The relationship between inflammatory markers and mortality in patients undergoing proximal femoral nail fixation for intertrochanteric femur fractures

İntertrokanterik kırık nedeniyle proksimal femur çivisi uygulanan hastalarda inflamatuar indekslerle mortalitenin ilişkisi

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Abstract

Aim: This study aimed to investigate the predictability of mortality based on biomarkers measured using complete blood count in geriatric patients who underwent proximal femoral nail fixation for intertrochanteric femur fractures.

Methods: We included in this retrospective study 247 patients who had undergone proximal femoral nailing due to osteoporotic intertrochanteric femur fracture. The patients were divided into two groups according to 1-year mortality outcome: group A, survivors (n=162), and group B, deceased patients (n=85). Preoperative demographic information, the number of days until surgery, C-reactive protein (CRP) level, hemoglobin level, platelet-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammatory index (SII) were recorded.

Results: No statistically significant differences were found between the groups in terms of sex, type of anesthesia, leukocyte count, and neutrophil level ($p>0.05$), but statistically significant differences were found in age, number of days until surgery, CRP level, hemoglobin level, lymphocyte count, and platelet count ($p<0.05$). The NLR significantly increased in the group with mortality ($p<0.05$), while SII and PLR yielded similar results in both groups ($p>0.05$). In the receiver-operating characteristic curve analysis, the NLR, SII, and PLR areas under the curve for mortality were 0.598, 0.549, and 0.569, respectively.

Conclusion: None of the biomarkers investigated in this study showed an ability to distinguish patients with higher mortality risks. Therefore, these biomarkers may be recommended not as predictive of mortality but as supportive parameters for determining patients' overall clinical statuses.

Keywords: Biomarkers; inflammation; intertrochanteric fractures; mortality determinants

Öz

Amaç: Bu çalışmanın amacı, intertrokanterik femur kırıkları sonrası proksimal femoral çivileme uygulanan geriatrik hastalarda tam kan sayımındaki biyobelirteçlerle mortalite öngörülebilirliğini araştırmaktır.

Yöntem: Osteoporotik intertrokanterik femur kırığı nedeniyle proksimal femoral çivileme uygulanan 247 hasta çalışmamıza dahil edildi. Hastalar iki gruba ayrıldı. Grup A, ameliyat sonrası birinci yılı sağ kalan hastaları (n=162), Grup B ise aynı dönemde ölen hastaları içeriyordu (n=85). Preoperatif demografik bilgiler, ameliyata kadar geçen gün sayısı, C-reaktif protein (CRP), hemoglobin, platelet-lenfosit oranı (PLR), nötrofil-lenfosit oranı (NLR) ve sistemik immün-inflamatuar indeks (SII) incelendi.

Bulgular: Cinsiyet, anestezi türü, lökosit ve nötrofil seviyeleri açısından gruplar arasında istatistiksel olarak anlamlı bir fark bulunmamakla birlikte ($p>0.05$), yaş, ameliyata kadar geçen gün sayısı, CRP, hemoglobin, lenfosit ve trombosit seviyeleri açısından gruplar arası anlamlı fark bulunmuştur ($p<0.05$). NLR seviyesi, mortalite gösteren Grup B'de anlamlı olarak yüksek iken ($p<0.05$), SII ve PLR her iki grupta benzer sonuçlar verdi ($p>0.05$). ROC analizinde, mortalite için NLR, SII ve PLR için eğri altında kalan alan değerleri sırasıyla 0.598, 0.549 ve 0.569 idi.

Sonuçlar: Bu çalışmada, mortalite riski yüksek olan hastaları ayırt etme imkânı veren bir biyobelirteç bulunamamıştır. Bu nedenle, bu biyobelirteçlerin mortalite öngörülebilirliği için değil de, hastanın genel klinik durumu içinde destekleyici parametreler olarak kullanılabileceği önerilmelidir.

Anahtar Sözcükler: Biyobelirteçler; inflamasyon; intertrokanterik kırıklar; ölüm oranı belirleyicileri

Received/*Geliş* : 25.09.2023
Accepted/*Kabul*: 13.11.2023

DOI: 10.21673/anadoluklin.1363996

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INTRODUCTION

With the increase in the elderly population due to the extension of life expectancy, the incidence of osteoporotic hip fractures has also been increasing. In 2000, approximately 1.6 million hip fractures occurred worldwide, and this number is expected to increase to 4.5 million by 2050 (1,2). The morbidity and mortality risks associated with these fractures are public health concerns. Recent publications highlight 1-year mortality rates of up to 33% (3). This high mortality rate may be explained by the fact that elderly individuals with low physiological reserves and comorbidities are subjected to trauma due to the fracture itself and the metabolic burden imposed by the major surgery required to treat it (4,5). Therefore, this indicates the importance of identifying patients at higher risk of developing complications.

Intertrochanteric femur fracture, a subtype of osteoporotic hip fracture, is not only the most common subtype but also one of the most common fractures, accounting for approximately 10% of all fractures (6). In recent studies, certain biomarkers measured using complete blood count after intertrochanteric hip fractures have been used to predict postoperative mortality (7-11). Measurable biomarkers such as platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) are recommended for assessing stress levels at hospital admission and during early and late postoperative periods to predict mortality (12-15).

Elevated PLR has been significantly associated with all-cause mortality in the general population, with a more pronounced effect in the elderly population (16). The NLR is used to predict postoperative mortality risk in abdominal, cardiovascular, and oncological surgeries (5,17,18). The SII was initially described in 2014 to predict postoperative prognosis in patients with hepatocellular carcinoma and has since been used to determine the prognoses of other malignancies, coronary artery diseases, stroke, and various diseases (19-22).

In most previous studies, the mortality rate among patients with femoral fractures and the parameters in complete blood count were compared, regardless of subtype of fracture and surgical method. The aim of this study was to investigate the predictability of mortality based on parameters measured using complete blood count in geriatric patients who underwent proximal femoral nail fixation for intertrochanteric femur fractures. The primary outcome of this study was to determine the relationship of 1-year mortality with biomarkers in patients who had undergone proximal femoral nail surgery. The secondary outcome was to examine the effects of age, sex, time until surgery, and type of anesthesia on mortality.

MATERIALS AND METHODS

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Giresun Training and Research Hospital (date: 19.06.2023, decision no: 08). In our hospital's database, we retrospectively searched for patients who had undergone surgery between January 1, 2020, and June 30, 2022. As a result, we found that 277 patients had undergone proximal femoral nailing (PFN) surgery in our hospital. Patients aged over 60 years who had undergone PFN due to osteoporotic intertrochanteric femur fractures were included in the study. Patients who had malignancies, had received chemotherapy or radiotherapy, had pathological or open fractures, had previously undergone surgery on the same or opposite hip, had undergone revision surgery due to implant failure, had multitrauma or polytrauma, and had comorbidities that could cause elevated inflammatory parameters, such as systemic infections or inflammatory diseases, were excluded from the study. Considering these criteria, 30 patients were excluded from the study (Figure 1). This resulted in a total of 247 included patients, of whom 74 were male and 173 were female. Their ages ranged from 60 to 103 years (mean ± standart deviation (SD), 82.3 ±10.1 years).

All patients' sex, age, number of days until surgery, type of anesthesia, and 1-year mortality status were noted. Hemoglobin level (g/dL), C-reactive protein (CRP) level (mg/L), leukocyte count (10^9/L), neutrophil count (10^9/L), lymphocyte count (10^9/L), and platelet count (10^9/L) were assessed in blood samples taken immediately after hospital admission (Table 1). The PLR was calculated by dividing platelet count by the lymphocyte count, and the NLR was calculated by dividing the neutrophil count by the lymphocyte count. The SII was calculated using the formula platelet x neutrophil count/lymphocyte count.

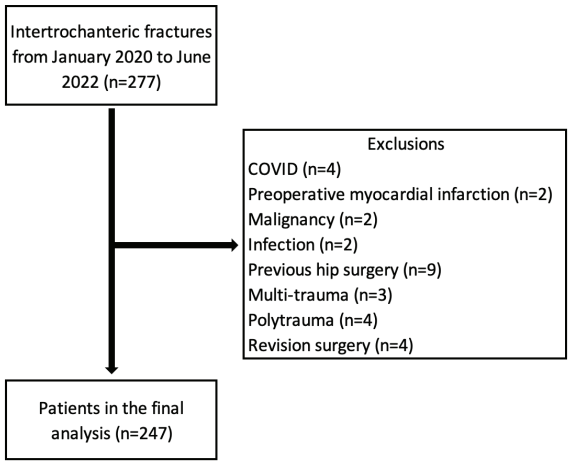

Figure 1. Flow diagram of study participants.

Surgical Procedure and Follow-up

In this study, the included patients underwent closed reduction in the lateral decubitus position followed by PFN by the same team. During their hospital stays, all patients received thromboembolism prophylaxis in accordance with the standard procedures. Radiographic follow-ups for fracture union and implant failure were conducted at the second, fourth, and sixth weeks; third and sixth months, and the first year after surgery.

Statistical Analyses

Statistical Package for the Social Sciences software for Windows, version 11.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Descriptive statistics, including mean, standard deviation, median, minimum, maximum, count, and percentage, were provided. To evaluate whether PLR, NLR, and SII can be used as predictors of mortality, receiver-operating characteristic (ROC) curves were used to create a threshold value. To determine the significance level, the Pearson chi-square test was used for two-variable criteria, and the Mann-Whitney *U* test was used for multivariable criteria. The statistical significance level was set at $p<0.05$.

RESULTS

When the patients were divided into two groups according to 1-year mortality results, group A consisted of 162 surviving patients (66%), and group B consisted of 85 deceased patients (34%). When the groups were compared, age, the number of days until surgery, and CRP level were statistically significantly higher in group B (p=0.001). The hemoglobin level, lymphocyte count, and platelet count were significantly lower in group B (p=0.001). No significant differences were found between the two groups in terms of sex, type of anesthesia, leukocyte count, and neutrophil level ($p>0.05$; Table 2).

Regarding the biomarkers, the NLR level was significantly higher in the group with mortality (group B; $p<0.05$), while SII and PLR yielded similar results in both groups ($p>0.05$; Table 2). The threshold values for SII and PLR were 889.8 and 152.8, respectively, which were statistically insignificant in relation to mortality (p=0.20 and p=0.076). For NLR, the threshold value was 7.4, and its association with mortality was statistically significant, although the area under the curve (AUC) failed (p=0.009, AUC: 0.598, sensitivity: 61.1%, specificity: 56.1%; Figure 2).

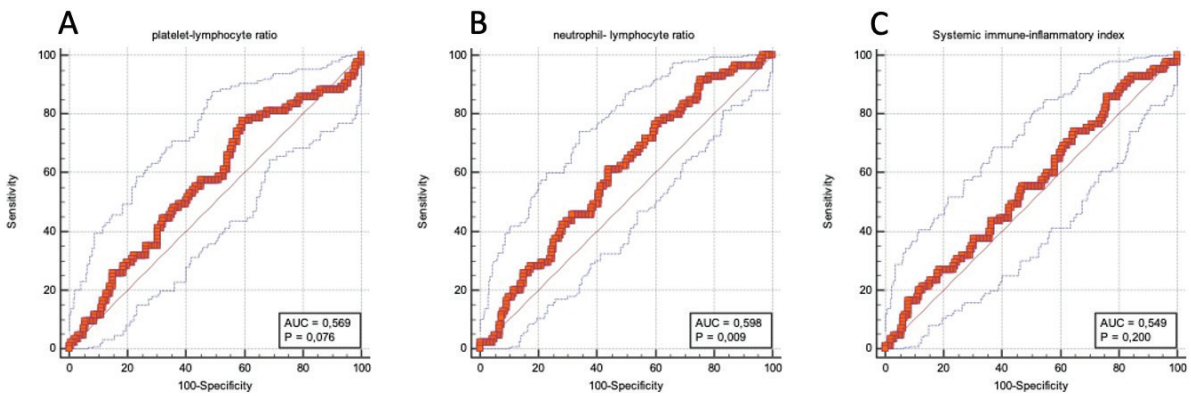

Figure 2. ROC curve of platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), systemic immune-inflammatory index for predicting 1-year survival.

Table 1. Statistical data of all patients

Variables			Number (n=247)
Age		mean (SD)	82,3 (10,1)
Sex	Female	n (%)	173 (70)
	Male	n (%)	74 (30)
Anesthesia type	Spinal	n (%)	221 (89)
	General	n (%)	26 (11)
Mortality	Yes	n (%)	85 (34)
	No	n (%)	162 (66)
Time to surgery (days)		n (%)	1,99 (1,24)
Hemoglobin (g/dl)		mean (SD)	11,5 (1,78)
CRP[a] (mg/L)		mean (SD)	23,81 (38,5)
Leukocyte (×109/L)		mean (SD)	11,01 (3,54)
Neutrophil (×109/L)		mean (SD)	8,93 (3,52)
Lymphocyte (×109/L)		mean (SD)	1,41 (0,77)
Platelet (×109/L)		mean (SD)	242,15 (73,31)
NLR[b] (×109/L)		mean (SD)	8,23 (5,64)
PLR[c] (×109/L)		mean (SD)	208,58 (108,56)
SII[d] (×109/L)		mean (SD)	1964,32 (1468,23)

n: Number, SD: Standard deviation, a: C-reactive protein; b: neutrophil-lymphocyte ratio; c: platelet-lymphocyte ratio; d: systemic immune-inflammatory index

Table 2. Statistical data of patients according to mortality

Variables	Group A (n:162)		Group B (n:85)		p value
	mean±SD	median	mean±SD	Median	
Age	79.9 (10.1)	82	87.3 (8.1)	89	<0.001
Time to surgery (days)	1.8 (1.1)	1	2.3 (1.3)	2	<0.001
Hemoglobin (g/dl)	11.7 (1.7)	11.7	11.1 (1.8)	11.3	0.009
CRP[a] (mg/L)	16.4 (28.8)	4.7	37.8 (49.5)	14.9	<0.001
Leukocyte (×109/L)	11.0 (3.6)	10.9	11.1 (3.5)	10.8	0.966
Neutrophil (×109/L)	8.8 (3.6)	8.7	9.1 (3.3)	9.0	0.534
Lymphocyte (×109/L)	1.5 (0.7)	1.3	1.3 (0.8)	1.1	0.001
Platelet (×109/L)	250.4 (70.7)	240.5	226.4 (76)	222	0.009
NLR[b] (×109/L)	7.72 (5.5)	6.9	9.2 (5.8)	7.9	0.012
PLR[c] (×109/L)	201.2 (101.7)	172.0	222.7 (119.9)	195.1	0.075
SII[d] (×109/L)	1875 (1388)	1563.14	2134.4 (1603.5)	1661.5	0.202

n: Number, SD: Standard deviation, a: C-reactive protein; b: neutrophil-lymphocyte ratio; c: platelet-lymphocyte ratio; d: systemic immune-inflammatory index

DISCUSSION AND CONCLUSION

In this study, the study groups were similar in terms of sex and type of anesthesia. However, age, the number of days until surgery, and CRP level were statistically significantly higher in the non-survivors (group B). When we analyzed the biomarkers in relation to the mortality rates, the NLR was significantly higher in group B. The SII and PLR were similar between the two groups.

Systemic inflammation is characterized by neutrophilia, lymphopenia, and thrombocytosis in peripheral blood. Leukocytes form a physiological response to stress that manifests as an increase in neutrophils and a decrease in lymphocytes. Although the primary function of platelets is in hemostasis and the coagula-

tion system, chronic inflammatory processes lead to increased platelet counts due to the proliferation of the megakaryocyte lineage (23).

However, the numerical values of blood cells can be directly influenced by the psychological, pathological, and physical factors present during patient blood sampling. Therefore, in the assessment of systemic inflammation, the use of the ratios of blood components is considered more effective than the use of their absolute numerical values. Various biomarkers that can be easily calculated with simple mathematical formulas have been identified for this purpose. These biomarkers are widely accepted as good indicators of systemic inflammatory response and are thus recommended for the diagnosis, monitoring, and risk assessment of various diseases, including cancer (17,18,24). Parameters such as the NLR, PLR, and SII are used to predict the severity and mortality of various inflammatory conditions, especially cancer (25,26). Over time, these biomarkers have also begun to be used in orthopedic disorders (7,8,10,12-15,27).

Wang et al. found that among patients with hip fractures, those with high PLRs (≥189) had an 18% higher 1-year mortality rate than those with lower PLRs (<189) (11). In our study, the PLR threshold value was 152. When comparing the survivors and nonsurvivors according to threshold values, no significant association was found between PLR and mortality.

In elderly patients undergoing orthopedic surgery, NLR values >8.5 were associated with postoperative myocardial infarction, infection, and early mortality (28). Özbek et al. also found that among patients undergoing PFN due to pertrochanteric fractures, those with high NLRs (≥5.2) had significantly higher 1-year mortality rates than those with lower NLRs (<5.2) (AUC: 0.861, sensitivity: 84.6%, specificity: 78.6%) (8). In our study, when comparing NLRs based on a threshold value of 7.4, the performance of the data for interpreting the results was poor (AUC: 0.598, sensitivity: 61.1%, specificity: 56.1%).

SII might be a better parameter than NLR and PLR in representing the balance of these roles in the systemic inflammation cycle (29). Wang et al. found that in patients with osteoporotic hip fractures, each 100-unit increase in SII was associated with an 8% increase in 1-year mortality (15). Bala also demonstrated that elevated SII in patients undergoing hemiarthroplasty for hip fractures was associated with mortality (27). However, in our study, no significant association was found between SII and mortality.

Considering all these factors, we think inflammatory biomarkers are not practical to use for predicting mortality. Studies have reported different threshold values for mortality biomarkers. As biomarkers have been examined in various clinical conditions, their threshold values differ. Although many studies have shown the relationship between mortality and these biomarkers, the discrepant cutoff values in each clinical situation make these biomarkers impractical to apply in clinical practice.

A study based on the Norwegian Hip Fracture Register with data from 73,000 patients found that mortality was significantly higher in patients who underwent operation after the first 48 hours (30). Similarly, in our study, mortality increased as waiting time until surgery increased. Moreover, consistent with the literature, the elevated CRP levels and decreased lymphocyte counts in our study were more pronounced in the group with mortality (31,32).

A study that examined the effect of preoperative hemoglobin level on mortality in patients with hip fractures found that as hemoglobin levels decreased, the risk of 30-day mortality increased (33). Another study that involved approximately 72,000 patients with hip fractures found that as platelet counts decreased, mortality increased (34). In our study, both hemoglobin levels and platelet counts were lower in the group with mortality.

While post-hospitalization and postoperative complications significantly affect mortality, identifying preoperative modifiable risk factors also has the potential to reduce mortality. A complete blood count is an easily applicable, inexpensive, and rapid test in patients admitted to the hospital. Biomarkers that can be easily calculated from this test have been recommended in many studies as prognostic and mortality markers for orthopedic and other diseases. In our study, although numerical differences were found in the group with mortality, no statistically significant contribution that could be added to clinical practice was found. Therefore, these biomarkers may be recommended not as predictive of mortality but as sup-

portive parameters for determining patients' overall clinical statuses.

The retrospective nature of this study, the fact that all parameters were only obtained from blood samples taken at the time of initial emergency room admission after trauma, the lack of examination of other parameters that could affect mortality (e.g., body mass index), and the lack of knowledge about the time to reach the emergency are limitations of this study. In addition, immune status, which can change with age, and the stress response to the fracture were unstandardized aspects of the study. However, the strength of this study lies in its compatibility with the literature due to its 34% mortality rate and the elimination of differences secondary to surgery with the use of the same type of implant in a single fracture type.

In conclusion, NLR, PLR, and SII measured at the time of hospital admission are insufficient for predicting mortality after surgery for osteoporotic hip fractures. To universally accept these biomarkers as predictors of risk factors, prospective studies with larger sample sizes are needed, and efforts should be made to minimize conditions that can affect blood cell counts.

Conflict-of-Interest and Financial Disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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