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Risk Factors of the 2-Year Mortality after Bipolar Hemiarthroplasty for Displaced Femoral Neck Fracture

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Purpose: This study investigates the relationship between preoperative neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-C-reactive protein ratio (LCR), albumin, and 2-year mortality in elderly patients having hemiarthroplasty for displaced femoral neck fracture (FNF).
Materials and Methods: We retrospectively reviewed 284 elderly patients who underwent hemiarthroplasty for Garden type IV FNF from September 2014 to September 2020. Using the receiver operating characteristic curve, optimal cutoff values for LCR, NLR, and albumin were established, and patients were categorized as low or high. Associations with 2-year mortality were evaluated through univariate and multivariate Cox regression analyses.
Results: Of the 284 patients, 124 patients (45.9%) died within 2 years post-surgery. The optimal cutoff values were: LCR at 7.758 (specificity 58.5%, sensitivity 25.0%), NLR at 3.854 (specificity 39.2%, sensitivity 40.0%), and albumin at 3.750 (specificity 65.9%, sensitivity 21.9%). Patients with low LCR (<7.758), high NLR (≥3.854), and low albumin (<3.750) had a statistically significant reduced survival time compared to their counterparts.
Conclusion: Lower preoperative LCR and albumin levels, along with higher NLR, effectively predict 2-year mortality and 30-day post-surgery complications in elderly patients with Garden type IV FNF undergoing hemiarthroplasty.

Key Words: Femoral neck fractures, Hemiarthroplasty, Mortality, Marker, Laboratory

INTRODUCTION

In general, hip fractures are more common in females than males, and the incidence increases with age[1]. Certain risk factors can also increase the risk of sustaining a hip fracture, including osteoporosis, a family history of hip fractures, a sedentary lifestyle, and certain medications. Regarding epidemiological trends, increasing incidence of hip fractures has been reported in some regions of the world, while a stable or decreasing trend has been reported in others[2,3]. This trend may be influenced by changes in lifestyle and demographic factors, such as an aging population and changes in physical activity levels. Identification of modifiable risk factors that can influence mortality and research on effective treatment options are critical in the effort to address this important issue.

The use of immune-inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and C-reactive protein-to-albumin ratio

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(CAR) as potential predictors of non-oncological mortality after various surgical procedures, including surgery for treatment of hip fractures, has increased in recent years. Several studies have examined this association[4-8]. In addition, a recent dissertation examined the relationship between immune inflammation indices and mortality in elderly patients with femoral neck fractures[9]. Of note, a link between the lymphocyte-to-C-reactive protein ratio (LCR) and NLR, as emerging biomarkers of systemic inflammation, to reduced survival rates in patients with other diseases such as colon cancer has been reported[10,11]. Albumin, which is regarded as a marker of nutritional status and overall health, may be a factor in the prognosis and outcomes of patients with Garden type IV fractures. Hypoalbuminemia has shown an association with increased morbidity and mortality in various medical conditions, including orthopedic injuries and surgical patients. In the context of Garden type IV fractures, low levels of albumin may be an indication of poor nutritional status and impaired healing capacity, potentially contributing to adverse outcomes[12].

Given the differences in treatment approaches and mortality rates among hip fracture patients[13,14], considering hip fractures as a homogeneous condition can be challenging. Therefore, the aim of the authors of this study is to demonstrate the clinical significance of LCR, NLR, and albumin specifically for assessment of Garden type IV FNFs.

Among other factors, LCR, NLR, and albumin have emerged as potential predictors of 2-year mortality for patients undergoing bipolar hemiarthroplasty (BHA). A retrospective study of elderly patients with FNFs was conducted in order to assess the value of these biomarkers for prediction of mortality and postoperative complications. The study compared the group of patients who died within two years with the group that did not in order to assess the effectiveness of LCR, NLR, and albumin for prediction of mortality, as well as their clinical benefits.

MATERIALS AND METHODS

1. Trial Design and Study Settings

Study design, setting, and patient study were performed according to the Declaration of Helsinki and followed the recommendations of the STROBE guidelines. This study was approved by the Institutional Review Board (IRB) of Busan Medical Center (approval No. 2022-12-001). The need for Informed Consent was waived by the IRB. Our study population consisted of 284 patients who underwent surgery performed by a single orthopedic surgeon between September 2014 and September 2020, consecutive elderly patients (age ≥65 years) undergoing hemiarthroplasty for treatment of Garden type IV FNF. Total hip arthroplasty (THA) is often our preferred approach for patients who are younger than 65 years old, healthier, and have a better overall functional status, particularly those classified as Koval grade 1. THA offers several advantages, including the potential for improved long-term outcomes and the preservation of joint function.

The study included patients who met specific criteria, including age over 65 and a diagnosis of Garden type IV FNF. Patients who underwent cementless hemiarthroplasty within four weeks of diagnosis were also included. However, those with time to surgery over four weeks, severe dementia or other psychiatric conditions, concomitant multiple fractures, pathological fractures, or those who were lost to follow-up were excluded from the analysis. A retrospective analysis of 270 patients was ultimately conducted (Fig. 1).

2. Cementless BHA Procedure and Postoperative Care

All patients underwent cementless BHA while under spinal anesthesia, and received an intrathecal injection of 0.2 mL/kg of bupivacaine (Heavy Marcaine™; AstraZeneca). Before the surgery, patients received instructions on performance of various exercises, including straight leg lifting, knee flexion/extension, and ankle dorsiflexion/plantarflexion, to aid in their rehabilitation. To prevent any postoperative complications, patients received instruction on postural adjustments and wore medical compression stockings throughout their hospital stay.

3. Outcome Assessment

Monitoring of the patient group was performed over a period of two years, and a phone-based death inquiry was conducted with both patient and guardian. The following information was collected: surgery date, sex, age, current height and weight, medical history, type of anesthesia used, Adjusted Age-adjusted Charlson Comorbidity Index Score (AACCIS), and American Society of Anesthesiologists score (ASA). Analysis of preoperative laboratory results including white blood cell count, red blood cell count, hemoglobin level, platelet count, neutrophil count, lymphocyte count, monocyte count, basic cell count, absolute neutrophil count, glomerular filtration rate, albumin level, C-reactive protein level (CRP), and erythrocyte sedimentation rate was also performed.

A two-step process was applied in order to extract mean-

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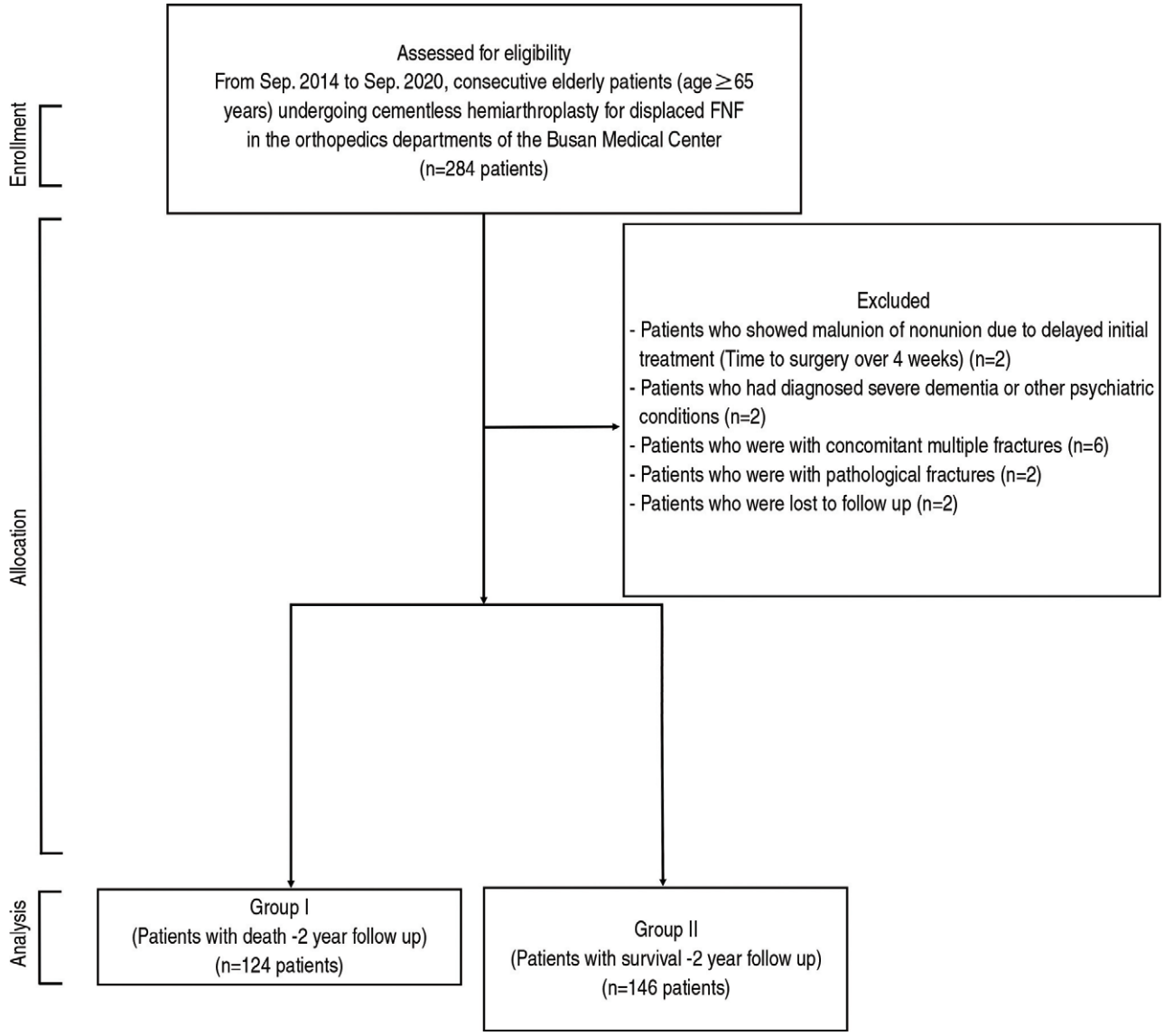

Fig. 1. Flow chart for patient selection.
FNF: femoral neck fracture.

ingful variables from this extensive list. First, a thorough review of the literature was conducted in order to identify laboratory factors that have been previously reported as potential predictors or indicators of outcomes in hip fracture surgery and related fields. Use of this process allowed us to focus on laboratory variables that have established or emerging associations with surgical outcomes and patient prognosis. Second, based on the findings from the literature review, a rigorous statistical analysis was performed in order to determine which specific variables among the collected laboratory results showed the strongest associations with the outcome of interest, which, in our study, was the 2-year mortality rate for patients who underwent BHA for treatment of Garden type IV FNF. Use of this process enabled selection of the most relevant and meaningful laboratory variables, including LCR, NLR, and albumin, which showed potential associations with the outcome of interest.

The number of doses administered by patient-controlled analgesia, the amount of rescue analgesics, and occurrences of nausea and vomiting were recorded. Analysis of Koval classification grade, T-cane walking duration, general postoperative complications, and duration of hospitalization was also performed.

4. Statistical Methods

Statistical analysis was performed using IBM SPSS Statistics software (ver. 26.0; IBM). Continuous variables were presented as mean±standard deviation or median values with interquartile ranges. A comparison of differences between the low-LCR and high-LCR groups, as well as between high the NLR, low NLR groups, and high albumin, low albumin groups, was performed using Independent Student's *t*-tests for data showing a normal distribution. Categorical variables were presented as numbers and percentages (%) and analysis was performed using chi-square or Fisher's exact test, as appropriate.

The optimal cutoff values for LCR, NLR, and albumin were determined using receiver operating characteristic (ROC) curves, using the Youden index in order to maximize sensitivity and specificity. The area under the curve (AUC) was calculated for determination of the significance of the ROC, and the significance level was set at $P<0.05$.

Univariate and multivariate Cox proportional hazard models were employed for analysis of 2-year mortality. Kaplan–Meier curves were used for estimation of patient survival and comparison was performed using the Tarone–Ware test. Statistical analyses were performed using IBM SPSS Statistics software (ver. 26.0) and R software (ver. 3.6.5; R Foundation for Statistical Computing). Statistical significance was defined as $P<0.05$, using a two-sided test.

RESULTS

1. Patients' Characteristics

The study population included 270 participants, with a distribution of 94 males and 176 females, and a mean age of 75.73 years (range, 65-99 years), as shown in Fig. 1. Of these, 124 patients (45.9%) died during the 2-year postoperative follow-up period, while no mortality occurred during the perioperative period.

2. Optimal Cutoff Values for LCR, NLR, and Albumin

The cutoff values for LCR, NLR, and albumin were 7.758, 3.854, and 3.750, respectively, based on the analysis of the receiver operating characteristic curve with a maximum Youden index. The results for the AUC for LCR, NLR, and albumin were 0.609, 0.609, and 0.624, respectively, indicating a fair predictive accuracy. The statistical significance of these biomarkers was confirmed by their *P*-values, which were all below 0.05. Specifically, the *P*-values for LCR, NLR, and albumin were 0.036, 0.003, and 0.001, respectively (Table 1). The ROC curves for LCR, NLR, and albumin are shown in Fig. 2.

3. Relationships between Patients' Data and Preoperative LCR, NLR

The association between patient characteristics and LCR and NLR parameters is shown in Table 2; 270 patients were analyzed. Of these, 157 patients (58.1%) were under the age of 75 and 113 patients (41.9%) were over 75 years old. The results for both the LCR and NLR groups showed similar trends; significant differences in age, sex, albumin, neutrophil, lymphocyte, CRP, LCR, and NLR were observed between the groups based on the optimal cutoff value. Of note, significantly higher mortality occurred among patients who were over 75 years old, female, had hypoalbuminemia, high neutrophil levels, low lymphocyte levels, high CRP levels, low LCR levels, and high NLR levels (Table 2).

4. Relationships between Clinical Variables and 2-Year Mortality (Kaplan–Meier Curve)

The results of survival analysis showed a median survival time of 20±1.16 months for patients with high LCR (≥7.758), while the median survival time was 15±3.06 months for those with low LCR (<7.758). Similarly, the median survival time was 20±1.88 months for patients with

Table 1. Optimal Cutoff Values for LCR, NLR, and Albumin

Variable	AUC (cutoff value)	Sensitivity	Specificity	95% CI	*P*-value
LCR	0.609 (7.758)	0.585	0.250	0.538-0.680	0.036*
NLR	0.609 (3.854)	0.392	0.400	0.539-0.678	0.003**
Albumin	0.624 (3.750)	0.659	0.219	0.555-0.694	0.001**

LCR: lymphocyte-to-C-reactive protein ratio, NLR: neutrophil-to-lymphocyte ratio, AUC: area under the curve, CI: confidence interval.
* $P<0.05$, ** $P<0.01$.

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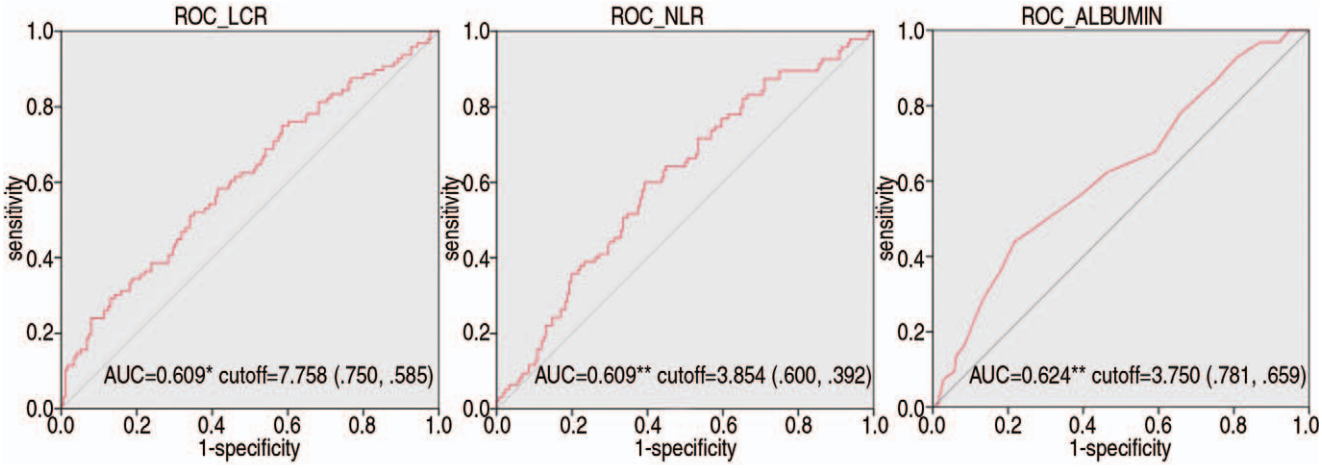

Fig. 2. The receiver operating characteristic curve (ROC curve) of lymphocyte-to-C-reactive protein ratio (LCR), neutrophil-to-lymphocyte ratio (NLR), and albumin.
AUC: area under the curve.

low NLR (<1.208), compared to 16±3.85 months for those with high NLR (≥1.208). In addition, the median survival time was 20 months for patients with high albumin (≥3.750), compared to 18 months for those with low albumin (<3.750) (Fig. 3).

The hazard ratios of the covariates are shown in Fig. 4. Significant results were obtained for sex, red blood cell, neutrophil, lymphocyte, monocyte, eosinophil, and AACCIS. Sex, neutrophil, lymphocyte, monocyte, eosinophil, AACCIS, and ASA showed positive coefficients, indicating an increased risk rate (hazard ratio [HR]). Conversely, red blood cells and ASA showed negative coefficients, indicating a decreased risk rate (HR).

5. Comparisons of Postoperative Complications

The results of comparison between the survival and death groups based on pain levels, walking ability, and surgery-related outputs are shown in Table 3. Koval classification was the only factor that showed a significant difference between the two groups (P=0.023), while no statistically significant difference was observed for any other factors.

The comparison of general complications, length of stay, and postoperative ambulatory functions between the two groups is outlined in Table 4. Of particular interest, postoperative nausea and vomiting (PONV) and delirium were the only factors that showed a statistically significant difference between the survival and death groups (P=0.013 and P=0.032, respectively).

DISCUSSION

Our retrospective study evaluated 2-year mortality in patients with garden type IV FNF who were treated with BHA. The 2-year survival rate was 54.1%, and our findings indicated that a lower LCR, a high NLR, and low albumin are markers for prediction of 2-year complications and mortality in these patients. High NLR, low LCR, and low albumin showed an association with significantly higher odds of in-hospital mortality. Based on our findings, we suggest that LCR can be regarded as a reliable predictor of in-hospital complication risk, and both high NLR and low LCR as useful prognostic markers for overall mortality risk.

NLR and LCR are both indicators of systemic inflammation; the former reflects the relative increase in neutrophil count and decrease in lymphocyte count, and the latter indicates decreased lymphocyte count relative to CRP levels. While NLR may be more indicative of later stages of inflammation, LCR could exhibit greater sensitivity in detecting early inflammation. Thus, low LCR and high NLR can be useful as independent predictors of in-hospital complications and mortality[15].

Our study provides evidence of the significance of preoperative LCR levels (<7.758) as a potential predictor of postoperative complications and prolonged hospital stays in patients with garden type IV FNF undergoing BHA. Consistent with previous studies[16], as a result of our multivariate analysis, hypoalbuminemia and AACCIS≥6 were identified as independent risk factors for 2-year mortality (P=0.041 and P=0.040, respectively), possibly due to their association with a vulnerable physiological state. Of note,

Table 2. Relationships between Patients' Characteristics and Preoperative LCR, NLR

Characteristic	Total (n=270)	Low LCR (n=175)	High LCR (n=95)	*P*	High NLR (n=145)	Low NLR (n=115)	*P*
Age				0.024*			0.031*
≤75 yr	157 (58.1)	53 (30.3)	63 (66.3)		45 (31.0)	70 (60.9)	
>75 yr	113 (41.9)	122 (69.7)	32 (33.7)		100 (69.0)	45 (39.1)	
Sex				0.032*			0.042*
Female	153 (56.7)	96 (54.9)	65 (68.4)		102 (70.3)	64 (55.7)	
Male	117 (43.3)	79 (45.1)	30 (31.6)		43 (29.7)	51 (44.3)	
Affected side				0.165			0.255
Left	137 (50.7)	88 (50.3)	53 (55.8)		79 (54.5)	61 (53.0)	
Right	133 (49.3)	87 (49.7)	42 (44.2)		66 (45.5)	54 (47.0)	
Anemia (Hb <12 for male, Hb <11 for female)				0.209			0.289
Yes	83 (30.7)	55 (31.4)	24 (25.3)		46 (31.7)	41 (35.7)	
No	187 (69.3)	120 (68.6)	71 (74.7)		99 (68.3)	74 (64.3)	
Hypoalbuminemia (<3.750 g/dL)				<0.001***			<0.001***
Yes	115 (42.6)	80 (45.7)	18 (18.9)		71 (49.0)	52 (45.2)	
No	155 (57.4)	95 (54.3)	77 (81.1)		74 (51.0)	63 (54.8)	
AACCIS				0.128			0.012*
1-3	7 (2.6)	5 (2.9)	0 (0.0)		1 (0.7)	6 (5.2)	
4-5	127 (47.0)	82 (46.9)	48 (50.5)		51 (35.2)	48 (41.7)	
≥6	136 (50.4)	88 (50.3)	47 (49.5)		93 (64.1)	61 (53.0)	
ASA class				0.101			0.078
I-II	201 (74.4)	129 (73.7)	60 (63.2)		28 (19.3)	77 (67.0)	
III-IV	69 (25.6)	46 (26.3)	35 (36.8)		117 (80.7)	38 (33.0)	
Neutrophil (50-70%)	68.19	70.68	63.73	<0.001***	77.89	59.97	<0.001***
Lymphocyte (×10³/L)	20.40	17.94	24.79	<0.001***	12.61	26.99	<0.001***
CRP (mg/dL)	8.64	12.82	1.15	<0.001***	9.66	7.76	<0.001***
LCR	24.79	-	-		10.25	37.10	<0.001***
NLR	4.84	5.68	3.32	<0.001***	-	-	<0.001***
2-Year mortality							
Yes	128 (47.4)	86 (49.1)	36 (37.9)	<0.001***	71 (49.0)	51 (44.3)	<0.001***
No	142 (52.6)	89 (50.9)	59 (62.1)	<0.001***	74 (51.0)	64 (55.7)	<0.001***

Values are presented as number (%) or mean only.
LCR: lymphocyte-to-C-reactive protein ratio, NLR: neutrophil-to-lymphocyte ratio, Hb: hemoglobin, AACCIS: Adjusted Age-adjusted Charlson Comorbidity Index Score, ASA: American Society of Anesthesiologists, CRP: C-reactive protein.
* $P<0.05$, *** $P<0.001$.

a previous study also identified allogeneic transfusion as a predictor of 1-year mortality in elderly patients who have undergone surgery for treatment of FNFs[17]. Our findings suggest that preoperative monitoring and management of these factors could potentially lead to improved patient outcomes and reduced mortality risk.

Our study found an association of a high NLR (≥3.854) on admission with fractures and worse outcomes in orthogeriatric patients, indicating its potential for use as an additional biomarker for therapeutic selection and preventive intervention. Elevated NLR, which is linked to the systemic inflammatory-immunological process of osteoporotic fractures and other age-related diseases[18,19], is influenced by various age-related co-morbid conditions and fractures[20,21]. In addition, a high NLR may be suggestive of a high probability of perioperative infectious complications, suggesting its potential use in guiding empirical antibiotic therapy. However, conduct of additional research is needed to determine whether patients with elevated NLR can benefit from administration of preoperative cardiovascular medications and/or antibiotics[22,23].

Bohl et al.[24] reported higher rates of mortality, sepsis, and unplanned intubation for patients with hypoalbuminemia. The findings of our study also demonstrated a significant

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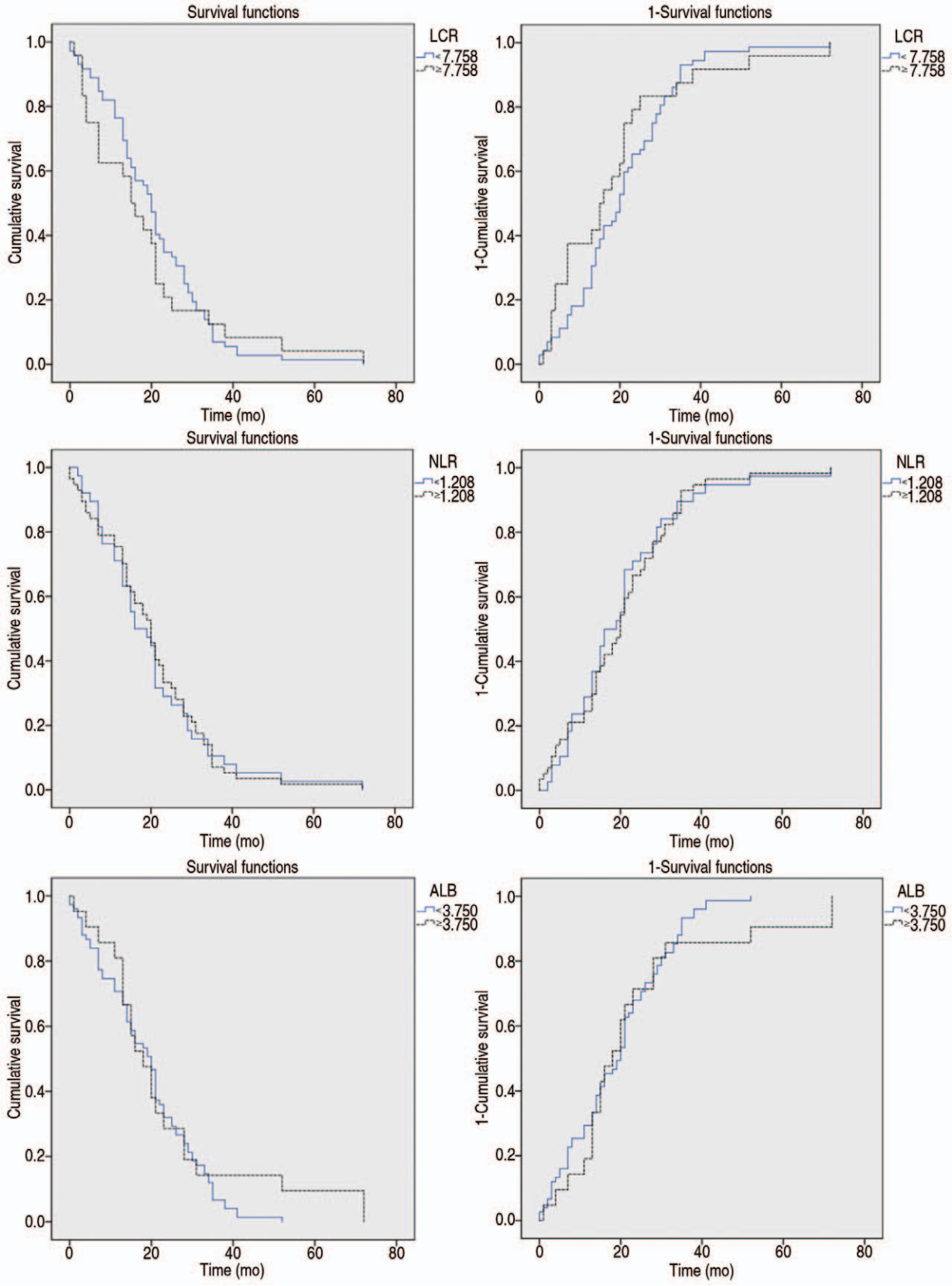

Fig. 3. Kaplan–Meier curve of lymphocyte-to-C-reactive protein ratio (LCR), neutrophil-to-lymphocyte ratio (NLR), and albumin (ALB).

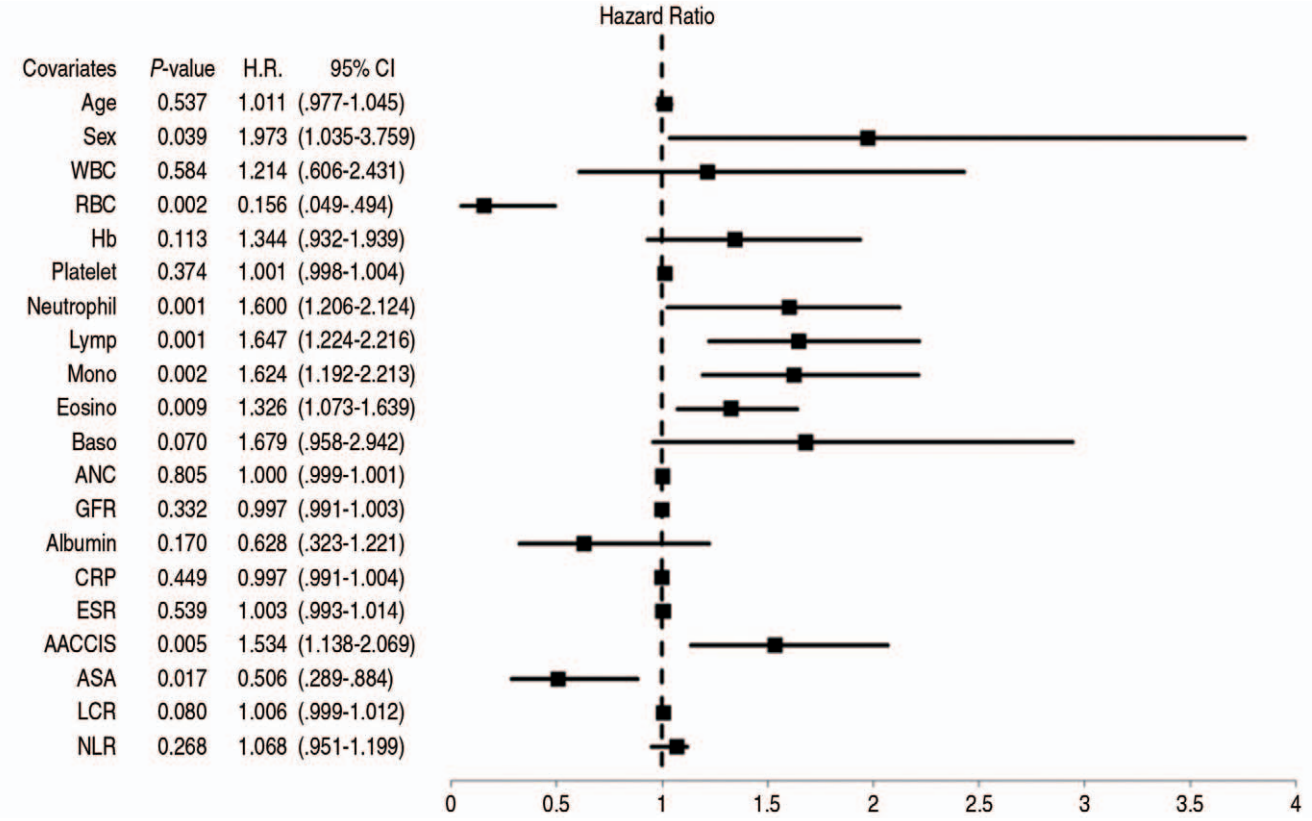

Fig. 4. Hazard ratio (HR) of covariates.
CI: confidence interval, WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin level, Lymp: lymphocyte count, Mono: monocyte count, Eosino: eosinophil, Baso: basic cell count, ANC: absolute neutrophil count, GFR: glomerular filtration rate, CRP: C-reactive protein level, ESR: erythrocyte sedimentation rate, AACCIS: Adjusted Age-adjusted Charlson Comorbidity Index Score, ASA: American Society of Anesthesiologists score, LCR: lymphocyte-to-C-reactive protein ratio, NLR: neutrophil-to-lymphocyte ratio.

association between hypoalbuminemia and increased mortality risk, with an albumin hazard ratio of 0.628 (Fig. 4). Noncompliance with instructions for postoperative rehabilitation can increase the risk of complications and mortality, underscoring the importance of early implementation of preventive protocols for this population in order to improve post-surgical quality of life and reduce mortality rates.

Compared with previous studies, our findings concur with existing evidence supporting the prognostic significance of inflammatory markers and albumin in hip fracture surgery. However, our study focuses specifically on Garden stage type IV FNFs, a distinct fracture subtype associated with higher rates of morbidity and mortality. Inclusion of the less commonly studied LCR parameter can result in enhanced understanding of inflammatory markers in this context with an emphasis on its potential as an independent predictor of patient outcomes.

Several underlying factors influence the observed associations between inflammatory markers and mortality in hip fracture surgery in the elderly. Systemic inflammation, as demonstrated by elevated NLR and decreased LCR, is known to contribute to impaired healing and increased susceptibility to complications. In addition, immune function and the body's ability to respond to surgical stress are influenced by albumin, a marker of nutritional status and overall health. These markers were identified as predictors of mortality, underscoring the importance of considering systemic inflammation and nutritional status in the preoperative assessment and management of patients with Garden stage type IV FNF.

In conclusion, our study provides valuable insights into the significance of inflammatory markers and albumin levels as prognostic indicators in patients undergoing BHA for treatment of Garden stage type IV FNF. The significant associations observed between LCR, NLR, albumin, and patient survival provide evidence of their potential clinical utility in risk stratification, treatment decision-making, and postoperative management.

Interpreting the findings of our study while keeping its lim-

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Table 3. Patients' Chracteristics and Intraoperative Volume Loss

	Survival group (n=142)	Death group (n=128)	*P*-value
Mean age (yr)	76.24	77.49	0.236
Sex			0.314
Male	60 (42.3)	43 (33.6)	
Female	82 (57.7)	85 (66.4)	
Mean BMI (kg/m^2)	22.08	22.05	0.405
Koval classification (grade)			0.023*
I	74	63	
II	21	17	
III	15	8	
IV	8	9	
V	10	8	
VI	6	11	
VII	8	12	
Mean operation time (min)	131.57	138.15	0.078
Mean blood loss (mL)	343	279	0.065
Mean urine output (mL)	360.02	279.67	0.059

Values are presented as mean only, number (%), or number only.
BMI: body mass index.
* $P<0.05$.

Table 4. Complications and Length of Stay and Ambulation Function of Survival and Death Groups

	Survival group (n=142)	Death group (n=128)	*P*-value
General complication			
Pressure sore	1	2	0.571
Pneumonia	2	3	0.875
DVT	0	0	-
PONV	0	6	0.013*
Delirium	3	10	0.032*
Local complication	0	-	-
Length of stay (day)	39.26	44.54	0.073
T-cane walking (day)	11.52	11.97	0.402

DVT: deep vein thrombosis, PONV: postoperative nausea and vomiting.
* $P<0.05$.

itations in mind is important. Because this study was retrospective and non-randomized, causality could not be established. Our sample size was relatively small; only 270 patient records were reviewed over a 2-year period, therefore, conduct of additional research may be necessary in order to obtain more accurate results. While our findings were adjusted for covariates including comorbidities and medications, there may be confounders that were not measured, such as the initiation of complementary therapies that were not accounted for.

Another limitation of our study is that no statistically significant relationship was observed between the biomarkers examined and the other risk factors considered. Despite extensive efforts to evaluate potential associations, the results of our data analysis did not show significant correlations. Conduct of future studies including larger sample sizes or alternative methodologies may be necessary in order to further examine the underlying mechanisms and unravel the intricate interplay between these biomarkers and other factors. In addition, because our data was primarily from an Asian cohort at a single center, there may be potential bias in our findings that should be considered.

CONCLUSION

Assessment of preoperative levels of LCR, NLR, and albumin can be performed for prediction of 2-year mortality and postoperative complications in elderly patients with displaced FNF undergoing hemiarthroplasty. Intensive care and rigorous follow-up strategies may be beneficial to patients with low levels of LCR and albumin, and high levels of NLR who are at higher risk.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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