







Neutrophil-Lymphocyte Ratio and C-Reactive Protein-Albumin Ratio as Predictors of Union Complications in Proximal Humerus Fractures

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ABSTRACT

Objective: Classification systems play a crucial role not only in determining diagnostic and therapeutic strategies but also in predicting patient prognosis. As the severity of trauma increases, the complexity of fractures and the classification level also tend to rise accordingly. In this study, we aimed to investigate how inflammatory markers that reflect trauma severity – such as the neutrophil-to-lymphocyte ratio (NLR) and the C-reactive protein-to-albumin ratio (CAR) – vary according to the NEER classification of proximal humerus fractures, and whether these markers can predict complications related to fracture healing.

Materials and Methods: This retrospective study reviewed patients with proximal humerus fractures treated with plate-screw osteosynthesis between January 2016 and January 2022 at a single medical center. 171 patients were grouped by bone union status and NEER classification. Non-union (5.4%) was defined as the absence of radiographic healing signs up to 6 months post-operatively. Blood samples for routine full blood count and biochemical analysis were collected within the first 24 h of emergency department admission for surgical evaluation. The correlation between the number of Neer fragments and inflammatory biomarkers was assessed. In addition, the association between inflammatory biomarkers and fracture healing was analyzed.

Results: The non-union rates of 3-part and 4-part fractures were higher than those of 2-part fractures. ($p=0.047$, $p=0.048$). However, there was no significant difference in blood parameters between the two groups. No statistically significant differences in C-reactive protein, Albumin, CAR, or NLR levels were found among Neer fracture types.

Conclusion: Inflammatory status may not have been affected by union or Neer classification, but integrating these classifications into multivariate union models for proximal humerus fractures might yield more scientifically rigorous and precise outcomes.

Keywords: C-reactive protein-to-albumin ratio, Neutrophil-lymphocyte ratio, Proximal humerus non-union

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INTRODUCTION

Fracture healing is a complex biological process influenced by a variety of clinical factors. Age, sex, osteoporosis, and chronic comorbidities have traditionally been utilized to predict fracture prognosis.^[1] Despite this, the role of systemic inflammatory status – particularly outside the context of overt infection – remains underexplored in present fracture healing models. Following a traumatic fracture, neutrophils are rapidly mobilized into circulation and, by the end of the 1st week, differentiate into tissue macrophages. These macrophages secrete cytokines that activate lymphocytes, thereby initiating and supporting tissue regeneration. However, excessive cytokine induction may disrupt this balance and impair bone union.^[2] Among inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR) has shown a strong correlation with various post-fracture outcomes, including delirium, thromboembolic events, and mortality.^[3,4]

In addition, C-reactive protein-to-albumin ratio (CAR), a marker reflecting both nutritional and inflammatory status, has been associated with the prognosis of various malignancies and with post-operative minor and major complications.^[5,6] Given this background, both NLR and CAR have emerged as promising markers for evaluating the severity of trauma and the extent of systemic inflammatory response. Their potential utility in predicting fracture healing outcomes remains a compelling subject for further investigation.

Fracture radiological classification systems are developed to establish diagnostic and treatment strategies and to predict prognosis.^[7] Consequently, some fracture classifications have demonstrated a relationship between fracture severity and these biomarkers indicating an inflammatory response.^[8–10] It remains unclear whether the Neer classification system, the most commonly used system for proximal humerus fractures, is influenced by the severity of inflammation.

Non-union following surgery for proximal humerus fractures represents significant morbidity and necessitates secondary surgical interventions.^[11,12] There is a paucity of studies investigating the relationship between these complications and pre-operative blood tests. This study aims to elucidate the relationship between CAR and NLR ratios and the Neer fracture classification. In addition, it seeks to examine the association between these biomarkers and post-operative union complications. We hypothesize that higher pre-operative CAR and NLR are significantly associated with higher Neer fracture classification grades, and that elevated CAR and NLR are independent risk factors for post-operative union complication.

MATERIALS AND METHODS

After receiving approval from the study ethics committee (Approval Number: 2025/115), the medical records of patients with proximal humerus fractures treated with plate-screw osteosynthesis between January 2016 and January 2022 were retrospectively reviewed at a single center. The study was conducted in accordance with the Declaration of Helsinki. Patients aged 18 and older who presented to the emergency orthopedic clinic with shoulder trauma, were diagnosed with proximal humerus fractures, and underwent plate-screw osteosynthesis as treatment and had a minimum of 6 months of radiological follow-up after surgery were included in the study. Exclusion criteria included inaccessible medical records, pathological fractures, ongoing oncological treatment, multiple traumas, additional infection findings during hospitalization, albumin replacement within the first 24 h of hospitalization due to rheumatologic disease, and the use of non-steroidal anti-inflammatory drugs (NSAIDs) or bisphosphonates before the fracture. Specifically, three patients with pathological fractures, fourteen with multiple fractures, two with bilateral proximal humerus fractures, seven with upper respiratory tract infections, one with rheumatoid arthritis, one with ankylosing spondylitis, three using NSAIDs, and two with inaccessible medical records were excluded from the study. Ultimately, 171 patients were included in the study out of the initial 204 patients (Fig. 1).

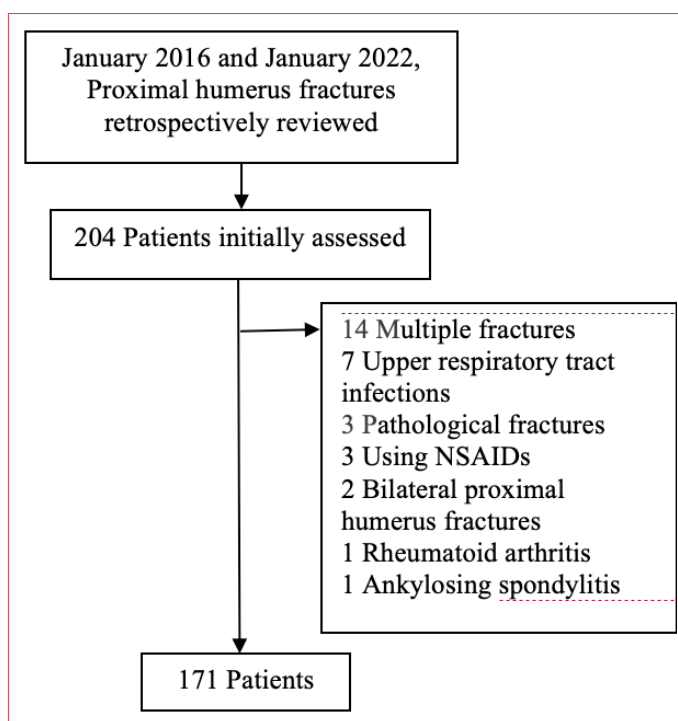


Figure 1. The patient flow chart in our study.

Neer fracture classification images, including standard AP axillary radiographs and computed tomography, were obtained from the hospital image archiving unit. Evaluations were independently conducted by two experienced orthopedic surgeons, and any discrepancies were resolved through joint re-evaluation. Patients were classified according to the Neer system based on the number of fragments.

Non-union was defined as the absence of radiographic evidence of fracture healing within 6 months post-operatively, characterized by distinct sclerotic borders between fracture fragments and the absence of trabecular bone formation.^[13] At 6 months, compared to early post-operative imaging, the occurrence of significant displacement between fracture fragments accompanied by broken screws was classified as a non-union complication (Figs 2 and 3). Union complications were subsequently confirmed through tomographic evaluation.^[5,13] Furthermore, post-operative screw cut-out or screw cut-through was categorized as union complications.^[13]

Routine hemogram and biochemistry blood samples for anesthesia preparation were collected from each patient within the first 24 h of emergency room admission. Laboratory tests previously evaluated as prognostic factors were analyzed from these blood samples, including hemoglobin (Hb) (g/dL), white blood cell count (K/ μ L), neutrophil count (mg/dL), lymphocyte count (mg/dL), platelet count (mg/dL), albumin (g/dL), C-reactive protein (CRP) (mg/dL), NLR, platelet/lymphocyte



Figure 2. Displacement with screw cut through at 6 months was defined as non-union.



Figure 3. At the 9-month follow-up, reduction loss and a sclerotic border on the medial side.

ratio, and CAR.^[3-5,14] The patients were divided into two groups: Those with complete fracture healing and those with non-union complications. The relationship between the number of Neer fragments and blood parameters was analyzed in these patients.

All patients were treated using a deltopectoral approach in the semi-chaise longue position under general anesthesia. Blood samples were collected within 24 h of the trauma. Surgeries were performed by two experienced trauma surgeons (each with over 10 years of experience). Proximal humerus locking plates and screws produced by Response Medical were used in all operations. Antibiotic prophylaxis was administered for 48 h post-surgery. Post-operative follow-up included a control visit 2 weeks later, with outpatient clinic records maintained.

Statistical Analysis

SPSS 21.0 for Windows was used for statistical analysis. Descriptive statistics were provided as numbers and percentages for categorical variables and as means, standard deviations, minimums, maximums, and medians for numerical variables. Due to the non-normal distribution of numerical variables, independent two-group comparisons were made using the Mann–Whitney U test, and independent multiple-group comparisons were made using the Kruskal–Wallis test. Group proportions were compared using the Chi-Square Test. Cohen's D test was performed for effect analysis. Relationships between numerical and ordinal variables were examined using Spearman Correlation Analysis. A binary logistic regression analysis was used to examine the risk factors associated with non-union complications. A multivariate analysis was performed using age, Hb level, albumin level, NLR, CAR, charlson comorbidity index (CCI) score, Neer fracture type, time to surgery, and sex. The statistical alpha significance level was set at $p < 0.05$.

RESULTS

The age and gender demographics of the patients are shown in Table 1. Non-union was observed in 5.8% of the patients (n=10). There was no gender difference between patients who had complications and those with complete union ($p=0.516$). A statistically significant difference was found in the Neer fracture types of patients with union complications ($p=0.046$). Among these patients, the incidence of Neer 3-part and 4-part fractures was high, while no Neer 2-part fractures were observed (Table 1). Post hoc comparisons revealed statistically significant differences in healing between 2- and 3-part fractures ($p=0.047$) as well as between 2- and 4-part fractures ($p=0.048$). Multivariate regression analysis revealed a statistically significant association between Neer fracture type and the risk of non-union (Table 2).

The mean time to surgery was 6.1 days. There was no significant relationship between union complications and the time to surgery ($p=0.737$). In addition, no significant difference was found in the age-adjusted CCI, nor in the present blood parameters between the two groups (Table 3). There was no statistically significant difference between the number of Neer fragments and CRP, Albumin, CAR, and NLR levels (Table 4). There was no correlation between the number of Neer fragments and CRP, Albumin, CAR, and NLR (Table 5).

Table 1. Comparison of Neer fracture type, side, and gender between two groups

	Non-union		Total n (%)	p*
	No n (%)	Yes n (%)		
Sex	161 (94.2)	10 (5.8)	171 (100)	0.516
Male	89 (55.3)	7 (70.0)	96 (56.1)	
Female	72 (44.7)	3 (30.0)	75 (43.9)	
Side	69 (42.9)	6 (60.0)	75 (43.9)	0.416
Left	92 (57.1)	4 (40.0)	96 (56.1)	
Neer	49 (30.4)	0 (0.0)	49 (28.7)	0.046
3	97 (60.2)	8 (80.0)	105 (61.4)	
4	15 (9.3)	2 (20.0)	17 (9.9)	

*Chi-square test.

Table 2. Multivariate analysis parameters associated with fracture healing

	Multivariate	
	Hazard ratio (95% confidence interval)	p
Age (year)	0.089	0.405
CCI*	−0.203	0.079
Neer classification	0.176	0.028
Side	−0.049	0.528
Sex	0.072	0.382
Time to surgery	0.096	0.223
Albumin (g/dL)	−0.049	0.537
Hemoglobin (g/dL)	−0.041	0.632
NLR*	0.053	0.505
CAR*	0.043	0.627

*CCI: Carlson index; NLR: Neutrophil/lymphocyte ratio; CAR: C-Reactive protein/albumin ratio.

DISCUSSION

The pre-operative inflammatory markers of the patients included in our study were not affected by the type of fracture and the number of fragments. The number of fragments may be a risk factor for non-union complication ($p=0.046$). However, there seems to be no relationship between union problems and pre-operative inflammatory status ($p=0.747$, $p=0.87$).

CRP is a key biomarker of acute inflammation and increases in response to various conditions, such as trauma and infection. However, the inflammatory response triggered by trauma or surgical intervention is generally more limited and resolves more rapidly compared to infection.^[15] Therefore, dynamic monitoring of CRP levels and the CAR in the post-operative period may provide more clinically meaningful insights for the early prediction of potential complications. In a study by Swarnkar et al.^[16] involving patients who underwent abdominal surgery, post-operative CRP and CAR levels were found to be effective predictors of complications. In the orthopedic surgery literature, particularly after prosthetic procedures, persistent elevation or further increase in CAR has been identified as a significant risk factor for periprosthetic joint infection. After total knee arthroplasty, failure of CRP and CAR levels to decline, or a secondary rise in these markers, raises clinical suspicion of infection.^[17,18] In our own patient cohort, pre-operative CAR values assessed after trauma were above the reference ranges reported in the lit-

Table 3. Comparison of age, Carlson index, and blood test result between two groups

	Non-union			95% confidence interval of the difference Lower- upper	Cohen's D	p*
	No Mean±SD (Min-Maks) (Median)	Yes Mean±SD Min-Maks (Median)	Total Mean±SD (Min-Maks)			
Age	54.5±14.6 18–90 (56)	55.5±11.2 35–68 (57)	54.5±14.4 (18–90)	(–10.33)–(8.26)	0.07	0.800
Carlson index	1.5±2.1 0–12 (1)	0.8±1.0 0–3 (0.5)	1.4±2.1 (0–12)	(–0.67)–(2)	0.47	0.476
Hemoglobin	11.2±1.9 1.4–16.5 (11.1)	11.0±1.6 7.4–12.9 (11.15)	11.2±1.9 (1.4–16.5)	(–1.04)–(1.44)	5.75	0.887
White blood cell	11.2±3.8 2.68–21.86 (10.8)	10.5±3.0 5.3–15.81 (10.6)	11.2±3.7 (2.68–21.86)	(–1.68)–(3.09)	0.25	0.662
Monocyte	0.88±1.50 0.11–13.6 (0.66)	0.69±0.34 0.25–1.2 (0.675)	0.87±1.46 (0.11–13.6)	(–0.74)–(1.13)	0.72	0.948
Neutrophil	9.50±7.10 0.83–86.8 (8.39)	8.44±2.68 4.2–12.7 (8.36)	9.44±6.92 (0.83–86.8)	(–3.40)–(5.51)	3.8	0.720
Lymphocyte	1.62±1.45 0.39–13.7 (1.35)	1.35±0.80 0.36–3.12 (1.06)	1.60±1.42 (0.36–13.7)	(–0.64)–(1.18)	0.26	0.576
Albumin	3.87±2.22 2.2–31 (3.7)	3.66±0.33 3.1–4 (3.805)	3.86±2.16 (2.2–31)	(–1.18)–(1.6)	0.13	0.777
CRPμ	56.0±70.4 0.43–364 (27)	52.8±55.4 5–141 (32.5)	55.8±69.4 (0.43–364)	(–41.66)–(47.97)	0.74	0.801
NLRμ	8.81±13.50 0.4–163.8 (6.5)	8.80±7.06 2.5–25.9 (6.7)	8.81±13.20 (0.4–163.8)	(–1.93)–(0.83)	1.56	0.818
PLRμ	218.0±150.3 21.8–1096.7 (178.1)	255.1±144.2 51.3–550 (225.4)	220.1±149.8 (21.8–1096.7)	(–144.61)–(59.41)	1.58	0.252
LMRμ	2.50±2.19 0–20.8 (2.1)	2.11±0.97 0.9–3.8 (1.9)	2.48±2.14 (0.0–20.8)	(–0.98)–(1.76)	1.1	0.808
CARμ	0.234±0.184 0.025–1.578 (0.195)	0.225±0.057 0.152–0.336 (0.201)	0.233±0.179 (0.025–1.578)	(–0.10)–(0.12)	0.06	0.282

*Mann–Whitney U test. μ CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; LMR: Lymphocyte/monocyte ratio; CAR: C-reactive protein/albumin ratio.

erature; however, these values did not appear to be reliable predictors of post-operative bone healing complications. This finding is also statistically supported by a small effect size (Cohen's $d=0.06$). In contrast, CRP and CAR levels measured and monitored over time in the post-operative period appear to provide more reliable results in the early detection of complications.^[19]

Most studies in the literature have focused on mortality rather than post-operative fracture complications. There is limited literature investigating the relationship between pre-opera-

tive CAR and post-fracture complications.^[8,9] Although studies investigating the association between aseptic non-union and inflammatory status exist in the literature, to the best of our knowledge, there are no publications specifically examining the relationship between pre-operative inflammatory status and aseptic non-union in patients with proximal humerus fractures.

Another parameter indicating systemic inflammatory status is NLR. The NLR ratio, similar to the CAR ratio, has been used to predict the severity of cardiovascular disease after hip frac-

Table 4. Association between Neer type and inflammation markers

	NEER			p
	2	3	4	
	Ort.±SD Min-Maks (Median)	Ort.±SD Min-Maks (Median)	Ort.±SD Min-Maks (Median)	
CRP*	45.5±55.5 0.43–235 (22)	59.6±71.7 0.59–333 (29)	61.3±89.5 2.9–364 (23)	0.642
Albumin	3.83±0.57 2.7–4.8 (3.9)	3.66±0.55 2.2–4.8 (3.7)	5.18±6.66 3.1–31 (3.6)	0.193
CAR*	0.24±0.22 0.11–1.58 (0.2)	0.22±0.14 0.09–1.19 (0.19)	0.26±0.24 0.03–1.14 (0.21)	0.870
NLR*	11.39±22.97 1.41–163.77 (6.62)	7.59±5.13 0.40–25.92 (6.47)	8.94±8.14 2.52–31.36 (5.99)	0.747

*CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, CAR: C-reactive protein/albumin ratio.

Table 5. Correlation between neer type and inflammation markers

	NEER	
	r	p
CRP*	0.061	0.431
Albumin	–0.138	0.072
CAR*	0.029	0.706
NLO*	–0.034	0.657

*CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; CAR: C-reactive protein/albumin ratio.

ture in some types of cancer.^[3,20,21] Johan et al.^[22] reported that pre-operative NLR is associated with tissue healing in patients with type 3 open fractures. Increased NLR may affect tissue healing and fracture healing. However, there are limited studies in the literature showing the relationship between aseptic non-union patients and NLR. In this study, conducted with proximal humerus fractures, the fact that no significant relationship was found between CAR and NLR may be due to the limited number of patients.

Fracture classification systems are performed to group fractures with similar fracture patterns to predict complications and guide the surgeon.^[8,23] Therefore, there is a relationship between some accepted fracture classifications and systemic inflammatory status.^[8,9] Wang et al.^[8] stated that the Schatzker classification reflected the severity of trauma and was related to inflammation markers. The generally accepted and most

commonly used classification system for proximal humerus fractures is the Neer classification. In our study, there was no relationship between pre-operative NLR and CAR after proximal humerus fractures and the Neer classification system. Therefore, the Neer classification may not reflect the systemic inflammatory status.

The primary limitation of our study is its retrospective design. Patient selection bias is inevitable among the proximal humerus fracture patients included in the study. Another limitation is the fact that avascular necrosis and non-union, despite being distinct entities, were not evaluated separately. Humeral head collapse and screw penetration may occur secondary to avascular necrosis.^[24] Changes in fracture reduction and plate-screw osteosynthesis during the post-operative period were considered as a non-union complication. Another notable limitation of the study is the potential variation of NLR and CRP levels in postmenopausal osteoporotic patients.^[25] Due to the retrospective nature of the study, sufficient data regarding osteoporosis status and bone mineral density were unavailable. However, patients with a history of bisphosphonate use were excluded based on their medical records. Our sample size may have limited our ability to detect significant differences; however, the effect size suggests a potential association with the NLR ratio (Cohen's $d=1.56$). In contrast, for the CAR ratio, neither the p-value nor the effect size indicated a meaningful difference between the groups (Cohen's $d=0.06$). These findings suggest that CAR may not have a substantial effect in this context; however, definitive conclusions are constrained by the limited sample size.

CONCLUSION

Proximal humerus fractures are among the most common intra-articular fractures and are frequently associated with significant shoulder mobility impairments. The complexity of the fracture, including the number of fragments, serves as a critical predictor for potential complications in fracture union. Systematic monitoring of the body's inflammatory response, alongside an analysis of its progression patterns, provides valuable insights for establishing evidence-based and effective clinical judgments.

DECLARATIONS

Ethics Committee Approval: The study was approved by Istanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (No: 2025/115, Date: 26/03/2025).

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