self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) pain scales.

Results: A total of 122 patients with a mean age 39.4±11.5 years were included in the study (group IB, n=62 and group PR, n=60). The TCHS of group PR was significantly lower than group IB (p=0.030). Better VAS, DASH and MWS scores were found in group PR at months 3, 6, and 12 (p=0.002, p=0.007, p=0.02 for VAS; p=0.01, p=0.01, p=0.01 for DASH; p<0.001, p<0.001, p=0.01 for MWS). The ratio of neuropathic pain according to DN4 and S-LANSS scores of group PR was also significantly lower than group IB at 6- and 12- month visits (p=0.21, p=0.023 for DN4; p=0.034, p=0.038 for S-LANSS).

Conclusion: The administration of low dose PR for 2 weeks following distal radius fracture surgery is beneficial for wrist function, chronic pain, and opioid consumption.

Keywords: Pregabalin, distal radius fracture, infraclavicular block, postoperative analgesia, chronic post-surgical pain, visual analog scale

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INTRODUCTION

Chronic post-surgical pain (CPSP) is defined as the pathological pain that persists beyond 2 months after surgery despite a lack of any local complications (1). Nearly one-third of patients present with varying degrees of CPSP at the end of 1st year following surgical procedures (1). Many factors are considered responsible for the development of CPSP. Among these, the presence of perioperative pain and its intensity are recognized as the most important patient-related factors. Effective control of perioperative and postoperative pain may improve patient satisfaction, early rehabilitation, and functional outcomes.

Brachial plexus block is a commonly preferred technique in surgical procedures of the upper extremity not only for improving intraoperative comfort by providing regional anesthesia but also for offering postoperative analgesia (2). This includes interscalene, infraclavicular, or supraclavicular blockade depending on the anatomic site to which it is applied. Major advantages of regional anesthesia include effective postoperative pain control, reduced need for opioids, and faster recovery after surgery than is offered by general anesthesia (3,4).

Pregabalin (PR) is a gabapentinoid derivative that has widespread use in the management of acute and chronic pains. PR reduces sensitization at peripheral neuron terminals and central neurons by decreasing calcium influx into the terminal presynaptic area (5). In addition, as PR decreases the need for opioids, opioid complications are decreased (6-8).

The aim of our study was to evaluate the effects of PR on wrist function and CPSP in patients who underwent infraclavicular brachial plexus block for surgical repair of distal radius fracture, retrospectively. We hypothesized that in distal radius fracture surgery, oral PR administration that was added to the infraclavicular block (IB) for multimodal pain control would decrease the risk of chronic pain by enhancing the effects of the block.

METHODS

Current study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

After obtaining approval from the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Ethics Committee (decision no: 807, date: 09.01.2018), adult patients (≥18 years) in whom surgical strategy was preferred due to the partial intra-articular distal radius fracture between 2012 and 2017 were evaluated from hospital medical records retrospectively. Written informed consent form was obtained from the patients.

Exclusion criteria included any chronic or acute rheumatologic condition; osteoporotic, open, or pathological fracture that occurred secondary to poly-trauma or high-impact trauma; known hypersensitivity to PR or local anesthetics, failed IB, not having regular clinical records or one-year follow up. One hundred twenty two of 194 patients met the inclusion criteria and were divided into two groups. Group IB received brachial block with a standard postoperative analgesia regimen and group PR received brachial block plus standard protocol and oral PR.

All patients underwent standard ultrasound-guided infraclavicular brachial plexus block (SonoSite M-Turbo; SonoSite, Bothell, WA, USA) by the anesthesiologist, as described in the literature (Figure 1) (9,10). After establishing infraclavicular blockade, the orthopedic surgeon performed an open reduction and internal fixation with a volar locking plate (Acumed, Andover, UK).

The standard postoperative analgesia in both groups consisted of paracetamol 15 mg/kg IV 4 times a day. In case of severe pain [a score >3 on a visual analog scale (VAS)], intravenous tramadol 2 mg/kg was added. Nonsteroidal anti-inflammatory drugs were avoided due to their union-delaying effects. Group PR was initially administered oral PR 300 mg 1 hour before the surgery and were then maintained on oral PR 25 mg BID (two times a day) for two weeks in addition to standard analgesia protocol.

Each patient wore a splint for 2 weeks after surgery to ensure proper wound healing. The splint was removed for therapy and put back on after the treatment. Wrist motion and strength exercises were started as soon as the sutures and splint were removed (11).

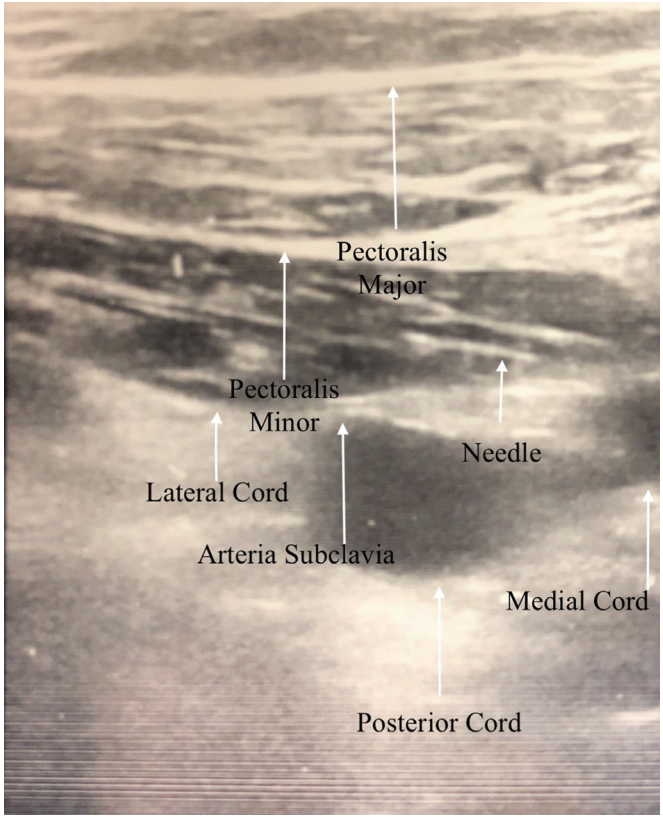

Figure 1. Section view of ultrasound-guided infraclavicular block

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The disability of the arm shoulder and hand (DASH), Mayo wrist score (MWS) and VAS scores were used to assess wrist functions and pain severity at 3-, 6- and 12-month visits. CPSP was evaluated by douleur neuropathique 4 (DN4) and the Self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) pain scales at 6- and 12- month visits. The DN4 questionnaire consists of 10 items used to identify pain of predominantly neuropathic origin based on the patient's current symptoms and signs and patients with score ≥ are considered to have neuropathic pain (12).

The S-LANSS scale consists of 7 items and patients with score ≥12 is considered to have neuropathic pain (13). Tramadol consumption of patients during hospital stay (TCHS) was also evaluated from the medical records.

Statistical Analysis

The statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS 24.0, SPSS Inc, Chicago, IL, USA). The Kolmogorov-Smirnov test was performed to assess the distribution of the data. Case numbers and percentages were used for demographic variables. Quantitative data were analyzed using independent sample t-test, and Pearson chi-square test was performed to compare the qualitative data. A p-value <0.05 was considered statistically significant.

RESULTS

Out of 194 patients with distal radius fractures, 122 patients who had regular follow-up were analyzed in the study, consisting of 62 patients in group IB and 60 patients in group PR. The mean age was 39.4±11.6 years (range: 23-58 years), and there were 78 women and 44 men. There was no significant difference regarding average follow-up between two groups (group IB 15.13±3.85, group PR 14.85±3.88; p=0.58). Ninety patients had B1 fractures, and 32 patients had B3 fractures according to the AO classification. While dominant side was affected in 72 patients, non-dominant side was affected in 50 patients (Table 1).

The incidence of TCHS, nausea and vomiting in Group PR were significantly lower than group IB (group PR=8.3%, Group IB=22.6%, p=0.030 for TCHS; group PR=1.7%, group IB=11.3%, p=0.032).

Table 1. Descriptive analyse of type and side of fracture, sex of patients

		n	%
Groups	Group A	62	50.8
	Group B	60	49.2
AO class	B1	90	73.8
	B3	32	26.2
Side	Dominant	72	59
	Non-dominant	50	41
Sex	Male	78	63.9
	Female	44	36.1

Group PR had statistically significantly lower VAS and DASH scores and higher MWS score than Group B at months 3, 6, and 12 months (VAS scores, p=0.002, p=0.007, and p=0.02; DASH scores p=0.001, p=0.001, and p=0.001; MWS p<0.001, p<0.001, p=0.010) respectively (Table 2).

The incidence of patients with CPSP regarding to DN4 and S-LANSS scales was significantly lower in group PR than group IB at 6 and 12 months (p=0.021 and p=0.023 for DN4; p=0.034 and p=0.038 for S-LANSS respectively) (Table 3).

DISCUSSION

The principal finding of the study was that adding PR to IB with distal radius surgery reduced the risk of CPSP and improved wrist functions. Only a few trials were carried out to evaluate the efficacy of PR in conjunction with IB for postoperative multimodal analgesia in upper extremity surgery. The prospective randomized trial performed by Cegin et al. (13) reported that administration of 150 mg PR before infraclavicular nerve block

Table 2. Evaluation of 3rd, 6th and 12th months DASH, VAS, and Mayo wrist scores

		Group B	Group P	p-value
		Mean ± SD	Mean ± SD	
DASH score (month)	3rd	21.04±3.36	15.73±2.16	0.001
	6th	16.07±2.13	11.12±1.86	0.001
	12th	9.78±1.89	5.52±1.72	0.001
VAS score (month)	3rd	2.87±0.95	2.03±1.09	0.002
	6th	1.74±0.72	1.16±0.87	0.007
	12th	0.94±0.57	0.56±0.62	0.02
Mayo wrist score (month)	3rd	25.48±2.82	31.13±4.45	0.001
	6th	66.06±3.87	77.48±3.43	0.001
	12th	90.37±4.73	92.43±3.86	0.010

DASH: disabilities of the arm, shoulder and hand, VAS: visual analogue scale, SD: standard deviation

Table 3. Incidence of CPSP assessed by S-LANSS and DN4 scores at 6th and 12th month's visit

S-LANSS	CPSP	Group IB		Group PR		p-value
		n	%	n	%	
6th month	-	45	58	50	83	0.031
	+	17	42	10	17	
12th month	-	46	74	56	93	0.044
	+	16	26	4	7	
DN4						
6th month	-	43	69.4	52	86.7	0.021
	+	19	30.6	8	3.3	
12th month	-	49	79	56	93.3	0.023
	+	13	21	4	6.7	

CPSP: chronic post-surgical pain, S-LANSS: Self-completed Leeds Assessment of Neuropathic Symptoms and Signs Pain scale, DN4: douleur neuropathique four

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reduced postoperative anxiety and increased the block quality in patients who underwent upper extremity bone surgery. In another study, Egol et al. (14) evaluated 187 patients who underwent open reduction volar plate fixation for distal radius fractures and compared general anesthesia and IB retrospectively. The IB had significantly more favorable effects on VAS and DASH scores within the first 6 months compared to that of general anesthesia (15). At 12 months, pain and DASH scores were similar between the two groups. The difference could be attributed to the fact that postoperative addition of PR might increase the efficacy of the block, prolong its duration of action, and increase the analgesic activity.

Chronic pain, unlike acute pain, is a compel-to-manage condition with a low likelihood of being adapted to it (16). Its underlying pathology is thought to involve disturbances in several mechanisms of the central and peripheral nervous systems such as neuroplasticity, pain modulation, and central sensitization (17). Acute pain after surgery is estimated to progress to chronic pain in 10-50% of patients, which makes prevention of transition to chronicity very critical (17). PR acts as a potent ligand for alpha 2-delta subunits of the voltage-gated calcium channels in the nervous system. Such action results in a reduction in the depolarization-induced influx of calcium, hence a reduction in the release of excitatory neurotransmitters including glutamate, noradrenaline, dopamine, and serotonin. The reduction of these neurotransmitters is suggested to lead to central desensitization (18). Owing to this effect on acute pain, perioperative use of PR may inhibit the evolution of acute pain to chronic pain (19). Several studies involving cases of distal radius fracture surgery reported the prevalence of chronic pain as high as 16-30% (20,21). In the current study, the incidence of one-year chronic pain assessed by the DN4 and S-LANSS scales were 21% and 19.4% in group IB, respectively, which were similar to the literature. However, the incidence of chronic pain according to DN4 and S-LANSS scales scores in group PR (DN4, 6.7%; S-LANNS, 6.7%) was significantly lower than group IB (p=0.038). This also suggests that PR administration for 2 weeks after IB is effective for reducing CPSP.

In orthopedic practice, the efficacy of PR has been studied in elective surgical procedures such as knee, hip arthroplasty, and carpal tunnel release. While these have suggested that PR reduce the need for opioids and thereby decrease the rates of side effects like nausea and vomiting, its efficacy for acute and chronic postoperative pain and function remains controversial. Buvanendran et al. (6) reported diminished postoperative chronic pain in patients who underwent total knee prosthesis surgical and received 300 mg PR in the preoperative period, followed by a 14-day course of 50-150 mg PR twice daily. On the other hand, YaDeau et al. (22) administered 50 to 150 mg PR twice daily starting just before surgery until the first postoperative day in patients undergoing total knee arthroplasty and reported no effect on postsurgical acute or chronic pain, opioid use, or adverse effects of analgesics such as increased sedation and patient dissatisfaction. While these two contradictory studies both used combined epidural regional anesthesia and postoperative patient-controlled epidural analgesia as a standard approach, Buvanendran et al. (6) administered infiltrative anesthesia for establishing multimodal analgesia as compared with femoral blockade used in the latter study (7-22). The different outcomes of these studies might be explained by the distinctive multimodal analgesia regimens, dosages, and duration of administration.

The effects of PR administration or type of anesthesia on opioid consumption and related side effects are controversial. For instance, Hadzic et al. (23) investigated the effects of IB vs general anesthesia added on perioperative infiltrative local analgesia in both groups who underwent hand and wrist surgery. Acetaminophen, IV Morphine and codeine were used for postoperative analgesia protocol. The rates of opioid consumption, nausea and vomiting were reported significantly higher in general anesthesia group (23). On the other hand, Rundgren et al. (24) and O'Neil et al. (25) also compared the anesthesia methods in the patients who underwent distal radius surgery and noted that the anesthesia method (regional or general) was not effective on total opioid consumption. In current study, we found that perioperative low dose PR addition to IB reduced the incidence of in-hospital opioid consumption, nausea, and vomiting. This combination seemed to be effective to lower opioid consumption and related side effects. Different results may depend on choosing different anesthesia techniques and multimodal analgesia methods.

Study Limitations

Our study had some limitations, including involvement of only a single center, having a retrospective design, and a lack of opioid doses and long-term outcomes.

CONCLUSION

Low dose PR administration for 2 weeks after IB reduced the incidence and severity of chronic pain and improved functional outcomes in patients who underwent open reduction and plate fixation for distal radius fracture. Thus, addition of PR to regional anesthesia seems to be an efficacious alternative for successful postoperative pain management following distal radius surgery.

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Clinical Research Ethics Committee (decision no: 807, date: 09.01.2018).

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The Importance of Screening Tests and Amniocentesis in Approach to Pregnant Women Over the Age of Thirty-Five

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ABSTRACT

Objective: Our goal was to evaluate the approach to the increased risk of fetal chromosomal anomaly in pregnant women over thirty-five years of age.

Methods: We retrospectively examined pregnant women over the age of 35 who underwent interventional procedures for fetal karyotype analysis in the Perinatology Clinic of University of Health Sciences Turkey Kanuni Sultan Süleyman Training and Research Hospital. Regardless of the indication for karyotype analysis, pregnant women over the age of 35 who underwent karyotype analysis were included in the study.

Results: Abnormal karyotype was detected in 76 (8.7%) of a total of 867 pregnant women examined in the study. Of 76 abnormal karyotypes, 51 were found as trisomy 21 (67.7%), 15 as trisomy 18 (21%), and 3 as trisomy 13 (4%). Three fetal karyotype analyzes revealed Turner syndrome (4%), 1 Klinefelter syndrome (1.3%), 2 mosaic trisomy 21 (2.6%) and 1 mosaic Turner syndrome (1.3%). In the patients who underwent interventional procedures primarily because of advanced maternal age, abnormal karyotype was detected in 6 (1.9%) of them. The rates of abnormal karyotype results for double, triple and quadruple tests were 6.4%, 1.9% and 5.8%, respectively.

Conclusion: The use of a triple test has no definite impact on the results of pregnant women of older age. When there is no fetal abnormality in the ultrasound, double and quadruple tests may be requested or since the fetal death rate is minimal in amniocentesis, it can be recommended directly without performing any screening tests in pregnant women with older age.

Keywords: Advanced maternal age, amniocentesis, Down sendrome, chromosomal anomaly, karyotype analysis

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INTRODUCTION

The rate of pregnancies in older ages is increasing day by day. Advanced maternal age is a significant risk factor of chromosomal abnormalities (1,2). While trisomy 21 is the most prevalent chromosomal abnormality in live births, other genetic abnormalities such as trisomy 13, trisomy 18, Turner syndrome, and Klinefelter syndrome may also be found in newborns (3,4). To determine the likelihood of a fetal chromosome abnormality, double test, triple test, or quad test may be used. In these tests, in addition to prenatal ultrasonography, certain hormone levels in the maternal blood with maternal age are considered when determining the risk ratio. Advanced maternal age also causes high-risk screening test results by causing changes in biochemical parameters that increase the likelihood of chromosomal abnormalities (5). Tests and/or fetal ultrasonographic evaluation will identify pregnancies with a high probability of chromosomal anomalies (6). In high-risk pregnancies, a fetal chromosome analysis is recommended.

The interventional methods used to determine chromosomes differ depending on the week of pregnancy. Between 11-14 weeks of gestation, chorionic villus sampling (CVS); between 16-20 weeks, amniocentesis and >20 weeks, cordocentesis can be performed. Amniocentesis is the most common procedure (7). While interventional procedures are often used to diagnose chromosomal abnormalities, fetal DNA analysis [non-invasive prenatal test (NIPT)] in maternal blood has gained popularity in recent years. This non-invasive procedure is not widely performed in our country because it is a costly test with no government warranty. Since it cannot be used to make a conclusive diagnosis, it can be used as a powerful screening tool for the time being.

METHODS

Ethical approval for our study was obtained from İstanbul Esenyurt University, dated 17.02.2022 and numbered 2022/02-14. We retrospectively examined pregnant women over the age of 35 who underwent interventional procedures for fetal karyotype analysis in the Perinatology Clinic of University of Health Sciences Turkey Kanuni Sultan Süleyman Training and Research Hospital between 2014-2017. The study protocol was reviewed and approved by the local ethics committee. The patients' gestational weeks ranged from 12 to 22 weeks. The research involved pregnant women who underwent karyotype analysis only because they were over 35 years old, had a fetal anomaly on ultrasound examination, had an elevated risk (>1/250) in their double, triple, or quadruple test results or had a history of fetal chromosomal anomaly in their previous pregnancies. Patients who were pregnant to twins and who had a positive fetal DNA (cell-free DNA) analysis for chromosomal abnormalities were excluded from the study.

The research involved a total of 867 patients. Amniocentesis was performed in 685 patients, CVS in 148, and cordocentesis in 34. The interventional procedures were carried out by perinatology specialists.

Statistical Analysis

Frequency analysis was used to characterize nominal and ordinal parameters, frequency and percentage were used to describe categorical data.

RESULTS

In our research, 867 patients were included. There were 308 patients who underwent interventional procedures primarily because of advanced maternal age (Table 1). Abnormal karyotype was detected in 6 (1.9%) of them. In the group with advanced maternal age and serum biochemical screening tests; 1) Double test: Karyotype analysis was performed in 132 patients and 9 (6.4%) had abnormal karyotype. 2) Triple test: Abnormal karyotype was observed in 2 (1.9%) of 105 patients. 3) Quadruple test: Trisomy 21 was observed in 6 of 103 patients (5.8%).

Karyotype analysis was performed in 180 patients due to advanced maternal age and pathological ultrasonographic findings. Normal karyotype was found in 128 (71.2%) and abnormal karyotype was determined in 52 (28.8%) patients. In 24 patients with advanced maternal age and a birth history with chromosomal anomalies in their previous pregnancy, trisomy 21 was detected in only 1 (4.2%) patient. Abnormal karyotype was detected in 76 (8.7%) of a total of 867 pregnant women examined in the study and the distribution of chromosomal abnormalities was summarized in Table 2.

DISCUSSION

As the number of advanced maternal age pregnancies increases, screening and diagnosis of fetal chromosomal abnormalities have become more important. The prevalence of fetal chromosome abnormalities increases with the increase of maternal age (2).

Table 1. The distribution of karyotype analysis based on indications

Karyotype analysis indication	Normal karyotype	Abnormal karyotype	Total
Only advanced age	308 (98.1%)	6 (1.9%)	314
Advanced age + double test	132 (93.6%)	9 (6.4%)	141
Advanced age + tripple test	103 (98.1%)	2 (1.9%)	105
Advanced age + quadruple test	97 (94.2%)	6 (5.8%)	103
Advanced age + pathological ultrasound finding	128 (71.2%)	52 (28.8%)	180
Advanced age + history of chromosomal anomalies in previous pregnancy	23 (95.8%)	1 (4.2%)	24
Total	791 (91.3%)	76 (8.7%)	867

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Table 2. The result of karyotype analysis

Chromosomal anomaly	Number
Trisomy 21	51 (67.1%)
Trisomy 18	15 (19.7%)
Trisomy 13	3 (4%)
Turner syndrome	3 (4%)
Klinefelter syndrome	1 (1.3%)
Mosaic trisomy 21	2 (2.6%)
Mosaic turner send	1 (1.3%)
Total	76 (100%)

Chromosome abnormalities are detected by invasive methods after genetic counseling in pregnant women, which are required according to the results of double, triple, and quadruple tests, in which different biochemical analytes are used. The most common invasive test is amniocentesis (7).

The most important risk factor for chromosome number abnormalities is maternal age. The indications for interventional procedures that we conduct are similar to those reported in the literature (8). Apart from positive prenatal screening tests, the most important reason for amniocentesis is advanced maternal age (9,10). Advanced maternal age was shown to be the most common indication for amniocentesis in a sample of 6,041 pregnant women, and positive serum screening tests were found to be the second most common cause (11).

The incidence of chromosomal anomalies in amniocentesis, which is the most frequently performed interventional procedure, has been given between 1-6% in the ACOG guideline and in the literature (8,10,12). In our study group, this rate was found to be 8.7%. We believe that this elevated incidence was attributed to pregnant women referred to our clinic after a fetal anomaly was detected in an ultrasound scan. Excluding the pregnant women with fetal anomaly on ultrasound, abnormal karyotype was observed in 24 (3.5%) of the remaining 687 pregnant women, which was similar to the literature.

In our study, we applied interventional procedures to 308 pregnant women only because of advanced maternal age and we detected chromosome anomalies in 6 of them (1.9%). Xiao et al. (13) found the rate of detecting chromosomal abnormality as 2.79% in older pregnant women and 2.23% in those with biochemical marker abnormalities in maternal serum and showed that advanced maternal age was an independent indication for amniocentesis. In another study, Zhu et al. (14) found that the incidence of trisomy 21 increased significantly in women aged 39 and over. According to the literature, fetal abnormalities identified by prenatal ultrasonography have the highest positive predictive value for identifying chromosomal anomalies in amniocentesis (6). Danisman et al. (8) found the rate of chromosomal abnormality to be 10.5% in this group. In another study by Kagan et al. (5), chromosome anomalies were found in 15% of fetuses diagnosed as having congenital abnormality by prenatal ultrasonography.

Our chromosomal anomaly prevalence was 28.8% in pregnant women with advanced age in whom pathological ultrasonography findings were observed in ultrasonography. We think our rate is high because, as a third-step referral clinic, we observe a greater number of fetal abnormalities on ultrasound than the national average. Furthermore, the majority of patients referred due to early fetal ultrasound findings such as cystic hygroma, omphalocele, and holoprosencephaly, which are frequently associated with chromosomal defects, increases our chromosomal anomaly rate.

Chromosomal abnormality was detected as 4.2% in patients who underwent interventional procedures due to fetal anomaly in previous pregnancy. In the literature, this rate has been given as 3.2% (8). In our study, fetal chromosomal abnormality was detected in only 1 of 24 pregnant women who had a birth history with chromosome anomaly in their previous pregnancy. The results were similar but for this group the number of patients was low in our study.

Detection rates will increase with the addition of ultrasonography to maternal serum biochemical markers and the use of ultrasonographic markers such as nasal bone evaluation (15). As a result, we evaluated advanced maternal age in our sample using double, triple, and quadruple tests separately. The rate of fetal chromosome anomaly was 6.4% in the double test group and 5.8% in the quadruple test group. Fetal chromosome anomaly was detected in 2 of 105 patients with a rate of 1.9% who were evaluated as high risk by examining the triple test. This was similar to the rate of the patients without any screening test. Therefore, triple test appears to be a poor test in screening for chromosomal abnormalities in advanced maternal age. In our study, as in the literature, our rate of detecting chromosomal anomalies increased in the double test in which nasal bone and nuchal translucency were evaluated compared to the triple and quadruple tests.

Trisomy 21 is the most common chromosomal anomaly among live births (3,4,16). Ocak et al. (11) found the frequency of trisomy 21 as 46% among fetal chromosome abnormalities after amniocentesis. In an analysis performed on 13,795 pregnant women, trisomy 21 was the most common, with 35.6%, among chromosomal anomalies after fetal karyotype analysis (17). In our study, among the abnormal karyotypes, Trisomy 21 was found to be the most common with a rate of 67.1%.

In the case of pregnant women with advanced maternal age who underwent both maternal serum test and NIPT, the rate of fetal chromosomal abnormality was shown to be higher than those who received only maternal serum test screening or fetal DNA screening in maternal blood (18). We did not incorporate patients who were admitted to our clinic with a positive NIPT test. In our country NIPT is not widely used as it is not paid for by insurances due to its cost. In the future, fetal chromosome determination will be made easier and with less risk in case of widespread use.

In the study of Bornstein et al. (19), the benefit of genetic amniocentesis for the only advanced maternal age, far outweighed the risk of fetal death associated with amniocentesis. In another study, performing invasive intervention only because of

advanced maternal age was found to be more costly and the risk of fetal demise was higher, therefore, the authors recommended to use maternal serum analytes and ultrasound with advanced maternal age (20). In our study, in 180 patients with pathology on ultrasound, 5 fetal demises were observed after the procedure. Three of these 5 fetuses had large cystic hygroma and 2 had hydrops fetalis. However, no fetal loss due to invasive procedures was observed in 687 pregnant women whose fetuses appeared normal on ultrasound.

Study Limitations

Our clinic is a tertiary center where fetuses with pathological ultrasound findings are frequently referred, therefore the results may be different according to a population-based study.

CONCLUSION

In conclusion the risk of chromosomal abnormalities for fetuses with a high risk of Down syndrome in the triple test was found to be comparable to that of pregnant women who received regular amniocentesis due to advanced age without any test. Therefore, it does not seem reasonable to advise triple testing for pregnant women of old age. Instead, double, or quadruple test screening may be performed, or direct amniocentesis may be recommended as the risk of miscarriage is very low.

Ethics Committee Approval: Ethical approval for our study was obtained from İstanbul Esenyurt University, dated 17.02.2022 and numbered 2022/02-14.

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