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Original Article

Predictive prognostic value of neutrophil–lymphocytes ratio in acute coronary syndrome

Rajesh Bajari, Sandeep Tak *

S.N. Medical College, Jodhpur 342011, India

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ABSTRACT

Objective: To assess the relationship between neutrophil–lymphocytes ratio (NLR) at admission and patient outcome over a period of six month in subjects with acute coronary syndrome (ACS).
Methods: A total of 435 consecutive patients presenting with ACS were enrolled and 400 patients completed the study. Patients were categorized into 2 groups: the NLR group 1 (NLR $\leq$ 5.25; n = 265, 66.25%) and the NLR group 2 (NLR $>$ 5.25; n = 135, 33.75%). The primary outcomes were in-hospital and 6 months mortality.
Results: Forty-seven (11.8%) patients died during 6 months follow up. Higher mortality was seen in NLR group 2 (42/135, 34.1%) compared to NLR group 1 (5/265, 1.9%) with p value $<$0.001.
Conclusion: Our study suggest that elevated NLR ($>$5.25) is independently associated with higher all-cause mortality rate up to 6 months period irrespective of ACS type.

1. Introduction

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality. India suffers the highest loss in potentially productive years of life, due to deaths from CVD.[1] Ischemic heart disease (IHD) is the single most important contributor to this increasing burden of CVD and acute coronary syndrome (ACS) is one of the most common admitting diagnosis in patients with CVD. Early mortality (first 30 days) from acute myocardial infarction (MI) is 30% with more than half of these deaths occurring before the individual reaches the hospital. Mortality is fourfold higher in elderly patients (>75 year) as compared with younger patients.[2]

Elevated white blood cells (WBC) play important role in vascular injury, development of an atherosclerotic plaque, its rupture and thrombosis.[3] The relationship between inflammation and MI was suggested more than 50 years ago.[4] Since then overwhelming evidences supporting that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of atherosclerosis have emerged.[4–7] Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation may lead to ACS.[8] Neutrophils are speculated to mediate plaque rupture and thrombosis by secreting proteolytic enzymes causing vascular damage, activation of coagulation pathways, micro vascular plugging and myocyte necrosis, mediated by secretion of pro-inflammatory cytokines.[9–13] Physiological stress and the subsequent activation of the neurohormonal system during ACS lead to cortisol release, which in turn mediates lymphopenia through apoptosis.[14] Thus, neutrophil–lymphocytes ratio (NLR) may act as a combined surrogate marker for both the reactive and adaptive components of the inflammatory response.

ACS is often accompanied with leukocytosis and it is thought to be associated with short term mortality and morbidity.[15–19] The neutrophil count and NLR represent the balance between neutrophil and lymphocyte levels in the body and can be indicators of systemic inflammation.[20,21] Some clinical trials have reported an association between increased absolute neutrophil count (ANC) in peripheral blood and short-term post-MI adverse outcomes and worse angiographic findings.[22–24] There are some reports regarding the value of monocyte count in predicting heart failure following MI.[24–26] NLR may also reflect the myocardial remodeling responses after reperfusion injury.[27]

Amongst different hematological indices, it has been observed that the NLR has the highest predictive value in predicting death/MI in high risk patients.[28] It has also been observed that NLR predicts the long term mortality in patients hospitalized with ST elevation myocardial infarction (STEMI)[29] and in patients undergoing percutaneous coronary intervention (PCI).[30,31] Inflammatory

* Corresponding author at: S.N. Medical College, 38B, West Patel Nagar, Jodhpur 342011, India.
E-mail addresses: rajesh.bajari@gmail.com (R. Bajari), drstak@yahoo.com (S. Tak).

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biomarkers, such as C-reactive protein (CRP) are used in clinical practice for cardiac risk stratification in stable CAD as well as in ACS.[13,32] Studies suggests a role of neutrophil count and NLR as an independent predictor of poor outcome or recurrence of cardiovascular events in patients with acute cardiovascular disease as well as in stable CAD.[33–36,12,37–41]

Hemogram is an inexpensive, easily available test, routinely done in all admitted patients. Measurement of a simple inflammatory marker like NLR could improve the risk stratification of ACS patients. This study is aimed at evaluating the predictive value of NLR in determining cardiac specific and all cause morbidity and mortality in the Indian patients with ACS.

2. Methods

This study included 435 patients admitted in department of medicine and department of cardiology at Dr. S.N. Medical College with ACS. Acute coronary syndrome including STEMI, non-STEMI, and unstable angina (UA) were diagnosed and classified using the definition and criteria published by American College of Cardiology and European Society of Cardiology. After informed consent, patients meeting inclusion criteria were enrolled. A patient who died in emergency immediately after arrival or required CPR at home or in emergency department was excluded. A venous blood sample was taken before any medical intervention. Hemogram was done by flow cytometry using Sysmex XS-800i analyzer. The NLR was calculated using the absolute count method. All patients were managed on standard protocol for ACS and were followed for 6 months. Approval was taken from institutional ethical committee before starting the study.

2.1. Statistical analysis

The statistical analysis was performed using student's "*t*" test and Chi-square test. Continuous variables were summarized as mean ± SD (standard deviation) and comparisons between continuous variables utilized the student *t* test. In our study, *p* value < 0.05 was considered as significant with either negative or positive correlation on account of biological variability. Categorical variables were summarized as percentages of the group total and comparisons between groups were analyzed using Chi-square test. NLR was utilized as both a continuous and categorical variable, based on relative risk of mortality. Assessment of the bivariate relationship between mortality and each risk factor was performed using data from 400 patients. Variables identified as significant (p-value <0.05) during univariate analysis were then fitted in a logistic regression model by a enter elimination method. This adjusted for confounders and enabled determination of variables of interest associated with increased risk of mortality or major cardiovascular adverse outcomes. Receiver operating curve (ROC) was constructed to obtain area under the curve (AUC), and to predict cut-off values of NLR that could be used to predict mortality. Constructed ROC (Fig. 1) gave cut-off NLR > 5.25 with a sensitivity of 89.36%, specificity of 75.07%, positive predictive value (PPV) of 32.4%, negative predictive value (NPV) of 98.1%, AUC = 0.843 and p value <0.001.

3. Results

A total of 435 patients of ACS were enrolled out of which 35 patients dropped out. Results of remaining 400 patients were analyzed. Majority of patients presented with STEMI (237–59.25%) and rest were with NSTEMI/UA. Patients were divided in two groups according to cut-off value (5.25) of NLR: NLR group 1 (NLR ≤ 5.25) had 265 patients and NLR group 2 (NLR > 5.25) included 135 patients. Forty-seven (11.8%) patients died during 6 months follow up.

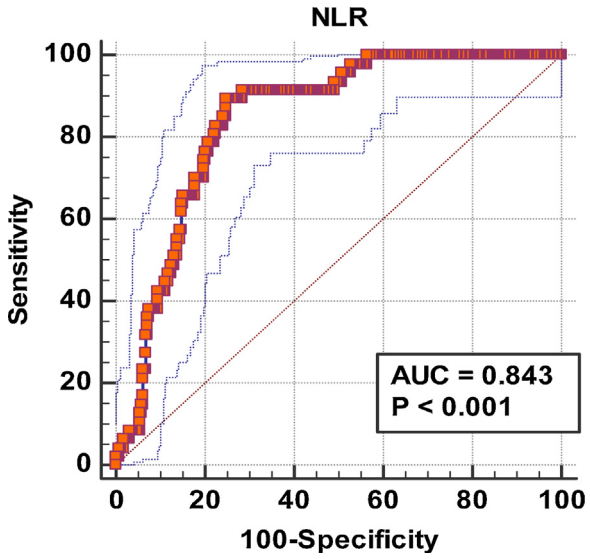

Fig. 1. Receiver operating curve (ROC) depicting NLR as a prognostic tool for mortality risk stratification in ACS patients. Disease prevalence = 11.8%, sample size = 400, AUC = 0.843. Cut-off NLR is >5.25 with a sensitivity of 89.36%, specificity of 75.07%, positive predictive value (PPV) of 32.4% and negative predictive value (NPV) of 98.1%.

Clinical and demographic data of patients are given in Table 1. Difference of mean age between both the groups was statistically significant with higher age was seen in NLR group 2. Significantly higher mortality was seen in NLR group 2 compared to NLR group 1, (42/135, 34.1%) vs. (5/265, 1.9%), with p value <0.001 (Fig. 2). Table 2 compares mortality data among two NLR groups at the time of admission and during 1 month and 6 month period and higher mortality was seen in NLR group 2 compared NLR group 1($p < 0.001$). Further sub analysis revealed that NLR group 2 had significantly higher acute left ventricular failure

Table 1
Patients characteristics among two NLR group.

Variable	Group1 NLR ≤ 5.25	Group2 NLR > 5.25	*p* value
N	265 (66.25%)	135 (33.75%)	
Age (mean ± SD; years)	59.4 ± 11.30	62.51 ± 13.11	$p < 0.02$
Male	189 (71.3%)	99 (73.3%)	
Female	76 (28.7%)	36 (26.7%)	
BMI (kg/m^2)			
18–22.9	52 (19.6%)	37 (27%)	
23–27.4	146 (55%)	70 (51.9%)	
27.5–32.4	52 (19.6%)	17 (12.5%)	
32.5–37.4	13 (4.9%)	6 (4.4%)	
≥37.5	2(0.7%)	5 (3.7%)	
ACS type			
STEMI	150 (56.6%)	87 (64.4%)	>0.2
NSTEMI/UA	115 (43.4%)	48 (35.6%)	
Co morbidities and risk factor			
Preexisting IHD	60 (22.6%)	28 (20.7%)	>0.7
Hypertension	96 (36.2%)	52 (38.5%)	>0.7
Diabetes mellitus	54 (20.4%)	34 (25.2%)	>0.3
Obesity	67 (25.3%)	28 (20.7%)	>0.5
Hyperlipidemia	57 (21.5%)	32 (23.7%)	>0.7
Smoking	85 (32.1%)	49 (36.3%)	>0.5
Alcoholic	29 (10.9%)	12 (8.9%)	>0.7
Tobacco chewer	70 (26.42%)	26 (19.3%)	>0.2
Outcome			
Survivor	260 (98.1%)	93 (68.9%)	$x^2 = 73.66$, $p < 0.001$
Non-survivor	5 (1.9%)	42 (34.1%)	

Difference of mean age between both the groups was statistically significant. Above data shows that higher % of mortality was seen in NLR group >5.25 and difference of % mortality between the two NLR groups was statistically significant.

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