Indian Heart Journal 69 (2017) S46–S50

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

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

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ARTICLE INFO

Article history:
Received 12 September 2016
Accepted 31 January 2017
Available online 7 February 2017

Keywords:
Neutrophil–lymphocytes ratio (NLR)
Acute coronary syndrome (ACS)
Mortality

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

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http://dx.doi.org/10.1016/j.ihj.2017.01.020

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.

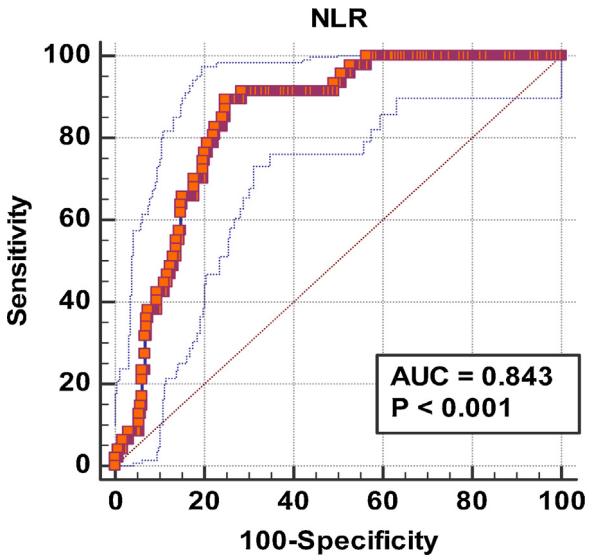

Fig. 1. Receiver operating curve (ROC) depicting NLR as a prognostic tool for mortality risk stratification in ACS patients. Disease prevalence = 11.8%, sample size = 400, AUC = 0.843. Cut-off NLR is >5.25 with a sensitivity of 89.36%, specificity of 75.07%, positive predictive value (PPV) of 32.4% and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

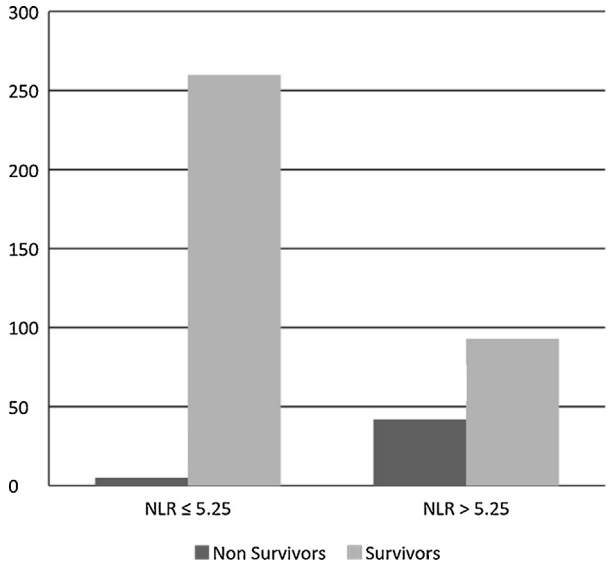

Fig. 2. Survival outcome among two NLR groups.

(21.5% vs. 8.3%) and cardiogenic shock (27.4% vs. 8.3%) as compared to group 1 ($p < 0.001$) but difference in ventricular arrythmia (6.7% vs. 3.8%; $p > 0.2$) was insignificant (Table 3).

Patients who died were compared with those who survived in terms of mean ANC, mean NLR, mean age and co-morbid diseases, revealing that non-survivors were older than survivors and mean NLR and mean ANC were significantly higher among non-survivors ($p < 0.001$). Preexisting IHD and hypertension as co-morbid diseases have significant impact on mortality (Table 4).

We did a separate analysis based on according ANC, with ANC cut-off value (7920 cells/ml) arrived by ROC. Subjects were divided in two groups; ANC group 1 (ANC ≤ 7920) had 220 patients whereas ANC group 2 (ANC > 7920) included 180 patients. Higher mortality was seen in ANC group 2 compared to ANC group 1 (22.8% vs. 2.7%): more number of deaths were seen in ANC group 2 at the time of admission (7.8% vs. 1.8%), at 1 month (10% vs. 0%) and at 6 month (5% vs. 0.9%) with $p < 0.01$. Patients in ANC group 2 had higher morbidity in terms of prolonged hospitalization rate and readmission rate as compared to those in ANC group 1 (p value <0.001).

We also did logistic multivariate regression analysis of mortality: higher age (OR = 1.17; $p < 0.001$), female sex (OR = 0.27; $p < 0.006$), mean ANC (OR = 1.00; $p < 0.001$), mean NLR (OR = 1.24; $p < 0.001$) and preexisting IHD (OR = 3.61; $p < 0.003$) had significant impact on mortality (Table 5). Difference in mean NLR of patients having STEMI and NSTEMI/UA was statistically significant: 4.84 ± 3.87 and 4.12 ± 3.19 respectively but

Table 2
Mortality and morbidity data comparison in two NLR group.

Duration		Group1 NLR ≤ 5.25 (n = 265)	Group2 NLR > 5.25 (n = 135)	p value
During first admission	Death	3 (1.1%)	15 (11.1%)	$x^2 = 20.72$, $p < 0.001$
	Morbidity[a]	48 (18.1%)	54 (40%)	$x^2 = 22.55$, $p < 0.001$
At 1 month	Death	0 (0%)	18 (13.3%)	$x^2 = 41.14$, $p < 0.001$
	Morbidity[a]	5 (1.7%)	9 (6.67%)	$x^2 = 6.05$, $p < 0.02$
At 6 month	Death	2 (0.8%)	9 (6.7%)	$x^2 = 23.52$, $p < 0.001$
	Morbidity[a]	17 (6.4%)	20 (14.8%)	$x^2 = 7.51$, $p < 0.01$
Total	Death	5 (1.9%)	42 (31.1%)	$x^2 = 36.67$, $p < 0.001$
	Morbidity[a]	70 (26.4%)	83 (61.5%)	$x^2 = 46.56$, $p < 0.001$

Results show that higher numbers of deaths and morbidity were seen in the NLR group 2 and difference was statistically significant.

[a] Morbidity data includes prolonged hospitalization, readmission, post-MI complication, i.e. acute LVF, cardiogenic shock and ventricular tachyarrhythmia.

Table 3
Immediate complications in two NLR group during hospital stay.

Immediate complications	Group1 NLR ≤ 5.25 (n = 265)	Group2 NLR > 5.25 (n = 135)	p value
Acute LVF	22 (8.3%)	29 (21.5%)	$x^2 = 13.96$, $p < 0.001$
Cardiogenic Shock	22 (8.3%)	37 (27.4%)	$x^2 = 28.96$, $p < 0.001$
Ventricular Arrhythmia (VT and VF)	10 (3.8%)	9 (6.7%)	$x^2 = 1.65$, $p > 0.2$

Immediate complications including LVF and cardiogenic shock were more and statistically significant in patients having more NLR (>5.25)

Table 4
Demographic, clinical and laboratory data comparison in survivors and non-survivors.

Variable	Non-survivors	Survivors	p value
N	47 (11.75%)	353 (88.25%)	
Age (mean ± SD; years)	68.82 ± 12.49	59.1 ± 11.48	$p < 0.001$
Male	27 (57.45%)	261 (73.93%)	$x^2 = 5.59$, $p < 0.02$
Female	20 (42.55%)	92 (26.06%)	$x^2 = 5.59$, $p < 0.02$
BMI (mean ± SD; kg/m^2)	26.5 ± 4.8	25.64 ± 4.8	$p > 0.3$
ANC (mean ± SD; cells/ml)	10,297.02 ± 2810.67	7678.22 ± 3380.89	$p < 0.001$
NLR (mean ± SD)	7.92 ± 3.46	4.10 ± 3.39	$p < 0.001$
ACS type			
STEMI	25 (53.2%)	212 (60%)	$p > 0.5$
NSTEMI/UA	22 (46.8%)	141 (40%)	$p > 0.5$
Co morbidity and risk factors			
Preexisting IHD	20 (42.6%)	68 (19.3%)	$x^2 = 13.11$, $p < 0.001$
Hypertension	26 (55.3%)	122 (34.6%)	$x^2 = 7.66$, $p < 0.01$
Diabetes mellitus	13 (27.7%)	75 (21.2%)	>0.5
Obesity	14 (29.8%)	81 (22.9%)	>0.3
Hyperlipidemia	8 (17%)	81 (22.9%)	>0.5
Smoking	16 (34%)	118 (33.4%)	>0.9
Alcoholic	5 (10.6%)	36 (10.1%)	>0.9
Tobacco chewer	4 (9%)	92 (26%)	$x^2 = 7.0$, $p < 0.01$

Preexisting IHD and hypertension had statistically significant impact on mortality. Mean NLR, male preponderance and 6 month morbidity were higher in STEMI patients compared to NSTEMI/UA patients and this difference was statistically significant but difference of mortality at 6 month was statistically insignificant.

Table 5
Logistic multivariate regression analysis of mortality among ACS population.

Variable	Mortality in 6 month (n = 47/400)			
	95% CI	Odds ratio	Std. error	p value
Age (in years)	0.072 (1.03–1.11)	1.07	0.018	**0.001**
Sex	−1.28 (0.11–0.69)	0.27	0.471	**0.006**
BMI (kg/m^2)	0.0015 (0.92–1.08)	1.00	0.042	0.97
WBC (cells/ml)	−0.00025 (0.99–1.00)	0.99	0.0002	0.26
ANC (cells/ml)	0.00019 (1.00–1.00)	1.00	0.00004	**0.001**
NLR	0.22 (1.21–1.35)	1.24	0.040	**0.001**
ACS type	−0.22 (0.34–1.83)	0.80	0.423	0.59
IHD	1.28 (1.51–8.60)	3.61	0.443	**0.003**
HTN	0.89 (0.99–5.97)	2.43	0.457	0.05
DM	−0.46 (0.25–1.53)	0.62	0.455	0.30
Obesity	0.68 (0.70–5.24)	1.80	0.52	0.20
Hyperlipidemia	1.00 (0.99–1.00)	1.00	0.004	0.70
Smoking	0.72 (0.74–5.64)	2.05	0.517	0.16
Alcoholic	0.52 (0.47–6.01)	1.68	0.648	0.42
Tobacco chewing	−1.04 (0.10–1.18)	0.35	0.621	0.09

mortality and morbidity do not vary significantly irrespective of ACS type.

Our results shows that elevated NLR (>5.25) is independently associated with higher all cause mortality and morbidity irrespective of ACS type. Overall mortality in NLR group 1 was 1.9% compared to 34% in group 2. ANC is also a good predictor of mortality and morbidity but NLR is statistically better predictor of mortality.

4. Discussion

Hemogram is a basic investigation done in all admitted patients and NLR can be easily calculated from it. Review of literature suggested that NLR can be used as marker of systemic inflammation and it may be an independent prognostic marker. There are several studies that had attempted to answer the use of NLR as prognostic marker in ACS patients; however, there is no large prospective Indian study to look in to this issue. There is also paucity of Indian study of NLR in healthy subjects.

In our study, patients were divided in two groups based on cut-off value of NLR 5.25 which provided highest predictive power of mortality (sensitivity of 89.36%: 95% CI, specificity of 75.07%: 95% CI, positive predictive value of 32.4% and negative predictive value of 98.1%). NLR may vary according to age, sex and race.[42–44] In our study NLR increased with age: NLR group 1 ($\leq$5.25) had mean age of 59.4 $\pm$ 11.3 and NLR group 2 (NLR > 5.25) with their mean age of 62.51 $\pm$ 13.11. Difference of mean age in both group was statistically significant ($p < 0.02$).

It seems NLR is not affected by other cardiac risk factors like hypertension, diabetes, obesity, hyperlipidemia, smoking, and smokeless tobacco use. Difference of above data in both group was not statistically significant ($p > 0.05$) in our study. However, preexisting IHD and HT had correlation with increased NLR. A study by Sawant et al. also indicate that other variables had no effect on NLR, this suggest that NLR is an independent prognostic marker in ACS.[42]

Our study suggest that on admission higher NLR value (>5.25) is associated with higher cardiovascular or all-cause mortality in hospital, at 1 month and at 6 month and difference was highly significant ($p < 0.001$). Overall mortality in NLR group 1 was 1.9% compared to 34% in group 2. Several other studies had results suggesting higher NLR associated with high mortality, though cut-off value of NLR differs and none of studies had such a wide variation in two groups.[29,36,45–48]

In a study about relation of NLR with presence of complexity of CAD, it was observed that patients with complex CAD had a significantly higher NLR value 2.3 median (1.8–3.0) compare to 1.6 median (1.2–3.3) (p value <0.001).[49] Another study also found that increasing NLR was associated with more severe CAD.[50]

In our study, morbidity data included prolonged hospitalization, post MI complication, i.e. acute LVF, cardiogenic shock and ventricular tachyarrhythmia and readmission. Subjects in NLR group 2 had prolonged hospital stay (40% vs. 18.1%) which was statistically significant. Statistically significant incidence of acute left ventricular failure and cardiogenic shock was also noted in NLR group 2 (p value <0.001). Incidence of ventricular tachyarrhythmia was higher in NLR group 2 but was not statistically significant (p value > 0.2). Readmissions were higher in NLR group 2 (>5.25) at 1 month and 6 months, and it was statistically significant (p value <0.02 and <0.01 respectively). A study by Ghaffari et al. showed incidence of VT was also significantly more in higher NLR group.[51] Another study showed that the incidence of heart failure increased with increment of NLR.[43] Sawant et al. also found significant association between higher NLR and increased morbidity like congestive heart failure.[42] In this study, mean NLR and mean ANC was higher in those patients who had STEMI compare to NSTEMI/UA. Difference was statistically significant (p value <0.05) and 6 month morbidity was more among STEMI patients compare to NSTEMI/UA patients and it was statistically significant.

In present study, 47 (11.8%) subjects died at 6 months. Difference in variables like old age, female sex, preexisting IHD and HT among non-survivors and survivors were statistically significant (p value <05) and for mean ANC and mean NLR, difference was highly significant (p value <0.001).

We also analyzed subjects based on optimal cut-off value of ANC, i.e. 7920 cells/ml which provided highest predictive power of mortality. Data showed that mortality risk increased significantly with on admission high ANC (p value <0.01). Prolonged hospitalization rates and readmission rate in 6 month was highly significant (p value <0.001) but difference of readmission rate in 1 month was insignificant (p value >0.5). Other studies also concluded that increase in ANC is associated with increased morbidity and mortality in patients with ACS and those undergoing PCI.

The logistic multivariate regression analysis of mortality among ACS population in our study showed that higher age, female sex, mean ANC, mean NLR and preexisting IHD had significant impact on mortality. Similar results were seen in other studies.[45,46,53,54]

Current study has demonstrated that patients presenting with ACS, an on admission elevated NLR is independently associated with higher all cause mortality and higher morbidity rates at admission, at 1 month and at 6 month. ANC is also a good predictor of mortality and morbidity among ACS population but NLR is statistically better predictor.

Our study has some inherent limitations. We did not include patients who died in emergency immediately after arrival or required CPR at home or in emergency department. Duration of ACS symptoms may have important impact on NLR levels but was not addressed in current study. Alternative concomitant etiologies for elevated NLR may have been present and not accounted for, e.g. occult infection or malignancy, though chances are low as we followed the patients up to 6 months.

A multi-centre study with larger population size and diversity is warranted to best determine the prognostic role of NLR, its best predictive cut-off value, and sampling time.

5. Conclusion

In this prospective study, we followed 400 subjects of ACS for six month. On admission, higher NLR is associated with significant risk of mortality during hospital stay, at 1 month and 6 month. Other factors that had impact on mortality include higher age, female sex, and pre-existing IHD. Prolonged hospitalization due to post MI complications was more in patients with on admission high NLR. Readmission rates at 1 month and 6 months period were higher in patients with high mean NLR. In our study, significant cut-off of NLR is 5.25, cut-off of ANC is 7920 cells/ml, and NLR is better predictor of mortality compared to ANC. NLR is a readily available, inexpensive, and reproducible prognostic indicator and can be utilized as stand-alone prognostic indicator for patients with ACS.

Conflicts of interest

The authors have none to declare.

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