

Association of Increased Neutrophil to Lymphocyte Ratio to in-Hospital Outcome of Acute anterior Myocardial Infarction Patients Subjected to Thrombolytic Therapy with Streptokinase

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ABSTRACT

Background: Myocardial infarction mainly contributes to morbidity and mortality around the globe. Thrombolytic therapy with streptokinase is the primary treatment strategy for patients with the presentation of ST-segment-elevated acute myocardial infarction. The absolute number of neutrophils and the number of lymphocytes ratio (NLR) has been identified as a potential new biomarker in recent times that is capable of singling out individuals who are at risk of cardiovascular events in future. Although, there are several studies conducted on STEMI patients undergoing primary percutaneous coronary intervention (PCI), there is still paucity of literature for the assessment of NLR prognostic value in patients with STEMI who are likely to receive streptokinase therapy as treatment.

Objective: To assess the correlation between increased NLR and in-hospital outcome in acute anterior MI patients subjected to streptokinase therapy.

Material and Methods: The study was a retrospective cohort conducted over a period of six months from 01, 06, 2021 to 30, 11, and 2021. All the patients admitted consecutively during this period received streptokinase therapy. The patients were grouped with respect to NLR, i.e., high NLR and low NLR. The cut-off point for dividing into these two groups was set as 4.50 as an average of studies previously conducted. The study endpoints in-hospital outcomes and the secondary end point was short-term mortality.

Results: A total of 250 patients were presented with acute MI. Complications were reported in 115 patients (46%) whereas 46 deaths (18.4%) were reported. More complications were reported in patients present in the group with higher NLR, (n=83 vs. 27, 62.8 % vs. 22.8 %, p < 0.0001), as well as death (n=35 vs. 11, 26.5 % vs. 9.3 %, p < 0.0001) in hospital compared to the group with lower NLR. The mean of NLR for whole cohort was noted to be 5.1 ± 1.9 . Mean NLR of the patients who died in the hospital was comparatively higher than the patients who were discharged alive (7.02 vs. 4.72, p < 0.0001). Moreover, NLR is an independent mortality predictor, with OR 2.011 (95% CI 1.622 2.494, p < 0.0001).

Conclusion: high NLR (using 4.50 as cut-off value) is in association with a higher rate of complications and death during stay in the hospital in acute MI patients which are subjected to streptokinase. Moreover, NLR being high was also useful for the prediction of short-term mortality.

Key Words: Myocardial infarction, Thrombolytic therapy, Streptokinase, Neutrophil, Lymphocyte.

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INTRODUCTION

Myocardial infarction is a main reason for morbidity and mortality globally.¹⁻³ The increase mortality rate is seen because of the failure to pump blood adequately. Thrombolytic therapy with streptokinase is the chief medicament strategy for patients which present the ST-segment-elevated acute myocardial infarction.⁴⁻⁶ The timely diagnosis of acute myocardial infarction can lead to early management by thrombolytic therapy.

For quite some time, it is known that there is a major role of inflammatory processes in coronary artery disease.⁷⁻¹⁰ In the initial phases of atherosclerotic plaque, monocytes and lymphocytes are observed, while neutrophils are

observed to take part in disruption of plaque and thrombotic occlusion.^{8,11} The inflammation serves as a trigger for bone marrow to release white blood cells (WBCs), importantly neutrophils.¹¹ Minor increase in the inflammatory biomarkers can indicate the forthcoming cardiovascular events and helps in identifying the patients who are at high risk for those cardiovascular events, particularly in intermediate risk group.⁹ Inflammatory indicators such as CRP and neutrophils increase as cardiac illnesses such as acute heart failure and acute coronary syndrome (ACS), particularly STEMI, worsen.¹¹⁻¹³ Therefore, these biomarkers are under study which can help identify patients at high risk so that they can be managed aggressively.

Among the inflammatory markers, the ratio of absolute neutrophil count to lymphocyte count (NLR) has recently been recognized as new potential biomarker that can identify the individuals who are at greater risk for cardiovascular events in the future.¹⁴⁻²⁰

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A number of proteolytic enzymes, for example myeloperoxidase, are released by activated neutrophils which play role in tissue injury.²¹ The patients with acute coronary syndrome has commonly been observed with low lymphocyte count, the explanation to which is elevated cortisol levels.²² The neutrophils and lymphocytes when combined into a single variable, NLR, has verified to be the most capable simple predictor of leukocyte count for worse outcome.^{23,24}

NLR has been observed to show association with the severity of coronary artery disease^{25, 26} and slow flow post PCI. It also has been observed to be a predictor of in-hospital^{27, 28} and 3-year mortality.^{29, 30} Moreover, NLR is a low-cost, readily available and easy to estimate test compared to other markers.

Numerous studies report regarding STEMI patients during primary percutaneous coronary intervention (PCI).^{20, 28, 30-33} However, there is scarcity of literature that evaluates the prognostic value of NLR in STEMI patients who have to be treated with streptokinase therapy. Streptokinase therapy is a widely available inexpensive treatment and hence a preferable choice of treatment in our setting.

The purpose of the preliminary study was to assess the correlation between increased NLR and in-hospital outcome in STEMI patients subjected to streptokinase therapy.

MATERIAL AND METHODS

Study Setting and Design

The retrospective study was design at DHQ Hospital Bathkela Malakand from 01/06/2021 to 30/11/2021. The study was conducted using the data obtained via consecutive convenient sampling. All the patients that showed the acute anterior wall myocardial infarction and were added progressively at the center between the study time period were enrolled in this present study.

Study Participants

All the patients presented with acute MI and underwent the treatment of thrombolytic therapy with streptokinase at our care center were added in our study. The additional basis added displays of acute anterior wall myocardial infarction that sustained over the time period of 30 mins. The excluded patients were the ones with sepsis, hematological malignancy, recent injury and treated with PCI.

Before allocating to the treatment, all the data of patients were seen which was the age of the patients, gender of the patients and associated factors were being monitored which includes the annals of diabetes mellitus, hypertension, Smoking any family history of cardiac disease. The vitals were checked which includes the heart rate of patient at admission time, systolic blood pressure and the time period of the chest pain patient is presenting. Samples of venous blood were acquired at the time of admission prior to the thrombolysis for cardiac enzymes, complete blood counts (CBC) and serum creatinine. Analyzation of the samples were done under one hour of their acquisition. Diatron ABACUS 380 (ISO-9001 certified) automated cell counter was used for doing CBC as well as absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and total leukocyte count (TLC). Ratio of ALC and ANC was taken as NLR. Record files from the hospitals were used for the collection of data. All the patients were completely examined at the time of the admission and all the patients were looked after till the time of discharge or death of the patients which were subjected to the streptokinase therapy.

The patients were grouped with respect to NLR, i.e., high NLR and low NLR. The cut-off point for dividing into these two groups was set as 4.50 as an average of studies previously conducted.^{30, 34-36}

Treatment Protocol

After the well-informed consent, the patients were given the thrombolytic therapy with streptokinase. It was given about 1.5 million units of dose with dilution of 100ml with saline water within a hour. The diabetes, systolic blood pressure heart rate was kept on check. Patients also received the 300mg aspirin orally with nitroglycerine were given to maintain the 110 mm hg systolic blood pressure. ECG was also recorded for the initial 2 hours. 12-Lead ECG was conducted before the thrombolytic treatment and at 90min afterwards from the patients with ST elevation of acute myocardial infarction. The total of ST elevation was recorded by hand caliper at 80ms above the J point in leads I aVL, V₁ to V₆ for anterior wall.

Patient successful reperfusion is shown by the = 70% ST-resolution (Full ST-resolution) in patients of acute MI, subjected to streptokinase therapy representing a positive outcome whereas ST-resolution failure (<30% ST-resolution) shows subjects with failed myocardial reperfusion, which

shows that patients are subjected to the more or worse effects.

Study End Points

The primary end point was in-hospital outcomes; re-infarction, left ventricular failure, stroke, bleeding, and arrhythmias. The secondary end point was short-term mortality.

Statistical Analysis

All data was statistically analyzed by the use of Statistical Package for Social Sciences version (SPSS) 20.0. categorical variables were presented as frequency (%) whereas continuous variables were expressed as mean \pm standard deviation (S.D). Chi square test and independent t test was used for the comparison of categorical variables continuous variables, respectively.

RESULTS

A total of 250 patients were presented with acute

MI and were included in the study. Based on the cutoff value of NLR i.e., 4.5, division of cohort was done into two groups. Group 1 where NLR was <4.5 consisted of 118 patients, making up 47.2% of the total patients, whereas group 2 where NLR was ≥ 4.5 consisted of 132 patients. The mean age of the patients was 55.98 ± 3.25 and 56.3 ± 2.87 years in low and high NLR group, respectively. The total number of males included in the study were 199 (79.6 %) and the females were 51 (20.4 %). The patients of both the low and high NLR did not differ in terms of demographic data and the associated risk factors. However, significant difference was observed with respect to blood parameters: serum creatinine ($p = 0.0007$), total leukocyte count ($p = 0.0001$), absolute neutrophil count ($p < 0.0001$) and lymphocyte count ($p < 0.0001$). The baseline and demographic characteristics of patients belonging to low and high NLR groups are enlisted in table 1.

Table 1. Demographic and Baseline Characteristics of the Patients Subjected to Streptokinase Therapy (n = 121).

| Variable | Low NLR n = 118 | High NLR n = 132 | P - value |
|--|--------------------|---------------------|-----------|
| Age (mean \pm S.D) | 55.98 \pm 3.25 | 56.3 \pm 2.87 | 0.40 |
| Gender | | | |
| Male n (%) | 95 (80.5 %) | 104 (78.7 %) | 0.72 |
| Female n (%) | 23 (19.5 %) | 28 (21.2 %) | |
| Associated Factors | | | |
| Diabetes mellitus n (%) | 43 (36.4 %) | 45 (34.1 %) | 0.70 |
| Hypertension n (%) | 48 (40.6 %) | 57 (43.1 %) | 0.68 |
| Smoking n (%) | 69 (57 %) | 73 (55.3 %) | 0.78 |
| Family history of cardia disease, n (%) | 36 (30.5 %) | 42 (31.8 %) | 0.82 |
| Heart rate on admission (beats/min) (mean \pm S.D) | 69.4 \pm 9.1 | 70 \pm 8.1 | 0.58 |
| Systolic BP, mm Hg (mean \pm S.D) | 120.3 \pm 25.2 | 122.3 \pm 26.5 | 0.54 |
| Blood Parameters | | | |
| Serum creatinine (mg/dl) (mean \pm S.D) | 0.9 \pm 0.10 | 1.03 \pm 0.40 | 0.0007 |
| Total leukocyte count ($\times 10^9$ cells/liter) | 11.15 \pm 3.1 | 12.9 \pm 3.9 | 0.0001 |
| Absolute neutrophil count ($\times 10^9$ cells/liter) | 7.7 \pm 2.8 | 11.09 \pm 3.1 | <0.0001 |
| Lymphocyte count ($\times 10^9$ cells/liter) | 2.4 \pm 1.3 | 1.26 \pm 0.3 | <0.0001 |

Complications were reported in 115 patients (46%) whereas 46 deaths (18.4%) were reported. More complications were reported in patients present in the group with higher NLR, (n=83 vs. 27, 62.8 % vs. 22.8 %, $p < 0.0001$), as well as death

(n=35 vs. 11, 26.5 % vs. 9.3 %, $p < 0.0001$) in hospital compared to the group with lower NLR. The in-hospital outcomes of the patients who went through streptokinase therapy are given in table 2.

The mean of NLR for whole cohort was noted to be 5.1 ± 1.9 . Mean NLR of the patients who died in the hospital was comparatively higher than the

patients who were discharged alive (7.02 vs. 4.72, $p < 0.0001$).

Table 2. In-Hospital Outcome of Patients Subjected to Streptokinase Therapy

| Variable | Low NLR n = 118 | High NLR n = 132 | P - value |
|----------------------|--------------------|---------------------|-----------|
| Re-infarction | 3 (2.5 %) | 13 (9.8 %) | 0.01 |
| Heart failure | 2 (1.6 %) | 1 (0.75 %) | 0.53 |
| Stroke | 1 (0.84 %) | 3 (2.2 %) | 0.38 |
| Cardiogenic shock | 1 (0.84 %) | 8 (6.0 %) | 0.02 |
| Bleeding | 1 (0.84 %) | 0 (0%) | 0.29 |
| LV ejection fraction | 49 ± 9 | 46 ± 8 | 0.005 |
| Arrhythmias | | | |
| Ventricular | 8 (6.7 %) | 24 (18.2 %) | 0.006 |
| Others | 10 (8.4 %) | 25 (18.9 %) | 0.01 |

Regression analysis demonstrated NLR as an independent mortality predictor, with OR 2.011 (95% CI 1.622 - 2.494, $p < 0.0001$). The ROC curve analysis showed the area under the curve (AUC) as 0.805 (95% CI: 0.737 - 0.872, $p < 0.0001$) (Figure 1).

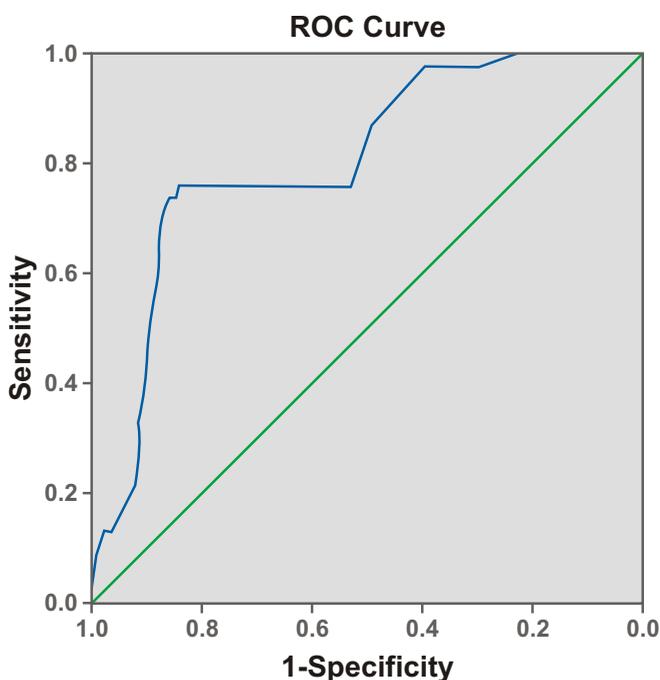


Figure 1. ROC Curve for the Prediction of in-Hospital Mortality by NLR. AUC: 0.805, 95% (0.737 - 0.872). p-value: <0.0001.

DISCUSSION

Myocardial Infarction still remains the one of the foremost causes of death in the world although the thrombolytic therapy with its agent streptokinase has gain a huge support in reducing the mortality rate due to its wide usage and easy access and also it shows the good result in improving the lesion at the area of lumen which is infarcted.² The present research shows the in-hospital outcome of acute anterior MI patients with high NLR subjected to thrombolytic therapy with streptokinase. The prognostic value of NLR (for adverse events and deaths) in STEMI patients thrombolysed with streptokinase has been evaluated by the authors.

Depending on the initial clinical presentation, STEMI is associated with greater rates of early and late mortality and morbidity.^{34,37} Risk stratification of patients having STEMI at earlier basis is related to improved outcomes. As increased NLR is a predictor of increased complications risk, it can also play role in risk stratification of STEMI patients.^{14,38}

In the current study, we observed that NLR is an important predictor of in-hospital mortality in STEMI patients. Additionally, greater number of complications amid hospital stay and lower ejection fraction was observed in patients with increased NLR³⁵. Consequently, this study supports and highlights the role of NLR to predict

death and complications in MI patients as demonstrated by some other studies conducted previously.^{10, 36, 39} Also, it supports the proposal that says NLR is a significant predictor of short-term mortality after STEMI.^{20, 40, 41}

Research on atherosclerosis has emphasized on inflammation in term of risk stratification and pathogenesis.^{42, 43} It has been demonstrated by Arruda-Olson, Reeder⁴⁴ that increased neutrophil count has an independent association with the increased heart failure incidence and long-term mortality in MI patients. A range of proteolytic enzymes, for example myeloperoxidase, are released by activated neutrophils which play their role in tissue injury.²¹ In patients with acute coronary syndrome, a common finding is the decreased lymphocyte count which is explained by increased levels of cortisol that induces apoptosis.²² In MI patients, decreased lymphocyte and CD4 cell count with inverted CD4/CD8 ratio is observed.⁴⁵ Moreover, it was reported by Horne et al.⁴⁶ that relatively decreased count of lymphocytes was related to worse clinical outcome. These two variables combined, neutrophils and lymphocytes (i.e., NLR) has manifested to be the most powerful tool to predict the adverse outcome.^{16, 46} Our study showed that patients with high NLR had elevated count of neutrophils and decreased count of lymphocytes in comparison to the patients who had low NLR. A positive impact of exercise and diet is observed on NLR by Wang et al.⁴⁷ The NLR values might also be modulated by other therapies based on guideline (i.e., statins)

Furthermore, in our study, we did not demonstrate significant differences for stroke and heart failure between the two groups which can be attributed to their low incidence. One other prominent finding of this study is that the increase in NLR is related to lower LVEF. This relationship may be associated with decreased epicardial and microvascular perfusion because of the rheological changes linked with relative and absolute neutrophilia^{20, 48} Which might be related to release of proinflammatory cytokine and lack of flexibility of cytoskeleton.⁴⁹

Our study possessed some limitations. Firstly, no comparison of NLR and other inflammatory markers was made to further assess the predictive role of NLR. However, a positive correlation has been observed between NLR and other inflammatory markers by some studies.^{11, 41} Moreover, other variables as risk factor were not

taken into consideration. It was a single-center but not multi-center study with relatively small sample size. Lastly, after discharge, morbidity (re-infarct, re-hospitalization, progressive heart failure) were not studied.

A prospective long-term study with a larger sample size is required to assess the predictive role of NLR for mortality and complications in a larger scale setting. There is need for further studies on assessing the ability of anti-inflammatory (lowers the NLR) treatment in decreasing the rate of deaths as well as complications and so, resulting in improvement of outcome for the patients presenting acute coronary syndrome.

CONCLUSION

The results drawn from this study depicted that a high NLR (using 4.50 as cut-off value) is in association with a higher rate of complications and death during stay in the hospital in acute MI patients which are subjected to streptokinase. Moreover, NLR being high was also useful for the prediction of short-term mortality.

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DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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AUTHOR'S CONTRIBUTION

The following authors full fill authorship criteria as per ICMJE guidelines;

Razaq HU: Idea conception, drafting the work, final approval, agreed to be accountable for all the work.

Ali K: Design of the work, data acquisition, critical revision, final approval, agreed to be accountable for all the work.

Aqsa: Data analysis, Data interpretation, drafting of the work, final approval, agreed to be accountable for all the work.