Neutrophil Lymphocyte Ratio: A Prognostic Marker in Acute ST Elevation Myocardial Infarction

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ABSTRACT

Objective: To investigate if neutrophil lymphocyte ratio (NLR) predicts in-hospital adverse events and mortality, and short-term (30-day) mortality in ST-elevated myocardial infarction (STEMI) patients thrombolysed with streptokinase (SK).

Study Design: An observational study.

Place and Duration of Study: Rawalpindi Institute of Cardiology, from June 2014 till January 2015.

Methodology: The STEMI patients, thrombolysed with SK had blood samples at admission, analysed for complete blood counts and NLR calculated. They were grouped into two, low and high NLR, taking 4.50 as cut-off. Chi square test was used to compare rate of adverse events and death in hospital stay. Mann-Whitney test was used to compare median NLR between patients died and discharged alive. Logistic regression analysis was used to estimate predictive ability of NLR for 30-day mortality.

Results: 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. Median NLR in patients died was higher than those discharged alive (7.46 vs. 4.70, p <0.0001). Regression analysis showed NLR an independent predictor of mortality (OR 1.131 at 95% CI, p = 0.029). Age, serum creatinine, Killip class were other predictors (p=0.002 and p=0.02, respectively). ROC curve showed AUC 0.908 (p <0.0001).

Conclusion: A high NLR predicted increased in hospital complication rate, and in-hospital as well as 30-day mortality in STEMI patients thrombolysed with streptokinase.

Key Words: Neutrophils-lymphocyte ratio. Myocardial infarction. Mortality. Thrombolysis. Streptokinase.

INTRODUCTION

Inflammation has been shown to underlie many cardiovascular diseases, especially those involving atherosclerosis as pathogenic mechanism like coronary artery disease.[1-3] Inflammation is involved in initiation, progression, and destabilisation of atherosclerotic plaque.[1] Systemic inflammation is known to be associated with inflammation of vessel wall.[1] Lymphocytes and monocytes are found in the early phases of plaque; whereas, neutrophils have a role in acute plaque disruption and thrombotic occlusion.[1,4] Bone marrow responds to inflammation by releasing white blood cells, especially neutrophils.[4] Agents like statins and clopidogrel have been found to improve outcomes through exerting anti-inflammatory effect in addition to their well known mechanisms of action.

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Small elevations in inflammatory biomarkers can point to upcoming cardiovascular events and can identify patients at increased risk for cardiovascular events, especially in the intermediate risk group.[2] The predictive value of these markers is independent of traditional risk factors.[2] Inflammatory markers like CRP, neutrophils etc. rise in acute worsening of cardiac diseases like acute heart failure, acute coronary syndrome, especially ST elevated myocardial infarction (STEMI).[4-6] Thus these biomarkers are being researched for identifying patients with acute coronary syndrome at high risk so that aggressive management can be done of this group. That is why these novel biomarkers are being studied for prognostic role.[7-9] Studies have shown various hematological indices such as total leukocyte count, neutrophils and monocytes to have role in prognosis of STEMI patients. However, neutrophil lymphocyte ratio (NLR) has been shown to be more predictive in some studies.[10-12] Furthermore, NLR is an inexpensive, widely available test and can be easily calculated in comparison to other inflammatory markers.

Most studies have been conducted on STEMI patients undergoing primary percutaneous coronary intervention (PCI).[13-16] To the authors' knowledge, no study has evaluated role of NLR in prognosis of STEMI patients undergoing fibrinolysis with streptokinase (SK). Fibrinolysis with SK is inexpensive and widely available.

Therefore, the treatment offered mostly in our hospitals. Authors could not find any study conducted on the prognostic value of NLR in the region.

The purpose of this study was to evaluate the association of elevated NLR in STEMI patients with in-hospital adverse events and to define its predictive role for short-term mortality.

METHODOLOGY

This study was an observational study, started after obtaining approval from Ethical Review Board of the Institute. Consecutive convenient sampling technique was employed. From June 2014 to January 2015, three hundred and twenty consecutive patients presented to emergency department of Rawalpindi Institute of Cardiology (RIC) with STEMI, were recruited after obtaining written informed consent.

Patients with sepsis, recent (three months) surgery or trauma, hematological malignancy or patients on current or recent (three months) steroid therapy and patients at extremes of ages (less than 25 years of age or more than 75 years), late for fibrinolysis or those with contraindication to fibrinolysis, referred to RIC after fibrinolysis and patients not willing, were excluded. Patients presented to RIC with acute STEMI within 12 hours of symptom onset, thrombolysed with SK and not having any of above mentioned exclusion criteria, were included.

STEMI was defined according to diagnostic criteria given by AHA/ESC guidelines.[17] All patients were thrombolysed with SK and given treatment for ACS, according to the contemporary guidelines.[17] Venous blood samples were drawn on admission before thrombolysis for complete blood counts (CBC), serum creatinine and cardiac enzymes. Samples were analysed within one hour of being drawn. CBC analysis including total leukocyte count (TLC), absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) was done with automated cell counter Diatron ABACUS 380 (ISO-9001 certified). NLR was calculated as ratio of ANC and ALC. Data was collected from hospital record files, supplemented by direct interviewing of patients. Patients were followed for a minimum of one month via telephone and, if needed, by outpatient follow-up record.

Primary end points were in-hospital adverse cardiac events and in-hospital death. Secondary end point was short-term (one-month) mortality. In-hospital adverse cardiac events include cardiogenic shock, heart failure, reinfarction/post MI angina, tachyarrythmias or blocks and stroke. Cardiogenic shock was defined as hypotension (SBP ≤90 mmHg or drop in MAP =30mmHg) not attributable to hypovolemia or sepsis, and, therefore, believed to be due to decreased cardiac output. Reinfarct was defined if ST elevation (1mm or more ST elevation in two consecutive all leads other than V2 and V3 for which ≥2 mm for males and ≥1.5 mm for females) recurs or new pathognomonic Q waves associated with ischemic symptoms for 20 minutes or longer and 20% rise in cardiac troponin I level after the incident MI during hospital stay. Post MI angina included ischemic pain with or without new ST/T change.

Heart failure was defined as appearance of fine crepts at least upto mid chest with raised JVP along with a consistent chest X-ray, not attributable to renal pulmonary edema.

Arrythmias included supraventricular (AF, SVT) or ventricular (VT/VF) arrythmias or persistent sinus bradycardia or advanced AV blocks requiring treatment with antiarrythmics or electrical cardioversion or temporary pacing in case of AV blocks. Transient AV blocks or transient bradycardia not requiring any treatment or requiring minimal treatment that is 0.5 mg atropine, or NSVT or ventricular ectopics coming under umbrella of reperfusion arrythmias, were excluded.

All analyses were performed by SPSS 19. Categorical variables were presented as percentage and frequency and continuous variables as median and interquartile ratio (IQR). Patients were divided into two groups according to NLR, i.e. low NLR and high NLR. The cut-off point for this division was taken as 4.50 as an average of previous studies.[8,9,13,15] Chi square test was used to compare categorical variables and Mann-Whitney test was used to compare continuous variables. Logistic regression analysis and ROC curve was used to assess predictive ability of NLR and other variables for short-term mortality. P-value ≤0.05 (two sided) was considered statistically significant at 95% confidence interval.

RESULTS

A total of 320 patients entered analysis after exclusion, with median age (IQR) of 56 (13) years and 258 (80.6%) were males and 62 (19.37%) were females. Table I shows baseline characteristics of two NLR groups.

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, (n=106 vs. 39, 63.5% vs. 25.5%, p <0.0001), and death (n=32 vs. 17, 19.2% vs. 11.1%, p=0.046) in hospital than those in low NLR group. Table II shows the rates of in hospital complications in the two groups.

Median NLR in patients died in hospital was higher than those discharged alive (7.46 vs. 4.70, p <0.0001). As compared to patients discharged alive, patients who died in hospital were older (median age of 60 vs. 55 years, p <0.0001) and were more likely to be females (36.7% vs.15.9%). Patients who died in hospital also had higher median serum creatinine (non-significant difference at p=0.054) and higher Killip class (12.2% vs. 1.8% for Killip IV).

Table I: Baseline characteristics in patients of low and high NLR group.

Characteristics	Low NLR group (n* = 153)	High NLR group (n* = 167)
Age (median(IQR))	55 (12)	57 (13)
Sex (male)	125 (81.7%)	133 (79.6%)
Hypertension	71 (46.4%)	4 (44.3%)
Diabetes mellitus	38 (24.8%)	53 (31.7%)
Serum creatinine**	0 .9 (0.20)	1.03 (0.40)
TLC***	11.17 (3.91)	12.29 (3.99)
ANC***	7.47(2.94)	10.09 (3.65)
ST resolution	96 (62.7%)	79 (47.3%)
Type of MI		
Anterior	68 (44.4%)	68 (40.7%)
Inferior	56 (36.6%)	53 (31.7%)
Extensive anterior	12 (7.8%)	27 (16.2%)
Lateral	6 (3.9%)	4 (2.4%)
Killip class		
I	115 (75.2%)	111 (66.5%)
II	30 (19.6%)	33 (19.8)
III	5 (3.3%)	13 (7.8%)
IV	2 (1.3%)	9 (5.4%)

*n = number of patients;   **mg/dl;   ***10⁹Xcells/liter
TLC (Total leukocyte count), ANC (Absolute neutrophil count)
Values are shown as median (IQR) for continuous variables and as frequency (percentage) for categorical variables.

Table II: In-hospital complications in low and high NLR groups.

Complication	Low NLR group (n=153)	High NLR group (n=167)	P-value
Re-infarct/post MI angina	3 (2%)	16 (9.6%)	0.004
Cardiogenic shock	17 (11.1%)	46 (27.5%)	<0.0001
Heart failure	11 (7.2%)	32 (19.2%)	0.002
Arrythmias:			
Ventricular	10 (6.5%)	30 (18.0%)	<0.0001
Others*	13 (8.5%)	31 (18.6%)	<0.0001
Stroke	1 (0.7%)	3 (1.8%)	0.381

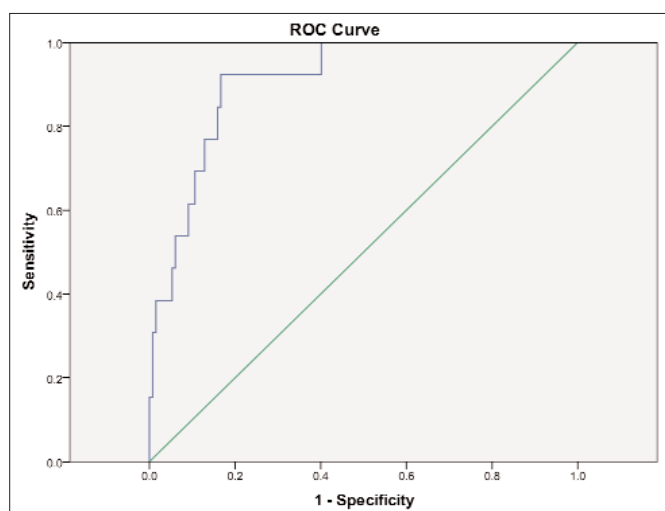*include supraventricular tachyarrythmias and AV blocks

Figure 1: ROC curve for prediction of short-term mortality by NLR.
Area under curve (95% confidence interval): 0.908 (0.842- 0.974).
p-value: <0.0001.

Regression analysis showed NLR an independent predictor of mortality, with OR 1.131 (95% CI 1.017-1.258, p=0.029). Age and serum creatinine were other predictors (p=0.002 and p=0.02). ROC curve showed AUC as 0.908 (95% CI 0.842 - 0.974, p <0.0001), respectively (Figure 1).

DISCUSSION

The authors evaluated prognostic value of NLR (for adverse events and deaths) in patients with STEMI thrombolysed with streptokinase.

STEMI has a high early and late morbidity and mortality rate dependent upon initial clinical presentation.[18] Early risk stratification of STEMI patients improves outcomes. As high NLR predicts high risk of complications, NLR can contribute to risk stratification of patients with acute ST elevation myocardial infarction.[19,20]

This study supports the role of NLR in predicting complications and death in myocardial infarction patients shown by some previous studies.[14-16] Also it adds to the proposal saying NLR predicts short-term mortality after STEMI.[14,21-23] In contrast, mortality rate was higher in this study, which we attribute to wide range of age and Killip class being included, i.e. older patients up to 75 years of age and patients with higher Killip class (cardiogenic shock, pulmonary edema), and cardiac arrest at presentation were not excluded.

This study had some limitations. Firstly, NLR was not compared for its predictive role with other inflammatory markers. However, some studies have shown positive correlation between NLR and other inflammatory markers.[4,23] Additionally, patients with deranged renal function were not excluded. NLR at admission was used only, NLR 24 hours after admission was not used in addition. Considering short half life of neutrophils, repeated measurements of NLR may provide better prognostic information.[22] However, it has been shown that initial and last NLR correlate well in their prognostic role.[22] For stroke, there was no significant difference between the two NLR groups, this could be attributed to the low incidence of stroke. Additionally, transient/ reperfusion arrhythmias were not included as adverse events, smoking as risk factor was not studied (smoking can contribute to chronic inflammatory process), sample size was relatively small, and study was conducted in single centre and not multi-ethnic. And finally, cause mortality (not cardiovascular mortality) was taken as secondary end point, and morbidity after discharge (re-infarct, progressive heart failure, re-hospitalisation) was not studied.

There could be arguments related to NLR, like optimal cut-off point being widely vary between different studies, which can be due to confounding factors like Lab techniques and ethnic variation. Further, physiological states like exercise and catecholamine release affecting inflammation can be pointed out. However, these have been shown to affect absolute neutrophil and lymphocyte counts (ANC and ALC), but not change the ratio that is NLR. NLR is easily calculated from the cell counts obtained by a readily available, rapid and

economical test on blood sample. High NLR has been shown to be associated with poor angiographic findings, larger infarct sizes and increased rate of long- and short-term mortality. NLR has incremental prediction independent of other risk scores like the Global Registry of Acute Coronary Events (GRACE) score.

A long-term prospective study on a larger scale is needed to evaluate whether the predictive role of neutrophil lymphocyte ratio for mortality is maintained in larger time scale. Further studies are needed on whether anti-inflammatory (NLR lowering) treatment will decrease death and complication rate and, therefore, improves outcome in patients with acute coronary syndrome and ST elevation myocardial infarction.

CONCLUSION

The results of this study show that a high NLR (using 4.50 as cut-off value) is associated with a higher rate of complications and death during hospital stay after STEMI. High NLR also predicted short-term mortality.

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