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Prognostic implications of neutrophil lymphocyte ratio in acute myocardial infarction

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Abstract---Background: Neutrophil Lymphocyte Ratio (NLR) is a readily available marker that conveys important information about the complex inflammatory activity in the vascular bed during the active phase of the syndrome. Hence it provides relevant information regarding the risk of mortality in patients who are admitted with acute myocardial infarction. Objectives: To estimate the neutrophil lymphocyte ratio in STEMI and NSTEMI of acute myocardial infarction. Materials and Methods: A total of 190 patients with acute myocardial infarction who fulfilled the inclusion criteria were selected. The neutrophil lymphocyte ratio was calculated in STEMI as well as NSTEMI and the value was compared. Patients were then categorized into three groups based on NLR. The relation of neutrophil lymphocyte ratio with the morbidity and mortality of acute myocardial infarction was then studied. Results : The mean age of patients in this study was 59.46 ± 15.29 years. In this study, 63.1 % were males and 37.9 % were females. The mean NLR value in acute myocardial infarction in this study was 6.175 ± 2.26 . The mean NLR value among patients with STEMI is 6.49 ± 2.30 while among patients with NSTEMI is 5.86 ± 2.17 . Though the value is higher in STEMI, the difference was not statistically significant in this study. In this study we also compared the NLR grading with the morbidity and mortality parameters. In this study, statistically significant correlation was found between higher NLR grading and complications like acute decompensated heart failure, arrhythmias, LV dysfunction in admission echocardiography, need for prolonged ICU stay, mechanical ventilation and mortality.

Conclusion: High NLR value has significant association with complications like ADHF, arrhythmias, LV dysfunction in admission echocardiography, need for prolonged ICU stay, need for mechanical ventilation and in-hospital mortality in acute myocardial infarction irrespective of the type of ACS.

Keywords---neutrophil lymphocyte ratio (NLR), acute myocardial infarction, mechanical ventilation.

Introduction

Coronary artery disease continues to be the major health problem in the world and it has become an increasingly important disease in developing countries. Atherosclerosis is the main pathophysiological process that causes many events of clinical syndromes from chronic stable angina to ACS. Leucocytes and neutrophils have many important influence on formation of arterial thrombus and elevated leucocyte cause capillary plugging of micro vessels and causes direct vascular injury and thrombus formation and that ultimately leads to myocardial necrosis. Acute coronary syndrome (ACS) is associated with many hereditary and acquired predisposing factors especially inflammation may play a role in myocardial ischemia. Atherogenesis represents an active inflammatory process rather than simply a passive vascular injury with infiltration of lipids¹. Neutrophil Lymphocyte Ratio (NLR) is a readily available marker that conveys important information about the complex inflammatory activity in the vascular bed during the active phase of the syndrome. Simple ratio (N/L) obtained from a universally available low cost test (CBC with differential) provides relevant information regarding the risk of mortality in patients who are admitted with acute myocardial infarction. A review of literature revealed several studies from across the globe showing a variation in the Neutrophil Lymphocyte Ratio between patients with ischemic heart disease and normal population.^{2,3,4} But only few studies were reported from South India. The usefulness of NLR as an inflammatory biomarker in acute myocardial infarction is also least studied.^{2,5} The aim is to estimate NLR in acute myocardial infarction (both STEMI and NSTEMI) and to assess its usefulness as a prognostic tool in acute MI.

Materials and Methods

Prospective observational study done in 10 months from the date of IRB approval in Medicine and Cardiology Departments on Patients admitted in the departments of General medicine and Cardiology in Govt Medical College Kottayam with acute myocardial infarction

Sample Size

$$\text{Sample size} = (Z_{1-\alpha/2})^2 \cdot \frac{SD^2}{d^2}$$

where $Z_{1-\alpha/2}$ = Is standard normal variate. As in majority of studies p values are considered significant below 0.05 hence 1.96 is used in formula

SD = Standard deviation of variable. Value of standard deviation can be taken from previously done study or through pilot study

d = absolute error or precision

Sample size = $1.96 \times 1.96 \times 2.6 \times 2.6 = 190$ {standard deviation from previous study = 2.6} 0.37×0.37 [mean = 3.7 ; d = 10% of mean]

Association between neutrophil to lymphocyte ratio and severity of coronary artery disease (International Journal of Advances in Medicine Jagadish HR et al. Int J Adv Med. 2018 Apr;5) .⁷

Inclusion Criteria

Patients with confirmed acute myocardial infarction

Exclusion Criteria

Blood dyscrasias, known concurrent infections, HIV, patients on chemotherapeutic drugs and steroids, inflammatory disorders like collagen vascular diseases, recent blood transfusion and acute myocarditis, Sepsis. The study was conducted in this institute after obtaining the ethical clearance from the Institutional Review Board and Department of General Medicine, Government Medical College Kottayam. Informed consent was obtained from all subjects who took part in the study. The privacy of the patient and confidentiality of the clinical data was maintained throughout the study. The information collected was used only for the purpose of this study. The study was done at no added cost to the patients, and did not affect the treatment given to them.

A total of 190 patients in the departments of General medicine and Cardiology diagnosed as acute myocardial infarction who fulfilled the inclusion criteria were selected and were subjected to detailed history, physical examination, biochemical and radiological investigations as per the well-designed proforma after obtaining consent. The neutrophil lymphocyte ratio was calculated in STEMI as well as NSTEMI and the value was compared. Patients were then categorized into three groups based on NLR. The relation of neutrophil lymphocyte ratio with the morbidity and mortality of acute myocardial infarction was then studied. Clinical history included age, sex, history of diabetes, hypertension, smoking, previous history of coronary artery disease. Clinical examination included vitals, general examination and systemic examination including detailed examination of cardiovascular system. Clinical symptoms like chest pain, duration, associated autonomic symptoms, pulse rate, blood pressure, basal crackles, S-3 gallop are conderied with myocardial infraction.

Laboratory investigations like Complete blood cell with differential count using auto analyser taken at the time of admission, RFT, lipid profile, cardiac enzymes-, Troponin I, ECG are done. Imaging-ECHO-ejection fraction, motion abnormalities, septal defects, valvular abnormalities are done. Complications (acute decompensated heart failure, arrhythmias, cardiogenic shock, pericarditis, ischemic mitral regurgitation, ventricular septal rupture), duration of hospital and ICU stay (more than 48 hrs), need for mechanical ventilation and mortality are

noted. Fourth Universal Definition of Myocardial Infarction (2018) is considered in study⁸

NLR Grading - A normal range of NLR is between 1-2, the values higher than 3.0 are considered to be pathological. NLR is influenced by many factors including age, race, medication, chronic disease like coronary artery disease, stroke, diabetes, obesity, psychiatric problems, cancer of solid organs, anemia and stress. Hence a definite cut off value could not be ascertained to NLR. Since all the prior studies have categorized the study population to low and high NLR groups^{9, 10} in this study also, we have grouped patients into 3 homogenous groups by taking the prior cut off values into consideration. The study population was hence categorized into those with NLR<3, NLR between 3-6 and NLR >6.

Statistical Analysis

Data was coded and entered in Microsoft Excel sheet and analyzed using IBM SPSS software version 24. Quantitative variables were presented as mean and standard deviation. Categorical variables were summarized using frequency and percentage. Statistical testing of association of various factors were done using Pearson Chi square test and independent sample t test. p value less than 0.05 was considered as statistically significant.

Results

Among the patients admitted with acute myocardial infarction in the departments of Cardiology and General Medicine, Government Medical College Kottayam from 1st August 2020, a total of 190 consecutive STEMI and NSTEMI patients who met the inclusion criteria were enrolled in this study. Admission NLR value was calculated based on which the study population was categorized into 3 groups and the relation with each variable was studied.

Table 1
Demographic characteristics of the study population

Age in years	Frequency	Percent
≤40	22	11.6
41 - 50	36	18.9
51 - 60	41	21.6
61 - 70	39	20.5
71 - 80	31	16.3
>80	21	11.1
Total	190	100
Mean + SD	59.46+15.29	
Gender		
Male	118	62.1
Female	72	37.9
NLR Grading		
<3	26	13.7

3-6	50	26.3
>6	114	60

Among the study population, 11.6% of the patients were below 40 years of age. 18.9% of patients between 41-50 years, 21.6% patients between 51-60 years, 20.5% patients between 61-70 years, 16.3% patients between 71-80 and 11.1% of patients were above 80 years of age. The mean age of patients included in this study was 59.46 ± 15.29 years. Out of 190 patients enrolled in this study, 62.1 % were males and 37.9 % were females

Table 2
Distribution of neutrophil lymphocyte ratio in STEMI and NSTEMI

NLR grading	STEMI		NSTEMI	
	n	%	n	%
<3	11	11.6	15	15.8
3-6	22	23.1	28	29.5
>6	62	65.3	52	54.7
TOTAL	95	100	95	100
Mean+SD	6.175+2.26			

Among patients presented with STEMI 65.3% had NLR >6, 23.1% had NLR between 3-6 and 11.6% had NLR <3. In patients with NSTEMI 54.7% had NLR >6, 29.5% had NLR between 3-6 and 15.8% had NLR <3. The mean NLR value of the entire study population is 6.175 ± 2.26 .

Table 3
Distribution of complications in the study population

	Frequency	Percent
ADHF		
Yes	38	20
No	152	80
Arrhythmia		
Yes	32	16.8
No	158	83.2
Shock		
Yes	11	5.8
No	179	94.2
Other Complications		
Yes	5	2.6
No	185	97.4
Other Complications		
Pericarditis	1	20
Ischemic mitral regurgitation	2	40

Ventricular septal rupture	2	40
LV Dysfunction		
Yes	114	60
No	76	40
ICU Stay		
Yes	59	31.1
No	131	68.9
Mechanical Ventilation		
Yes	48	25.3
No	142	74.7

The study population was categorized into 3 groups based on admission NLR. First group of patients had NLR value <3, which constituted about 13.7% of the population. Second group had NLR between 3-6 and this constituted about 26.3% of the study population. Rest 60% were categorized into third group and had NLR >6. Out of 190 patients included in the study 20% of patients developed ADHF while it was absent in 80% of the patients. 16.8% of patients developed arrhythmia as a complication of acute myocardial infarction while 83.2% did not. 5.8% of the study population developed cardiogenic shock as a complication of acute myocardial infarction. Rest 94.2% did not develop cardiogenic shock. Only 2.6% developed other complications like pericarditis, ischemic mitral regurgitation and ventricular septal rupture. Acute myocardial infarction, 60% had LV dysfunction in admission echo and 40% had good LV function. Among 190 patients included in the study, 31.1% had prolonged ICU stay in the hospital whereas 68.9% did not. 25.3% required mechanical ventilation during hospital stay and 74.7% did not require mechanical ventilation.

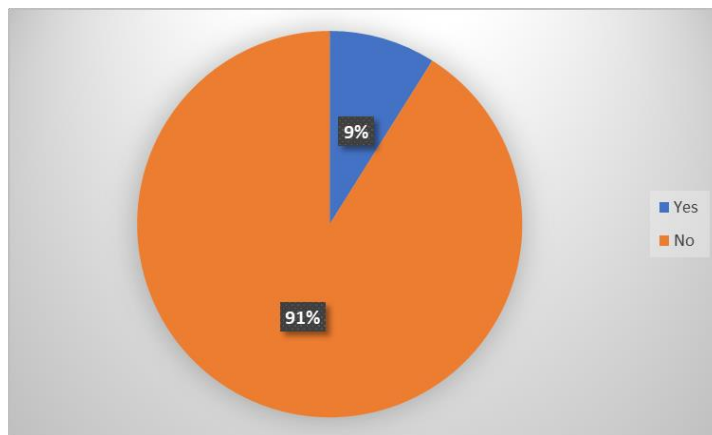


Figure 1. Mortality in present study

Out of 190 patients enrolled in the study, 8.9% patients succumbed to death during hospitalization. 91.9% of the patients survived.

Table 4
Mean NLR in STEMI and NSTEMI

ACS	N	NLR		T test	
		Mean	sd	t	p
STEMI	95	6.49	2.30	1.937	0.054
NSTEMI	95	5.86	2.17		

The mean NLR value among patients with STEMI is 6.49 ± 2.30 . The mean NLR value among patients with NSTEMI is 5.86 ± 2.17 . This data is statistically insignificant. Hence no difference was noted in NLR value between patients with STEMI and NSTEMI in this study.

Table 5
Correlation between NLR grading and complications

ADHF	NLR GRADING						Total		x ²	df	p
	<3		3-6		>6						
	n	%	n	%	n	%	n	%			
Yes	1	3.8	5	10	32	28.1	38	20	12.006	2	0.002
No	25	96.2	45	90	82	71.9	152	80			
Arrythmia											
Yes	1	3.8	5	10	26	22.8	32	16.8	7.70	2	0.021
No	25	96.2	45	90	88	77.2	158	83.2			
Cardiogenic Shock											
Yes	1	3.8	2	4	8	7	11	5.8	0.79	2	0.674
No	25	96.2	48	96	106	93	179	94.2			
Other Complications											
Yes	0	0	1	2	4	3.5	5	2.6	1.12	2	0.570
No	26	100	49	98	110	96.5	185	97.4			
LV Dysfunction											
Yes	6	23.1	20	40	88	77.2	114	60			
No	20	76.9	30	60	26	22.8	76	40			
Prolonged ICU stay											
Yes	3	11.5	9	18	47	41.2	59	31.1	14.12	2	0.001
No	23	88.5	41	82	67	58.8	131	68.9			
Mechanical Ventilation											
Yes	1	3.8	14	28	33	28.9	48	25.3	7.334	2	0.026
No	25	96.2	36	72	81	71.1	142	74.7			

Acute MI patients with NLR >6 developed ADHF, arrhythmia, LV dysfunction, prolonged ICU and required mechanical ventilation which is more frequently than in the other two groups which is statistically significant. This might be because of the overall lower incidence of cardiogenic shock and other complications in acute myocardial infarction which is statistically insignificant.

Table 6
Correlation of NLR and mortality

Mortality	NLR GRADING						Total		χ^2	df	p
	<3		3-6		>6						
	n	%	n	%	n	%	n	%			
Yes	0	0	2	4	15	13.2	17	8.9	6.538	2	0.038
No	26	100	48	96	99	86.8	173	91.1			
Total	26	100	50	100	114	100	190	100			

About 13.2% of acute MI patients with NLR > 6 and around 4 % of patients with NLR value between 3-6 expired. None among NLR<3 expired. This data is statistically significant. Hence acute MI patients with NLR>6 had higher mortality compared to other two groups with low NLR.

Discussion

In present study mean age of patients in this study was 59.46 ± 15.29 years. The maximum number of patients were in the age group 51-60. In the study conducted by Denis Xavier et al, the mean age of patients presented with acute myocardial infarction was 57.5 ± 12.1 .¹¹ In this study ,63.1 % were males and 37.9 % were females. In the study conducted by Chawla et al 72.4% were males.¹² The mean NLR value in acute myocardial infarction was 6.175 ± 2.26 . In the study conducted by Divyaprakash et al, ⁷ the mean NLR was 3.7 ± 2.6 . They also concluded that an NLR of 2.34 or higher was an independent predictor of CAD. But this NLR value was obtained when CAD patients were compared with healthy population. But in this study we have enrolled only patients with acute myocardial infarction which could explain the higher mean NLR in this study. The mean NLR value among patients with STEMI is 6.49 ± 2.30 while among patients with NSTEMI is 5.86 ± 2.17 . Though the value is higher in STEMI ,the difference was not statistically significant in this study. This was consistent with the study conducted by Elisabeth Setianingrum et al which concluded that NLR was higher in acute myocardial infarction patients than normal subjects but there was no significant in NLR difference between STEMI and NSTEMI¹³.

In this study we also compared the NLR grading with the morbidity and mortality parameters. Based on NLR, the study population was divided into 3 categories and each parameter was separately studied. Morbidity parameters included complications like ADHF, cardiogenic shock, arrhythmias, other complications, LV dysfunction in admission echo, need for prolonged ICU stay and mechanical ventilation. About 28.1% of acute MI patients with NLR > 6 developed acute decompensated heart failure as a complication in this study .This data is statistically significant and is consistent with the study conducted by Sawant et al which stated that higher NLR value was associated with increased morbidity like congestive heart failure¹⁴. About 22.8 % of acute MI patients with NLR > 6 developed arrhythmia as a complication of acute myocardial infarction which was definitely higher compared to the other two groups. This data is statistically significant and is consistent with the study conducted by Samad Ghaffari et al. But in the study conducted by Bajari et al⁵ ,this was not statistically significant.

Around 7% of acute MI patients with $NLR > 6$ developed cardiogenic shock as a complication of acute MI. Though this proportion was higher than that of other 2 groups, it was not statistically significant in this study. This might be due to the overall low incidence of cardiogenic shock in this study. But in the study conducted by Bajari et al,⁵ statistically significant incidence of cardiogenic shock was seen in patients with higher $NLR > 5.25$. About 3.5% of acute MI patients with $NLR > 6$ and 2 % of patients with NLR between 3-6 developed other complications such as pericarditis, ischemic mitral regurgitation and ventricular septal rupture. This data is statistically insignificant. The incidence of these complications was too low to make a meaningful association.

About 77% of acute MI patients with $NLR > 6$ had LV dysfunction echocardiographically at admission in our study. This data was statistically significant. So LV dysfunction as a complication of acute MI was observed more frequently in patients with $NLR > 6$. About 41.2 % of acute MI patients with $NLR > 6$ required prolonged ICU stay during the course of the disease which was higher than the other two groups. This data was statistically significant. So the need for prolonged ICU stay in acute MI was more frequently observed in patients with $NLR > 6$ in our study. Similar results were also obtained in the study conducted by Bajari et al.⁵ About 28.9 % of acute MI patients with $NLR > 6$ required mechanical ventilation during the course of the disease, which was higher compared to other two groups. This data is statistically significant. Hence the requirement for mechanical ventilation was more frequently observed in patients with $NLR > 6$ in this study. About 13.2% of acute MI patients with $NLR > 6$ and around 4 % of patients with NLR value between 3-6 expired during hospitalization. None among $NLR < 3$ expired. Hence we could conclude that mortality in acute MI patients was significantly higher in patients with $NLR > 6$ in this study. This was consistent with the study conducted by Bajari et al⁵ which stated that higher NLR is associated with significant risk of mortality during hospital stay.

Conclusion

The mean NLR of patients with acute myocardial infarction in this study is 6.175 ± 2.26 . The mean NLR value of patients with STEMI is 6.49 ± 2.30 and NSTEMI is 5.86 ± 2.17 . Though the value is higher in STEMI compared to NSTEMI, no statistically significant difference was noted in NLR value between STEMI and NSTEMI in this study. High NLR value has significant association with complications like ADHF, arrhythmias, LV dysfunction in admission echocardiography, need for prolonged ICU stay, need for mechanical ventilation and in-hospital mortality in acute myocardial infarction irrespective of the type of ACS. No statistically significant association was noted between NLR and occurrence of cardiogenic shock and other complications of acute myocardial infarction like pericarditis, ischemic mitral regurgitation and ventricular septal rupture in this study.

Limitations

NLR is an acute inflammatory marker which can be altered in multiple medical conditions though we have excluded most of the conditions. Acute MI can present to a

tertiary care centre at different timeline; only admission NLR was considered in our study.

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