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THE PROGNOSTIC VALUE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO IN PREDICTING IN-HOSPITAL OUTCOMES FOR PATIENTS WITH NON-ST-ELEVATION ACUTE CORONARY SYNDROME

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Abstract

Objective: To investigate the association between admission neutrophil-to-lymphocyte ratio (NLR) and clinical outcomes during hospitalization in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) at a major cardiac center in Pakistan.

Study Design: A cross-sectional study

Place and Duration: This study was conducted at Peoples University of Medical and Health Sciences for Women Shaheed Benazirabad Nawabshah from November 2023 to November 2024

Methods: This study enrolled 156 patients aged 18–80 years with NSTE-ACS (unstable angina or non-ST-elevation myocardial infarction [NSTEMI]) after ethical approval and informed consent. NLR was calculated from admission blood samples and stratified as low-risk (<3.0), intermediate-risk (3.0–6.0), and high-risk (>6.0). Outcomes included symptom profiles, ejection fraction, arrhythmias, contrast-induced nephropathy (CIN), and mortality. Data were analyzed using IBM SPSS version 21, with statistical significance at $p<0.05$.

Results: Of 156 patients (60.3% male, mean age 51–60 years), 51.3% (n=80) were low-risk, 32.1% (n=50) intermediate-risk, and 16.6% (n=26) high-risk. Significant differences included shortness of breath prevalence (19.4% low-risk vs. 42.3% high-risk; p=0.004), ejection fraction (20–40%: 28.8% low-risk vs. 53.8% high-risk; p=0.019), neutrophils (60±8.90% low-risk vs. 85±3.00% high-risk;

p<0.001), and lymphocytes (33.5±7.02% low-risk vs. 9.5±2.25% high-risk; p<0.001). In-hospital trends showed arrhythmias (3.8% low-risk vs. 12.5% high-risk; p=0.073), CIN (2.5% low-risk vs. 9.6% high-risk; p=0.078), and mortality (1.3% low-risk vs. 3.8% high-risk; p=0.263), with uniform hospital stays (median 3 days; p=0.311).
Conclusion: Elevated NLR is associated with worse symptom severity, reduced ejection fraction, and trends toward increased complications in NSTE-ACS, supporting its prognostic value in resource-limited settings. Larger studies are needed for validation.

Keywords: Neutrophil-to-lymphocyte ratio (NLR), Non-ST-elevation acute coronary syndrome, Inflammatory biomarkers, In-hospital outcomes

Introduction

With lifestyle-driven increasing comorbidities changing the landscape of cardiovascular health, emergency cardiac care systems all around the world have been facing a significant burden. The rates of cardiovascular morbidity and mortality are disproportionately high in South Asia, and most prevalent of all is coronary artery disease (CAD) [1]. The literature notes that in Asia, the prevalence and mortality rates of cardiovascular diseases (CVD) are about 35 percent of the total deaths, 3850.8 per 100,000 and 152.2 per 100,000 individuals, respectively [1, 2].

Acute coronary syndromes (ACS), especially non-STelevation ACS (NSTE-ACS), contribute a substantial portion of hospitalizations and have been known to vary widely within diverse populations [3]. NSTE-ACS, or unstable angina and non-ST elevation myocardial infarction (NSTEMI), is defined as myocardial ischemia without ST-segment elevation persistence [4, 5]. Patients with NSTE-ACS have high risks of experiencing adverse outcomes, i.e., major adverse cardiovascular events (MACE), including recurrent myocardial infarction, heart failure, and death, despite improvements in pharmacological and interventional therapies [5]. Sudden cardiac death is a feared complication of ACS, which is frequently accompanied by debilitating functional and economic impairments [6]. Risk stratification and early detection of vulnerable patients are central to prevent myocardial damage and maximize therapeutic outcomes [3]. Additionally, recognizing inflammation as a key driver in the pathophysiology of coronary artery disease has opened new avenues for evaluating immune cell-based biomarkers that reflect the balance between pro-inflammatory and anti-inflammatory processes [3, 7]. Among various inflammatory biomarkers, the neutrophil-to-lymphocyte ratio (NLR), derived from routine complete blood count analysis, has emerged as a simple, cost-effective, and readily available indicator of systemic inflammation and immune imbalance [8]. Elevated NLR indicates neutrophil predominance, associated with enhanced inflammatory activity, while relative lymphopenia may signify stress-induced apoptosis or immune suppression [8, 9]. In cardiovascular contexts, NLR integrates hematological markers of acute phase response, offering prognostic insights beyond traditional risk factors [9]. Recent evidence underlines its utility in stratifying patients with NSTE-ACS, where higher admission NLR correlates with increased lesion complexity, as assessed by SYNTAX scores, and greater clinical risk via GRACE scoring systems [9, 10].

Research has consistently demonstrated the prognostic utility of admission NLR in NSTE-ACS patients. Elevated NLR levels are independently associated with poorer left ventricular function, increased lesion complexity, and higher long-term mortality following percutaneous coronary intervention (PCI) [11]. For instance, a retrospective cohort study highlighted NLR's predictive efficacy for long-term prognosis in new-onset ACS, showing higher NLR values linked to adverse events such as recurrent myocardial infarction and heart failure [12]. A meta-analysis further substantiates these findings. This meta-analysis of 90 studies involving 45,990 ACS patients reported that elevated NLR is a robust diagnostic and prognostic marker, with higher ratios in NSTEMI compared to other ACS subtypes, correlating with increased major adverse cardiovascular events (MACE) and all-cause mortality [13].

Despite advancements in emerging therapeutics and interventional procedures, NLR has been linked to increased risk of myocardial infarction, infarct size, MACE, and delayed recovery [14]. Its

accessibility from a routine complete blood count test adds to its clinical utility, particularly in low-resource settings [15]. This study investigates the association between NLR and clinical outcomes during hospitalization in patients admitted with NSTE-ACS, using data from a major cardiac center in Pakistan.

Methodology

This cross-sectional study involved the recruitment of consecutive patients with a diagnosis of NSTE-ACS, which included NSTEMI or unstable angina, after securing approval from the hospital's ethical review board. Adherence to the Declaration of Helsinki was maintained by acquiring verbal informed consent from all participants.

Patients aged 18–80 years presenting with symptoms suggestive of NSTE-ACS within 48 hours of onset were eligible for inclusion. Patients with recent surgery, trauma, malignancy, active infection, or those on immunosuppressive therapy were excluded to avoid confounding elevations in inflammatory markers.

NSTE-ACS diagnosis was based on clinical presentation (central chest pain lasting over 20 minutes, sensations of heaviness or pressure in the chest extending to the jaw or arms, or dyspnea with a respiratory rate above 18 breaths per minute) and ECG findings (significant T-wave inversions, transient elevation, or ST depression of 1 mm or greater). Troponin-I assays further classified patients into unstable angina (normal troponin) or NSTEMI (elevated troponin).

Upon admission, a 2-3 ml blood specimen was obtained by skilled nursing staff and placed in ethylenediaminetetraacetic acid (EDTA) tubes for prompt transfer to the on-site emergency department laboratory. Samples were promptly processed to assess total and differential leukocyte counts using an automated hematology analyzer. The NLR was calculated as the quotient of neutrophils divided by lymphocytes, with categorization into low-risk (<3.0), intermediate-risk (3.0-6.0), and high-risk (>6.0) groups.

In-hospital monitoring captured occurrences of new ST-T changes, atrial fibrillation, contrast-induced nephropathy (CIN), and death. ST-T changes encompassed ST depression (1 mm or more in leads other than aVR), ST elevation (1 mm or more), or T-wave inversion (any downward deviation). Atrial fibrillation was identified on 12-lead ECG by irregular R-R intervals with typical QRS morphology (including left or right bundle branch block) and absent or indistinct P waves. CIN was defined as a creatinine rise exceeding 0.5 mg/dL or an estimated glomerular filtration rate (eGFR) reduction of more than 20%.

Data analysis employed IBM SPSS version 21. Stratification occurred by NLR risk categories, enabling comparisons of demographics, clinical features, and hospital outcomes. Descriptive statistics comprised means with standard deviations (SD), medians with interquartile ranges (IQR), and percentages. Statistical tests such as analysis of variance or the Kruskal-Wallis test for continuous data, and chi-square tests for categorical data, were applied, considering a significance threshold of p less than 0.05.

Results

The study cohort comprised 156 patients with NSTE-ACS. Of the total 156 patients, 80 (51.3%) were classified as low risk (NLR < 3.0), 50 (32.1%) as intermediate risk (NLR 3.0-6.0), and 26 (16.6%) as high-risk (NLR > 6.0). The majority were male (n=94, 60.3%) and aged 51-60 years (n=64, 41%). Chest pain was the most common symptom across all groups, with 90% in low-risk, 88% in intermediate-risk, and 80.8% in high-risk groups. The NLR, admission neutrophil count, and lymphocyte count significantly differed between the groups ($p<0.001$). Ejection fraction also varied significantly ($p=0.019$), with more high-risk patients having an ejection fraction of 20-40%.

Table 1. Demographic and clinical characteristics of NSTE-ACS patients stratified by NLR risk categories.

	NLR Ratio			**p-value**
	Low risk (NLR < 3.0)	**Intermediate risk (NLR: 3.0 to 6.0)**	**High risk (NLR > 6.0)**	
Total (N)	80 (51.3%)	50 (32.1%)	26 (16.6%)	
Sex				
Male	57.5% (46)	60.0% (30)	69.2% (18)	0.389
Female	42.5% (34)	40.0% (20)	30.8% (8)	
Age (years)				0.523
20-50 years	18.8% (15)	24.0% (12)	23.1% (6)	0.423
51-60 years	44.8% (36)	40.0% (20)	30.8% (8)	
61-70 years	25.0% (20)	28.0% (14)	34.6% (9)	
>70 years	11.3% (9)	8.0% (4)	11.5% (3)	
Chest pain (CP)	90.0% (72)	88.0% (44)	80.8% (21)	0.426
CP duration (hours)	24 [IQR: 12-48]	24 [IQR: 5-48]	24 [IQR: 5-48]	0.032
Shortness of breath (SOB)	19.4% (15)	24.0% (12)	42.3% (11)	0.004
SOB duration (hours)	48 [IQR: 24-48]	24 [IQR: 4-36]	24 [IQR: 5-48]	0.038
Diagnosis				0.271
Unstable angina	12.5% (10)	10.0% (5)	7.7% (2)	
NSTEMI	87.5% (70)	90.0% (45)	92.3% (24)	
Admission ECG findings				0.347
Atrial fibrillation	1.3% (1)	2.0% (1)	3.8% (1)	0.520
ST-T changes	72.5% (58)	70.0% (35)	80.8% (21)	
Admission lymphocytes	33.5 ± 7.02	18.2 ± 2.50	9.5 ± 2.25	<0.001
Admission neutrophils	60 ± 8.90	75 ± 5.20	85 ± 3.00	<0.001
NLR	2.0 [IQR: 1.5-2.3]	3.6 [IQR: 3.2-4.5]	8.2 [IQR: 7.0-10.0]	<0.001
Ejection fraction				0.019
20-40%	28.8% (23)	39.0% (19)	53.8% (14)	
40-55%	40.0% (32)	38.0% (19)	30.8% (8)	
55-65%	31.3% (25)	23.0% (11)	15.4% (4)	

Among patients, complications varied across the NLR groups. New ST-T changes occurred in 3.8% (n=3) of low-risk, 2.0% (n=1) of intermediate-risk, and 1.9% (n=1) of high-risk patients (p=0.524). Arrhythmias were observed in 3.8% (n=3) of low-risk, 5.0% (n=2) of intermediate-risk, and 12.5% (n=3) of high-risk patients (p=0.073). The occurrence of PVCs was exclusive to high-risk patients (23.1%, n=3; p=0.152). The need for dialysis was seen in 1.9% (n=1) of intermediate-risk and 3.8% (n=1) of high-risk patients (p=0.214). Mortality was 1.3% (n=1) in low-risk and 3.8% (n=1) in high-risk (p=0.263). Hospital stays were consistent across groups (p=0.311).

Table 2: In-hospital complications and outcomes in NSTE-ACS patients based on NLR

	NLR Ratio			**P-value**
	Low risk (NLR < 3.0)	**Intermediate risk (NLR: 3.0 to 6.0)**	**High risk (NLR > 6.0)**	
In-hospital new ST-T changes	3.8% (3)	2.0% (1)	1.9% (1)	0.524
In-hospital arrhythmias	3.8% (3)	5.0% (2)	12.5% (3)	0.073
PVCs	0% (0)	0% (0)	23.1% (3)	0.152
VT/VF	25.0% (1)	20.0% (1)	50.0% (2)	0.601
Atrial fibrillation	33.3% (1)	50.0% (1)	66.7% (2)	0.698
Bradyarrhythmia	60.0% (3)	40.0% (2)	33.3% (1)	0.491
Contrast-induced nephropathy	2.5% (2)	3.5% (2)	9.6% (3)	0.078
Need for dialysis	0% (0)	1.9% (1)	3.8% (1)	0.214
Hospital stay (days)	3 [IQR: 2-4]	3 [IQR: 2-4]	3 [IQR: 2-4]	0.311
In-hospital mortality	1.3% (1)	0% (0)	3.8% (1)	0.263

*PVCs=premature ventricular contractions, VT/VF=ventricular tachycardia/ventricular fibrillation

Discussion

This study investigates the association between NLR and clinical outcomes during hospitalization in patients admitted with NSTE-ACS, using data from a major cardiac center in Pakistan. In our cohort of 156 patients, the stratification revealed a predominance of low-risk individuals (51.3%), with progressively fewer in intermediate (32.1%) and high-risk (16.6%) categories based on NLR thresholds of <3.0, 3.0-6.0, and >6.0, respectively. These proportions align with patterns observed in a study by Avci et al. who demonstrated that elevated NLR was a significant predictor of in-hospital mortality in NSTEMI patients, reporting an AUC of 0.783 with a cut-off value of 3.625 [16].

Demographic profiles in our analysis demonstrated a male majority (60.3%) and peak incidence in the 51-60 age group (41%), with no significant differences across NLR strata ($p=0.389$ for sex; $p=0.523$ for age). This consistency echoes findings from a meta-analysis of 90 studies, which reported similar gender and age distributions without NLR-linked variations in baseline demographics [13]. However, contrasting evidence emerges from a study by Zengin et al., which conversely associated high NLR with younger age in coronary slow flow NSTE-ACS, predicting recurrent infarction (hazard ratio 1.48; $p<0.01$), diverging from our neutral demographic profile [17].

Hematological parameters showed marked disparities, with neutrophils rising (60% to 85%, $p<0.001$) and lymphocytes declining (33.5% to 9.5%, $p<0.001$) in higher NLR categories. This finding corroborates a study by Yang et al. associating NLR with inflammatory shifts in ACS severity [18]. Ejection fraction in our study varied significantly, with 53.8% of high-risk patients in the 20-40% range. This is consistent with a meta-analysis by Banahene et al. indicating NLR's role in predicting reduced ventricular function post-ACS [19]. Yet, a cohort study by Lin et al. contrasted this by reporting no NLR-EF association in NSTE-ACS subsets, highlighting potential influences from revascularization timing [20].

In the current study, arrhythmia demonstrated an increasing pattern, which is consistent with a study by Zhang et al. linking high NLR to elevated in-hospital arrhythmia risk through multivariate logistic regression (odds ratio 1.45, $p<0.05$), attributing it to neutrophil-mediated myocardial inflammation [21]. A variation is specific subtypes was seen in our study with premature ventricular contractions exclusive to the high-risk group, ventricular tachycardia/ventricular fibrillation showing no clear trend, atrial fibrillation increasing modestly, and bradyarrhythmia decreasing. These findings are similar to the meta-analysis by Pruc et al. associating NLR with arrhythmic events in acute coronary syndrome, including ventricular arrhythmias as markers of adverse remodeling [13]. For CIN rates

that increased in our study, a retrospective cohort study in 418 ACS patients undergoing PCI demonstrated NLR as an independent risk factor (OR 2.12; 95% CI 1.34-3.36; p=0.001), with cut-offs >3.5 yielding higher incidence (15.2% vs. 4.8%), opposing our non-significant trend and highlighting potential underpowering in smaller samples [22].

In this study, in-hospital mortality displayed a slight increase in high-risk patients, similar to trends in an observational study where higher NLR predicted elevated mortality (8.5% vs. 1.8%), though our non-significance may stem from smaller sample size [8]. Hospital stays remained uniform at a median of 3 days (p=0.311), consistent with some cohorts showing no NLR impact on duration [23]. Yet, this contrasts with a study by Diniz et al. where elevated NLR correlated with prolonged stays (β=0.131, p<0.05), possibly reflecting differences in comorbidity management [24].

This study is limited by its single-center design, which may restrict generalizability to broader populations. The relatively small sample size of 156 patients could reduce statistical power, potentially contributing to non-significant findings in some outcomes. Furthermore, the absence of detailed clinical and laboratory investigations to identify causes of elevated NLR introduces potential confounders. As a result, larger, multicenter studies are required to confirm NLR's role in risk stratification for NSTE-ACS patients in similar settings.

Conclusion

This study highlights the potential of admission NLR ratio as a valuable biomarker for risk stratification in patients with NSTE-ACS. Our findings reveal that elevated NLR correlates with significant hematological shifts, reduced ejection fraction, and trends toward increased in-hospital complications such as arrhythmias and contrast-induced nephropathy, though statistical significance was limited in some areas. These observations reinforce NLR's role in identifying high-risk subsets amid persistent inflammatory burdens, offering a cost-effective tool for resource-constrained settings. Nonetheless, the non-significant associations in mortality and other outcomes highlight the need for larger, multicenter trials to refine its prognostic utility and integrate it with established scoring systems for enhanced patient management.

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