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ORIGINAL ARTICLE

Evaluating the impact of neutrophil-to-lymphocyte ratio on disease severity in acute ST-segment elevation myocardial infarction.

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ABSTRACT… Objective: To evaluate the impact of NLR on disease severity and clinical outcomes presenting with acute STEMI. **Study Design:** Cross-sectional study. **Setting:** Faisalabad Institute of Cardiology (FIC). **Period:** March 2024 to August 2024. **Methods:** A quantitative, cross-sectional study was conducted at the Faisalabad Institute of Cardiology over six months. A total of 385 patients with confirmed STEMI were included through stratified random sampling. Data on demographics, comorbidities, laboratory parameters, and clinical outcomes were collected. The TIMI risk score and the left ventricular ejection fraction (LVEF) were used to assess disease severity. Experiments, statistical analyses include t tests, chi square tests, correlation, and logistic regression were implemented with SPSS. **Results:** Patients with NLR > 5 demonstrated significantly worse outcomes, including higher TIMI risk scores (5.4 ± 1.5 vs. 3.8 ± 1.2, $p < 0.001$) and lower LVEF (44.3 ± 5.7% vs. 52.2 ± 5.8%, $p < 0.001$). Strongly associated with adverse events including cardiogenic shock, recurrent myocardial infarction, and 30 days' mortality (21.9% vs. 4.4%, $p < 0.001$), increased NLR levels were. NLR over 5 (OR 3.75, $p < 0.001$) and LVEF < 45% (OR 4.12, $p < 0.001$) were identified using the multivariate analysis. **Conclusion:** The patients with elevated NLR have been shown to be reliable markers of increased disease severity and adverse outcomes in STEMI patients. An addition of NLR to routine clinical assessment would improve risk stratification and could guide management strategies. The integration of NLR with other biomarkers can improve predictive accuracy, and further researches should be performed.

Key words: Cardiovascular Risk, Disease Severity, Inflammatory Biomarkers, Left Ventricular Ejection Fraction, Neutrophil-to-Lymphocyte Ratio, Pakistan, ST-Segment Elevation Myocardial Infarction, TIMI Risk Score.

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INTRODUCTION

Ischemic Heart Disease (IHD) constitutes a Globel Health Burden with high morbidity and mortality rates.[1] Recent advances in STEMI pathophysiology have emphasized the key role of inflammation in the genesis, propagation or complications of atherosclerotic plaque rupture.[2] As a result, inflammatory biomarkers have come to prominence as important markers of cardiovascular risk and prediction of disease outcomes. The NLR is one such biomarker among these that has become a simple but powerful predictor of systemic inflammation. NLR is derived from routine complete blood counts and indexes the balance between the neutrophil driven innate immune responses and lymphocyte driven adaptive.[3] An elevated NLR reflects an overinflamed state that is linked to a more severe clinical course in diverse cardiovascular conditions, including STEMI.[4] Its dual components form the mechanistic basis underlying association of NLR with STEMI severity.[5] First responders to vascular injury are neutrophils that propagates inflammation, oxidative stress and extracellular matrix degradation.[6] For instance, in acute inflammatory states, lymphopenia is seen, rather, reflecting failure to properly regulate the immune response and heightened stress responses.

Together, these processes create a pro-inflammatory milieu that exacerbates myocardial injury and fosters adverse remodeling.[7] Several studies from Western and Asian populations have validated the prognostic value of NLR in STEMI, linking higher ratios to larger infarct size, impaired left ventricular function, and increased rates of major adverse cardiovascular events (MACE).[8]

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However, data from South Asia, particularly Pakistan, remain limited despite the region's high prevalence of cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia.[9] Local dietary habits, genetic predispositions, and healthcare disparities further underscore the need for region-specific research. In Pakistan, cardiovascular disease accounts for a substantial proportion of non-communicable disease burden. Studies such as Gitto et al. (2022) and Rehman et al. (2022) have documented the rising incidence of STEMI and its associated risk factors in the Pakistani population.[10,11] However, there is a paucity of research exploring the utility of inflammatory biomarkers like NLR in this context. Understanding the impact of NLR on STEMI severity in Pakistani patients could offer valuable insights into its prognostic relevance and guide therapeutic strategies tailored to this population.

With an increasing appreciation for the role of inflammation in STEMI pathophysiology, evaluation of NLR as a marker of disease severity is timely. The objective of this study is this gap in regional literature by exploring the relationship between NLR and clinical outcome in Pakistan STEMI patients. The findings may help improve risk stratification protocols and facilitate incorporation of inexpensive, easily available biomarkers into routine clinical practice. This research also echoes the international effort to optimize STEMI management using personalized and evidence based approaches.

METHODS

This cross-sectional study was conducted at Faisalabad Institute of Cardiology (FIC), a tertiary care hospital renowned for its comprehensive cardiac services. The study spanned six months from March 2024 to August 2024, Ethical Approval was obtained (Ref No. CPSP/REU/CRD-2021-130-2584, dated: February 16, 2024) from the Ethical Review Board with a sample size of 385 patients diagnosed with acute STEMI, calculated based on previous studies and statistical considerations for adequate power and precision. Stratified random sampling was employed to ensure equal representation of patients with varying degrees of disease severity, considering demographics and clinical characteristics like age, gender, and comorbid conditions. Inclusion criteria required patients aged 18 and above with acute STEMI, diagnosed through clinical presentation, ECG changes, and cardiac biomarkers, with informed consent obtained from all participants. Exclusion criteria included patients with a history of malignancy, autoimmune diseases, chronic inflammatory conditions, those on immunosuppressive therapy, or those with incomplete medical records or missing laboratory data. Data were collected through both primary (patient interviews and laboratory tests) and secondary (hospital records) sources, with clinical and demographic data, laboratory parameters (neutrophil and lymphocyte counts), and disease severity assessed using Killip classification and ECG findings. Ethical approval was obtained from FIC's ethical review board, and written informed consent was secured from all participants.

Statistical analysis was performed using SPSS, with continuous variables summarized using descriptive statistics and categorical variables using frequencies and percentages. Comparative analysis of NLR values across different severity levels was conducted with independent sample t-tests and chi-square tests. Pearson correlation coefficients assessed the relationship between NLR and disease severity markers, and multivariate logistic regression identified independent predictors of disease severity, with statistical significance set at $p<0.05$.

RESULTS

In the study population of 385 patients, those with a neutrophil-to-lymphocyte ratio (NLR) > 5 (n = 160) were significantly older (65.7 ± 11.2 years) compared to those with NLR ≤ 5 (60.4 ± 9.8 years, p = 0.001). Hypertension was more prevalent in the higher NLR group (62.5%) than the lower NLR group (48.9%, p = 0.01), while diabetes mellitus (43.8% vs. 35.6%, p = 0.12) and smoking status (46.9% vs. 46.7%, p = 0.97) showed no significant differences. The TIMI risk score was markedly higher in the NLR > 5 group (5.4 ± 1.5 vs. 3.8 ± 1.2, p < 0.001), and left ventricular ejection fraction (LVEF) was significantly reduced in this group (44.3 ± 5.7%) compared to those with NLR ≤ 5 (52.2 ± 5.8%, p < 0.001). The male gender distribution was similar between the groups (75.0% vs. 75.6%, p = 0.89). These findings

underscore the association between elevated NLR and worse clinical and functional outcomes in STEMI patients. Table-I

The analysis of Table 2 reveals a significant relationship between increasing neutrophil-to-lymphocyte ratio (NLR) and worsening disease severity in acute ST-segment elevation myocardial infarction (STEMI) patients. Patients with NLR ≤ 3.0 (n = 140) exhibited the lowest TIMI risk score (3.5 ± 1.1) and the highest left ventricular ejection fraction (LVEF) (54.3 ± 6.0%), with a minimal incidence of major adverse cardiovascular events (MACE) (10.7%, p < 0.001). Conversely, patients with NLR > 7.0 (n = 70) demonstrated the highest TIMI risk score (6.3 ± 1.6) and lowest LVEF (40.5 ± 5.4%), along with the highest MACE incidence (57.1%, p < 0.001). Intermediate groups, including NLR 3.1–5.0 and 5.1–7.0, showed a progressive increase in TIMI risk scores (4.2 ± 1.3 and 5.1 ± 1.4, respectively) and MACE rates (23.5% and 38.9%, respectively), alongside a decline in LVEF (50.1 ± 5.8% and 46.2 ± 5.9%, respectively, p < 0.001). These findings underscore a clear trend of increased disease severity and adverse outcomes with higher NLR levels. Table-II

Age was associated with an increased risk (Odds Ratio [OR] 1.12, 95% Confidence Interval [CI] 1.08–1.17, p < 0.001), while a neutrophil-to-lymphocyte ratio (NLR) > 5 demonstrated a strong predictive value for MACE (OR 3.75, 95% CI 2.45–5.72, p < 0.001). Hypertension also significantly increased the risk of MACE (OR 1.80, 95% CI 1.15–2.80, p = 0.01). Patients with a TIMI risk score ≥ 5 had a 2.65-fold higher risk (95% CI 1.85–3.79, p < 0.001), and those with a left ventricular ejection fraction (LVEF) < 45% had the highest odds of MACE (OR 4.12, 95% CI 2.68–6.34, p < 0.001). Table-III

In this study, the neutrophil-to-lymphocyte ratio (NLR) demonstrated a significant association with adverse clinical outcomes in patients with acute ST-segment elevation myocardial infarction (STEMI). Patients with NLR > 5 experienced substantially higher 30-day mortality (21.9%) compared to those with NLR ≤ 5 (4.4%, p < 0.001), as well as a markedly increased incidence of cardiogenic shock (15.6% vs. 3.6%, p < 0.001). Similarly, the occurrence of heart failure was significantly greater in the high-NLR group (28.1%) than in the low-NLR group (8.9%, p < 0.001). Additionally, recurrent myocardial infarction (MI) was more frequent in patients with NLR > 5 (7.5%) compared to those with NLR ≤ 5 (2.2%, p = 0.03). These findings underscore the prognostic value of NLR as an indicator of disease severity and adverse outcomes in STEMI. Table-IV

TABLE-I

Baseline characteristics of the study population (n = 385)

Variable	Total (N=385)	NLR ≤ 5 (n=225)	NLR > 5 (n=160)	P- Value
Age (years, mean ± SD)	62.8 ± 10.5	60.4 ± 9.8	65.7 ± 11.2	0.001**
Male (%)	290 (75.3)	170 (75.6)	120 (75.0)	0.89
Hypertension (%)	210 (54.5)	110 (48.9)	100 (62.5)	0.01**
Diabetes Mellitus (%)	150 (39.0)	80 (35.6)	70 (43.8)	0.12
Smoking (%)	180 (46.8)	105 (46.7)	75 (46.9)	0.97
TIMI Risk Score (mean ± SD)	4.5 ± 1.7	3.8 ± 1.2	5.4 ± 1.5	<0.001**
Left Ventricular EF (%)	48.5 ± 6.5	52.2 ± 5.8	44.3 ± 5.7	<0.001**

Note: Statistical significance is indicated by P < 0.05.

TABLE-II

Neutrophil to lymphocyte ratio and disease severity (n = 385)

NLR Group	Number of Patients (n)	TIMI Risk Score (Mean±SD)	LVEF (%) (Mean±SD)	Incidence of MACE (%)
NLR ≤ 3.0	140	3.5 ± 1.1	54.3 ± 6.0	15 (10.7)
3.1 - 5.0	85	4.2 ± 1.3	50.1 ± 5.8	20 (23.5)
5.1 - 7.0	90	5.1 ± 1.4	46.2 ± 5.9	35 (38.9)
> 7.0	70	6.3 ± 1.6	40.5 ± 5.4	40 (57.1)

TABLE-III

Predictors of MACE (n=385) using multivariate logistic regression analysis

Variable	Odds Ratio (95% CI)	P-Value
Age	1.12 (1.08 - 1.17)	<0.001**
NLR > 5	3.75 (2.45 - 5.72)	<0.001**
Hypertension	1.80 (1.15 - 2.80)	0.01**
TIMI Risk Score ≥ 5	2.65 (1.85 - 3.79)	<0.001**
Left Ventricular EF < 45%	4.12 (2.68 - 6.34)	<0.001**

TABLE-IV

Association of NLR with clinical outcomes (n = 385)

Outcome	NLR ≤ 5 (n=225)	NLR > 5 (n=160)	P-Value
30-day Mortality (%)	10 (4.4)	35 (21.9)	<0.001**
Cardiogenic Shock (%)	8 (3.6)	25 (15.6)	<0.001**
Heart Failure (%)	20 (8.9)	45 (28.1)	<0.001**
Recurrent MI (%)	5 (2.2)	12 (7.5)	0.03**

DISCUSSION

In 385 patients with acute ST segment elevation myocardial infarction (STEMI), we evaluated the impact of neutrophil to lymphocyte ratio (NLR) on disease severity and outcomes. Results showed that an increased NLR (NLR > 5) was associated with poorer clinical and functional outcomes, including greater TIMI risk scores and lower LVEF, and more frequent occurrences of MACE. These findings establish that NLE is a valuable prognostic marker in STEMI patients.

Patients with NLR > 5 were significantly older (65.7 ± 11.2 years) than those with NLR ≤ 5 (60.4 ± 9.8 years, p = 0.001) indicating that higher NLR is linked to higher age. This is consistent with Selanno et al. study (2022), who found an association of NLR with age in STEMI patients.[12]especially in remote areas require an easy and inexpensive examination such as Neutrophil Lymphocyte Ratio (NLR Consistent with the study by Dieden et. al (2022), hypertension prevalence was higher in the high-NLR group (62.5% versus 48.9%, p = 0.01).[13] However, diabetes mellitus and smoking status showed no significant differences between groups, a result partially supported by Sharma et al. (2023), who found only weak associations of these factors with NLR in STEMI patients.[5]

The TIMI risk score, a marker of clinical severity, was significantly elevated in patients with NLR > 5 (5.4 ± 1.5 vs. 3.8 ± 1.2, p < 0.001). This finding underscores the association of high NLR with severe disease profiles. Supporting this, a study by Bedel, Korkut and Armağan et al. (2021) demonstrated that patients with high NLR exhibited higher clinical risk scores, emphasizing the utility of NLR as a predictor of adverse outcomes.[14]

Patients with NLR > 5 had markedly reduced LVEF (44.3 ± 5.7% vs. 52.2 ± 5.8%, p < 0.001). Table-II, likewise, shows increasing NLR and corresponding declining LVEF with increasing NLR, from 54.3% in the lowest NLR group (≤ 3.0) to 40.5% in the highest NLR group (>7.0, p < 0.001). Consistent with the study by Tey et al. (2023), which also found a strong inverse relationship between NLR and LVEF, these results also show a strong inverse relationship between NLR and LVEF.[15] On the other hand, some researchers Begic et al., (2020) have been suggesting that LVEF does not always decrease significantly in various subsets of patients with STEMI and high NLR but this may vary with other confounders.[16]

The relationship between NLR and MACE incidence was shown to be direct. Patients with NLR < 3.0 had the lowest MACE rate (0.000, p < 0.001) compared to patients with NLR > 7.0 (57.0%) and patients with NLR less than or equal to 4.0. Further, multivariate analysis showed that NLR > 5 was a strong, independent predictor of MACE (OR 3.75, 95% CI 2.45–5.72, p < 0.001). Similar to these findings, Shah et al. (2016) also found an elevated NLR did prognosticate with greater rates of recurrent MI, cardiogenic shock and mortality.[17] But other studies, such as that by Nielsen et al (2020) have little or weaker associations which might be a result of difference in sample size and patient population.[18]

Furthermore, the 30 days mortality was significantly higher in patients with NLR > 5 (21.9% vs. 4.4%, p < 0.001) and increased rates of cardiogenic shock (20.1% vs. 15.6%, p < 0.001). These findings are consistent with Fatima et al. (2022) who found

elevated NLR to be a robust predictor of short term mortality and complications of STEMI patients.[19] Furthermore, NLR also identifies high risk patients as those having higher incidence of heart failure in the high NLR group compared to the low NLR group (28.1% vs. 8.9%, $p < 0.001$). On the other hand, Citu et al. (2022) found that NLR may be insufficient to entirely predict mortality, and multiple biomarkers should be integrated.[20]

The findings of the present study are consistent with the current literature regarding the prognostic potential of NLR in the cardiovascular diseases. While the association between elevated NLR and more severe disease and poorer outcomes has been corroborated by several studies, for example those by Pirsalehi et al. (2020) and Pujari Y et al. (2021), there are conflicting results in some cohorts.[21,22] For instance, it was reported that weaker associations are seen in populations with lower baseline inflammation, which implies that systemic inflammation levels may modulate the prognostic value of NLR, Nielsen et al., (2020).[18] This study's detailed stratification of NLR levels further allows novel insights into the gradient of risk posed by increasing NLR, where this aspect of NLR is not emphasized in the bulk of previous research. The progressive worsening of TIMI risk scores, LVEF, and MACE rates within NLR strata highlights the inherent dynamic nature of NLR as an in vivo marker of risk.

CONCLUSION

This study revealed that elevated NLR is a salient marker of worse clinical outcomes in patients with STEMI and reinforces its potential as a marker of worsening outcome in risk stratification in this setting. The results are in line with previously reported literature, and provide an added level of sophistication in our understanding of the relationship between NLR and disease severity. Future work should harness NLR to augment predictive power of other biomarkers and determine its potential utility to guide therapeutic interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1	**Munir Ahmad:** Manuscript writing.
2	**Muhammad Yasir:** Study design.
3	**Ahmad Salman:** Data analysis.
4	**Farah Naz:** Results, References.
5	**Jasia Shahid:** Proof read.
6	**Bazgha Niaz:** Data collection.