

Prognostic Value of the Neutrophil–Lymphocyte and Platelet–Lymphocyte Ratios in Predicting One-Year Mortality in Patients with Hip Fractures and Aged Over 60 Years

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Abstract

Aim: In this study, we aimed to determine the effect of neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) on one-year mortality in patients with hip fractures and aged over 60 years.

Materials and Methods: The S72.00, S72.10, and S72.20 codes were screened according to International Classification of Disease-10, and 560 patients were included as cases of hip fractures. Blood counts on admission and clinical data were obtained from medical data. Predictors of one-year mortality were evaluated.

Results: In total, 116 out of 560 patients (20.7%) included in the study died during the one-year follow-up. When the patients' characteristics were compared according to one-year mortality (survivor and non-survivor groups), significant differences were detected for age, lymphocyte count, NLR, and PLR ($p < 0.05$). When a Cox regression model was created to assess the factors predicting one-year mortality, the hazard ratios of NLR and PLR were 1.059 (1.022–1.097, $p = 0.002$) and 0.997 (0.994–0.999, $p = 0.01$), respectively.

Conclusion: In the study, in predict mortality among patients aged over 60 years and who had hip fractures, the NLR and PLR were observed to be higher in the survivor group than in the non-survivor group. However, when the specificity of these values is considered, it is obvious that they are not sufficiently reliable for clinical use.

Keywords: Hip fracture, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, one-year mortality

Introduction

Since the human lifespan has increased in recent years, there has been an increase in the geriatric population. Hip fractures, which are commonly seen among the elderly, are injuries with high mortality and morbidity rates, resulting due to the limited physiological reserves of the elderly, their preoperative medical conditions, trauma, and major surgical combinations (1, 2). The average lifespan among the elderly who received treatment for hip fractures is shorter than the lifespan of those who did not receive treatment in the same age group (3). Except for the direct effect of trauma, reactions, such as systemic inflammatory response syndrome, might develop in pa-

tients with hip fractures in a manner similar to that for multi-trauma patients; this is considered a significant mortality factor for the patient group involved. Therefore, considering the factors that might be related to the degree of the inflammatory response in patients with hip fractures could give an idea regarding mortality (4).

The white blood cell (WBC) count is regarded a well-defined inflammatory indicator and/or stress indicator, whereas the neutrophil–lymphocyte ratio (NLR), which is calculated through the division of absolute neutrophil count by absolute lymphocyte count, is asserted to be a new indicator of the inflammatory response. A high correlation has been detected between the NLR and acute coronary syndrome, non-ST myocardial infarcts, ischemic and hemorrhag-



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ic strokes, pulmonary embolisms, and several types of cancer (5-7), while the platelet-lymphocyte ratio (PLR) is calculated through the division of absolute platelet count by lymphocyte count. The PLR has been claimed to have potential as a marker to help identify thrombotic activity and inflammation in certain oncological and cardiac diseases (8, 9). In previous studies, a number of factors in hip fractures that could lead to mortality have been analyzed. However, there are a limited studies show that the subtypes of leukocyte and thrombocyte counts, especially NL and PL, are associated with severe clinical conditions and mortality in major surgical procedures in the literature (10-12). In this study, we aimed to determine the prognostic value of the NLR and PLR on one-year mortality in patients who have hip fractures and aged over 60 years.

Materials and Methods

Study population

This retrospective, case-control study was designed after obtaining approval by the local ethics committee. The diagnostic coding of patients who were admitted to the emergency department (ED) of a training and research hospital between January 2009 and March 2015 was screened from the electronic database of the hospital. The diagnostic coding was performed by scanning the International Classification of Disease-10 (ICD-10) codes on patients with the S72.00 (femur neck fracture, closed), S72.10 (perthrochanteric fracture, closed), and S72.20 (subtrochanteric fracture, closed) codes. We obtained death data of patients from the national death notification system. Those with high-energy trauma, a hematological disease, an infectious and inflammatory disease, a recent myocardial infarction, severe renal disease (glomerular filtration rate <30 mL/min), severe liver disease, immunosuppression, and a history of malignancy and those aged under 60 years were excluded from the study. Overall, 694 patients were found to have the three ICD codes (S72.00, S72.10, S72.20); 134 patients were excluded (56 patients aged <60 years, 27 patients had missing data, 18 had high-energy trauma, 2 had active malignancy, 28 had chronic renal failure, and 3 had severe liver disease). Finally, 560 patients were included in the study for statistical analyses (Figure 1).

Data collection

The demographic data of the patients, whole blood count parameters obtained on admission [such as WBC count, NLR, red blood cell distribution width (RDW), hemoglobin level, platelet count, PLR, and mean platelet volume (MPV)], fracture types of the patients, duration of hospital stay, and comorbidities and their outcomes at the hospital (discharge, death) were recorded in study forms. It was obtained from Public Health Association death notification system whether patients are survived at present. The patients were divided into two groups as survivor and non survivor according to one year mortality.

Laboratory parameters

The laboratory results were evaluated according to the first venous blood samples taken on admission to the ED. Total blood cell counts and its subtypes were analyzed using an automated blood cell counter (Cell-dyn, 3700, Abbott, USA). The NLR was calculated as the ratio of the neutrophil count to the lymphocyte count, and the PLR was calculated as the ratio of platelet count to lymphocyte count.

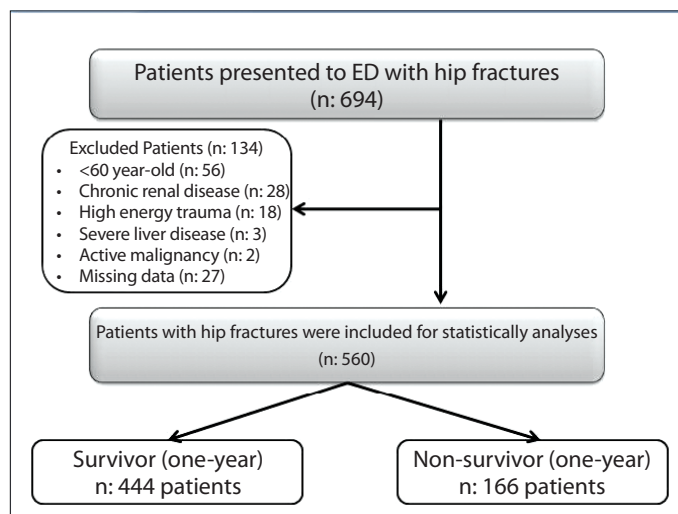


Figure 1. Flow chart of patients

Table 1. Demographics and some laboratory findings of the patients [median (IQR 25%–75%)]

Age (years)	80 (74–85)
Sex (female), n (%)	348 (62.1)
Comorbidities, n (%)	
Hypertension	264 (47.1)
Congestive heart failure	24 (4.3)
Chronic renal disease	27 (4.8)
Diabetes mellitus	121 (21.6)
Coronary artery disease	98 (17.5)
Hemoglobin level (g/dL)	11.8 (10.5–13.1)
WBC count (10 ³ /μL)	9.9 (7.8–12.1)
Neutrophil count (10 ³ /μL)	7.8 (5.8–10.3)
Lymphocyte count (10 ³ /μL)	1.2 (0.8–1.6)
Red blood cell distribution width (%)	14.9 (13.9–16.4)
Platelet count (10 ³ /μL)	212 (169–257)
Mean platelet volume (fL)	8.3 (7.7–9)
NLR	6.7 (4–11)
PLR	181 (126–256)
Type of fracture, n (%)	
Head	9 (1.6)
Neck	424 (75.7)
Perthrochanteric	127 (22.7)
30-day mortality, n (%)	27 (4.8)
One-year mortality, n (%)	116 (20.7)
IQR: interquartile range; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; WBC: white blood cell	

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences 15.0 (SPSS Inc.; Chicago, IL, USA). Demograph-

Table 2. Patients' characteristics according to long-term (one-year) mortality [median (IQR 25%-75%)]

	Survivor	Non-survivor	p
Age (years)	80 (74–84)	83 (77–87)	<0.001*
Sex (female), n (%)	282 (63.5)	66 (56.9)	0.1
Comorbidities, n (%)			
Hypertension	205 (46.2)	59 (50.9)	0.3
Congestive heart failure	15 (3.4)	9 (7.8)	0.03*
Chronic renal failure	22 (5.0)	5 (4.3)	0.7
Diabetes mellitus	103 (23.2)	18 (15.5)	0.07
Coronary artery disease	72 (16.2)	26 (22.4)	0.1
Hemoglobin level (g/dL)	11.8 (10.5–13.1)	11.9 (10.3–13.1)	0.5
WBC count (10 ³ /μL)	10 (7.9–12.1)	9.8 (7.7–12.1)	0.8
Neutrophil count (10 ³ /μL)	7.8 (5.7–10.3)	7.8 (5.9–10.1)	0.6
Lymphocyte count (10 ³ /μL)	1.2 (0.9–1.6)	1 (0.7–1.4)	0.004*
Red blood cell distribution (%)	14.8 (13.8–16.3)	15 (14.1–16.5)	0.1
Platelet count (10 ³ /μL)	214 (172–257)	206 (159–263)	0.3
Mean platelet volume (fL)	8.3 (7.7–9)	8.2 (7.6–9)	0.5
NLR	6.6 (3.9–10.9)	7.2 (4.7–12.2)	0.04*
PLR	178 (119–248)	197 (140–289)	0.02*
Type of fracture, n (%)			
Head	6 (1.4)3 (2.6)		
Neck	336 (75.7)	88 (75.8)	0.5
Perthrochanteric	102 (23)	25 (21.6)	

*p<0.005. IQR: interquartile range; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; WBC: white blood count

ic data related to the patients were expressed as number, percentage, median values, and interquartile range (IQR, 25%–75%). The Kolmogorov–Smirnov test was used to assess the normal distribution of the variables. Non-parametric parameters were analyzed using the Mann–Whitney U test. To determine the cut off values of the NLR and PLR between the survivor and non-survivor groups, a receiver operating characteristic (ROC) curve was generated, and the area under curve (AUC) was calculated. Multivariate Cox regression models were used to evaluate the relationship of one-year mortality with the NLR and PLR. Age, sex, comorbidities, hemoglobin level, WBC count, lymphocyte count, neutrophil count, MPV, RDW, and the type of fracture were included multivariate Cox regression model. Finally, for two groups, which were created according to the cut off values of NLR and PLR, survival rates were calculated using the Kaplan–Meier curve for one-year mortality. The 95% confidence intervals (95% CIs) were calculated whenever appropriate, and a p value of <0.05 was considered statistically significant.

Results

A total of 560 patients diagnosed with femur fractures were included in the study for statistical analyses; 348 patients (62.1%) were women and median age of all patients was 80 years (IQR, 25%-75%, 74-85). The median NLR and PLR were 6.7 (4-11) and 181 (126-256), respec-

tively. In total, 27 patients (4.8%) died within 30 days and 116 (20.7%) died within 1 year. The demographics and some laboratory results of all patients are shown in Table 1.

When patients' characteristics were compared according to the one-year mortality of patients (survivor–non-survivor), significant differences were detected for age, lymphocyte count, the NLR, and the PLR (p<0.05). While the median NLR was 6.6 (3.9-10.9) in the survivor group, it was 7.2 (4.7-12.2) in the non-survivor group (p=0.04). While the median PLR was 178 (119-248) in the survivor group, it was 197 (140–289) in the non-survivor group (p=0.02) (Table 2).

Laboratory parameters

The cutoff NLR was obtained regarding the differences between the survivor and non-survivor groups using ROC analysis. For the NLR, the AUC was estimated as 0.56 (95% CI, 0.50–0.61), and the best cutoff NLR was 3.9 (sensitivity, 80%; specificity, 25%) (Table 3, Figure 2).

When survival rates were calculated using the Kaplan–Meier curve for one-year mortality according to cutoff NLR (3.9), the estimated mean of survival day was 314 (95% CI, 295-332) in patients with an NLR of <3.9 and the estimated mean of survival day was 306 (95% CI, 295-316) in patients with an NLR of >3.9. However, the difference

Table 3. Prediction performance of the NLR and PLR for long-term (one-year) mortality

	NLR (Cut-off: 3.9)	PLR (Cut-off: 131)
Sensitivity	80 (71–87)	80 (71–87)
Specificity	25 (20–28)	29 (25–33)
Positive likelihood ratio	1.06 (0.96–1.18)	1.13 (1.02–1.26)
Negative likelihood ratio	0.81 (0.5–1.21)	0.68 (0.4–1)
Accuracy	56 (50–61)	56 (50–62)

NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio

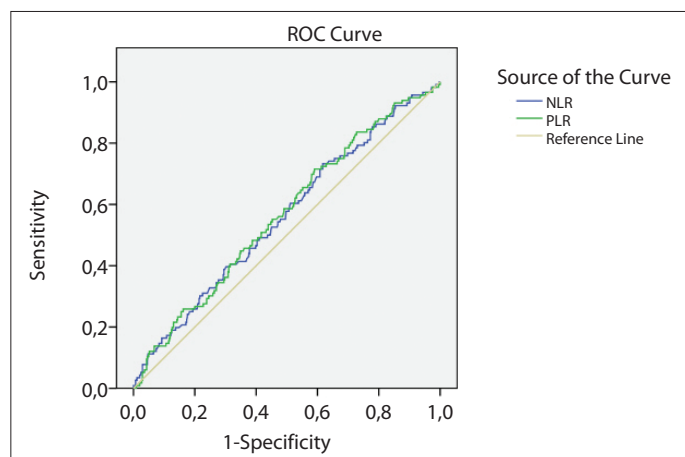


Figure 2. ROC curve of the NLR and PLR to predict mortality
NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; ROC: receiver operating characteristic

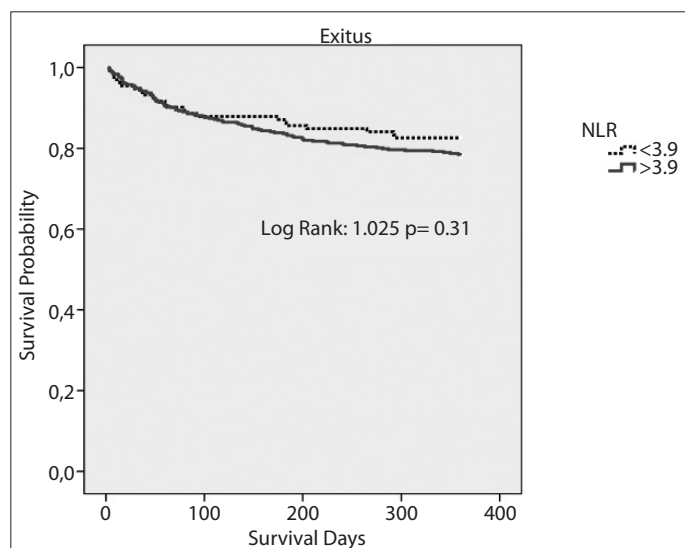


Figure 3. Comparison of Kaplan–Meier survival curves of the NLR
NLR: neutrophil–lymphocyte ratio

between the groups was not statistically significant (log-rank test, 1.025; p=0.3) (Figure 3).

When the Cox regression model was created to assess the factors predicting one-year mortality, the hazard ratio (HR) of the NLR was 1.059 (1.022–1.097; p=0.002; Table 4).

Table 4. Cox regression model to predict long-term (one-year) mortality

	Wald	p value	HR (95% CI)
Age (years)	8.89	0.03	1.03 (1.01–1.06)
Sex	1.15	0.2	0.7 (0.5–1.1)
Comorbidities, n (%)			
Hypertension	1.06	0.3	1.2 (0.8–1.6)
Congestive heart failure	2.24	0.1	1.7 (0.8–3.5)
Chronic renal failure	0.03	0.8	0.9 (0.3–2.2)
Diabetes mellitus	4.04	0.04	0.5 (0.3–0.9)
Coronary artery disease	2.95	0.08	1.4 (0.9–2.3)
Hemoglobin level (g/dL)	0.001	0.9	0.9 (0.8–1.1)
WBC count (10 ³ /μL)	0.58	0.4	1 (1–1)
Neutrophil count (10 ³ /μL)	0.08	0.7	1 (1–1)
Lymphocyte count (10 ³ /μL)	0.40	0.52	1 (1–1)
Red blood cell distribution (%)	0.83	0.36	1.04 (0.9–1.1)
Platelet count (10 ³ /μL)	3.55	0.06	1 (1–1)
Mean platelet volume (fL)	0.17	0.67	0.9 (0.7–1.1)
NLR	9.97	0.002	1.05 (1.02–1.09)
PLR	6.01	0.01	0.997 (0.994–0.999)
Type of fracture	1.04	0.7	2.2 (0.4–11.5)

CI: confidence interval; HR: hazard ratio; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; WBC: white blood cell

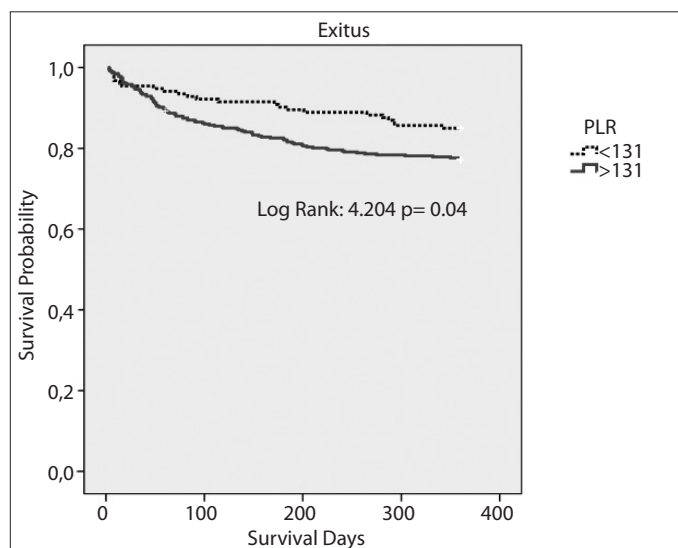


Figure 4. Comparison of Kaplan–Meier survival curves of the PLR
PLR: platelet–lymphocyte ratio

Platelet–lymphocyte ratio

The cutoff PLR was obtained regarding the differences between the survivor and non-survivor groups by ROC analysis. For the PLR, the AUC was measured as 0.56 (95% CI, 0.50–0.62), and the best cutoff PLR was 131 (sensitivity, 80%; specificity 30%) (Table 3, Figure 2).

When survival rates were calculated using the Kaplan–Meier curve for one-year mortality according to the cutoff PLR (131), the estimated mean of the survival day was 325 (95% CI, 310–340) in patients with a PLR of <131 and the estimated mean of survival day was 301 (95% CI, 290–312) in patients with a PLR of >131. The difference between the groups was statistically significant (log-rank test, 4.204; $p=0.04$) (Figure 4).

When the Cox regression model was created to assess the factors predicting one-year mortality, the HR of the PLR was 0.997 (0.994–0.999, $p=0.01$) (Table 4).

Discussion

In the study, wherein we researched the NLR and PLR for predicting mortality among patients aged over 60 years and who had hip fractures, both NLR and PLR were observed to be higher in the survivor group than in the non-survivor group. However, when the specificity of these values is considered, it is obvious that these values are not sufficiently reliable for clinical use. Likewise, according to the cut off values, which were determined using ROC analysis, when the survey of the patient groups were evaluated using Kaplan–Meier life analysis in terms of one-year mortality, there were no differences in the survey based on the NLR, whereas there was a statistical difference based on the PLR. However, we believe that this difference does not contribute significantly to clinical use in practice.

The markers for inflammation were considered in a very large disease group (13, 14). In an effort to study the state of the inflammatory response in the body and to what extent it is stimulated, biomarkers such as WBCs, acute-phase reactants, and adhesion molecules and cytokines were used. In routine practice, the WBC count is used for the diagnosis and follow-up of diseases and is noted in many scoring systems (13). WBCs play an important role in the systemic inflammatory response. Jilma et al. (14) studied changes in the types of WBC after inflammation and found that the neutrophils in circulation increased in number and that the number of monocytes and lymphocytes decreased. In recent years, the NLR has been regarded as a parameter that shows a high level of neutrophils, which is indicative of an acute inflammatory response, and the poor health condition as well as the negative effects of the low level of lymphocytes, which reflect physiological stress (15). In the previously conducted studies, the NLR has been reported as a new cardiovascular risk factor (16, 17). However, there are few studies in which risk analyses of patients were considered in the preoperative period of the surgical population. In the study by Vaughan-Shaw et al. (10), it was claimed that the NLR could be used as an independent predictor in the survey prediction among geriatric patients who require emergency abdominal surgery. Hip fractures mostly affect the geriatric population that often has more than one health problem. On average, an old person usually has more than one disease (18, 19). Among these diseases, cardiac, respiratory, and cerebral diseases and malignancies are largely responsible for mortality and morbidity in the geriatric population (20, 21). Further, these diseases are associated with chronic inflammation. This highlights the relationship between the NLR and the progression of the disease in patients with chronic illnesses. Forget et al. (11) evaluated the NLR after surgery for hip fractures. They researched the relationships between patients' NLRs on admission and postoperatively on the second and fifth days with adverse clinical events in the

hospital and mortality after discharge and suggested that NLR alone is a risk factor but that it cannot be used as a predictor for mortality. In contrast, a study by Sedlar et al. (12) focused on the effect of early postoperative period and subacute inflammatory response [WBC count, NLR, C-reactive protein level, interleukin-6 level, and soluble adhesion molecule level] on the long-term mortality but did not to confirm the effect of acute inflammatory response. Our study is based on the baseline NLR that we obtained when patients were admitted to the ED in the preoperative period, and we do not consider that the NLR can be used as an indicator in predicting mortality.

Increased platelet activity is closely associated with atherosclerosis and thromboembolic states. It has been suggested that the PLR is a new indicator showing chronic inflammation. In particular, the PLR has been introduced as a potential marker to determine excess thrombotic activity and inflammation in oncologic and cardiac disorders (22, 23). In several recent studies, it has been suggested that the PLR is associated with major adverse cardiovascular outcomes and that it is an independent marker of mortality in some oncological diseases (24, 25). In a study by Turkmen et al. (26), the PLR was shown to be superior to the NLR in predicting the severity of inflammation. Similarly, Neofytou et al. (27) suggested that the PLR was superior in diagnosing colorectal cancer. To our knowledge, our study is the first to determine the predictive value of the PLR and hip fractures. Although we found a statistically significant difference with the PLR in living analyses in terms of one-year mortality, we believe that this difference (estimated mean of survival day; survivor for 325 days, non-survivor for 301 days) will not make a significant clinical contribution with regard to hip fractures.

Study limitations

Our study has several limitations. It is a single-center retrospective study, and data were obtained from patient files. The postoperative hematological parameters of the patients were not considered. Repetitive measurements of the NLR and PLR were not performed. The inflammatory process is complex, and other inflammatory parameters were not evaluated in this study. We used a single blood sample to calculate the NLR and included all-cause mortality as our endpoint. Considering the retrospective nature of our analysis, the results should be regarded only for generating a hypothesis and need to be confirmed in prospective trials.

Conclusion

It is important to identify new risk factors for mortality predictions after hip fractures in the geriatric age group. The NLR and PLR are simple measures, do not require additional expenses, and are inexpensive, universally available, rapidly accessible, and routine parameters. We found that in patients with a hip fracture, the NLR and PLR measured at admission were higher in the survivor group than in the non-survivor group. However, we believe that this difference does not make a significant contribution for use in clinical practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Keçiören Training and Research Hospital.

Informed Consent: Written informed consent was not obtained because of retrospective study.

Peer-review: Externally peer-reviewed.

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

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