

The Prognostic Value of Inflammation Indices in Predicting Postoperative ICU Admission and Mortality in Elderly Patients Undergoing Hip Fracture Surgery

Ökkeş Hakan Miniksar¹, Mehmet Kara², Muhammed Nuri Polat², Yeşim Andıran Şenaylı², Serhat Durusoy³, Hacı Ali Olçar³, Murat Korkmaz³

¹University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey

²Yozgat Bozok University Faculty of Medicine, Department of Anesthesiology and Reanimation, Yozgat, Turkey

³Yozgat Bozok University Faculty of Medicine, Department of Orthopedics and Traumatology, Yozgat, Turkey

Abstract

Objective: This study aimed to assess the predictive impact of various inflammation indices and inflammatory biomarkers on postoperative intensive care unit (ICU) admission and mortality following hip fracture (HF) surgery in elderly patients.

Materials and Methods: We retrospectively reviewed the data of 131 geriatric patients who underwent isolated HF surgery under regional anesthesia. The patients were divided into two groups: ICU admission (ICU, n=98) and non-ICU admission (non-ICU, n=33). The patients were also grouped as survival (n=122) and non-survival (n=9) according to postoperative mortality rates. The patients' clinical characteristics and inflammation indexes were compared between the two groups, and predictors of ICU admission were determined using a multivariate regression model.

Results: Advanced age and high American Society of Anesthesiologists (ASA) scores were observed in the ICU and Non-survivor groups. Urea and creatinine levels were significantly higher in the Non-survivor group. While inflammatory indices [systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio] were significantly higher in the ICU group (respectively, p=0.009, p=0.022, p=0.019), they did not differ significantly in the mortality group. Age, ASA score, and SII of the inflammation indices were determined to be independent predictors of postoperative ICU admission after HF surgery.

Conclusion: It was shown that advanced age, high ASA score, and high preoperative SII value were independent risk factors for postoperative ICU admission following HF surgery in elderly patients. SII can be used as an easily measured prognostic parameter on the ICU admission of these surgical patients in daily practice.

Keywords: Geriatrics, hip fracture, systemic immune-inflammation index, intensive care, mortality

Introduction

People on earth are getting older, and hip fractures (HF) are much more frequently seen in clinics due to aging. HF, mainly observed in elders, is a severe injury and causes a high mortality and morbidity of approximately 15-20% (1-4).

A decline in physical stamina and a rise in the prevalence of comorbidities are observed in elderly patients. Myocardial infarction, pulmonary thromboembolism, heart failure, and

infectious complications account for most mortality following HFs (2-5). These high-risk HF patients are usually treated in intensive care units (ICUs) after surgery, according to their clinical history and disease progression (6). The planned postoperative ICU admission of these high-risk patients helps to minimize adverse complications. Recognizing and targeting patients with adverse outcomes is an important part of treatment planning for geriatric HF surgery. A surgical patient's decision to be admitted to the ICU is not dependent on a single

Address for Correspondence: Ökkeş Hakan Miniksar, University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Ankara, Turkey

Phone: +90 312 336 09 09 **E-mail:** hminiksar@yahoo.com **ORCID:** orcid.org/0000-0001-5645-7729

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factor and is complex (1,2,6,7). We, clinicians, need to determine the preoperative predictors that will affect this ICU admission decision. Recognizing and targeting patients with adverse outcomes is an important part of treatment planning for geriatric HF surgery. Accurate prognostic predictors can provide valuable information on postoperative outcomes, and patients with such indicators can receive additional aggressive therapies to improve survival (4,7,8).

Several studies have shown the relationship between specific laboratory results and various factors causing ICU admission and mortality in elderly patients after HF surgery (9-11). According to previous reports, other inflammatory markers have also been associated with mortality (1-8). Therefore, in addition to these laboratory parameters, there is still a need in daily practice for an ideal readily measured marker, such as hematological parameters, to predict postoperative clinical outcomes. Nevertheless, to the best of our knowledge, no standard inflammatory biomarkers or a scoring system can be used in clinical practice to predict the postoperative outcomes of elderly HF surgery patients based on the inflammation status. Therefore, we assumed in our study that these indices could be independent predictors of ICU admission and mortality rates in elderly patients after HF surgery.

Our objective was to determine and evaluate the predictive value of several inflammatory indices and inflammatory biomarkers on prognosis in elderly patients undergoing HF surgery.

Materials and Methods

Ethical Statement

The Yozgat Bozok University Clinical Research Ethics Committee approved this retrospective observational single-center study in accordance with the Declaration of Helsinki (decision number: 2017-KAEK-189_2021.08.25_02, date: 25.08.2021). Informed consent: Retrospective study.

Study Design

This study reviewed the clinical findings of 163 patients who received isolated HFs because of minor trauma caused by falls at our department between January 2019 and May 2021. Patients included in the study had an American Society of Anesthesiologists (ASA) score of 2/3/4, were over 65 years of age, and were treated with regional anesthesia. General anesthesia, age under 65 years, hematologic abnormalities, infectious and inflammatory disease, intraoperative mortality, revision surgery, history of severe liver disease and malignancy, multiple traumas, and missing records were among the study's exclusion criteria. The study included 131 participants when the exclusion criteria were applied (Figure 1). STROBE guidelines were used during presentation preparations. (www.strobe-statement.org).

Study Participants

Demographic characteristics, comorbidities, ASA scores, intervention time, and patients' preoperative laboratory data were recorded. Both electronic and hard-copy hospital archives were evaluated to obtain data on patient files and perioperative

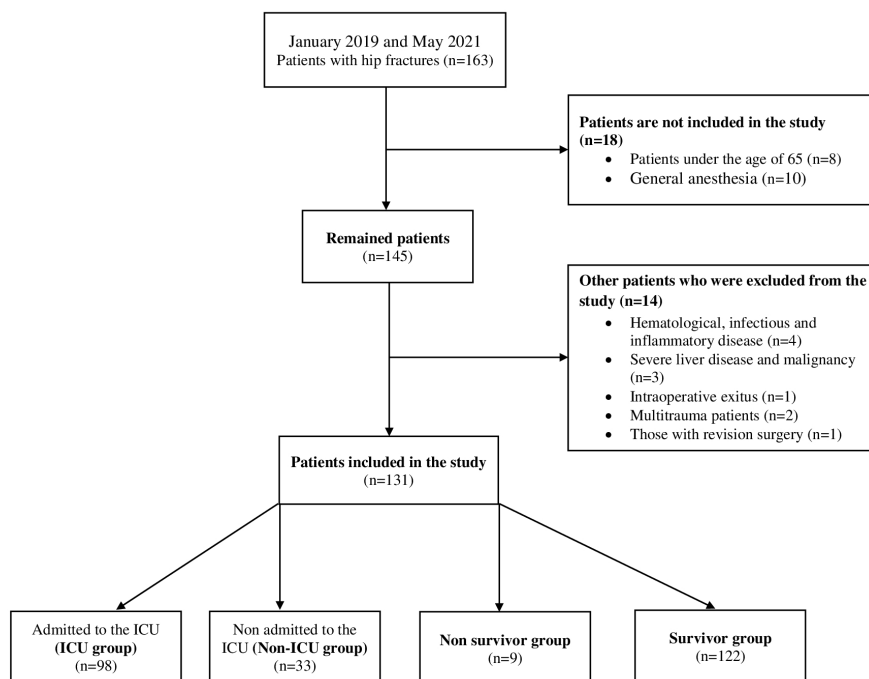


Figure 1. Flow chart of the study participants

ICU: Intensive care unit

anesthesia. The period between hospitalization and surgery was defined in days.

The patients were divided into two groups for evaluation: the ICU and Non-ICU groups. The anesthesiologist decided to admit the patient to the ICU on the basis of the patient's postoperative clinical status. This study included patients who underwent operations under regional anesthesia. For the ICU group, these patients were also evaluated as the Survivor group and Non-survivor group according to mortality. Medical departments such as cardiology, respiratory disease, or internal medicine evaluated all patients in the preoperative period. Consultation records were reviewed to evaluate the possible presence of comorbidities in the patients during the preoperative period. The patients who were admitted for the first time to the ICU were accepted. The team consisted of anesthetists, orthopedic surgeons, and internal medicine specialists who followed the patients postoperatively.

Laboratory Measurements

One day before surgery, venous blood samples [complete blood count (CBC)] were routinely taken from each patient and recorded in the hospital's medical records. Test results were obtained using a blood analyzer (Beckman Coulter®, LH 780, California, USA). The inflammatory indices were calculated from whole blood assays as follows: systemic immune-inflammation index (SII) [(neutrophils x platelets)/lymphocytes], neutrophil-to-lymphocyte ratio (NLR) (neutrophil/lymphocyte), neutrophil-to-platelet ratio [neutrophil/(lymphocyte x platelet)], platelet-to-lymphocyte ratio (PLR) (platelet/lymphocyte), and mean platelet volume/platelet.

Statistics

Statistics were analyzed using IBM SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Categorical data were presented in *n* and frequency, while continuous data were presented in mean \pm standard deviation (SD) and median (interquartile range; 25th–75th percentile). The Kolmogorov-Smirnov and Shapiro-Wilk tests checked the normality distribution. If more than 20% of the expected values in the cross tables were less than 5, or if at least one of the values was less than 2, Fisher's exact test was performed. All significant variables (age, ASA, SII, NLR, and PLR) were included in the multivariate logistic analysis after the univariate analysis. Factors that predict postoperative ICU admission were investigated using a backward stepwise multivariate logistic regression analysis. The Hosmer-Lemeshow test for goodness-of-fit statistics was used to determine the calibration validation and discrimination of this regression analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the parameters and inflammation indices with the most significant predictive value for postoperative ICU admissions, and the areas under the curve

(AUC) were calculated. A statistically significant difference was defined as a *p* value of 0.05.

Results

Demographic and Clinical Characteristics

A total of 131 patients in 163 met the inclusion criteria for statistical analysis with HF diagnoses who underwent surgery throughout the study period. The mean age (SD) of all patients was 82.66 (5.44), with 74 (56.5%) being female. Thirty-three patients (25.2%) and 98 patients (74.8%), respectively, comprised the Non-ICU and ICU groups. The patient's mean age in the ICU group was 83.6 years, compared with 80.4 years in the Non-ICU group (*p*=0.005). Nine patients (6.9%) were included in the Non-survivor group, whereas 122 patients (93.1%) were included in the Survivor group. In the Survivor group, the patients' median age ranged from 78 to 86 years; in the Non-survivor group, it was 90 to 94 (*p*=0.021). The difference in ASA physical status between the groups was statistically significant (*p*=0.002 for the ICU group and *p*=0.018 for the Survivor group). There was no statistically significant difference between the groups for the most common comorbidities, which were hypertension (58.0%), diabetes mellitus (29.8%), and coronary artery disease (27.5%) (Table 1).

Biochemical and Total Blood Count Parameters and Inflammation Indices

When laboratory parameters were examined, urea was significantly higher in the ICU and Non-survivor groups (*p*=0.002 and *p*=0.037, respectively). Creatinine was higher only in the Non-survivor group (*p*=0.047). SII (*p*=0.009), NLR (*p*=0.022), and PLR (*p*=0.019) inflammatory indices were significantly higher in the ICU group. Inflammation indices did not differ significantly in the Survivor groups (Table 2).

Risk Factors for ICU Admission Using Univariate and Multivariate Analysis

The results of univariate and multivariate logistic regression analyzes for ICU admission in patients undergoing HF surgery are shown in Table 3. In univariate analysis, the following preoperative variables were found to be important predictors of postoperative ICU admission: Age [odds ratio (OR): 1.128; 95% confidence interval (CI) 1.033–1.233; *p*=0.008], ASA (OR: 3.332; 95% CI 1.463–7.590; *p*=0.004), SII (OR: 1.001; 95% CI 1.000–1.001; *p*=0.013), NLR (OR: 1.117; 95% CI 1.014–1.231; *p*=0.025), and PLR (OR: 1.005; 95% CI 1.001–1.009; *p*=0.027). Multivariate analysis revealed that age (OR: 1.118; 95% CI 1.015–1.231; *p*=0.023), ASA (OR: 2.572; 95% CI 1.101–6.007; *p*=0.029) and SII (OR: 1.001; 95% CI 1.000–1.001; *p*=0.021) were independent predictors of postoperative ICU admission. Other important variables (NLR, PLR) were not independent predictors of ICU admission. The Hosmer-Lemeshow goodness-

Table 1. Comparison of demographic and clinical characteristics between the ICU admission and mortality groups

Variables	Non-ICU group (n=33)		ICU group (n=98)		p	Non-survivor group (n=9)		Survivor group (n=122)		p
	n	%	n	%		n	%	n	%	
Age (years), mean (SD) [25-75 p.]	80	(4)	83	(6)	0.005¹	90	[80-94]	81	[78-86]	0.021²
Time before surgery (days)	2	[1-2]	2	[1-2]	0.606 ²	1	[0-2]	1	[1-2]	0.376 ¹
Gender, female (n=74)	16	48.5	58	59.2	0.284 [#]	3	33.3	71	58.2	0.147 [*]
ASA physical status, II/III/IV	7	21.2	3	3.1	0.002[#]	0	0.0	10	8.2	0.018[*]
	21	63.6	65	66.3		3	33.3	83	68.0	
	5	15.2	30	30.6		6	66.7	29	23.8	
Comorbidities, n (%)										
Hypertension, (n=76)	19	57.6	57	58.2	0.067 [#]	5	55.6	71	58.2	0.877 [*]
Congestive heart failure, (n=22)	4	12.1	18	18.4	0.406 [*]	2	22.2	20	16.4	0.652 [*]
Diabetes mellitus, (n=39)	13	39.4	26	26.5	0.162 [#]	2	22.2	37	30.3	0.608 [*]
Cerebrovascular disease, (n=26)	5	15.2	21	21.4	0.434 [*]	4	44.4	22	18.0	0.055 [*]
Arrhythmia, (n=20)	3	9.1	17	17.3	0.254 [*]	3	33.3	17	13.9	0.118 [*]
Coronary artery disease, (n=36)	5	15.2	31	31.6	0.067 [*]	4	44.4	32	26.2	0.237 [*]
Chronic renal failure, (n=9)	2	6.1	7	7.1	0.832 [*]	1	11.1	8	6.6	0.602 [*]
Chronic lung disease, (n=17)	2	6.1	15	15.3	0.172 [*]	1	11.1	16	13.1	0.863 [*]

The values are presented as the mean (SD) and median [interquartile range] for continuous variables and number and percentage for categorical variable. Compared by the ¹independent t-test and ²Mann-Whitney U test for continuous variables. All statistically significant values are reported in bold. Compared by the ^{*}chi-square test and [#]Yates' correction for continuity. ICU: Intensive care unit, ASA: American Society of Anesthesiologists, MPV: Mean platelet volume, SII: Systemic immune-inflammation index, NLR: Neutrophil to lymphocyte ratio, NLPR: Neutrophil to lymphocyte, platelet ratio, PLR: Platelet to lymphocyte ratio, MPR: Mean platelet volume/platelet, SD: Standard deviation

Table 2. Comparison of laboratory parameters and inflammation indices between the ICU admission and mortality groups

Variables	Non-ICU group (n=33)		ICU group (n=98)		p ¹	Non-survivor group (n=9)		Survivor group (n=122)		p ²
	Mean	SD	Mean	SD		Median	25-75 p.	Median	25-75 p.	
Biochemical parameters										
Glucose (mmol/L)	161	78	158	75	0.833	133	107-161	135	108-183	0.504
Sodium (mmol/L)	138	5	138	7	0.682	138	137-139	138	136-140	0.945
Urea (mg/dL)	217	61	238	92	0.002	239	206-254	227	186-269	0.037
Creatinin (mg/dL)	0.97	0.48	1.06	0.50	0.390	1.31	0.89-1.39	0.89	0.74-1.14	0.047
Albumin (g/dL)	3.85	0.56	4.57	5.31	0.440	3.65	3.56-3.81	3.75	3.45-4.02	0.356
Total blood count										
Hemoglobin (g/dL)	12.73	2.08	11.85	2.02	0.033	11.90	10.1-12.7	12.05	10.9-13.4	0.598
Neutrophils (x10 ⁹ L)	0.03	0.03	0.04	0.03	0.056	0.05	0.02-0.08	0.03	0.01-0.05	0.277
Lymphocytes (x10 ⁹ L)	1.50	0.69	1.34	0.75	0.280	0.94	0.56-2.21	1.26	0.87-1.7	0.437
Platelets (x10 ⁹ L)	217	61	238	92	0.238	239	206-254	227	186-269	0.967
MPV (fL)	10.22	1.02	10.14	0.85	0.643	9.90	9.6-10.4	10.00	9.5-10.7	0.685
Inflammatory indices										
SII	1229.32	751.29	2132.54	1912.93	0.009	1210.60	1001.85-4007.51	1305.45	723.85-2466.98	0.601
NLR	6.04	3.73	8.58	5.88	0.022	10.02	3.44-16.76	6.71	3.80-10.52	0.385
NLPR	0.03	0.03	0.04	0.03	0.215	0.05	0.02-0.08	0.03	0.016-0.053	0.185
PLR	165.59	66.67	234.09	161.10	0.019	185.19	109.95-423.33	162.76	119.42-260.39	0.788
MPR	0.05	0.02	0.05	0.02	0.494	0.04	0.039-0.056	0.05	0.036-0.057	0.982

Data are presented as the mean (SD) and median [interquartile range (25-75. percentile)] for continuous variables and number and percentage for categorical variable. Compared by the ¹Independent t-test and ²Mann-Whitney U test for continuous variables. Statistical significance was set at 0.05. All statistically significant values are reported in bold. ICU: Intensive care unit, ASA: American Society of Anesthesiologists, MPV: Mean platelet volume, SII: Systemic immune-inflammation index, NLR: Neutrophil to lymphocyte ratio, NLPR: Neutrophil to lymphocyte, platelet ratio, PLR: Platelet to lymphocyte ratio, MPR: Mean platelet volume/platelet, SD: Standard deviation

of-fit test indicated a well-calibrated model ($\chi^2=6.933$; $df=8$; $p=0.544$).

Predictive Accuracy of SII for ICU Admission

ROC analysis determined the cut-off SII based on the differences between the ICU and Non-ICU groups. The cut-off point was established as 1001.61 (AUC of 0.646 95% CI 0.546-0.747) with 74% sensitivity and 55% specificity; $p=0.012$) for postoperative ICU admission SII (Figure 2).

Discussion

There is still no universal consensus, despite the large number of clinical trials that have been reported that have shown a relationship between several inflammatory markers and postoperative outcomes in elderly HF surgery patients. This study examined the relationship between postoperative ICU hospitalization, mortality, and serum inflammatory markers and indices in geriatric patients undergoing elective HF surgery. In the current study, several significant results were identified. First, patients admitted to the postoperative ICU, with observed

mortality had higher ASA scores and urea levels and were older. Second, although inflammation indices (SII, NLR, and PLR) were higher in the ICU group, they did not differ significantly in the mortality group. Third, advanced age, high ASA score, and SII of the inflammation indices were determined to be independent predictors of postoperative ICU admission after geriatric HF surgery.

In previous studies, advanced age was shown to be a risk factor for HF surgery (12,13). Forget et al. (12) developed a score that included age, gender, and NLR at the fifth day to estimate the risk of death at one year in elderly patients after HF surgery. Conversely, other studies have reported that advanced age is not a risk factor for mortality (14-16). In the current study, being old with a high ASA score was defined as an independent risk factor for admission to the ICU and mortality. A strong relationship between age and the ASA score is known. There is an increase in comorbidities associated with advanced age. This risky situation also contributes to postoperative mortality and ICU admission decisions. In addition, the high mean age of the included patients may have contributed to the results of our study. Although inconsistent results have been reported in the literature, our results indicate that advanced age is a significant risk factor for the prognosis of this critical surgery.

Recently, many studies have examined the relationship between inflammation and the outcomes of elderly patients. It has been reported that many inflammation markers are associated with prognosis in major orthopedic surgeries, such as HF. The most analyzed of these markers is NLR (13-18). Forget et al. (13) reported that mortality at one year was higher in patients with HF with an $NLR > 5$ at the fifth day. The NLR value at the time of admission of elderly patients who had undergone HF surgery may be used for mortality-related risk classification, according to Temiz and Ersözlü (18) report in another investigation. On the contrary, in the study by of Altinsoy et al. (17), it was reported that there was no relationship between NLR value and postoperative short-term mortality and morbidity in patients with HF. The authors consider the small number of non-survival

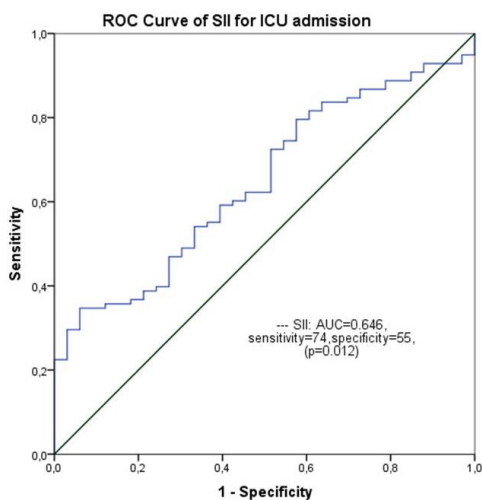


Figure 2. ROC curve of the relationship between SII and admission of ICU
 ICU: Intensive care unit, SII: Systemic immune inflammation index, ROC: Receiver operating characteristic

Variables	Univariate analysis				Multivariate analysis			
	OR	(95% CI)		p	OR	(95% CI)		p
		Lower	Upper			Lower	Upper	
Age	1.128	1.033	1.233	0.008	1.118	1.015	1.231	0.023
ASA	3.332	1.463	7.590	0.004	2.572	1.101	6.007	0.029
SII	1.001	1.000	1.001	0.013	1.001	1.000	1.001	0.021
NLR	1.117	1.014	1.231	0.025	--	--	--	--
PLR	1.005	1.001	1.009	0.027	--	--	--	--

Hosmer-Lemeshow test ($\chi^2=6.933$; $df=8$; $p=0.544$), Nagelkerke R Square =0.249, $p<0.001$. Multivariate Model's Adjusted $R^2=0.183$, p value <0.001 .
 CI: Confidence interval, OR: Odds ratio, ICU: Intensive care unit, ASA: American Society of Anesthesiologists, SII: Systemic immune inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

patients as the reason for this different result. Similarly, in our study, although preoperative NLR value was not associated with postoperative ICU mortality, it was associated with ICU admission. Elevated NLR was also found to be an independent predictor of admission to the ICU. There are few patients in the mortality group, and we must interpret our results cautiously.

In an experimental rat study, systemic inflammation mediators were reported as potential biomarkers in the diagnosis and prognosis of acute lung injury, a fatal complication after HF (19). In another clinical study, increased concentrations of inflammatory cytokines (tumor necrosis factor- α , interleukin (IL)-6, and IL-10) in elderly patients with HF represented independent risk factors for adverse postoperative outcomes (20). The underlying mechanism activates the inflammatory response of neutrophils activated after trauma. Increased stress is the cause of systemic changes that cause an increase in neutrophil counts and a decrease in lymphocyte counts. Vascular damage is induced by activated platelets and neutrophils, leading to endothelial dysfunction and coagulation disorders (21). SII, an inflammatory biomarker, depends on peripheral platelet, neutrophil, and lymphocyte counts, and it appears to be a useful prognostic indicator for some diseases (9,11). In a recent study, older patients with HF undergoing surgery had lower all-cause mortality when their SII was high (9). In our study, inflammation indices (SII, NLR, PLR) were predictors of ICU admission in univariate regression analysis, whereas SII was an independent risk factor in multivariate regression analysis. Therefore, we thought that an elevated SII level might be a possible predictor of admission to the ICU, an adverse postoperative outcome in older adults with HFs. In addition, it is crucial to determine preventive plans for postoperative ICU admission management according to this inflammation index in elderly patients with HF.

Another significant result of our study is that increased PLR, another inflammatory index, predicts admission to the ICU. Bala (22) reported that increased PLR on the second postoperative day was an effective predictor of survival in patients who underwent hemiarthroplasty. Similarly, another study showed that a high PLR (≥ 189) can result in increased one-year all-cause mortality in old HF patients (23). The authors reported that because PLR is an easily used simple indicator obtained during routine blood testing, it can be easily found in clinical practice. Although if the PLR level is high, the prognosis will be poor in these patients, the possible underlying mechanism is not precise. Additional research is necessary to understand the predictive ability of these inflammatory indices and to include the predictors in a new scoring system.

Furthermore, our study showed that urea and creatinine levels were significantly associated with ICU mortality and ICU admission. These risk factors have also been defined in other studies (24,25). Mosfeldt et al. (24) reported that 3-month

mortality in elderly patients with HF increased threefold in those with high creatinine levels. Laulund et al. (11) concluded that high creatinine plasma levels have predictive significance for mortality in patients with HF after performing a meta-analysis of 15 studies. Preoperative correction of abnormalities in these biochemical laboratory values associated with mortality may positively affect postoperative prognosis.

Study Limitations

However, it is essential to acknowledge that this study has several limitations. First, there may be selection bias because the study was retrospective and single-centered. As a result, we are forced to rely only on the outcomes of patients at our facility. Many parameters such as the type of ICU, capacity, patient population, and anesthesiologist-surgeon relationship can affect a patient's admission to the ICU. Second, various variables contributed to the patient's admission to the ICU. Third, a thorough study with a larger sample size is required to support the existing data because there were few patients in the Non-survivor group throughout the relevant period. The conclusion of a causal association between inflammatory indices and surgical outcomes is thus limited, despite the small sample size of patients.

Conclusion

The study's primary finding is that old age, a high ASA score, and a high preoperative SII value all independently increase the probability of an elderly patient with HF being admitted to the ICU after surgery. The SII value can be employed as an easily measured prognostic parameter in the routine management of critical surgical patients. The reproducibility and generalizability of our study findings need to be examined in more extensive multicenter clinical studies.

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Ethics

Ethics Committee Approval: The Yozgat Bozok University Clinical Research Ethics Committee approved this retrospective observational single-center study (decision number: 2017-KAEK-189_2021.08.25_02, date: 25.08.2021) in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ö.H.M., M.K., M.N.P., Concept: Ö.H.M., M.K., M.N.P., Y.A.Ş., S.D., H.A.O., M.K., Design: Ö.H.M., M.K., M.N.P., Y.A.Ş., S.D., H.A.O., M.K., Data Collection or Processing: Ö.H.M., M.K., M.N.P., Y.A.Ş., S.D., H.A.O., M.K., Analysis or Interpretation: Ö.H.M., Literature Search: Ö.H.M., Y.A.Ş., Writing: Ö.H.M., Y.A.Ş.

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

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