Heart Sci J 2024; 5(3): 39-44

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Original Article

Neutrophil-Lymphocyte Ratio (NLR) as A Predictor for Non-ST Elevation Myocardial Infarction (NSTEMI) in the Emergency Room

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ARTICLE INFO

Keyword :
Marker Inflammation;
NLR;
NSTEMI;
Troponin I.

ABSTRACT

Background: The usefulness of the NLR as an approach to identifying cases of acute coronary syndrome (ACS) needs to be improved.
Objective: This research was designed to determine the effectiveness of the NLR in identifying individuals who presented to the emergency room complaining of anginal due to ACS.
Material and Methods: The single-center cross-sectional study was performed at Saiful Anwar General Hospital in Malang, East Java, Indonesia, from July 2020 to December 2023. Patients were involved in this study with complaints of angina suspected of ACS. During further observation in the emergency room, based on the findings of the troponin I analysis, individuals were divided into unstable angina pectoris (UAP) and NSTEMI.
Result: Study results were collected from 282 individuals diagnosed with Non-ST Elevation Acute Coronary Syndrome (NSTEACS), with 75.9% male and a mean age of 58.39 ± 10.27 years**.** The NLR threshold was 4.5 (AUC: 0.78, 95% CI: 0.765–0.867, P <.001) assessed during admission, which showed a sensitivity of 79% and a specificity of 78% in accurately predicting the probability of subsequent troponin positivity. Multivariate analysis revealed that the NLR at hospitalization remained an essential marker of troponin positivity during follow-up.
Conclusion: In the end, NLR could be considered an initial test in emergency services to predict the diagnosis of NSTEMI in people experiencing angina.

1. Introduction

ACS is a serious cardiovascular condition that occurs due to the reduced flow of blood caused by the partial or complete blockage of coronary arteries. ACS is classified into STEMI, NSTEMI, and UAP. The diagnosis of STEMI can be established through history taking and electrocardiogram (ECG) examination. In contrast, distinguishing NSTEMI from UAP requires cardiac enzyme examination.[1,2] Despite this importance, the availability of cardiac enzyme examinations remains challenging, especially in remote areas.

Neutrophile-lymphocyte ratio (NLR), leukocyte, neutrophile, and lymphocyte percentages are essential markers of inflammation.[3,4] NLR was recognized as a reliable instrument for detecting cardiac events and fatalities.[5,6] Additionally, this marker had a predictive significance in individuals with ACS.[7,8] Lymphopenia is associated with the cortisol secretion generated by stress, and prior investigations demonstrated that it occurred during observations following acute cardiac damage.[9,6] Recent meta-analyses showed that a high NLR was associated with mortality and major adverse cardiovascular events (MACE), with an OR of 6.41 (95% CI: 2.65–15.5); p<0.001. A higher NLR value indicated a worse prognosis in ACS patients.[10,11] This research was conducted to assess the effectiveness of NLR, a recently discovered inflammatory marker, in identifying NSTEACS in patients presenting to the emergency room with chest pain.

2. Methods

Study Population

The single-center cross-sectional study was performed at Saiful Anwar General Hospital in Malang, East Java, Indonesia, from July 2020 to December 2023. A total of 282 NSTEACS patients were involved in this research with complaints of chest pain or angina with an onset of less than 48 hours. Two electrocardiograms (ECGs) were taken in the Emergency Room (ER) 5 minutes after medical contact and the following 30 minutes if ACS was not detected on the previous ECG. A brief history was taken regarding smoking habits, family history of CAD, prior history of MI, hypertension, diabetes, and any other noncardiac illnesses, followed by a complete physical examination.

The inclusion criteria were patients older than 18 years with a diagnosis of UAP or STEMI who were willing to take part in the study. whereas patients with a history of STEMI, severe hepato-renal insufficiency, severe physical trauma, NYHA IV heart failure, malignant arrhythmias, acute and chronic inflammatory diseases, a history of PCI or CABG, infectious diseases like sepsis, pericarditis, or myocarditis, blood abnormalities (leukemia, lymphoma, or other hematologic neoplasms), platelet malfunction, or thrombocytopenia will be excluded from the study.

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https://doi.org/10.21776/ub/hsj.2024.005.03.7
Received 25 December 2023; Received in revised form 12 January 2024; Accepted 29 January 2024
Available online 25 July 2024

ACS is proven by changes in the ECG that show signs of an infarction, ischemia, necrosis, or a significant rise in cardiac enzymes (Troponin) after angina. The cut-off values for Troponin I measurement were above 250 ng/L. If the initial value was insignificant, two serial measurements were performed in 3-6 hours for disposition decision. A delta of >20 ng/L indicated NSTEMI. Patients with a troponin level above the 99th percentile of 45 ng/L and a delta variation of 10–20 ng/L had to have a Troponin I test every six hours.[12,13] Coronary angiography was ordered for patients with ACS diagnosis.

Laboratory Analysis

During the observation in the emergency room, the peripheral vein was collected to obtain a complete blood count (NLR) and troponin I. The cardiac enzyme (troponin I biomarker) examination was performed twice, immediately, and six hours following the initial collection. For the analysis, the total white blood cell count was determined using a computerized haematology instrument for both whole and differential counts. Standard procedures were used to measure biochemical parameters.

Statistical Analysis

The data obtained from the study was analyzed using the SPSS version 17.0. The Kolmogorov-Smirnov test was applied to determine the normality of data distribution. The continuous variable was presented using the mean and standard deviation, while the categorical variable was summarized using numbers and percentages. In this study, bivariate analysis was carried out using chi-square in the NSTEMI and UAP groups. A Spearman correlation test was conducted between the NSTEMI and UAP groups on the patients' age, laboratory values, and comorbidities. A multivariate analysis determined each variable's impact on troponin level. Regression analysis was conducted using multivariate logistic regression for variables with a significance level (P) below 0.10. The data were presented as odds ratios (OR) and the confidence intervals (CIs) at 95%. Through the receiver-operating characteristic (ROC) curve assessments, the ideal cutoff for the NLR compared to high troponin concentrations was determined.

3. Result

In this study, there were 282 consecutive patients, with an average age of 58.39 ± 10.27 years. Around 75.9% of these patients were male. The participants were classified into the NSTEMI group or UAP group according to their, blood troponin levels. Table 1 displayed the baseline characteristics and biochemical, haematological, and demographic information for each group of patients. Cardiovascular risk factors such as a history of CAD, hypertension, smoking, and diabetes mellitus were comparable across both groups.

Table 1. Baseline Characteristics between NSTEMI and UAP patients.

Variable	NSTEMI N= 147	UAP N=135	P
Age, years	58.73 ± 10.22	58.01 ± 10.34	.161
Male gender, n (%)	116 (78.92)	98 (72.68)	.025
Random Blood Glucose, mg/dL	158 ± 13.8	110 ± 6.07	<.001
Creatinine (Cr) mg/dL	1.18 ± 0.92	1.08 ± 0.21	.321
High blood pressure, n (%)	67 (45.67)	72 (53.35)	.193
Diabetus melitus, n (%)	42 (28.6%)	43 (31.9%)	.549
Hyperlipidemia, n (%)	31 (21.18)	37 (27.42)	.215
Smoking, n (%)	99 (67.34)	87 (64.46)	.607
Family History, n (%)	19 (12.97)	24 (17.86)	.257
Coronary Artery disease, n (%)	48 (32.78)	54 (40)	.200
Urgent PCI with significant Stenosis	133(90.47)	0(100)	<.001
Haemoglobin, g/L	10.89± 1.99	11.07± 1.94	.473
Red Cell distribution width (RDW), %	13.94 ± 1.59	13.90 ± 1.74	.656
Platelet count, / mm^3	238 ± 90	271± 73	1.00
Mean platelet Volume, fL	10.56 ± 1.36	10.29 ± 1.41	.289
White blood cell count, $x10^3$ /mL	11.8 ± 4.3	7.1 ± 2.2	<.001
Neutrophil Count, x 10^3/mL	8.82 ± 1.18	4.62 ± 1.54	<.001
Lymphocyte count, x 10^3/mL	1.92 ± 1.78	2.21 ± 0.73	<.001
NLR	5.53 ± 1.49	3.683 ± 1.30	<.001

P = P Value ($p < 0.05$);
N = Frequency; CAD = *coronary artery disease*; PCI = *Percutaneous Coronary Intervention*; UAP = *Unstable Angina Pectoris*; NSTEMI= Non-ST Elevation myocardial Infarctions; NLR = *Neutrophil-Lymphocyte Ratio*; RDW = *Red Cell distribution width.*

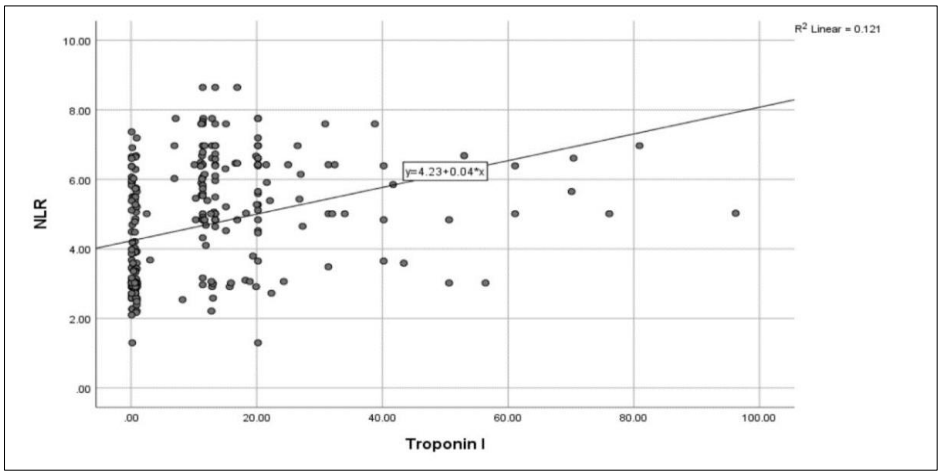

Figure 1. Correlation between NLR and troponin.
Note : P = P value ($p < 0.05$); r = Coefficient correlation

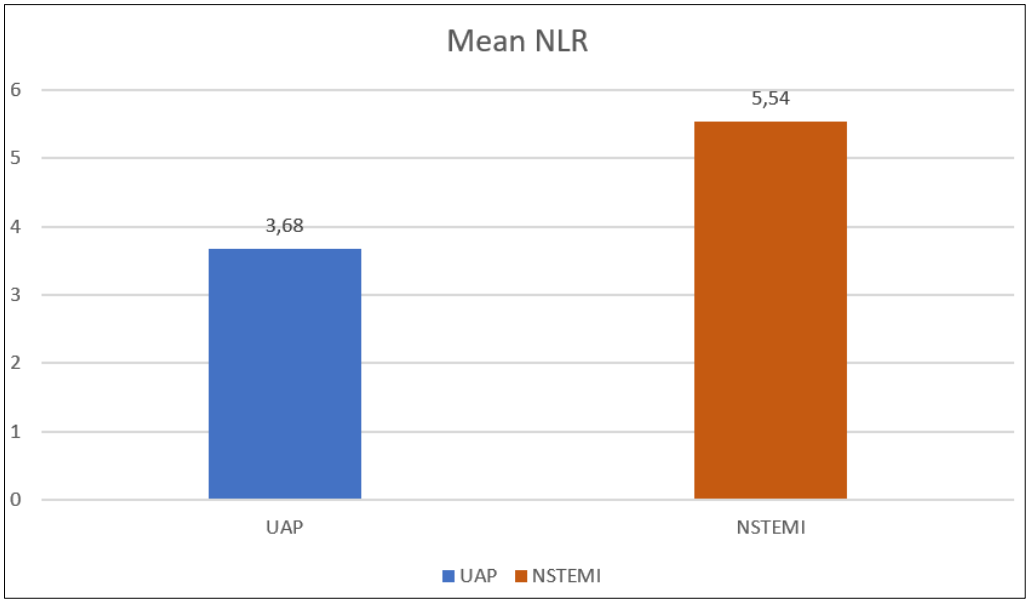

Figure 2. NLR value in the patient with NSTEMI and UAP.

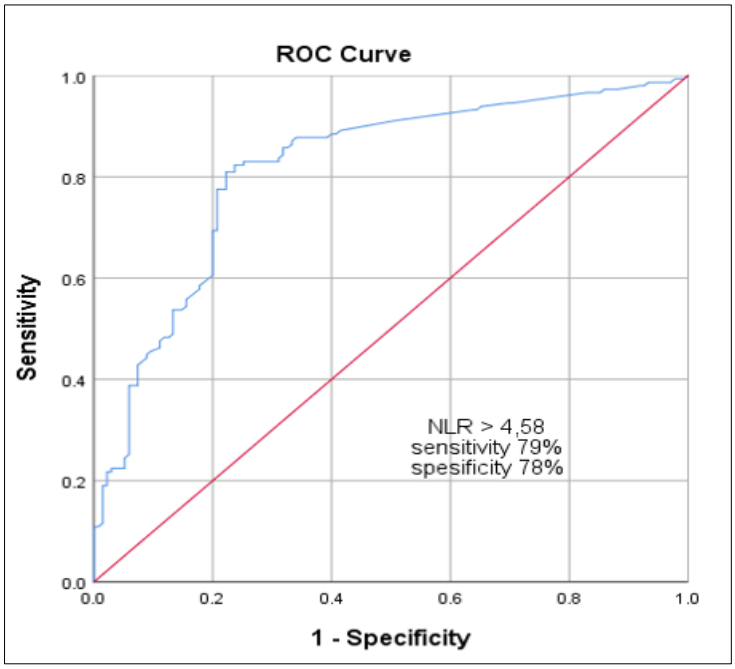

Figure 3. Receiving Operating Curve analysis of NLR in predicting NSTEMI.
Note : ROC = receiver-operating curve; NLR = *Neutrophil-Lymphocyte Ratio*;

Table 2. Multivariate analysis of clinical and laboratory parameters.

Variable	Odds Ratio (95% CI)	P
NLR	1.43 (1.28 – 2.17)	<.001
Age	0.87 (0.96 – 1.02)	.601
Hb	1.014 (0.97 – 1.05)	.382
Plt	1.00 (1.00 – 1.00)	.633
Glucose	1.006 (1.001-1.011)	.024
RDW	1.15 (0.87-1.518)	.325

Note : P = P value with Significant difference ($p < 0.05$); ; r = Coefficient correlation
N = Frequency; Hb = *Hemoglobin;* NLR = *Neutrophil-Lymphocyte Ratio*; PLT = Platelet count; RDW = *Red Cell distribution width*

The majority of participants in the troponin I-positive population who were diagnosed with NSTEMI were male. The NSTEMI group also showed higher levels of glucose, platelets, white blood cells, and neutrophils and lower levels of lymphocytes compared to the troponin-negative population diagnosed with UAP. The Spearman correlation test was performed on patients by comparing troponin I levels with NLR values. Troponin I was positively correlated with NLR with moderate strength, with a value of r = 0.427 and P < 0.001 (Figure 1). In addition, the NSTEMI group had a much higher NLR value (P <.001; Figure 2). Multivariate logistic regression showed that the more elevated NLR levels proved adequate to independently determine which people would have elevated troponin during the follow-up period. Using a 95% CI of 1.28–2.17 and a p-value of less than 0.001, the OR was determined to be 1.43 (Table 2). According to the ROC curve analysis for identifying troponin I positivity with an NLR > 4.58 threshold, the sensitivity rate was 79%, and the specificity was 78%. The ROC analysis produced an area under the curve (AUC) of 0.78 (95% CI: 0.765–0.867, P <.001). With this AUC value, a cutoff level of NLR > 4.58 achieved 79% sensitivity and 78% specificity in predicting troponin elevation. In general, the AUC value of 0.78 is considered quite good, indicating the model's reasonably effective capability to differentiate between the NSTEMI and UAP groups (Figure 3).

4. Discussion

Our research showed that higher admission NLR levels can successfully determine individuals diagnosed with NSTEMI based on positive troponin I results. This study was supported by several studies, which revealed that NLR can increase in patients with ACS.[8,14] Previous studies indicated a relationship between raised white blood cell (WBC) numbers and higher admission frequency and mortality in heart failure patients, as well as higher rates of mortality from cardiovascular disease in a brief period in persons with ACS.[15,16] Additionally, in predicting severe cardiovascular incidents in patients with PAD, increased WBC and neutrophil numbers had been shown to have prognostic relevance.[17,18]

The NLR gained recognition as a reliable indicator of inflammation and was utilized in several research investigations to predict unfavourable outcomes.[6] In a study of individuals with stable CAD, the researcher discovered a correlation between the NLR and the rate of death in individuals with cardiovascular disease. Among people who were receiving coronary PCI, an elevated NLR was found to be a predictor of extended death during the procedure.[6] Patients who were receiving initial PCI for STEMI were identified in another investigation as having an association between non-reflow or TIMI Flow 0 and the occurrence of significant cardiac problems.[19] Furthermore, NLR was shown to function as a prognostic tool for mortality in patients who suffered from STEMI and NSTEMI.[20,21] Although its prognostic importance has been explored in several cardiovascular disorders, NLR is not commonly used as a diagnostic tool for cases of acute ACS. The term “myocardial injury” for ACS refers to complaints of angina accompanied by a rise and/or decline in troponin values that exceed the upper reference limit established at the 99th percentile.[22]

Identifying myocardial damage through cardiac biomarkers plays a crucial role in diagnosing NSTEACS. This is because chest discomfort and ECG abnormalities tend to be nonspecific.[23,24,25] The development of innovative biomarkers such as high-sensitivity troponin I (hs-cTnI) has been facilitated to accurately assess the risk of ACS and determine its presentation.[26] This is necessary because traditional cardiac markers only start to increase 4 to 6 hours after the onset of symptoms.[13]

Several investigations showed a relationship between high troponin I values and C-reactive protein (CRP) values in individuals suffering from ACS. Regardless of the severity of the cardiac injury, elevated CRP levels were associated with short-term adverse outcomes.[27] A meta-analysis revealed contradictory data about CRP's short-term advantages while also demonstrating the long-term predictive significance of CRP. Inconsistent results with the predictive value of CRP for short-term outcomes, accompanied by expensive costs, did not support the routine use of CRP at hospital admission to evaluate possible ACS patients.[28,29] Our study aimed to confirm NLR, different white blood cell counts, and their early diagnostic utility as a replacement for expensive and affordable markers. From our research, Troponin I exhibited a moderately positive correlation with NLR ($r = 0.427$, $P < 0.001$). Additionally, the NSTEMI group demonstrated significantly higher NLR values. The NLR threshold during admission was 4.5 (AUC: 0.78, 95% CI: 0.765–0.867, $P < 0.001$), indicating a sensitivity of 79% and specificity of 78% in accurately predicting subsequent troponin positivity.

For many years, it had been recognized that individuals with ACS had an elevation in the total number of leukocytes and a change in the distribution of different leukocytes. Elevations of cortisol have been associated with these changes.[16,30,31] A study revealed that relative lymphopenia and an abrupt elevation in CK-MB were the first signs of acute MI. These findings were in line with our study, which showed that patients with NSTEMI had higher NLR values than the control group.[10,32]

During the development of ACS, there is a specific time interval between the appearance of symptoms and the subsequent increase in cardiac enzymes.[33] White blood cells and NLR can be considered as the reactive elements in the acute phase of inflammatory processes, which are the main causes of acute myocardial ischemia. Our analysis supported the hypothesis, which showed that patients with NSTEMI had higher NLR values than UAP, all of whom had acceptable entry troponin levels.

Irrespective of the risk factors for diabetes in patients with ACS, several studies have linked glucose on admission to a higher likelihood of incident MACE in the context of ACS. Hyperglycemia was connected to a broader infarct diameter and higher long-term mortality in non-diabetic patients receiving reperfusion therapy for STEMI.[34] In a large-scale investigation of ACS patients, high admission levels of glucose were revealed to be an excellent independent predictor of death in the hospital, particularly in nondiabetic populations.[35,36] The degree of myocardial injury causing troponin elevation may be reflected by the hyperglycemia brought on by stress following an ACS.

The main limitations of this research were the cross-sectional study, lack of long-term and in-hospital follow-up, and relatively small patient population. Another limitation was the lack of comparison with NLR and simultaneous measurement of other inflammatory markers. Low-grade chronic inflammation is associated with diabetes mellitus, obesity, smoking, hypertension, and hyperlipidemia. NLR serves as a prognostic factor for cardiovascular disease. Thus, the lack of data regarding the patient's initial leukocyte, neutrophil, and lymphocyte numbers before the ACS incident is another limitation. Additional large-scale prospective trials are required to establish the usefulness of enhanced NLR as a more practical diagnostic tool, either on its own or in conjunction with other biomarkers such as troponin.

5. Conclusion

Compared to troponin assays, which may not be easily accessible in all healthcare institutions, the NLR is a laboratory parameter that is almost consistently available in all healthcare facilities. NLR serves as a significant inflammatory marker with predictive capabilities and the potential to assist in the straightforward, cost-effective, rapid, and easily accessible diagnosis of NSTEMI. In general, the AUC value of 0.78 is considered quite good, indicating the model's reasonably effective capability to differentiate between NSTEMI and UAP patients.

6. Declaration

6.1 Ethics Approval and Consent to participate

The subjects in this study are humans, so ethical rules must be followed. This research has passed the ethical due diligence, approved based on the Certificate of Ethical Eligibility No. 400/263/K.3/302/2023 issued by the Health Research Ethics Committee at Dr. Saiful Anwar Malang.

6.2. Consent for publication

Not applicable.

6.3 Availibility of data and materials

Data used in our study were presented in the main text.

6.4 Competing interests

Not applicable.

6.5 Funding Source

Not applicable.

6.6 Authors contributions

Idea/concept: SA, IP. Design: LHZ. Control/supervision: SA, IP, BS, AFR. Data collection/processing: LHZ. Analysis/interpretation: LHZ, SA. Literature review: LHZ, SA. Writing the article: LHZ. Critical review: SA, IP. BS, AFR. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

6.7 Acknowledgements

We thank to Brawijaya Cardiovascular Research Center

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