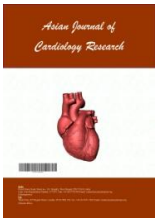

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Role of Neutrophil to Lymphocyte Ratio (NLR) In Conjunction with Coronary Artery Involvement as a Biomarker for the Magnitude of Current of Injury, Type of Intervention and Clinical Outcomes in STEMI

Mohammed Abdul Hannan Hazari[1], Kailas Laxman Rao[2], Bachi Tazneem[3], Sara Sana Ayesha Khanum[3*], Huma Quadri[3] and Syeda Kehkashan Jabeen[3]

[1]Department of Physiology, Deccan College of Medical Sciences, DMRL 'X' Road, Kanchanbagh, Hyderabad-500058, Telangana, India.
[2]Department of Cardiology, Owaisi Hospital and Research Centre, Deccan College of Medical Sciences, DMRL 'X' Road, Kanchanbagh, Hyderabad-500058, Telangana, India.
[3]Deccan School of Pharmacy, Darussalam, Aghapura, Hyderabad-500001, Telangana, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author KLR was the treating physician for these STEMI patients. Author MAHH contributed in conceptualisation, research design, data collection, data analysis and approved the final draft of the manuscript. Author BT helped in conceptualisation and research design. Authors SSAK and HQ contributed in data collection, data compilation, data analysis and drafting of the paper. Author SKJ helped in data collection. All authors read and approved the final manuscript.

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ABSTRACT

Background: The potential prognostic biomarker—neutrophil to lymphocyte ratio (NLR) can be used to predict the severity of STEMI. We conducted an observational study using this parameter together with the extent of coronary artery involvement from coronary angiogram and magnitude of ST-elevation on ECG to determine the prognosis and the length of hospital stay. The effect of early reperfusion with thrombolysis was also observed.

**Corresponding author: Email: sarasak2025@gmail.com;*

Methods and Results: 30 subjects (age 56.43 ± 13.98), with ST-elevation on ECG at admission, treated with streptokinase and undergoing angiogram were taken for the study. Repeated ECGs and complete blood picture on admission day, day 3, day of discharge and on the follow-up day were obtained. Out of 30 subjects, 15 received thrombolysis out of which 12 (80%) survived compared to the other 15 subjects who presented late, out of which 10 (66.6%) survived. Mean ST-elevation on the day of admission, on day 3, day of discharge and on follow up was found to be 0.39 ± 0.12, 0.18 ± 0.12, 0.05 ± 0.07, 0.00 ± 0.00 respectively. NLR values on admission day were 7.89 ± 4.98, day 3 (6.24 ± 5.05), day of discharge (4.34 ± 2.74) and on follow up (1.71 ± 1.40) indicating association of higher NLR values with magnitude of current of injury. NLR values as high as 18.5 were observed in expired subjects. The length of hospital stay was found to be 6.43 ± 5.03 days.

Conclusion: There was a linear decrement in ST-segment resolution with a decrease in NLR and can be attributed to the natural course of disease and type of intervention provided. Nevertheless, the univariate correlation between ECG and NLR on various days of treatment was not significant.

Keywords: STEMI; neutrophil to lymphocyte ratio; electrocardiogram; reperfusion; mortality; pharmacotherapy.

1. INTRODUCTION

Atherosclerosis is a major cause of cardiovascular disease and ST elevated myocardial infarction (STEMI) in particular. It is a chronic inflammatory process that leads to plaque formation. The rupture of the unstable plaque and consequent thrombosis leads to occlusion of the coronary arteries and necrosis of the myocardial tissue [1]. STEMI is a leading cause of morbidity and mortality and has several risk factors including hypertension, diabetes, smoking, alcohol consumption, etc. Leukocytes and its subtypes are considered as markers of inflammation as the tissues injuries lead to infiltration of these cells, neutrophils in particular at the site of injury [2]. Recently neutrophil to lymphocyte ratio (NLR) has emerged as a potential inflammatory biomarker to assess the prognosis of coronary artery disease (CAD) [3,4]. The ratio can be easily calculated from the complete blood picture (CBP) reports, which is inexpensive and available widely. There is strong evidence about the negative impact of elevated NLR. Arbel et al. (2012) in a study with a three-year follow-up of patients with cardiovascular diseases reported that NLR is associated with more severe CAD [5]. The reference values of NLR vary depending upon race and ethnicity. These variations need to be considered while proposing a cut-off value in a particular race [6].

According to a number of studies, in patients undergoing coronary angiography or percutaneous coronary intervention, NLR has been associated with adverse outcomes [7,8]. The diagnosis of STEMI is made with the evidence of ST-elevation on the electrocardiogram. The extent of infarction and number of infarct-related arteries (IRA) involved is determined using coronary angiogram and the need for percutaneous coronary intervention (PCI) is assessed [9]. The European and American guidelines for STEMI recommend primary percutaneous intervention (PPCI) over fibrinolysis for early reperfusion and better prognosis [10]. However, restoration of the normal blood flow immediately with thrombolytic therapy has been observed to be the most effective in patients with STEMI which can be observed from ST-segment resolution on ECG. This is referred to as “Electrocardiographic sign of spontaneous reperfusion (SR)” [11]. Nearly 30 deaths out of 1000 patients are prevented when patients are treated with fibrinolysis within 6 hours of the onset of symptoms. One of the most used fibrinolytic is streptokinase. It is a non-fibrin selective fibrinolytic which acts on the occluding thrombus and causes lysis to restore the blood flow or patency in the effected artery [12]. Residual thrombus can occur after mechanical thrombectomy or thrombolytic therapy. This thrombus can be removed via a more aggressive antiplatelet therapy together with thrombolytic therapy [13,14].

2. MATERIALS AND METHODS

A prospective observational study was conducted between October 2018 and March 2019. Firstly, informed consent of all subjects and / or their attendants was obtained by giving a brief explanation about the study and the laboratory tests to be performed. Demographic data (age, gender) and cardiovascular disease risk factors (hypertension, diabetes, smoking and alcohol consumption) were noted.

2.1 Study Patients

A total of 30 patients above 18 years of age with a diagnosis of STEMI on admission (mean age 56.43 ± 13.98) were enrolled in the study. STEMI was diagnosed according to typical symptoms of chest pain and shortness of breath before admission and with cumulative ST-segment elevation of ≥0.2mV in limb leads or ≥0.1 mV in at least two consecutive chest leads. Patients with ongoing infection or systemic inflammatory conditions, severe renal or liver disease, haematological disease and pregnant women were excluded from the study. Also patients with ECG showing left bundle branch block or patients with cardiogenic shock were excluded.

Electrocardiogram of all patients on the day of admission, day 3, on the day of discharge and on first follow-up was obtained and the magnitude of ST-elevation was measured at the J point from leads II, III, aVF for inferior wall myocardial infarction (MI); leads I, aVL, V5-V6 for lateral wall MI; leads V3-V4 for anterior wall MI; and leads V1-V2 for septal myocardial infarction.

2.2 Laboratory Measurements

Venous blood samples were collected from all patients at the time of admission, on day 3, at the time of discharge and on the first follow-up. Complete blood picture (CBP) was obtained from which neutrophil and lymphocyte counts were analysed. Neutrophil to lymphocyte ratio (NLR) was calculated by dividing neutrophil count by lymphocyte count.

Out of 30 subjects, only 12 of them underwent angiogram for suspected coronary artery block on the 3rd day of admission. Each coronary angiography was performed through the femoral artery access by two interventional cardiologists. A thorough review of the angiogram established the location of the lesions and the percentage of stenosis caused by the lesions. PCI was advised for stenosis >50% in any of the main arteries. The angiography reports revealed the need for PCI in almost all patients, with some requiring a single stent to some requiring as many as 3 stents or coronary artery bypass graft (CABG). Geriatric patients who could not undergo PCI were advised medical management.

2.3 Statistical Analysis

Statistical tests were performed using the SPSS version 17.0 statistical package for Windows (SPSS Inc., Chicago). The data was separated into a continuous and categorical type. Continuous data are expressed as mean and standard deviation (SD), while categorical data is represented by numbers and percentages. Whether there is a significant difference in the NLR was determined by recording the baseline parameters during the analysis which include age, gender, hypertension, diabetes, smoking, alcohol consumption, thrombolytic therapy, type of MI, type of coronary artery involvement, ST-segment elevation, NLR, type of intervention, and the length of hospital stay. Analysis of this data was performed by three different tests, Pearson's correlation test, repeated-measures ANOVA, with Mauchly's test of sphericity and Freidman test. The p values were determined and significance was fixed at $p<0.05$.

3. RESULTS

3.1 Baseline Demographics

Over 8 months (October 2018 - March 2019) 30 patients were enrolled who presented with a primary diagnosis of STEMI. The mean age was 56.43 ± 13.98, among them 20 (66.67%) patients were males and 10 (33.33%) were females. Overview of baseline characteristics and risk factors are given in Table 1.

Table 1. Baseline characteristics and clinical data of the study population

Data	Cases (n=30)
Age (years)	56.43 ± 13.98
Male	20 (66.67%)
Female	10 (33.33%)
CAD risk factors	
Hypertension	15 (50.00%)
Diabetes	8 (26.66%)
Smoker	7 (23.33%)
Alcoholic	5 (16.66%)

3.2 Complete Blood Picture Characteristics

Haematological analysis was carried out to calculate the inflammation associated with the injury based on neutrophil and lymphocyte count on day of admission, day 3, day of discharge and on first follow-up. The haematological parameters are included in the Table 2.

3.3 Electrocardiogram (ECG) Characteristics

The diagnostic determination of ST-elevation myocardial infarction (STEMI) was purely based on ECG changes. The 30 patients included in the study showed a significant elevation in the ST-segment on the day of admission. The changes in ST-segment were also noted on day 3, day of discharge and in follow up. These changes are represented in Table 3.

8 (26.67%) patients had anterior wall, 10 (33.33%) had inferior wall, 1 (3.33%) had lateral wall, 5 (16.67%) had anterolateral wall, 1 (3.3%) had anteroseptal wall, 3 (10%) had inferolateral and 2 (6.66%) had anterior with lateral wall myocardial infarction (MI) respectively.

3.4 Coronary Angiogram (CAG) Characteristics

The data based on vessel involvement in the patients is given in Table 4. Among the 30 patients, 16 (53.33%) patients had not undergone CAG due to unstable health conditions and some expired before the procedure was planned.

Table 2. Haematological characteristics of the study population

Haematological Parameters	Cases (n=30)
Haemoglobin (g/dl)	12.74 ± 2.76
RBC count (million cells.cumm)	4.49 ± 1.01
WBC (thousand/cumm)	12.03 ± 3.03
Neutrophil To Lymphocyte Ratio	
On day of admission	7.89 ± 4.98
Day-3	6.24 ± 5.05
Day of discharge	4.34 ± 2.74
Follow up	1.71 ± 1.40

Table 3. Electrocardiogram characteristics of the study population

Electrocardiogram	**Cases (n=30)**
Day of admission	0.39 ± 0.12
Day 3	0.18 ± 0.12
Day of discharge†	0.05 ± 0.07
Follow up†	0.00 ± 0.00

†Excluding missing data of subjects who expired

Table 4. Angiographic characteristics of the study population

Type of Vessel	**Number of Patients**
Single Vessel Disease	
RCA	3 (10.00%)
LAD	3 (10.00%)
LMCA	1 (3.33%)
Double Vessel Disease	
RCA + LCx	2 (6.66%)
RCA + LAD	2 (6.66%)
LAD + LMCA	1 (3.33%)
Triple Vessel Disease	
RCA + LCx + LAD	1 (3.33%)
LMCA + RCA + LCx	1 (3.33%)

RCA = Right coronary artery, LAD = Left anterior descending artery, LMCA = Left main coronary artery, LCx = Left circumflex artery

4. DISCUSSION

Clinical consequences of STEMI range from none or minimal sequelae to early death. STEMI can be treated with several therapeutic interventions, including pharmacologic treatments and invasive approach. Different combinations of pharmacologic treatments and invasive strategies are associated with different benefits and risks, which depend upon patients' baseline clinical profile and risk assessment [15].

A meta-analysis published in the International Journal of Cardiology in 2008 by Dentali et al. [15] explored the impact of neutrophil to lymphocyte ratio (NLR) on clinically important outcomes in acute coronary syndrome (ACS). Pooled data from 23 studies, for a total of >16,000 patients who met the predefined criteria was analysed and found that high NLR, measured on-admission, was associated with a higher mortality rate and with major clinical adverse outcomes. Overall in-hospital and long-term mortality appeared to increase in patients with higher NLR [15].

The findings of our study displayed similar outcomes with higher NLR value on admission. The cut-off value of NLR for our study was determined to be >3.8 which corresponded to the severity of coronary artery disease requiring immediate intervention. Those patients with values as high as 9 or above did not survive. It was also noted that patients who presented to the hospital within 12h of onset of symptoms had relatively lower NLR when compared to those who presented late and were subjected to thrombolytic therapy. The ratio in some of these patients increased during their hospital stay until they succumbed to the illness.

In patients with high NLR, early identification of major adverse cardiovascular events can be achieved by strict surveillance which can help in making treatment decisions, preventing complications and reducing hospital stay [15].

It is important to perform serial ECGs while the patient is still in the cardiac intensive care unit to identify high-risk patients which can expedite the treatment decisions, thereby, minimizing total ischemic time [16].

Our study involved the collection of electrocardiogram at 3 different times of the hospital stay and also at the first follow-up. The first one was obtained at the time of admission, which showed significant ST-elevation. The next two ECGs were collected on day 3 and on the day of discharge which showed relatively less to no elevations in the leads. ECG obtained on the follow-up rarely had any significant elevations.

We correlated the electrocardiographic findings and NLR and found that significant ST-elevation at admission was associated with higher NLR.

High NLR and ST-segment elevation were also associated with over 50% stenosis of the coronary arteries which required immediate intervention. Correlating these three parameters was found to help determine the severity of STEMI and observation was made that the course of treatment could be decided considering these parameters at the earliest.

5. CONCLUSION

There was a linear decrement in ST-segment resolution with the decrease in NLR and can be attributed to the natural course of disease and type of intervention provided. Nevertheless, the univariate correlation between ECG and NLR on various days of treatment was not significant. This study confirms the potential use of NLR along with the extent of coronary artery involvement and the magnitude of ST-elevation to predict the severity of STEMI. Time of admission has a great impact on mortality and the length of hospital stay with thrombolysis within 12 hours of the onset of symptoms proving beneficial effects.

LIMITATIONS

This study had a few flaws. Convenient sampling and the sample was relatively small to produce profound results. Moreover, it was a prospective observational study conducted for a short period.

CONSENT AND ETHICAL APPROVAL

Ethical approval was received for this study (Reference number: 2018/25/011) from the Institutional Review Board. Written informed consent was obtained from all subjects and/or their attendants. Study was carried out in accordance with the “National ethical guidelines for biomedical and health research involving human participants” laid down by Indian Council of Medical Research (ICMR). Available from https://icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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