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STUDY OF NEUTROPHIL TO LYMPHOCYTE RATIO AS A PROGNOSTIC MARKER IN ACUTE ST ELEVATED MYOCARDIAL INFARCTION

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ABSTRACT

Objectives: Previous studies have demonstrated the role of inflammation in acute STEMI. We examined cellular inflammatory response to STEMI in the blood and its association with in-hospital mortality and/or adverse clinical events. The neutrophil-to-lymphocyte ratio (NLR) was found to be a useful inflammatory marker for predicting adverse outcomes. We hypothesized that an elevated neutrophil-to-lymphocyte ratio would be associated with increased adverse outcomes in patients with acute STEMI. **Material and Methods:** The study consisted of 100 patients with acute STEMI who were admitted in various wards of M.B.S. Hospital, Kota in year 2018-20, after obtaining informed consent. The complete blood cell count (CBC) was obtained from all patients within 12-24 hours of the onset of symptoms. Total leukocytes were counted and differential count was obtained for neutrophils, lymphocytes and neutrophil/lymphocyte ratio (NLR) were evaluated. The patients were divided into two groups [High NLR and Low NLR] according to their admission NLR results. Association of cellular response (NLR) with the incidence of post-MI mortality/complications was assessed by using chi-square test with yates correction. **Results:** Results showed that patients with increased NLR at admission were having increased in hospital complication and mortality at 5 days. In-hospital mortality and post-STEMI complication rate were 9% and 42%, respectively. Patients in high NLR group had higher rate of complications (69.4% vs. 26.5%, p <0.001) and death (19.4% vs. 3.12%, p=0.018) in hospital than those in low NLR group. Cardiogenic shock (36.11% vs.3.12%, p <0.001), pulmonary edema (44.44% vs. 9.37%, p<0.001), heart failure (55.55% vs. 23.43%, p=0.003), arrhythmias (33.33% vs. 9.37%, p =0.006) occurred more in high NLR group. Risk factors were not found to have a major impact on NLR. Differences of the risk factor data in the both groups were not statistically significant (P > 0.05) in our study. **Conclusion:** It can be concluded that in patients with acute STEMI, NLR can be taken as simple, inexpensive, reproducible and universally available inflammatory biomarkers for determining in-hospital mortality and complications.

INTRODUCTION

Acute myocardial infarction (AMI) is the most common diagnosis in hospitalized patients in industrialized countries. In the United States, ~660,000 patients experience a new AMI, and 305,000 experience a recurrent AMI each year. About half of AMI-related deaths occur before the stricken individual reaches the hospital. The in-hospital mortality rate after admission for AMI has declined from 10 to about 5% over the past decade.[1]

Atherosclerosis is an inflammatory disease of arterial wall. The major risk factors (low HDL, high LDL, Hypertension, DM, Smoking) for atherosclerosis disturbing the normal functions of the vascular endothelium that leads the cascade of atheroma formation. AMI is caused by the rupture of the atherosclerotic plaque & inflammation plays a key role. Acute myocardial infarction induces an exacerbation of acute inflammation and stress response, which are characterized by an exaggerated mobilization of leucocytes (mostly neutrophils) in the necrotic area contributing to fibrotic scar formation, a cause of arrhythmia. Elevated neutrophil counts are associated with the development of heart failure and mortality in acute myocardial infarction.[2] Neutrophils also prompt the secretion of inflammatory mediators, aggravating myocardial ischemia and extending the infarct area.[3]

Lymphocyte count is depressed during acute stress conditions due to the excess of stress hormones. Low lymphocyte counts have been reported in acute myocardial infarction and associated with adverse clinical outcomes, advanced heart failure[4] and mortality in STEMI patients.[5]

The NLR is simply the number of neutrophils divided by the number of lymphocytes. Under physiologic stress (Endogenous cortisol and catecholamines), the number of neutrophils increases, while the number of lymphocytes decreases.[6] The NLR combines both of these changes, making it more sensitive than either alone. Neutrophils are seen as a marker of ongoing inflammation and lymphocytes as a marker of regulatory pathways. High NLR ratio indicates a subgroup of patients who will benefit from therapy with anti-inflammatory agents. It shows the balance that exists in-between the body's adaptive immunity and innate immunity and so indirectly between lymphocytes and neutrophils.[7]

In acute STEMI patients, elevated neutrophil counts and low lymphocyte counts are associated with the development of heart failure and mortality.[2,4] A high NLR is predictive of the development or worsening of CHF, shock, re-infarction, arrhythmias, death, and any adverse outcome in acute STEMI patients.[2,8,9-14]

MATERIALS AND METHODS

In this prospective observational study, 100 patients with STEMI admitted in various wards of M.B.S. Hospital, Kota in year 2018-20, were enrolled after obtaining an informed written consent. A detailed history was taken and examination was done as per the proforma in all cases. All patients were divided into two groups on The basis of NLR. The cutoff point value to differentiate High NLR to Low NLR is 4.60 (Low NLR: ≤4.6, High NLR: >4.6). Patients were followed up in the hospital for 5 days for development of complications and occurrence of mortality.

Inclusion Criteria:

(1) History of chest pain at rest or other symptoms suggestive of an acute MI with the most recent episode occurring within 24 hours of admission,
(2) Electrocardiographic (ECG) changes fulfilling current ECG criteria in the diagnosis of acute STEMI,
(3) Positive cardiac biomarkers

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ECG criteria for diagnosis of STEMI in the absence of LBBB:

New ST elevation at the J point in two contiguous leads with the following cut points

(1) ≥0.1 mV in all leads (except V_2-V_3),

(2) In leads V_2-V_3 the following cut points apply- ≥0.2 mV in men ≥40 years; ≥0.25 mV in men <40 years; ≥0.15 mV in women

Exclusion Criteria:

Following patients were excluded from the study:-

1. Patients with active or chronic inflammatory diseases, active infection, hematological disorder, history of severe liver disease, renal disease, malignancy and autoimmune disease.
2. Patients with recent trauma and surgery.
3. Patients on drugs that can affect WBC/differential Count.
4. Patients who are discharged before 5 days from hospital.
5. Patients not capable of giving consent (psychiatric patients) or not willing to participate in the study (who refused to give consent).

Laboratory test

At the time of hospital admission ECG was done and venous blood sample was taken for analysis of the following parameters using standard techniques: glucose, triglycerides, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and cardiac biomarkers. Differential leukocyte counts were measured with an automated hematology analyzer & Neutrophil to Lymphocyte ratio was calculated simply by dividing the neutrophil count to lymphocyte count.

Statistical Analysis

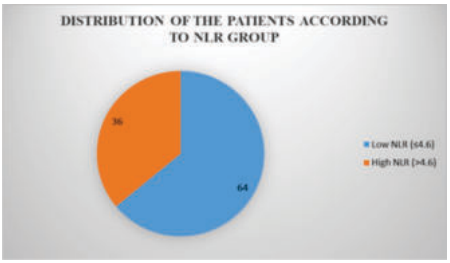
All collected data were analyzed using SPSS 12, Stata 8.0 and Graph Pad. Descriptive statistics were reported as Mean ± SD (range) for continuous variables and frequency (%) for dichotomous or discrete variables. Chi square 2 test were used for comparing categorical variables was used to determine the relationship between NLR to acute STEMI. P value <0.05 was considered as statistically significant.

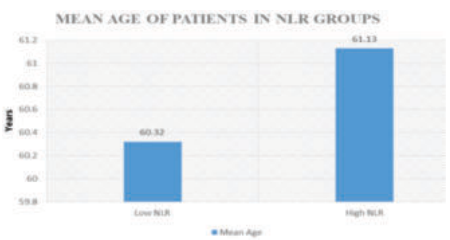
RESULTS

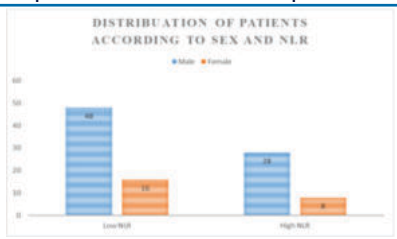
Results were compiled after studying the specific variables. One hundred patients with acute SETMI were evaluated in this study.

Table 1 shows the relationship between NLR group and patient baseline characteristics:

CHARACTERES		Low NLR (≤4.6)	High NLR (>4.6)
No. of Patients		64	36
Age (years)	Range	36-80	38-83
	Mean ±SD	60.32 ± 10.5	61.13 ± 11.81
Sex	Male	48	28
	Female	16	8







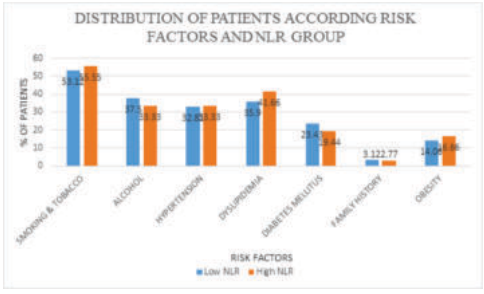
Total number of patients were 100, with 64, 36 in low and high NLR group respectively. Mean age was 60.32±10.5 and 61.13±11.81 in low and high group respectively.

There were 76 males and 24 females in the study with number of males/females of 48/16 and 28/8 in low and high group respectively.

There was a clear male preponderance in the cases of acute STEMI recruited in this study. The mean age of males in the study was 60.13 ± 11.44. The mean age of females in the study was 63 ± 10.8. There was no statistically significant difference between age and sex of both groups.

Table 2 shows distribution of patients according to risk factors and NLR group:

RISK FACTORS	Low NLR		High NLR		Total		P Value
	No.	%	No.	%	No.	%	
SMOKING & TOBACCO	34	53.12	20	55.55	54	54	0.980
ALCOHOL	24	37.5	12	33.33	36	36	0.842
HYPERTENSION	21	32.81	12	33.33	33	33	0.957
DYSLIPIDEMIA	23	35.9	15	41.66	38	38	0.725
DIABETES MELLITUS	15	23.43	7	19.44	22	22	0.833
FAMILY HISTORY	2	3.12	1	2.77	3	3	0.922
OBESITY	9	14.06	6	16.66	15	15	0.953



Out of many risk factors for Acute STEMI, smoking and tobacco was the most prevalent in our study group with the percentage of 54. Dyslipidemia came second (38%) followed by alcohol addiction (36%), hypertension (33%), diabetes (22%), obesity (15%), and family history (3%).

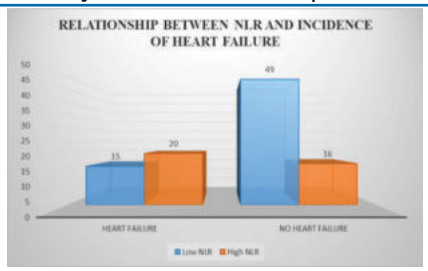
Table 3 and 4 shows the relationship between NLR group and incidence of heart failure among patients in the study:

NLR	Low NLR	High NLR	Total
Heart Failure	15	20	35
No Heart Failure	49	16	65
P value	0.003		

Number of patients in heart failure showed an increasing trend from low NLR (n=15) to high NLR group (n=20).

Table No. 4 Nlr Ratios According To Heart Failure Status (IN ALL PATIENTS)

NLR	RANGE	MEAN±SD
Heart Failure	1.2-10.4	6.16±2.75
No Heart Failure	1.1-8.3	3.51±1.53
P value	<0.001	



In our study Neutrophil to lymphocyte ratio (NLR) had statistically significant correlation with incidence of heart failure. There was strong statistically significant, and strong association between level of NLR group and incidence of heart failure with a p value of 0.003 and average NLR being 6.16 ± 2.75 in patients with heart failure and 3.51 ± 1.53 in those without heart failure.

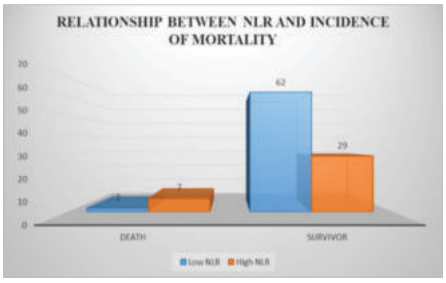
Table 5 and 6 shows the relationship between NLR group and incidence of mortality among patients in the study:

NLR	Low NLR	High NLR	Total
Death	2	7	9
Survivor	62	29	91
P value	0.018		

Table No. 6 Nlr According To Mortality Status (in All Patients)

NLR	RANGE	MEAN±SD
Death	4.5-10.4	8.14 ± 2.13
Survivor	1.1-10	4.08 ± 2.10
P value	<0.001	

Number of patient mortality showed an increasing trend from low NLR (n=2) to high NLR group (n=7).



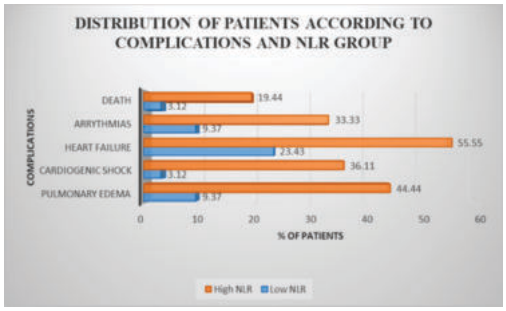
NLR had statistically significant correlation with incidence of mortality. There was strong statistically significant and strong association between level of NLR and incidence of mortality with a p value = 0.018 and average NLR being 8.14 ± 2.13 in patients with mortality and 4.08 ± 2.10 in those without mortality.

Table 7 shows distribution of patients according to complications and NLR group:

COMPLICATIONS	Low NLR		High NLR		Total		P value
	No.	%	No.	%	No.	%	
Pulmonary edema	6	9.37	16	44.44	22	22	<0.001
Cardiogenic shock	2	3.12	13	36.11	15	15	<0.001
Heart failure	15	23.43	20	55.55	35	35	0.003
Arrythmias	6	9.37	12	33.33	18	18	0.006
Death	2	3.12	7	19.44	9	9	0.018

The above table analyzes the distribution and relation between NLR and complications. In our study we found statistically significant and strong correlation between incidence of complication and level of NLR group with a p value of < 0.001.

Patients in high NLR group had higher rate of complications (63.5% vs. 25.5%, p <0.0001) in hospital than those in low NLR group. Cardiogenic shock (36.11% vs.3.12%, p <0.001), pulmonary edema (44.44% vs. 9.37%, p<0.001), heart failure (55.55% vs. 23.43%, p=0.003), arrhythmias (33.33% vs. 9.37%, p =0.006) occurred more in high NLR group.



DISCUSSION

In the current study, we evaluated the leukocytic response and NLR of STEMI patients and examined their possible association with in hospital mortality and post infarction complications. Our study has demonstrated that total neutrophil count and specifically NLR, which is low cost & simple test, is not only an independent marker but probably can predict the risk of complications including mortality post STEMI.

We demonstrated higher NLR was predictor of in-hospital mortality, total complications , post infarction pulmonary edema, cardiogenic shock and arrythmias. The results are consistent with a number of studies which showed the predictive value of NLR in patients with STEMI.

Similar reports by 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.[15] Horneet 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.[8]

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.[12] In our study 42% patients had complications, and 9% died in hospital. Patients in high NLR group had higher rate of complications (69.4% vs. 26.5%, p <0.001) and death (19.4% vs. 3.12%, p=0.018) in hospital than those in low NLR group.

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.[13] Similarly in our study higher total neutrophil counts and higher NLR were predictors of heart failure, mortality and arrythmias but high age was not showing association with mortality.

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 (42/135, 34.1%) 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.[16] Similarly in our study patients in high NLR group had higher rate of mortality (19.4% vs. 3.12%,

p=0.018) in hospital than those in low NLR group. Tamhane UU et al, at University of Michigan, retrospectively studied 2833 patients with ACS and stratified patients into low, medium and high risk groups at the time of their admission. They concluded that patients with high NLRs were significantly more likely to die both in hospital and at 6 months after discharge. The in-hospital mortality was 8.5% in high NLR group as compared to lowest NLR group in which it was 1.8%. The 6 months mortality was also higher 11.5% vs. 2.5%, respectively. This study findings and results are quite similar to our study, as mortality in our study was 7 (19.4%) in patients who were having high NLR and 2 (3.12%) in low NLR.[17]

Similarly, our study patients with evidence of heart failure either as pulmonary edema or cardiogenic shock had higher NLR ratio. According to the previously mentioned results in our study, it seems that NLR is an independent factor that is not affected by other cardiac risk factors like age, sex , hypertension, diabetes mellitus, dyslipidemia and smoking. Differences of the above data in the both groups were not statistically significant (P > 0.05) in our study.

CONCLUSIONS

In this review we observed the association between NLR and of STEMI patients (on admission) and the prognostic outcome with respect to development of heart failure and mortality of these patients on follow up in 5 days in hospital.

Our study found a statistically significant correlation between the Neutrophil to lymphocyte ratio in the development of heart failure and mortality. Numerous other studies have shown that patients with high NLR has been shown to have a higher risk of developing adverse events during the acute setting of STEMI.

The present study was designed to determine predictive role of NLR on admission for morbidity and mortality in patients of STEMI; where lack of resources keeps the access of so many to the best diagnostic methods, NLR may become an additional parameter for the preliminary approach of patients with acute STEMI.

Thus it can be concluded that in patients with acute STEMI, NLR can be taken as simple, inexpensive and reproducible biomarkers for determining in-hospital mortality and complications.

Ethical issues: All patients gave written informed consents and the study was approved by Ethics Committee.

Competing interests: The authors of the present work declare that there is no conflict of interest.

REFERENCES

1. Antman EM, Loscalzo J. ST-Segment Elevation Myocardial Infarction. Jameson JL, Kasper DL, Longo DL et al. (ed). Harrison's principles of internal medicine. 20th Edition. New York. Mc Graw Hill Education. 2018;269:1872-1885.
2. Arruda-Olson AM, Reeder GS, Bell MR, W, et al. Neutrophilia predicts death and heart failure after myocardial infarction: a community-based study. CircCardiovascQual Outcomes. 2009;2(6):656-62.
3. He J, Li J, Wang Y, et al. Neutrophil-to-lymphocyte ratio (NLR) predicts mortality and adverse-outcomes after ST-segment elevation myocardial infarction in Chinese people. Int J Clin Exp Pathol 2014;7(7):4045-4056.
4. Uthamalingam S, Patvardhan EA, Subramanian S, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol 2011; 107: 433-438.
5. Cho KH, Jeong MH, Ahmed K, et al. Value of early risk stratification using hemoglobin level and neutrophil-tolymphocyte ratio in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2011; 107: 849-856.
6. Onsrud M, Thorsby E. Influence of in vivo hydrocortisone on some human blood lymphocyte subpopulations. I. Effect on natural killer cell activity. Scand J Immunol. 1981;13(6):573-579.
7. Angkananard T, Anothaisintawee T, Ingsathit A, et al. Mediation effect of neutrophil lymphocyte ratio on cardiometabolic risk factors and cardiovascular events," Scientific Reports, vol. 9, no. 1, 2019.
8. Horneet BD, Anderson JL, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005;45:1638-1643.
9. Erkol A, Oduncu V, Turan B, et al. Neutrophil to lymphocyte ratio in acute ST-segment elevation myocardial infarction. Am J Med Sci. 2014;348:37–42.
10. Rudiger A, Burckhardt OA, Harpes P, et al. The relative lymphocyte count on hospital admission is a risk factor for long-term mortality in patients with acute heart failure. Am J Emerg Med. 2006;24:451–454.
11. Ertem AG, Ozcelik F, Kasapkara HA, et al. Neutrophil lymphocyte ratio as a predictor of left ventricular apical thrombus in patients with myocardial infarction. Korean Circ J. 2016;46:768–773.
12. Gul U, Kayani A.M, Munir R, et al. Neutrophil lymphocyte ratio: aprognostic marker in acute st elevation myocardial infarction. J Coll Phys Surg Pakistan. 2017;27:4–7.
13. Ghaffari S, Nadiri M, Pourafkari L, et al. The predictive value of total neutrophil count and neutrophil/lymphocyte ratio in predicting in-hospital mortality and complications after STEMI. J Cardiovasc Thorac Res. 2014;6:35–41.
14. Gazi E, Bayram B, Gazi S, et al. Prognostic value of the neutrophil–lymphocyte ratio in patients with ST-elevated acute myocardial infarction. Clin Appl Thromb Hemost. 2015;21:155–159.
15. Nunez J, Bodi V, Sanchis J, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long term mortality in ST segment elevation myocardial infarction. Am J Cardiol. 2008;101(6):747-52.
16. Bajari R, Tak S, Predictive prognostic value of neutrophil-lymphocytes ratio in acute coronary syndrome. Indian Heart Journal. 2017;69(4):S46-501.
17. Tamhane UU, Aneja S, Montgomery D, et al. Neutrophil/lymphocyte ratio aids risk stratification in ACS. Am J Cardiol 2008; 102: 653-7.