The prognostic value of total neutrophil count, neutrophil/lymphocyte ratio and left ventricular ejection fraction in predicting in-hospital mortality and complications after acute STEMI

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Abstract

Background: Leukocytosis, predominantly neutrophilia has previously been described following ST elevation myocardial infarction (STEMI). The exact contribution of this phenomenon to the clinical outcome of STEMI is yet to be shown. We examined cellular inflammatory response to STEMI in the blood by assessing total neutrophil count (TNC), neutrophil to lymphocyte ratio (NLR) and Left ventricular ejection fraction (LVEF) post myocardial infarction and their association with in-hospital mortality and/or adverse clinical events.

Methods: In this cross-sectional study, 50 patients who were admitted with the diagnosis of acute STEMI at Government medical college and Hospital, Amritsar were studied. The complete blood cell count (CBC) was done in all patients within 12-24 hours of the onset of symptoms. Total leukocyte count and differential leukocyte count were performed and neutrophil/lymphocyte ratio (NLR) was calculated. Left ventricular ejection fraction was assessed within one week of MI. Association of cellular response and ejection fraction with the incidence of post-MI mortality/complications like pulmonary edema, cardiogenic shock, arrhythmias and blocks were assessed by using ROC curve analysis and chi square test.

Results: In-hospital mortality and post-STEMI complication rate were 8% and 42%, respectively. Total neutrophil count (P=0.029) and Neutrophil to lymphocyte ratio (P=0.001) were predictors of mortality. High NLR (P<0.001) and lower LVEF (P<0.001) were predictors of total complications and cardiogenic shock. Pump failure in the form of acute pulmonary edema (6%) or cardiogenic shock (8%) occurred in 7 (14%) patients. Higher total neutrophil counts (P=0.009), higher NLR (P<0.001) and lower ejection fraction (P<0.001) were predictors of pulmonary edema. The frequency of ventricular tachyarrhythmias (VT/VF) at the first day was associated with higher NLR level (P=0.029). High TNC and low LVEF were predictors for first degree heart block and high NLR was predictor for third degree heart block and left bundle branch block.

Conclusion: A single CBC analysis along with routinely assessed parameter i.e. ejection fraction may help to identify STEMI patients at risk for mortality and heart failure, while neutrophil to lymphocyte ratio is the most valuable in predicting both.

Keywords: Acute Myocardial Infarction, ST Segment Elevation, White Blood Cell, Total Neutrophil Count, Neutrophil/Lymphocyte ratio, Left Ventricular Ejection Fraction.
Introduction

Coronary artery disease (CAD) is a major contributor of death and disability in India, and its overall prevalence has risen dramatically over the past two decades. Approximately, 3-4% of Indians in rural areas and 8-10% in urban areas have CAD.\(^1\)

Acute myocardial infarction induces an exacerbation of acute inflammation and stress response, which are characterized by an exaggerated mobilisation of leucocytes in the necrotic area. Among leucocytes, neutrophils are mobilized the most during acute myocardial infarction. Elevated absolute neutrophil counts are associated with the development of heart failure and mortality in acute myocardial infarction.\(^2\) On the other hand, lymphocyte count, another differentiated type of leucocytes, is depressed during acute stress condition due to the excess of stress hormones. Low lymphocyte counts have been reported in acute myocardial infarction and associated with adverse clinical outcomes.\(^3\)

The ratio of absolute neutrophil counts to lymphocyte counts (NLRatio) indicates the equilibrium between neutrophils and lymphocytes in circulation. It reflects the state of acute inflammation and ongoing stress response.\(^4\) In acute myocardial infarction, the equilibrium might swing to the extreme edge such that NLRatio increases due to excessive acute inflammation and stress response. Increased NLRatio has been reported in acute ST-elevation myocardial infarction (STEMI).\(^5\)

Several studies have reported that WBC counts provide independent and additional predictive value to short-term mortality risk stratification in patients with acute myocardial infarction.\(^6\) Proposed mechanisms responsible for this association include leukocyte-mediated no-reflow, leukocyte-mediated hypercoagulable state and indirect cardiotoxicity mediated through proinflammatory cytokines.\(^7\) The prognostic significance of different WBC subtypes varies in patients with acute myocardial infarction.\(^3,8\)

The measurement of left ventricular ejection fraction (LVEF) after acute myocardial infarction (AMI) has both prognostic and therapeutic implications and is a class I clinical practice guideline recommendation, as well as a core AMI performance measure recommended by the American College of Cardiology (ACC) and American Heart Association (AHA).\(^9\) Reduced LVEF is associated with greater mortality among patients with coronary artery disease and predicts increased risks of early all-cause mortality as well as sudden cardiac death after AMI.\(^10\)

Since neutrophils and lymphocytes act in immunologically different patterns, this study aimed at evaluating the predictive value of total peripheral neutrophil count, NLR along with LVEF in determining the prognosis of MI and the risk of major post-MI adverse events. We hypothesized that patients with high leukocytic response and NLR and lower LVEF were at higher risk of in-hospital death and complications after a documented STEMI.

Materials and Methods

In this prospective study participants were patients who presented with acute STEMI in medical emergency at Guru Nanak Dev Hospital attached to Government Medical College, Amritsar. The study group comprised of 50 patients of acute STEMI of age between 40 years and 70 years. The study was conducted after approval from institutional thesis and ethical committee. Patients with active inflammation or chronic inflammatory diseases, unstable angina, non-ST elevation MI, past history of surgery or prior MI, active inflammation, end stage liver and renal failure and cancer were excluded from the study. STEMI was determined using the third universal definition of myocardial infarction and criteria provided by American College of Cardiology (ACC) and European Society of Cardiology; In short: STEMI defined as an increase in cardiac troponin-I (cTNI) along with new ST-segment elevation measured from J point at least 0.2 mV in two adjacent V1-V3 leads or at least 0.1 mV in other leads within 24 hours after the onset of chest pain.

Complete blood cell count (CBC) was performed in all patients within 12-24 hours of onset of symptoms. After sampling, blood samples were evaluated for total WBC count, neutrophil, lymphocytes, and NLR. The information regarding demographic features, past medical history, patient’s outcome and the occurrence of major complications or mortality were collected. Twelve -lead ECG was done at admission, at 24 hours, 48 hours and 72 hours of admission. The diagnosis of arrhythmia was carried out as per American Heart Association (AHA) guidelines and treated accordingly.2-D Trans Thoracic Echocardiography (TTE) with doppler flow study was done using Colour Doppler Echocardiography (CDE) machine with an adult transducer of 2.5M Hz (Sonosite USA), during the first 7 days of hospitalization.
Cut off values of TNC, NLR and LVEF and their sensitivity, specificity and area under curve taken according to ROC curves in predicting in-hospital mortality.

### Table 1

| ROC Curve Analysis for predicting Mortality | Sensitivity | Specificity | Area under curve |
|--------------------------------------------|-------------|-------------|------------------|
| TNC Cut off=9.5                            | 75%         | 77%         | 0.750            |
| NLR Cut off=6.5                            | 100%        | 94%         | 0.924            |
| LVEF Cut off=39%                           | 75%         | 71.7%       | 0.837            |

**Results**

- The study included 50 STEMI patients and they were monitored for complications and mortality during their hospital stay.
- Majority STEMI patients were males (73%) older than 50 years. The mean age of the patients in our study was 55.98 ± 8.89 years.
- Smoking (52%) was the most significant risk factor followed by hypertension (44%), diabetes mellitus (22%) and dyslipidemia (30%).
- The most common complication after STEMI was sinus bradycardia followed by cardiogenic shock (8%), mortality (8%), VT within 24 hours (8%), then pulmonary edema (6%), first degree heart block (6%), RBBB (6%), VT/VF after 24 hours (4%), third degree heart block (4%), LBBB (4%), PSVT (2%). Overall complications occurred in 42% of total patients.
- NLR with cut off as 6.5 has 100% sensitivity and 94% specificity, while TNC with cut off as 9.5 has sensitivity 75% and specificity 77% and LVEF with cut off as 39% with specificity 75% and sensitivity 71.7%, as prognostic markers.
- In hospital mortality was present in 8% of patients. NLR and TNC were predictors for in-hospital mortality. NLR was highly significant with p value=0.001. LVEF was not significant predictor of in-hospital mortality after STEMI.
- Total complications were present in 42% of patients. NLR, TNC and LVEF were all predictors for total complications after STEMI. Out of these parameters. NLR and LVEF were highly significant predictor for post MI complications.
- Pulmonary edema was present in 6% of patients and was predicted by all three parameters with, TNC and NLR better than LVEF.
- Cardiogenic shock was present in 8% of patients. NLR and LVEF were better predictors. TNC was not a significant predictor.
- Arrhythmias were present in 28% of patients. NLR was a significant predictor for VT/VF within 24 hours with p value=0.029. TNC and LVEF were not significant parameters for predicting post MI arrhythmias.
- Blocks, both AV nodal and intraventricular were present in total 20% of patients. TNC and LVEF were predictors for first degree heart block after MI. NLR was a significant predictor for LBBB and third degree heart block.
Table 2 End points seen in our study after acute myocardial infarction

| End points* | Total | Percentage |
|-------------|-------|------------|
| Mortality   | 4     | 8%         |
| Total Complications | 21  | 42%        |
| Pulmonary edema | 3   | 6%         |
| Cardiogenic shock | 4   | 8%         |
| Sinus bradycardia | 5   | 10%        |
| PSVT        | 1     | 2%         |
| VT/VF after 24 hours | 2   | 4%         |
| VT/VF within 24 hours | 4  | 8%         |
| Atrial fibrillation | 2  | 4%         |
| 1st degree heart block | 3  | 6%         |
| 3rd degree heart block | 2  | 4%         |
| RBBB        | 3     | 6%         |
| LBBB        | 2     | 4%         |

Table 3 Mean value of TNC and NLR according to LVEF groups

| Parameters                  | LVEF<=39(Total=18) | LVEF>39(Total=32) | P value |
|-----------------------------|--------------------|-------------------|---------|
|                             | Mean               | S. D              | Mean    | S.D    |         |
| Total Neutrophil Count      | 9.92               | 3.001             | 7.16    | 2.843  | 0.002   |
| Neutrophil to lymphocyte ratio | 6.65              | 0.419             | 4.21    | 1.60   | 0.0001  |

Table 4 P- Value of TNC, NLR and LVEF for complications in STEMI

| Complications               | P value |
|-----------------------------|---------|
|                             | TNC     | NLR     | LVEF    |
| Mortality                   | 0.029   | 0.001   | 0.090   |
| Total complications         | 0.009   | <0.001  | <0.001  |
| Cardiogenic shock           | 0.193   | 0.001   | 0.005   |
| Pulmonary edema             | 0.004   | 0.004   | 0.017   |
| VT/VF within 24 hr          | 0.307   | 0.029   | 0.543   |
| VT/VF after 24 hr           | 0.479   | 0.368   | 0.674   |
| Atrial Fibrillation         | 0.479   | 0.368   | 0.674   |
| First degree heart block    | 0.004   | 0.124   | 0.017   |
| Third degree heart block    | 0.479   | 0.021   | 0.674   |
| LBBB                        | 0.368   | 0.054   | 0.074   |
Figure 1: Mean value of TNC and NLR according to LVEF groups

Figure 2: TNC, NLR and LVEF as parameters for predicting in hospital mortality after acute myocardial infarction

Figure 3: TNC, NLR and LVEF as parameters for predicting total complications after acute myocardial infarction
Figure 4: TNC, NLR and LVEF as parameters for predicting pulmonary edema after acute myocardial infarction

Figure 5: TNC, NLR and LVEF as parameters for predicting cardiogenic shock after acute myocardial infarction

**Discussion**

In the current study, we evaluated the leukocytic response and ejection fraction of STEMI and examined their possible association with in-hospital mortality and post-infarction complications. We demonstrated that 12-24 hours following STEMI the numbers of white blood cells, mostly in the form of neutrophils, are higher than known normal values. Increased neutrophil count was associated with higher in-hospital mortality, total complications, post-infarction pulmonary edema and occurrence of first degree heart block. The presence of neutrophilia after STEMI (higher than the cutoff value of 9.5×1000 cells/mm³) was predictive of pump failure and significant increase in the frequency of ventricular arrhythmias within the first post MI day. Comparably, higher NLR (with cut off value of 6.5) was also predictor of in-hospital mortality, total complications, post-infarction pulmonary edema and cardiogenic shock. High NLR was also associated with ventricular arrhythmias within first 24 hours of MI, with third degree heart block and LBBB. LVEF with cut off value as 39% was predictors of post MI complications, shock, pulmonary edema and first degree heart block. In our study, there was positive correlation between higher TNC, NLR values with lower LVEF.
Chatterjee et al. reported a higher mortality in patients with more intense increase in WBC count. Nunez et al. that showed highest neutrophil and lowest lymphocyte counts and maximum NLR in 12-24 hours following STEMI had a higher overall long-term mortality. Chia et al. showed that elevated leukocyte and neutrophil counts after primary PCI in patients with STEMI were associated with larger myocardial infarct size and lower LVEF and were independent predictors of cardiovascular outcome. Similarly, our study patients with evidence of heart failure either as pulmonary edema or cardiogenic shock had higher WBC count, neutrophil and NLR ratio.

The association between inflammation and atrial fibrillation is well studied. In our study there was no significant difference in total WBC, neutrophils or NLR between those with and without AF. Data regarding association of ventricular arrhythmias with CBC results are conflicting. Chatterjee et al. reported that pre-procedural elevated WBC count, neutrophilia and elevated NLR in patients undergoing PCI were significant predictors of ventricular arrhythmias. In our study, higher NLR was found in patients who developed VT/VF within the first day but the difference was not significant for arrhythmias beyond this time course. We postulated this might be secondary to the stress associated with cardioversion and possible cardiopulmonary resuscitation in these patients rather than a primary causative factor. Horne et al. found that neutrophil, lymphocyte and NLR were independent factors for predicting death/MI, however among them, NLR was more powerful predictor of the risk of death/MI.

Similar to our study Gul U et al showed that a total of 145 (45.3%) patients had complications; 49 (15.3%) died in hospital, and 13 (4.06%) died in 30 days. Patients in high NLR group had higher rate of complications (63.5% vs. 25.5%, p <0.0001) and death (19.2% vs. 11.1%, p=0.046) in hospital than those in low NLR group. Cardiogenic shock (27.5% vs.11.1%, p <0.0001), heart failure (19.2% vs. 7.2%, p=0.002), arrhythmias (18% vs. 6.5%, p <0.0001), reinfarct/angina (9.6% vs.2% p=0.004) occurred more in high NLR group. In study by Bajari R et al patients were categorized into 2 groups: the NLR group 1 (NLR5.25: n = 265, 66.25%) and the NLR group 2 (NLR > 5.25; n = 135, 33.75%). Higher mortality was seen in NLR group 2 (42/265, 1.9%) compared to NLR group 1 (5/265, 1.9%) with p value <0.001. The study suggest that elevated NLR (>5.25) is independently associated with higher all-cause mortality. Acet et al concludes that neutrophil to lymphocyte ratio, PDW and UA level are convenient, inexpensive and reproducible biomarkers for STEMI prognosis before primary angioplasty when these indicators are combined with the TIMI-STEMI risk score.

Ghaffari et al showed that high age, female gender, lower ejection fraction and absolute neutrophil count were predictors of mortality. Pump failure in form of acute pulmonary edema or cardiogenic shock occurred in 8.9% of patients. Higher leukocyte and neutrophil counts and higher NLR were predictors of failure. The frequency of ventricular tachyarrhythmias (VT/VF) on the first day was associated with higher neutrophil count and higher NLR level.

Our study concluded that TNC and NLR values are significantly higher in patients with lower ejection fraction. Similarly, Dogdu et al showed relationship between hematological parameters in patients with multivessel coronary artery artery disease and left ventricular systolic dysfunction. This study found a positive correlation between impaired left ventricular systolic functions and high NLR values. Karakas et al, divided patients into two groups according to LVEF and there RDW (red cell distribution width) and NLR were assessed at time of admission.Group 1 (systolic dysfunction, LVEF<50%) and Group 2 (preserved global systolic function, LVEF>50%), concludes that mean RDW and NLR were significantly higher in group 1 patients.Zhang et al demonstrated that hemoglobin, neutrophil/ lymphocyte ratio (NLR), Global Registry of Acute Coronary Event score, and post procedure left ventricular ejection fraction (LVEF) were independent predictors of MACEs. But Abrel et al concluded that high NLR was independently associated with lower ejection fraction (49+8 vs 46+8; P<0.001) and fewer hospital complications.

**Conclusion**

Thus it can be concluded that in patients with acute STEMI, TNC and NLR along with LVEF can be taken as readily ascertainable, inexpensive and reproducible biomarkers for determining in-hospital mortality and complications. It was seen that patients with lower
LVEF has higher TNC and NLR values. NLR has better predictive power out of three parameters with cut off as 6.5 having sensitivity 100% and specificity 94%.

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