The benefit of dynamic neutrophil-lymphocyte ratio and systemic immune-inflammation index in predicting survival in patients undergoing hemiarthroplasty

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Abstract. – OBJECTIVE: We aimed at investigating the relationship between the values of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII) in the preoperative and postoperative periods in patients who underwent hemiarthroplasty.

PATIENTS AND METHODS: The medical records of patients aged >65 years who underwent hemiarthroplasty due to hip fracture in our institution between January 2017 and December 2020 were examined. Dynamic Neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte ratio (dPLR), and systemic immune-inflammation index (dSII) were calculated using biomarker data (neutrophil, lymphocyte, and platelet counts) obtained at admission and on postoperative day 2 and 5.

RESULTS: A total of 176 individuals (119 females, 57 males) were included in the study. The PLR on postoperative day 2, and NLR and SII measurement on postoperative day 2 and 5 in patients were found to have significant predictive value in 1-year mortality rates. A 1-year increase in age was associated with a 4.9% increased risk of death at 1-year follow-up (p=0.006). A 1-unit increase in NLR on postoperative day 5 was associated with a 4.3% increased risk of death at 1-year follow-up (p=0.004).

CONCLUSIONS: The present study shows that our model for predicting the absolute mortality risk in patients can be improved by evaluating dSII, dPLR, and dNLR in the preoperative period and postoperative day 2 and 5. However, it cannot be said that the model has a discriminatory ability to exactly predict postoperative mortality. Nevertheless, these parameters may aid in the development of early therapeutic intervention to improve patient outcomes.

Key Words:

Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Systemic immune-inflammation index, Hip fracture, Mortality.

Introduction

Hip fracture is a leading cause of morbidity and mortality in the geriatric population[1]. Despite the advances in the patient care provided in the perioperative and postoperative periods, the mortality rate within 1 year after hip fracture operation has increased to 36%. The major causes of death include myocardial infarction, heart failure, pneumonia, and pulmonary embolism. An elevated neutrophil-to-lymphocyte ratio (NLR) in the postoperative period after hip fracture operation is a risk factor for postoperative mortality and cardiovascular complications[2]. Elevated NLR, especially on postoperative day 5, was shown to be associated with poor disease course in patients with COVID19, cancer, and infection[3].

The platelet-to-lymphocyte ratio (PLR) is a novel marker of systemic inflammation. It has shown great potential as a prognostic predictor in various diseases including inflammatory and cardiovascular diseases, in several malignancies, as well as COVID-19[4]. PLR is calculated by dividing the platelet count with the lymphocyte count. The increased platelet and decreased lymphocyte counts are associated with poor prognosis in patients with hip fracture following operation[4].

The systemic immune-inflammation index (SII) is a composite indicator that combines platelet, neutrophil, and lymphocyte counts. Several studies have shown that SII is associated with malignant tumors, coronary artery disease, acute ischemic stroke, and premature rupture of membranes[1]. Additionally, higher SII (≥834.89) has been recently defined as a favorable risk predictor to indicate osteoporotic fracture in patients with postmenopausal osteoporosis[5].

The dynamic profile of the vital hematological parameters of patients undergoing hemiarthroplas-

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ty for hip fracture was presented at three different time points. The literature search showed that there was a correlation between the dynamic profile of hematological parameters and mortality, and a significant difference was observed in the preoperative period and postoperative days 2 and 5[6].

To the best of our knowledge, this is the first study that evaluated the kinetic relationship between the preoperative and postoperative dynamic SII, NLR, PLR (dSII, dPLR, and dNLR) on specific days. Moreover, the present study describes their effect on mortality in patients aged >65 years who underwent hemiarthroplasty due to hip fracture. In this study, we aimed to investigate NLR, SII, and PLR values in the preoperative period and postoperative days 2 and 5 and evaluate their correlation with mortality.

Our first goal was to determine the most significant preoperative and postoperative predictive risk factors for postoperative mortality in patients aged >65 years with hip fracture. Further, this study aimed to establish and evaluate the performance of a predictive risk score based on these risk factors. Thus, as the second goal of this paper, it was crucial to analyze the prognostic value indicated by different hematological parameters and compare their performance as a potential alternative to each other. The improved ability to predict both in-hospital adverse clinical events and post-discharge mortality using these parameters may provide further benefit to the physician.

Patients and Methods

Study Design and Patient Selection

Planning the operation and postoperative care

The medical records of patients of aged >65years who underwent hemiarthroplasty due to hip fracture in our institution between 2017 and 2020 were examined. This study has been conducted in accordance with the principles set forth in the Helsinki Declaration and obtained the Ethics Committee Approval (Decision No. 2020-49) from the Health Sciences University Trabzon Kanuni Training and Research Hospital. We obtained the informed consent form in writing from all patients before the study. All patients underwent clinical follow-up after operation by a multidisciplinary medical team consisting of surgeons, geriatricians, anesthetists, and a supervisor internist.

The inclusion criteria were as follows:

1) age > 65 years, 2) a minimum of 1-year follow-up, and 3) low-energy hip fractures.

The exclusion criteria were as follows:

1) history of previous operation on the same hip, 2) intraoperative fractures, 3) fractures other than hip fractures, 4) high-energy hip fractures 5) fractures due to direct blunt trauma, 6) pathological fractures, 7) cancer patients, 8) patients under dialysis, and 9) severe liver disease.

Vital Status

For a complete and high-quality follow-up data, we obtained the survival status and the date of death (if it occurred) from the Turkish Social Security Institution using the national identification number of the patients. Causes of death were not available.

Blood Count

The blood counts obtained from all the patients were evaluated in our biochemistry laboratory on the day of hospitalization, and postoperative day 2 and 5. Complete blood counts were measured using automated hematology analyzer (Abbott, Cell-Dyn Ruby, IL, USA). The values of SII, NLR, and PLR were calculated based on the absolute total neutrophil, platelet, and lymphocyte counts. Samples collected up to 3 days before operation were used for calculating preoperative values.

Analysis Procedure

Follow-up

All patients were allowed to walk with the aid of a walker on postoperative day 1. After discharge, the patients were followed up in the outpatient clinic at 2, 4, and 8 weeks and 6 and 12 months after the operation. Further, the follow-up was continued once a year or until death. The survival status of the patients was determined either through hospital follow-up or governmental institution records. The mortality rate was recorded at 1 month, 6 and 12 months, and at the end of the study. The primary endpoint was determined as the day of death or the end of the study.

Determination of the Prognostic Risk Factors

In previous studies, advanced age and male gender were identified as risk factors in patients with hip fracture. Thus, age and gender were selected as variables with discriminatory ability[7].

The preoperative and postoperative total lymphocyte, platelet, and neutrophil counts, SII, NLR, and PLR were analyzed. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. SII was calculated using the following formula: platelet count × neutrophil count/lymphocyte count[5].

Results

A total of 176 individuals (119 females, 57 males) were included in the study. The baseline characteristics of the study population are presented in Table I. The mean age of the participants was 81.36±9.22 years. The median SII was 1007.7 (Interquartile range [IQR]:654.2-1496×10^9/L).

The mortality rates at 30 days, 6 month and 1 year were 8.0% (n = 14), 27.3% (n=48) and 36.4% (n = 64), respectively. As shown in Table II, the comparison of patients' characteristics between survivors and non-survivors based on 1-year mortality showed that age, PLR on 2nd day, and NLR and SII on 2nd and 5th days, were statistically significantly different between survivors and non-survivor groups. A significant increase was observed in PLR from the preoperative period to the postoperative day 5 in both the groups. Further, both the groups showed significant elevation in NLR on the 2nd postoperative day compared with the preoperative period; however, no significant difference in NLR was observed between the preoperative period and 5th postoperative day. SII on the 2nd and 5th postoperative days were found to be significantly higher than that in the preoperative period in both the groups. However, no difference was observed in SII between the 2nd and 5th postoperative days.

Univariable Cox proportional hazard models revealed that increasing age, higher NLR and SII on the 2nd and 5th postoperative days were significantly associated with higher hazard of death at 1-year follow-up (Table III). After adjusting for other variables in multivariable model, age, PLR, and NLR on the 5th postoperative day were identified as independent predictors of 1-year mortality. Results of the multivariable model revealed that, a 1 year increase in age was associated with

Table I. Baseline characteristics.

Characteristics	Total (n=176)
Age	81.36±9.22
Gender	
Male	57 (32.4)
Female	119 (67.6)
Platelet (×10^9/L),	195.0 (151.0-250.8)
Lymphocyte (×10^9/L)	12.0 (8.0-16.0)
Neutrophil (×10^9/L)	55.5 (42.3-77.8)
SII(×10^9/L)	1007.7 (654.2-1496)

Continuous data are summarized with mean±sd or median (25^{th}-75^{th} quartile). Categorical data expressed as frequency (%). SII: Systemic immune-inflammation index.

Table II. Comparison of patient characteristics between survivors and non-survivors (based on one-year mortality).

Variables	Survivor (n=112)	Non-survivor (n=64)	*p*
Age	80.04±9.81	83.68±7.62	0.011
Gender			0.153
Male	32 (28.6)	25 (39.1)	
Female	80 (71.4)	39 (60.9)	
PLR			
Preop	151.25 (112.06-233.65)^a	175.04 (124.66-248.13)^a	0.203
2nd	185.8 (127.55-246.83)^a	227.36 (153.17-312.81)^a	0.022
5th	229.19 (178.58-298.33)^a	256.07 (197.5-349.25)^a	0.087
NLR			
Preop	5.07 (3.47-6.93)^a	5.48 (3.97-7.53)^b	0.270
2nd	6.92 (4.86-9.36)^{ab}	8.71 (6.13-12.19)^{ab}	0.001
5th	4.12 (3.05-6.33)^b	5.7 (4.5-9.36)^b	<0.001
SII			
Preop	944.67 (627.5-1399.2)^{ab}	1121.41 (773.68-1627.22)^{ab}	0.09
2nd	1362.13 (946.9-1876.5)^a	1777.56 (1233.26-3006.51)^a	0.002
5th	1236.47 (907.75-1868.64)^b	1762.23 (1100.13-2748.95)^b	0.002

Values are expressed as n (%), means ± sd or median (25^{th}-75^{th} percentile). For categorical variables Pearson's chi-square are used. For continuous variables, if values are reported in means, *p*-values are calculated using independent samples *t*-test; if values are given in medians, *p*-values are calculated using Mann Whitney U test. [a,b,c] Same superscript letters indicate statistically significant difference between the measurement time points based on the Bonferroni adjusted Wilcoxon signed rank test.

Table III. Univariable and multivariable Cox proportional hazard models for the risk factors associated with 1-year mortality.

Variables	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.039 (1.009-1.070)	0.011	1.049 (1.014-1.086)	0.006
Gender				
Male	1.000 (reference)	-		
Female	1.457 (0.882-2.407)	0.142	1.667 (0.953-2.916)	0.073
Preop PLR	1.001 (0.999-1.004)	0.305	0.999 (0.994-1.005)	0.785
PLR 2nd	1.002 (1.000-1.004)	0.055	1.002 (0.998-1.006)	0.320
PLR 5th	1.001 (1.000-1.003)	0.124	1.004 (1.001-1.009)	0.009
Preop NLR	1.036 (0.980-1.095)	0.213	1.029 (0.902-1.173)	0.675
NLR 2nd	1.096 (1.049-1.144)	<0.001	1.073 (0.988-1.166)	0.093
NLR 5th	1.035 (1.017-1.053)	<0.001	1.043 (1.013-1.073)	0.004
Preop SII (per 100 units)	1.017 (0.992-1.043)	0.180	0.997 (0.924-1.075)	0.937
SII 2nd (per 100 units)	1.018 (1.005-1.030)	0.005	0.994 (0.958-1.031)	0.752
SII 5th (per 100 units)	1.019 (1.008-1.030)	0.001	1.023 (1.000-1.047)	0.055

SII value was divided by 100 to improve the interpretability of the results. HR: Hazard ratio, CI: Confidence interval. NLR: Neutrophil-to-lymphocyte ratio PLR: platelet-to-lymphocyte ratio SII: systemic immune-inflammation index.

4.9% increased hazard of death at 1-year follow-up (Hazard ratio[HR]: 1.049, 95% confidence interval[CI]:1.014-1.086, *p*=0.006), an increase of 10 units of PLR on the 5th postoperative day was associated with 4% increased hazard of death at 1-year follow-up (HR: 1.004, 95% CI: 1.001-1.009, *p*=0.009), and an increase of one unit of NLR on the 5th postoperative day was associated with 4.3% increased hazard of death at 1-year follow-up (HR: 1.043, 95% CI: 1.013-1.073, *p*=0.004). Moreover, multivariable analysis showed a borderline significance for SII on the 5th day, implying that, an increase of 100 units of SII on the 5th postoperative day was associated with 2.3% increased hazard of death at 1-year follow-up (HR: 1.023, 95% CI: 1.000-1.047, *p*=0.055).

ROC curve analysis (Figure 1) revealed that the preoperative and postoperative variables have the ability to determine the 1-year mortality. Table IV juxtaposes the characteristics of the predictive power of ROC curve analysis. The PLR, NLR and SII measurements on the 2nd postoperative day, as well as the NLR and SII measurements on the 5th postoperative day had a good ability to differentiate between survivors and non-survivors. For PLR an area under the curve (AUC) of 0.604 (95% CI: 0.517-0.690, *p*=0.022, optimal cut-off value ≥ 256.88) was obtained on the 2nd postoperative day. For NLR, AUCs of 0.652 (95% CI: 0.568-0.736, *p*=0.001, optimal cut-off value≥ 8.25) and 0.690 (95% CI:0.610-0.769, *p*<0.001, optimal cut-off value≥ 4.70) were obtained on the 2nd and 5th postoperative days, respectively. In case of SII, we found that SII ≥ 1800.94 $\times 10^9$/L on the 2nd postoperative day and SII ≥ 1500.78 $\times 10^9$/L on the 2nd postoperative day were the optimal cut-off values for differentiating between survivors and non-survivors (AUC of 0.638 [95%CI: 0.551-0.725, *p*=0.002]and 0.642 [95% CI: 0.556-0.729, *p*=0.002], respectively). Further, the results of the log-rank test of the Kaplan–Meier curves based on the dichotomized variables showed that the patients with high preoperative SII, high PLR, NLR and SII on the 2nd postoperative day, and high NLR and SII on the 5th postoperative day had worse 1-year mortality (Figure 2).

Discussion

The incidence of hip fractures in the geriatric population has tripled in the last 20 years, and a similar increase is observed in mortality rates[8]. In our study, the postoperative 30-day, 6-month, and 1-year mortalities after hip fracture operation were evaluated and predictive values for mortality were defined. dSII, dPLR, and dNLR were included in our analysis as the dynamic values, SII, PLR, and NLR were obtained on the day of admission and postoperative day 2 and 5 (SII, PLR, and NLR kinetics). We aimed to explore the prognostic value of dSII, dPLR, and dNLR in the early risk stratification of patients from time of hospital admission to the postoperative period in terms of overall survival regardless of known and unknown comorbidities. The prognostic value of SII, PLR, and NLR may ascertain the worse outcome of patients with ongoing inflammation. The cumulative effect of per-

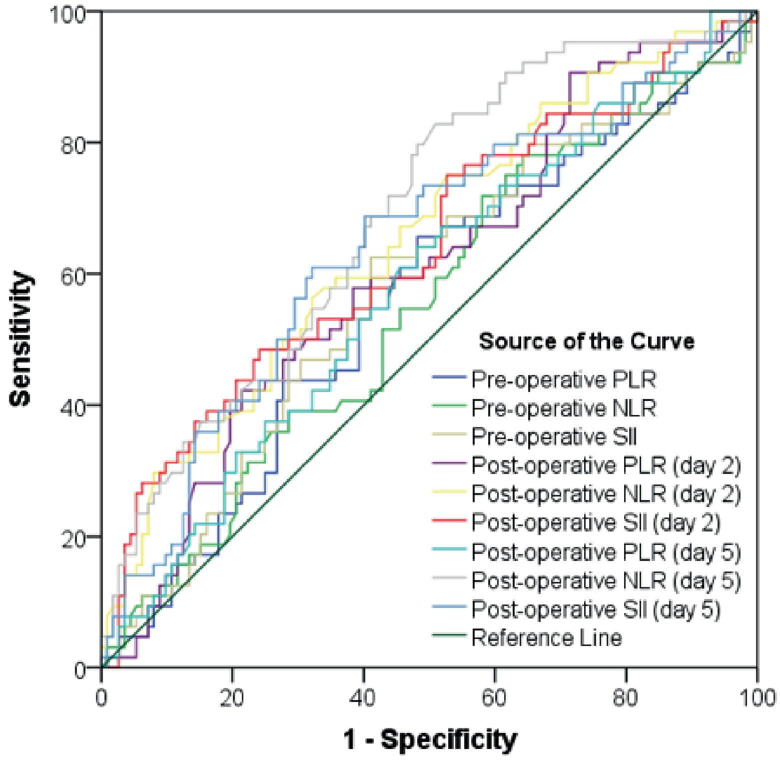

Figure 1. Receiver-operating characteristic (ROC) curves to detect the predictive ability of variables on 1-year mortality.

sistent acute inflammatory response and the body's response to it are believed to increase toxicity.

The present study confirms the previously demonstrated prognostic ability of dSII, dPLR, and dNLR in a vulnerable patient population. These measures provide clinicians with a simple and readily available tool to facilitate accurate prognosis prediction in patients with hip fracture. The low-cost SII, NLR, and PLR measurements are obtained via simple, near real-time calculations using routine laboratory test values without the need of high-cost assays. SII, PLR, and NLR are available at the time of patient presentation and can be used as rapid and simple parameters in clinical practice. The inflammatory response increases proinflammatory mediators and aggravates hyperinflammation. Inflammatory comorbid conditions accompanied with the gradual collapse of the immune system results in increased mortality and fatality rates[6].

Neutrophils increase the secretion of prostaglandins, growth factors, cytokines, and reactive oxygen species that lead to vascular damage and cause endothelial dysfunction by interfering with platelets. Geriatric patients who are under stress due to hip fracture, hemiarthroplasty, general anesthesia, and pain have difficulty maintaining homeostasis. Systemic changes caused by increased stress result in increased neutrophil counts and decreased lymphocyte counts. Increased SII, PLR, and NLR on postoperative day 2 and 5 are suggestive of increased stress[9].

The utility of SII, PLR, and NLR is limited to prognosis prediction in our study considering our goals; however, these measures can also enable the prediction of patient outcomes. We can improve the revalidation process using early and individualized interventions for high-risk patients and thus reduce mortality. This is possible by measuring the risk factors.

In their study involving 50 patients who underwent hemiarthroplasty, Temiz et al[10] have reported the NLR cut-off value as 5.34. In a study by Forget et al[9] comprising 237 patients with intracapsular or extracapsular hip fracture, the postoperative NLR cut-off value was 4.9 (sensitivity: 62.9%, specificity: 57.6%). In our study, unlike the literature, the cut-off value was 8.25 (sensitivity: 67%,

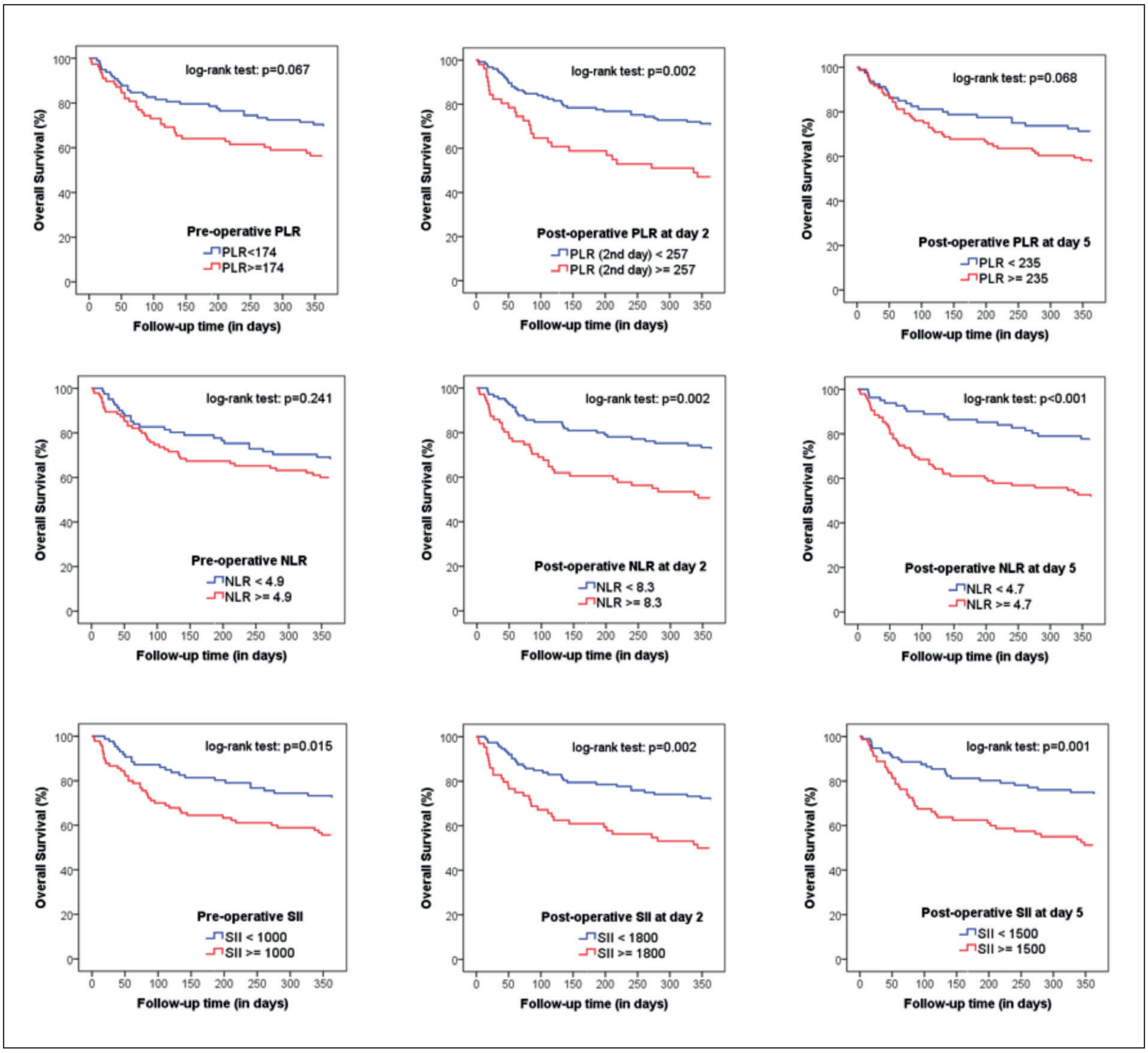

Figure 2. Kaplan-Meier survival analyses according to Platelet- Lymphocyte Ratio (PLR), Neutrophil-lymphocyte ratio (NLR), and Systemic immune-inflammation index (SII) at the pre-operative and post-operative times. *p*-value was estimated using the log-rank test.

specificity: 56%, p=0.001) on postoperative day 2 evaluation, whereas on postoperative day 5 was 4.7 (sensitivity: 71.19%, specificity: 56.2%, p< 0.001) similar to the literature.

In the study performed by Bingol et al[11] that included 345 patients with hip fracture, the cut-off value of NLRs calculated at the time of admission for 1-year mortality was 6.55 (sensitivity: 77%, specificity: 71.1%, p< 0.001). In our study, the values at the time of admission were not found to be significant, and postoperative values were considered as more significant.

Increased PLR is found to be significantly associated with increased all-cause mortality in the general population, particularly in the geriatric population[12]. Mathur et al[12] reported that the mean PLR was significantly higher in individuals who died than those who survived in the general population. Participants in the fourth quartile of PLR exhibit a significantly higher risk of death than those in the first quartile (19.8 *vs.* 13.9 per 1000 person-years). Wang et al[4] have reported a 18.06% increase in the annual mortality of patients with high PLR (≥189) compared with patients with low PLR (<189). Similarly, patients who died had significantly higher platelet counts, and PLR and lower lymphocyte counts than survivors. In our study, only the PLR (256.88)

Table IV. Diagnostic values of the ROC curve analysis to evaluate the discriminatory ability of each dichotomized variable on 1-year mortality.

	AUC (95%CI)	Optimal cut-off (≥)	Sensitivity	Specificity	*p*
Perop PLR	0.558 (0.469-0.647)	173.75	0.531	0.607	0.203
Preop NLR	0.550 (0.462-0.639)	4.90	0.594	0.491	0.270
Preop SII	0.577 (0.488-0.666)	1000.26	0.625	0.589	0.090
PLR 2nd	0.604 (0.517-0.690)	256.88	0.422	0.786	0.022
NLR 2nd	0.652 (0.568-0.736)	8.25	0.679	0.562	0.001
SII 2nd	0.638 (0.551-0.725)	1800.94	0.484	0.759	0.002
PLR 5th	0.578 (0.490-0.665)	235.58	0.641	0.518	0.087
NLR 5th	0.690 (0.610-0.769)	4.70	0.719	0.562	<0.001
SII 5th	0.642 (0.556-0.729)	1500.78	0.609	0.679	0.002

AUC: Area under the curve.

obtained on postoperative day 2 was significant (*p*= 0.022).

A recent study has showed that high PLR was associated with increased all-cause mortality in the geriatric patients but not in middle-aged or younger participants[12].

Wang et al[4] have found a HR of 1.05 for each 1-year age increment in patients with hip fracture (95% confidence interval [CI]: 1.01-1.08). Our study showed that a 1-year increment in age was associated with an increased HR of 4.9% at 1-year follow-up (HR: 1.049, 95% CI: 1.014-1.086, *p*=0.006).

Wang et al[1] have found that SII was associated with 1-year mortality as an independent risk factor in geriatric patients with hip fractures (HR = 1.08 per 100 units, 95% CI: 1.01-1.17). In our study, we revealed that SII was statistically significant, particularly on postoperative day 2.

A limitation of this study is related to the nutritional status of the patients. Malnutrition is a risk factor for worse outcomes after hip fracture and typically associated with lymphopenia.

Some significant data could not be collected in the study. In particular, we did not have relevant information about the degree of osteoporosis, which may reflect the most important comorbidities. In addition, the cause of death was known only in a limited number of patients.

Specifically, no exclusion criteria were applied to the parameters obtained, although patients who receive steroid therapy and have a smoking habit may show high neutrophil counts.

Platelets and neutrophils are involved in endothelial dysfunction, atherosclerotic plaque destabilization, and increased coagulation, causing further vascular damage. These effects depend on the magnitude and duration of the response. All this does not exclude the possibility that NLR on postoperative day 5 is a marker of frailty. Hormonal changes caused by stress include the secretion of cortisol, which increases the neutrophil count and decreases the lymphocyte count. All these factors may contribute to higher 1-year mortality in patients with NLR > 5 on postoperative day 5[13]. Despite these limitations, the PLR on postoperative day 2, and NLR and SII measurement on postoperative day 2 and 5 in patients over the age of 65 who underwent hemiarthroplasty were found to have significant predictive value in 1-year mortality rates. A 1-year increase in age was associated with a 4.9% increased risk of death at 1-year follow-up (*p*=0.006). A 1-unit increase in NLR on postoperative day 5 was associated with a 4.3% increased risk of death at 1-year follow-up (*p*=0.004). However, their individual performance in predicting mortality was relatively low depending on the time of collection. Therefore, these predictive values should be considered risk factors rather than predictive biomarkers.

Conclusions

Our study confirms the poor prognosis of patients undergoing hemiarthroplasty for traumatic hip fracture. Therefore, it is very important to identify novel risk factors for predicting mortality in geriatric patients.

In addition to age, gender, and other comorbidities, dSII, dPLR, and dNLR are simple and cost-effective markers. dSII, dPLR, and dNLR can be used as objective risk factors for infections, mortality, and morbidity in the early and late postoperative period after hemiarthroplasty. This study shows that our model for predicting the absolute mortality risk of patients can be improved by evaluating dSII, dPLR, and dNLR in the preoperative period and postoperative day 2 and day 5. However, it cannot be said that it has the discriminatory ability to exactly predict postoperative mortality. Nevertheless, these parameters may at least allow an early therapeutic intervention to improve patient outcomes.

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Conflict of Interest

The author has no conflict of interest to declare.

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Ethics Approval

This study has been conducted in accordance with the principles set forth in the Helsinki Declaration and obtained the Ethics Committee Approval (Decision No. 2020-49) from the Health Sciences University Trabzon Kanuni Training and Research Hospital. We obtained the informed consent form in writing from all patients before the study.

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