ORIGINAL ARTICLE

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE) IN STEMI PATIENTS WITH ELEVATED NEUTROPHIL-TO-LYMPHOCYTE RATIO UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION-A STUDY IN PAKISTANI COHORT

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Background: Cardiovascular diseases (CVDs) remain the leading cause of death globally, with approximately 20.5 million fatalities recorded in 2021, representing nearly one-third of all deaths.[1] Low- and middle-income countries (LMICs) bear a disproportionate burden, accounting for 80% of these cases.[1] ST-segment elevation myocardial infarction (STEMI), a severe form of coronary heart disease (CHD), continues to contribute significantly to global morbidity and mortality.[2] In countries such as India and China, STEMI accounts for 60–80% of hospital admissions related to myocardial infarction (MI). This study aimed to evaluate the association between an elevated neutrophil-to-lymphocyte ratio (NLR) and the occurrence of major adverse cardiovascular events (MACE) in patients with STEMI undergoing primary percutaneous coronary intervention (PPCI). **Methods:** A retrospective observational study was conducted at a tertiary care cardiac center in Rawalpindi, Pakistan, from December 2018 to May 2019. A total of 155 STEMI patients treated with PPCI were included. Patients with active infections, autoimmune disorders, hematologic malignancies, severe renal or hepatic impairment, or those receiving immunosuppressive therapy were excluded. NLR values were calculated from blood samples collected upon hospital admission, and patients were divided into two groups: those with elevated NLR (≥4.8) and those with lower NLR (<4.8). The primary outcome was in-hospital MACE, defined as mortality and non-fatal MI. Statistical analysis involved univariate and multivariate logistic regression to identify independent predictors of MACE. **Results:** Of the 155 patients, 39 (25.2%) experienced MACE. The incidence of MACE was significantly higher in the elevated NLR group (84.6%) compared to the lower NLR group (15.4%) (p= 0.001). Univariate analysis demonstrated a strong association between high NLR and increased MACE risk (OR: 2.11; 95% CI: 1.61–2.76; p=0.001). Multivariate analysis, after adjusting for confounding variables, confirmed NLR as an independent predictor of MACE (AOR: 2.08; 95% CI: 1.57–2.74; p=0.001). **Conclusion:** Elevated NLR is a significant predictor of MACE in STEMI patients undergoing PPCI. Given its simplicity and cost-effectiveness, NLR may serve as a valuable biomarker for early risk stratification and targeted intervention in STEMI management.

Keywords: Neutrophil-to-lymphocyte ratio; STEMI; Major adverse cardiovascular events; Primary percutaneous coronary intervention; Risk stratification; Pakistan

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INTRODUCTION

Cardiovascular diseases (CVDs) remain a leading cause of death globally, with approximately 20.5 million fatalities recorded in 2021, representing nearly one-third of all deaths.[1] Low- and middle-income countries (LMICs) bear a significant burden, accounting for 80% of these cases.[1] ST-segment elevation myocardial infarction (STEMI) is a severe form of coronary heart disease (CHD) and continues to be a major contributor to both morbidity and mortality worldwide.[2] In nations such as India and China, STEMI is responsible for 60–80% of hospital admissions related to myocardial infarction (MI).[3]

In Pakistan, STEMI remains a major public health concern. A recent study reported that 78.4% of MI cases in Pakistan were classified as STEMI, highlighting its dominance as an acute coronary event.[4] Furthermore, a retrospective study spanning five years documented 5,343 STEMI-related hospital admissions, emphasizing the growing burden of this condition.[5] Early risk stratification and timely

intervention are critical for reducing STEMI-related complications and mortality.[4, 5] Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion strategy, though patient prognoses vary due to individual risk factors and inflammatory responses.[6] Consequently, identifying cost-effective and reliable prognostic markers is essential to enhance risk assessment and optimize treatment strategies in STEMI patients undergoing PPCI.[6]

The neutrophil-to-lymphocyte ratio (NLR), derived from routine blood counts, has emerged as a potential marker of systemic inflammation and adverse cardiovascular events.[7] Studies have linked elevated NLR to platelet activation, endothelial dysfunction, and microvascular obstruction, all of which contribute to adverse outcomes in STEMI patients.[8–11] A meta-analysis including 35 studies and 28,756 patients found that elevated NLR was linked to a 3.52-times greater risk of in-hospital mortality and a 3.32-fold increased risk of long-term mortality. [11] Furthermore, high NLR has been associated with worse left ventricular function, higher incidence of arrhythmias, and increased likelihood of heart failure following STEMI.[8–11] Given its accessibility and cost-effectiveness, NLR has the potential to be integrated into routine risk stratification models for STEMI patients.

While NLR is a well-established inflammatory and prognostic marker in STEMI, its clinical implications and predictive accuracy within specific populations remain underexplored. The majority of studies have been conducted in Western and East Asian populations, with limited data available for South Asian, particularly Pakistani, STEMI patients. Given the unique demographic and clinical characteristics of the Pakistani population, including younger STEMI onset compared to Western populations**,** high burden of hypertension, diabetes mellitus, smoking, and dyslipidaemia, and differences in genetic predisposition, dietary patterns, and healthcare accessibility. Assessing the frequency of MACE in patients with elevated NLR specifically in Pakistani STEMI patients undergoing PPCI is critical to determine whether existing findings apply to this population. Thus, the aim of this study is to compare the frequency of MACE in STEMI patients with elevated versus non-elevated NLR during hospitalization undergoing PPCI at a tertiary care hospital, Karachi, Pakistan.

MATERIAL AND METHODS

This study was conducted at a tertiary care cardiac center in Rawalpindi, Pakistan, from December 2018 to May 2019. The research adhered to the STROBE guidelines for observational studies and was approved by the hospital's Ethics Review Committee (ERC). Written informed consent was obtained from all participants before inclusion.

The sample size was calculated using the WHO sample size calculator, assuming a 5% significance level (α), an estimated 80% prevalence of MACE among patients with elevated NLR[12], and an absolute precision of 6.3%. This yielded a final sample of 155 participants. Eligible patients were between 18 and 75 years old, diagnosed with STEMI, and underwent PPCI during hospitalization. Diagnosis was based on clinical symptoms such as shortness of breath, chest pain, dizziness, sweating, nausea, palpitations, and anxiety, along with ECG findings indicating ST-segment elevation in at least two contiguous leads (≥2 mm in men and ≥1.5 mm in women in leads V2–V3, or ≥1 mm in other contiguous leads). Patients were excluded if they had active infections (e.g., fever, chills), autoimmune disorders, hematologic malignancies, neoplastic diseases, severe renal dysfunction (eGFR <30 mL/min/1.73 m²), hepatic impairment, or were receiving immunosuppressive therapy or corticosteroids. Exclusion criteria were confirmed through a review of medical history, clinical examination, and laboratory investigations. A non-probability consecutive sampling technique was employed.

Data collection was carried out using a structured questionnaire administered by trained medical personnel. Information collected included demographic details, baseline clinical characteristics (age, gender, hypertension, diabetes, dyslipidaemia, and smoking status), and laboratory findings. Venous blood samples were obtained prior to thrombolysis for a complete blood count (CBC) analysis. These samples were processed within one hour using an automated haematology analyzer (Diatron ABACUS 380, ISO-9001 certified). The total white blood cell (WBC) count, neutrophil count, and lymphocyte count were recorded. The NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count. Based on NLR levels, patients were categorized into two groups: elevated NLR (≥4.8) and non-elevated NLR (<4.8). Participants were monitored for the development of MACE during hospitalization, which included mortality and non-fatal MI.

Statistical analysis was conducted using SPSS software version 20. Continuous variables, such as age, neutrophil count, lymphocyte count, and NLR, were expressed as mean±standard deviation (SD). Categorical variables, including gender, comorbid conditions (hypertension, diabetes, smoking, and hyperbilirubinemia), and MACE occurrence, were presented as frequencies and percentages. To compare the frequency of MACE between elevated and non-elevated NLR groups, the Chi-square test was used. Univariate and multivariate binary logistic regression

analyses were performed to determine predictors of MACE. Crude odds ratios (OR) with 95% confidence intervals (CI) were calculated for univariate analysis. Variables with a *p*-value ≤0.25 in univariate analysis were included in the multivariate logistic regression model to adjust for potential confounders. Adjusted odds ratios (AOR) with 95% CI were computed, and factors with a *p*-value ≤0.05 in the multivariate analysis were considered independent predictors of MACE.

RESULTS

A total of 155 patients participated in the study, with 85 (54.8%) being male. The mean age of the study population was 53.62±8.97 years. In terms of comorbidities, 27 patients (17.4%) had hypertension, 23 (14.8%) had diabetes, 34 (21.9%) were smokers, and 36 (23.2%) presented with hyperbilirubinemia. The mean neutrophil count recorded was 9546.83±985.07 /mm³, while the mean lymphocyte count was 2715.53±509.51 /mm³, resulting in a calculated neutrophil-to-lymphocyte ratio (NLR) of 4.21±2.15. (Table 1)

Among the total study population, 39 patients (25.2%) experienced major adverse cardiovascular events (MACE). (Figure 1) A comparison between the two NLR groups showed that 33 patients (84.6%) in the elevated NLR category developed MACE, whereas only 6 patients (15.4%) in the non-elevated NLR group experienced these events. This difference was statistically significant, indicating a higher risk of MACE in patients with elevated NLR (*p*=0.001). (Table 2)

Univariate analysis demonstrated a significant correlation between elevated NLR and increased MACE risk, with an odds ratio (OR) of 2.11 (95% CI: 1.61–2.76, *p*=0.001). Additionally, hypertension was found to be significantly associated with MACE (OR: 2.45, 95% CI: 1.02–5.88, *p*=0.044). Other factors, such as age (OR: 1.04, 95% CI: 0.99–1.08, *p*=0.090), male gender (OR: 1.93, 95% CI: 0.91–4.12, *p*=0.089), and diabetes (OR: 2.18, 95% CI: 0.86–5.54, *p*=0.100), exhibited a potential association with MACE but did not reach statistical significance. Smoking (OR: 1.58, 95% CI: 0.69–3.56, *p*=0.276) and hyperbilirubinemia (OR: 0.81, 95% CI: 0.33–1.96, *p*=0.643) were not significantly associated with MACE in univariate analysis.

Multivariate analysis, adjusting for potential confounding factors, confirmed that elevated NLR remained the sole statistically significant independent predictor of MACE, with an adjusted odds ratio (AOR) of 2.08 (95% CI: 1.57–2.74, *p*=0.001). The associations initially observed with age (AOR: 1.03, 95% CI: 0.97–1.08, *p*=0.308), male gender (AOR: 2.23, 95% CI: 0.85–5.83, *p*=0.100), hypertension (AOR: 1.95, 95% CI: 0.63–6.05, *p*=0.247), and diabetes (AOR: 1.26, 95% CI: 0.38–4.12) did not remain statistically significant following adjustment. (Table 3)

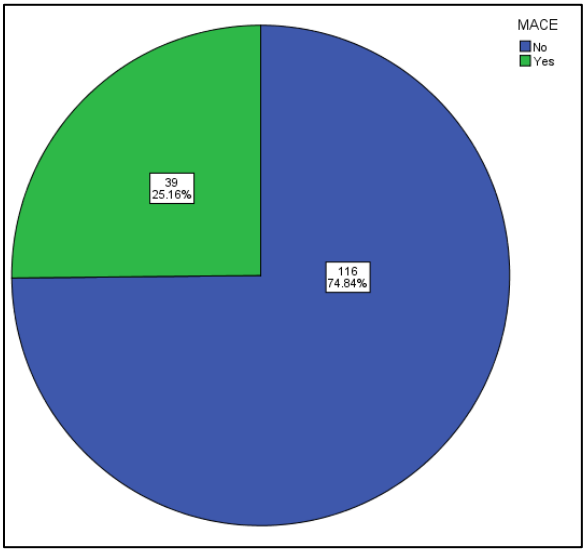

Figure-1: Frequency distribution of MACE (n=155)

Table-1: Baseline characteristics of the study sample (n=155)

Characteristics	n (%) or Mean±SD
Age (years)	53.62±8.97
Gender	
Female	70 (45.2)
Male	85 (54.8)
Hypertension	
Yes	27 (17.4)
No	128 (82.6)
Diabetes	
Yes	23 (14.8)
No	132 (85.2)
Smoking	
Yes	34 (21.9)
No	121 (78.1)
Hyperbilirubinemia	
Yes	36 (23.2)
No	119 (76.8)
Neutrophils counts (/mm^3)	9546.83±985.07
Lymphocytes counts (/mm^3)	2715.53±509.51
NLR	4.21±2.15

Table-2: Relationship between elevated NLR and MACE (n=155)

	MACE		
Elevated NLR	**Yes**	**No**	***p*-value**
Yes	33 (84.6%)	24 (20.7%)	
No	6 (15.4%)	92 (79.3%)	0.001*

Table-3: Factors associated with MACE in patients undergoing for PPCI (n=155)

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p*-value**	**AOR (95% CI)**	***p*-value**
Age (years)	1.04 (0.99-1.08)	0.090**	1.03 (0.97-1.08)	0.308
Gender				
Female	Ref		Ref	
Male	1.93 (0.91-4.12)	0.089**	2.23 (0.85-5.83)	0.100
Hypertension				
No	Ref		Ref	
Yes	2.45 (1.02-5.88)	0.044*	1.95 (0.63-6.05)	0.247
Diabetes				
No	Ref		Ref	
Yes	2.18 (0.86-5.54)	0.100**	1.26 (0.38-4.12)	0.706
Smoking				
No	Ref			
Yes	1.58 (0.69-3.56)	0.276		
Hyperbilirubinemia				
No	Ref			
Yes	0.81 (0.33-1.96)	0.643		
NLR	2.11 (1.61-2.76)	0.001**	2.08 (1.57-2.74)	0.001*

***Variables that met the threshold value of 0.25 for inclusion in the multivariate analysis*
**Variables significant at the <5% level of significance*

DISCUSSION

Our study demonstrates a significantly higher incidence of MACE in patients with elevated NLR (≥4.8) compared to those with non-elevated NLR. Among the 155 patients included, 25.2% experienced MACE, with 84.6% of these occurring in the elevated NLR group versus only 15.4% in the non-elevated NLR group (p=0.001). Furthermore, multivariate logistic regression analysis confirmed that elevated NLR remained an independent predictor of in-hospital MACE (AOR: 2.08; 95% CI: 1.57–2.74, p=0.001), even after adjusting for potential confounders such as age, gender, hypertension, diabetes, smoking, and hyperbilirubinemia. No other factors, including traditional cardiovascular risk factors, showed a statistically significant association with MACE after adjustment. These results emphasize the prognostic value of NLR in STEMI patients undergoing PPCI and suggest that systemic inflammation plays a crucial role in determining early adverse outcomes.

Our results align with international studies that have established NLR as a strong prognostic biomarker for adverse cardiovascular outcomes in STEMI patients.[8-15] Sawant et al. evaluated 250 STEMI patients undergoing revascularization and identified an NLR cut-off of 7.4 for predicting short- and long-term mortality. Kaplan-Meier survival curves showed that an NLR above this threshold was significantly associated with worse 30-day and 2-year survival rates.[16] In contrast, our study used a lower cut-off (≥4.8), which may reflect differences in inflammatory profiles and baseline characteristics of the Pakistani population.

A meta-analysis of 35 studies involving 28,756 STEMI patients found that an elevated NLR was associated with a 3.52-fold increased risk of in-hospital mortality and a 3.32-fold increased risk of long-term mortality.[11] Similarly, Pan *et al*. examined 636 STEMI patients and reported a significant correlation between high NLR and in-hospital mortality (r = 0.439, p<0.001).[17] Our findings are consistent with these studies, reinforcing the utility of NLR as an early predictor of MACE.

In South Asia, Her AY *et al*. evaluated 172 STEMI patients undergoing PPCI and found that an NLR cut-off of 5.8 was associated with a significantly higher rate of severe cardiovascular events (43.9% vs. 6.9%; p<0.001).[18] The variation in NLR cut-off values across studies suggests that population-specific factors, such as genetics, baseline inflammatory states, and healthcare access, may influence optimal thresholds.

Nationally, studies in Pakistan have reported that approximately 52.4–56% of myocardial infarction cases are STEMI, with a growing burden on healthcare facilities.[19,20] Given the limited availability of advanced inflammatory biomarkers in resource-constrained settings, our findings support the use of NLR as a cost-effective and easily accessible tool for risk stratification. By incorporating NLR into routine clinical assessments, high-risk patients can be identified early and managed more aggressively to improve outcomes.

The strong association between elevated NLR and increased MACE risk can be attributed to the role of inflammation in acute coronary syndromes.[11,21,22] Neutrophils contribute to myocardial damage by releasing pro-inflammatory cytokines, proteolytic enzymes, and reactive oxygen species, which exacerbate endothelial dysfunction and thrombus formation.[23,24] Conversely, lymphocytes play a regulatory role in modulating inflammation and

promoting myocardial healing.[23,24] An elevated NLR suggests an excessive neutrophil-driven inflammatory response, which has been linked to microvascular dysfunction, impaired coronary reperfusion, and increased infarct size, all of which contribute to poor cardiovascular outcomes.[11–16, 23,25]

Furthermore, inflammation-induced platelet activation and endothelial injury are known to promote hypercoagulability, increasing the risk of recurrent ischemic events, arrhythmias, and heart failure.[11,21,22] The significantly higher incidence of MACE in the elevated NLR group in our study supports the hypothesis that systemic inflammation, as reflected by NLR, serves as a critical determinant of early adverse outcomes in STEMI patients.

This study provides valuable insights into the prognostic role of NLR in a Pakistani STEMI cohort, addressing a gap in regional data. A key strength of our study is the use of a well-defined methodology, including standardized diagnostic criteria for STEMI, strict inclusion and exclusion criteria, and robust statistical adjustments to minimize confounding factors. Unlike some previous studies that used higher NLR thresholds, our study identified a lower cut-off (≥4.8), which may enhance early risk stratification in high-risk populations. Additionally, the use of prospectively collected data reduced the risk of selection bias, and our findings were validated using both univariate and multivariate analyses.

Despite its strengths, our study has some limitations. First, it was conducted at a single tertiary care center with a relatively small sample size (n=155), which may limit the generalizability of our findings. Larger, multicenter studies are needed to validate our results in diverse populations. Second, we only assessed in-hospital outcomes, and long-term prognostic implications of elevated NLR were not evaluated. Future studies should follow patients beyond hospitalization to determine whether NLR remains predictive of long-term cardiovascular mortality and morbidity. Third, we did not include other inflammatory markers, such as the platelet-to-lymphocyte ratio (PLR) or C-reactive protein (CRP), which could provide additional insights into the inflammatory burden in STEMI patients. Incorporating multiple inflammatory markers in future studies may improve risk stratification models. Lastly, while our study adjusted for key confounders, residual confounding due to unmeasured variables, such as socioeconomic factors, medication adherence, and dietary patterns, cannot be entirely ruled out. The findings of our study have significant clinical implications, particularly in resource-limited settings like Pakistan. Given the simplicity, affordability, and widespread availability of NLR as a biomarker, it can be easily incorporated into routine clinical assessments for STEMI patients. Early identification of high-risk patients using NLR could lead to more targeted interventions, such as intensified antiplatelet therapy, closer hemodynamic monitoring, and early use of mechanical circulatory support in selected cases.

In future, large, prospective, and multicentre studies are needed to establish standardized NLR cut-off values for risk stratification in different populations, the integration of NLR with other inflammatory and hematologic markers (e.g., PLR, CRP, interleukin-6) should be explored. Also, future trials should assess whether anti-inflammatory therapies targeting neutrophil-mediated inflammation can improve clinical outcomes in STEMI patients with elevated NLR.

CONCLUSION

STEMI patients with elevated NLR (≥4.8) have a significantly higher frequency of in-hospital MACE compared to those with non-elevated NLR. Given its cost-effectiveness and ease of availability**,** NLR may serve as a valuable prognostic marker for early risk stratification in STEMI patients undergoing PPCI. Routine NLR assessment at admission could help identify high-risk patients, allowing for early interventions to improve clinical outcomes.

AUTHORS' CONTRIBUTION

I Arshad Ali as principal investigator in this contributed in all aspects from synopsis, dissertation to fully study, I committed dedication and time in it. My co authors especially corresponding author helped me in different aspects of the study.

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