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Research Article

Neutrophils-Lymphocytes Ratio (NLR) and Platelet-Lymphocytes Ratio (PLR) as Predictors of NSTEMI Events

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Abstract: ACS is a manifestation of a complex process known as atherosclerosis. The pathogenesis of atherosclerosis is formed not only from cholesterol but also from the inflammatory response. NLR represents a balance between two essential response pathways, the regulation reflected by neutrophilia and the body's stress response, discussed by lower lymphocyte counts. platelet-lymphocytes (PLR) also showed that inflammation markers could be an independent predictor of left ventricular systolic dysfunction in patients with NSTEMI. Data analysis or statistical tests conducted in this study constitute the Independent T-Test to calculate the differences between the two data in standard data and an alternative test consisting of Mann-Whiney data that is not normal. The given ROC or AUC value has an excellent predictive ability if the angle deviation is above 45 degrees and the p-value <0.05. Statistical test results obtained mean differences representing the NSTEMI and Normal groups on the age variable, NLR, and PLR (p-value <0.05). NLR and PLR have the best predictor abilities in predicting NSTEMI opportunities (AUC> 0.80 or with a good predictive ability). NLR and PLR have an excellent predictive ability to predict NSTEMI events.

INTRODUCTION

Acute myocardial infarction is a clinical disease that is the leading cause of mortality globally [1–4]. The World Health Organization (WHO) in 2017 showed as many as 17.3 million people worldwide died from cardiovascular disease, or 31% of deaths worldwide. More than three-quarters of mortality from cardiovascular disease occur in low- and middle-income countries. Of the 16 million deaths under the age of 70 due to non-communicable conditions, 82% are in low and middle-income countries, and 37% are affected by cardiovascular disease. Of all deaths due to cardiovascular disease, 7.4 million (42.3%) caused by coronary heart disease (CHD) [1].

Myocardial infarction is considered as one part of acute coronary syndrome (ACS). Acute coronary syndrome describes myocardial ischemia and consists of unstable angina pectoris (UAP), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation of myocardial infarction (STEMI). It is necessary to examine cardiac biomarkers such as myoglobin, isoenzyme creatinine kinase (CK-MB), and high sensitivity troponin (high sensitivity troponin / hs-cTn) to determine between the UAP with NSTEMI [5–7].

ACS is a manifestation of a complex process known as atherosclerosis. The pathogenesis of atherosclerosis is formed not only from cholesterol but also from the inflammatory response. When the process of atherosclerosis begins, proinflammatory markers start to emerge. These proinflammatory markers are oxidized LDL (Ox-LDL), stimulatory proinflammatory cytokines (IL-1, TNF-α), adhesion molecules (intracellular adhesion molecules, oxide-selective), stimulant stimulation with proinflammation (IL-1, TNF-α), adhesion molecules (intracellular adhesion molecules, oxide-selectors), stimulant stimulation with hepatic effects (IL-6) or hepatic stimulation products such as serum amyloid A (SAA), C-reactive protein (CRP), and many others. Since the understanding of the role of inflammation in atherosclerosis has increased, so a large number of studies have been approved [8–10]. The importance ratio of neutrophils-lymphocytes (NLR) has increasingly investigated. NLR represents a balance between two essential response pathways, the regulation reflected by

neutrophilia and the body's stress response, discussed by lower lymphocyte counts [11]. Research with inflammatory markers conducted by Beckler et al. in 2015, consisting of platelet-lymphocytes (PLR), also showed that inflammation markers could be an independent predictor of left ventricular systolic dysfunction in patients with NSTEMI. In countries or hospitals with limited facilities and resources, the test is relatively inexpensive and is a very available parameter. These markers can be essential and contribute to establishing a diagnosis that exists in patients with chest pain [12].

If NLR and PLR could give significant results as biomarkers of NSTEMI, then NSTEMI can be more easily suspected even in health facilities that do not have sophisticated examination modalities. So that the incidence of NSTEMI can be reduced in the future, this study aims to determine the use of NLR and PLR as inflammatory biomarkers in NSTEMI.

EXPERIMENTAL METHODS

This research is a preliminary test with a cross-sectional research design to measure basic laboratory prediction parameters such as complete blood to predict the incidence of NSTEMI. This research conducted at Depati Hamzah Regional Hospital, Pangkalpinang, Bangka Belitung, from June 2020 to July 2020. The sample in this study were all patients who came to the Emergency Department of the Depati Hamzah Regional Hospital, Pangkalpinang, Bangka Belitung with the help of treatment in the period June 2019 June 2020.

The inclusion criteria of these patients were all patients who received a complete blood examination and electrocardiography (ECG). In this study, the exclusion criteria were patients with signs of simple heart failure, kidney disorders, strokes, liver disorders, and incomplete medical records. The minimum large sample required is 30 samples with a sampling method consisting of non-random consecutive sampling. The procedure of this study was to start with licensing with the hospital and medical records. Furthermore, secondary data in the form of medical records received in full-participation to see the data in the form of anamnesis complaints, complete blood, and ECG.

This study's independent variables include age and complete blood laboratory parameters containing erythrocytes, hematocrit, hemoglobin, MCV, MCH, MCHC, Platelets, RDW leukocytes, type of count, NLR, PLR, and ALC. The dependent variable in this study is the ECG results that state NSTEMI or normal. The reason for choosing the NSTEMI in this study was that no other ECG results were found in other patients, including STEMI. Before statistical testing, the normality test data used to use the Kolmogorov-Smirnov and Shapiro Wilk tests and variance between groups using the Levene Test. Data analysis or statistical tests conducted in this study constitute the Independent T-Test to calculate the differences between the two data in standard data and an alternative test consisting of Mann-Whiney data that is not normal. When the relationship between the two variables obtained by a significant average difference or p-value <0.05 between the two groups, this variable will be re-assessed its predictor ability by the ROC test in predicting NSTEMI events. The given ROC or AUC value has an excellent predictive ability if the angle deviation is above 45 degrees and the p-value <0.05. The accuracy of the test is further divided into five groups when the AUC value of 0.90 - 1.00 is considered very good, 0.80 - 0.90 is considered good, 0.70 - 0.80 is acceptable enough (fair), 0.60 - 0.70 is considered harmful, and 0.50 - 0.60 is considered a failure. Depati Hamzah Regional Hospital, Pangkalpinang, Bangka Belitung as a learning media for interns to conduct research. The submission of the research ethics review is carried out at the Islamic University of Indonesia with the filing number 11 / C / VII / 20.

RESULTS

As shown in figure 1, of 53 medical records that were assessed for eligibility, 23 medical records cannot be used because they have exclusion criteria. 30 medical records met the inclusion criteria.

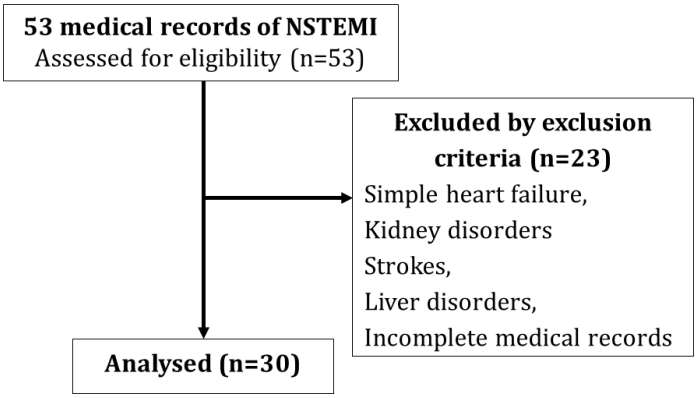

Figure 1. Flow Chart of the Eligibility Assessment

Respondents were generally female (56.7%) and diagnosed with NSTEMI in 12 (40%) respondents. All descriptive parameter data presented in table 1. Data normality test results for independent variables on dependent variables using the Shapiro Wilk test obtained normal data distribution on the variables of erythrocytes, hematocrit, MCV, RDW, leukocytes, count segment types, lymphocyte count types, monocyte count types, and ALC as well as abnormal data distribution on age variables, hemoglobin, MCH, MCHC, platelets, basophil type count, eosinophil type count, stem type count, NLR, and PLR. The Independent statistical t-test was taken as the mean difference representing the NSTEMI and Normal groups on leukocyte variables, calculating the type of segment, calculating the lymphocyte type, and ALC (p-value <0.05) and also not being recognized by the group-related mean. NSTEMI and Normal on erythrocyte, hematocrit, MCV, RDW, and monocyte type count variables (p-value> 0.05). (Table 2).

The Mann Whitney Test statistical test results obtained mean differences representing the NSTEMI and Normal groups on the age variable, NLR, and PLR (p-value <0.05) and found no associated mean between the NSTEMI and Normal groups on the hemoglobin variable, MCH, MCHC, platelets, basophil type count, eosinophil type count, and stem type count (p-value> 0.05). (Table 2)

Table 1. Basic Characteristics of Respondents

Variable	N (%)	Mean (SD)	Med (Min – Max)
Sex			
• Male	13 (43,3)		
• Female	17 (56,7)		
Diagnosis			
• NSTEMI	12 (40)		
• Normal	18 (60)		
Age		54 (18,07)	57,5 (16 – 83)
Erythrocytes		4,42 (0,61)	4,32 (3,24 – 5,89)
Hematocrit		35,18 (7,87)	37(13,90 - 48,80)
Hemoglobin		14,56 (8,18)	12,95 (8,90 – 48,80)
MCV		83,33 (9,44)	84 (59 – 98)
MCH		28,70 (2,75)	29 (20 – 33)
MCHC		33,50 (3,40)	34 (18,90 – 39)
Platelets		273,5 (95,10)	250 (77 – 545)
RDW		14,3 (2,09)	13,8 (10,90 – 18,10)
Leukocytes		8,66 (3,77)	7,55 (3,50 – 18,80)
Basophils		0,23 (0,43)	0 (0 – 1)
Eosinophils		3,17 (3,87)	1 (0 – 12)
Band Neutrophils		0,63 (1,27)	0 (0 – 5)
Segmented Neutrophils		61,73 (17,06)	63 (31 – 93)
Lymphocytes		27,63 (14,69)	29 (4 – 55)
Monocytes		7,27 (3,67)	7 (1 – 17)
NLR		4,51 (5,67)	2,19 (0,61 - 23,25)
PLR		1,85 (1,62)	1,23 (0,21 – 8,41)
ALC		205,65 (99,75)	204,6 (64,80 – 418)

Table 2. Differences in Mean Parameters of Complete Blood Laboratory between NSTEMI and Normal Patients

Parameter	Normality	Disease				p-value
		NSTEMI		Normal		
		Mean (SD)	Med (Min-Max)	Mean (SD)	Med (Min-Max)	
Sex	< 0,05	63,33 (15,63)	67 (32 – 83)	47,78 (17,23)	53 (16 – 69)	0,028
Erythrocytes	> 0,05	4,33 (0,75)	4,21 (3,24 – 5,89)	4,49 (0,52)	4,4 (3,72 – 5,70)	0,496
Hematocrit	> 0,05	35,58 (5,18)	36 (25 – 42)	34,91 (9,39)	37,5 (13,9 – 47,3)	0,822
Hemoglobin	< 0,05	12,06 (1,60)	12 (8,90 – 14,10)	16,23 (10,25)	13,35 (9,3 – 48,8)	0,134
MCV	> 0,05	82,67 (9,98)	85,5 (59 – 95)	83,9 (9,30)	84 (65 – 98)	0,747
MCH	< 0,05	28,25 (2,99)	29 (20 – 32)	29,08 (2,58)	29 (23 – 33)	0,595
MCHC	< 0,05	34,25 (1,96)	34 (31 – 39)	32,85 (4,25)	34 (18,9 – 36)	0,667
Platelets	< 0,05	289,17 (109,35)	(262,5 (164 – 545)	263,06 (86,03)	248(77- 501)	0,602
RDW	> 0,05	14,85 (1,75)	14,7 (12,3 – 18,1)	13,83 (2,30)	13,2 (10,9 – 18,1)	0,221
Leukocytes	> 0,05	11,16 (4,58)	10,15 (5,7 – 18,8)	6,99 (1,81)	7,1 (3,5 (10,7)	0,010
Basophils	< 0,05	0,25 (0,45)	0 (0 - 1)	0,22 (0,43)	0(0-1)	0,917
Eosinophils	< 0,05	2,83 (4,09)	1 (0- 12)	3,39 (3,82)	1,5 (0 – 12)	0,465
Band	< 0,05	-	-	1,06 (1,51)	0 (0 - 5)	0,079
Segmented	> 0,05	73,17 (15,38)	72 (42 – 93)	54,11 (13,76)	53,5 (31- 83)	0,001
Limphocytes	> 0,05	15,25 (9,63)	12,5 (4 – 33)	35,89 (11,3)	35,5 (11 – 55)	0,000
Monocytes	> 0,05	8,5 (4,25)	8,5 (3 – 17)	6,44 (3,07)	6 (1 – 15)	0,135
NLR	< 0,05	8,36 (7,34)	6,17 (1,27 – 23,25)	1,94 (1,59)	1,62 (0,61 – 7,55)	0,000
PLR	< 0,05	2,64 (2,07)	2,20 (0,87 – 8,41)	1,32 (0,98)	1,09 (0,21 – 4,65)	0,005
ALC	> 0,05	144,92 (82,67)	120,15 (64,80 -345)	246,12 (90,62)	244,5 (91- 418)	0,004

From the results of statistical tests on the average difference between the two groups, seven variables which could be used to predict the incidence of NSTEMI consisting of age, leukocytes, type count segments, lymphocyte count types, NLR, PLR, and ALC. These seven variables are answered back using the ROC Curve method. This trial used to test each of these variables' robust model in predicting NSTEMI based on ECG measurements. From the results of ROC analysis obtained 5 of 7 variables that have a deviation of 45 degrees, which means having a minimum predictive test capability both in predicting NSTEMI events. The fifth variable consists of age (AUC: 0.738 / p-value: 0.029), leukocytes (AUC: 0.775 / p-value: 0.012). (AUC: 0.822 / p-value: 0.003), NLR (AUC: 0.884 / p-value: 0,000), and PLR (AUC: 0.801 / p-value: 0.006) (Figure 2 and Table 3). From these observable variables, NLR and PLR have the best predictor abilities in predicting NSTEMI opportunities (AUC> 0.80 or with a good predictive ability). The trade-off in sensitivity and specificity of this study was carried out by variables consisting of age (cutoff value: 58.00), leucocytes (cutoff value: 7.30), segmented (cutoff value: 62), lymphocytes (cutoff value: 27), NLR (cutoff value: 2.30), PLR (cutoff value: 1.50), and ALC (cutoff value: 190) toward NSTEMI events (Figure 3 to 9).

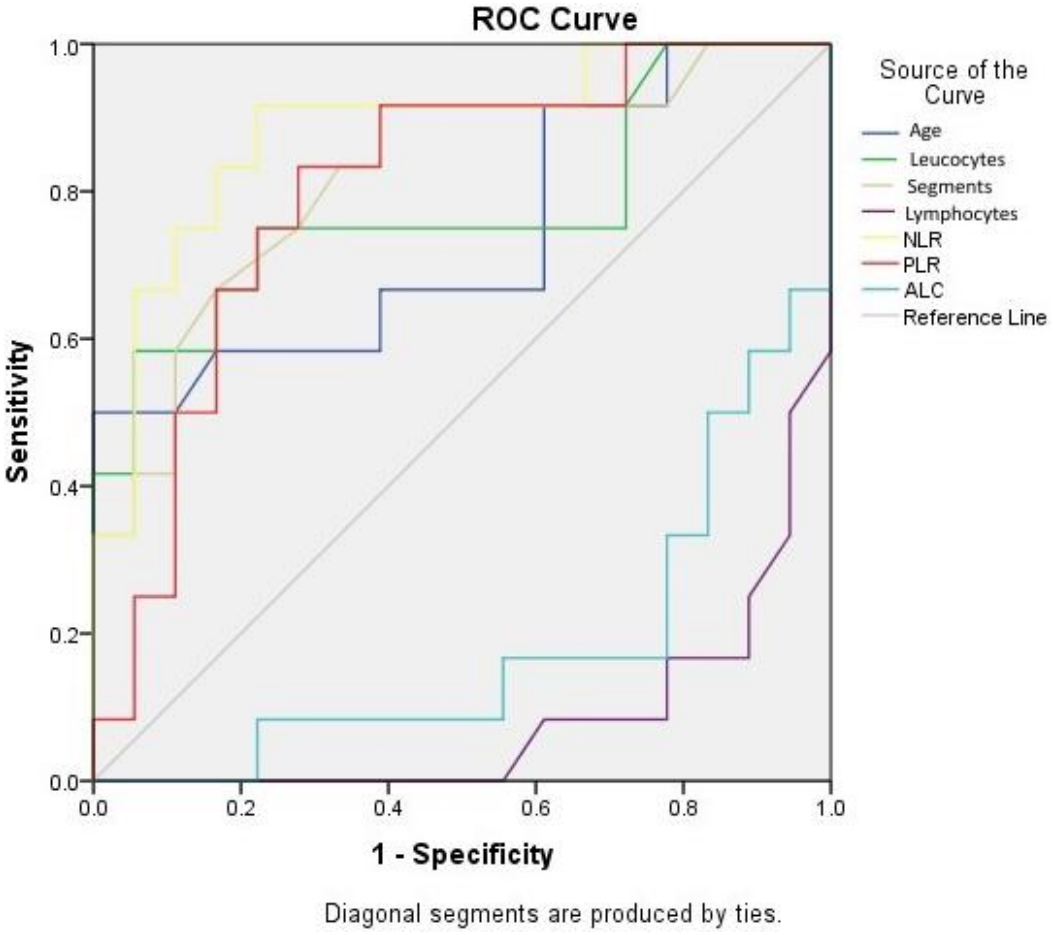

Figure 2. ROC Curve Predictor Parameters for NSTEMI Events

Table 3. Areas Under the Curve (AUC) Parameter Predictors of NSTEMI Events

				Asymptotic 95% Confidence Interval	
Variabel	**Area**	**Std. Error[a]**	***p-value***	***Lower Bound***	***Upper Bound***
Age	0.738	0.099	0.029	0.545	0.932
Leukocytes	0.775	0.096	0.012	0.587	0.964
Segmented	0.822	0.081	0.003	0.664	0.980
Limphocytes	0.081	0.049	0.000	0.000	0.178
NLR	0.884	0.066	0.000	0.756	1.000
PLR	0.801	0.083	0.006	0.638	0.964
ALC	0.181	0.081	0.003	0.022	0.339

The test result variable(s): Age, Leukocytes, Segmented, Limphocytes has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

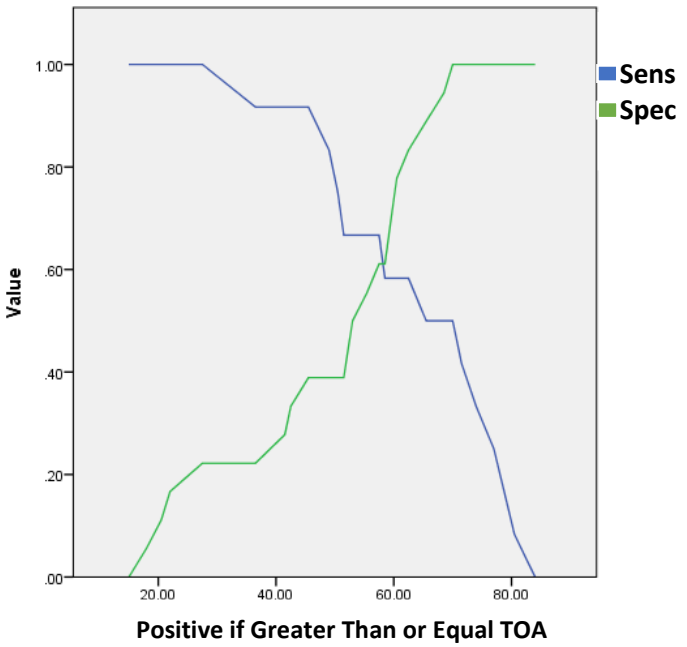

Figure 3. Sensitivity and Specificity of Age Variables on NSTEMI (Sens: Sensitivity; Spec: Specificity)

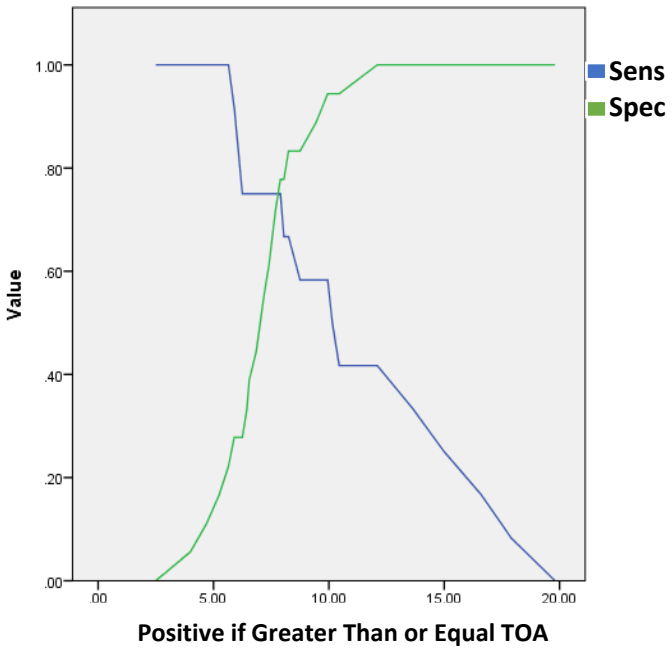

Figure 4. Sensitivity and Specificity of Leukocyte Variables on NSTEMI (Sens: Sensitivity; Spec: Specificity)

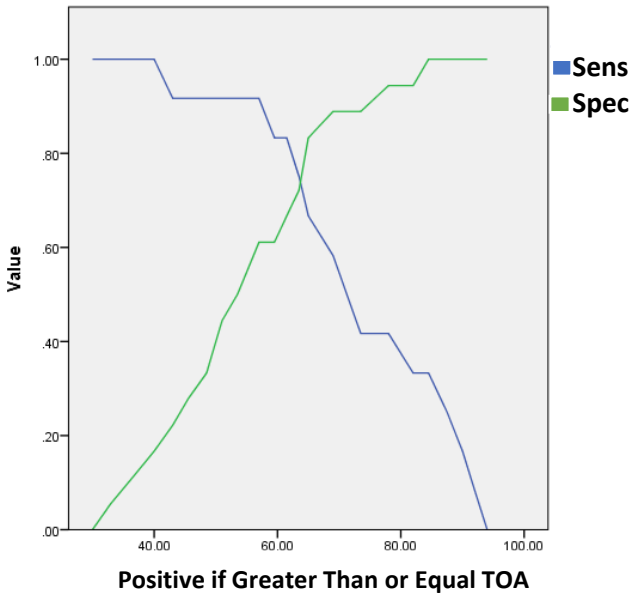

Figure 5. Sensitivity and Specificity of Segment Variables for NSTEMI (Sens: Sensitivity; Spec: Specificity)

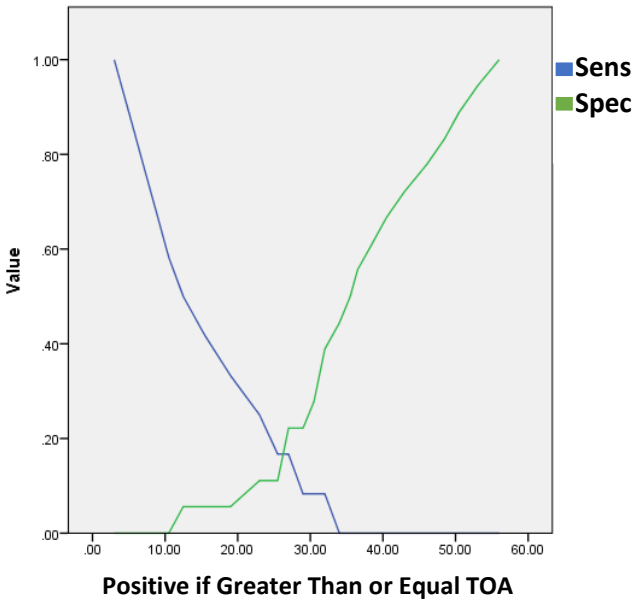

Figure 6. Sensitivity and Specificity of Lymphocyte Variables on NSTEMI (Sens: Sensitivity; Spec: Specificity)

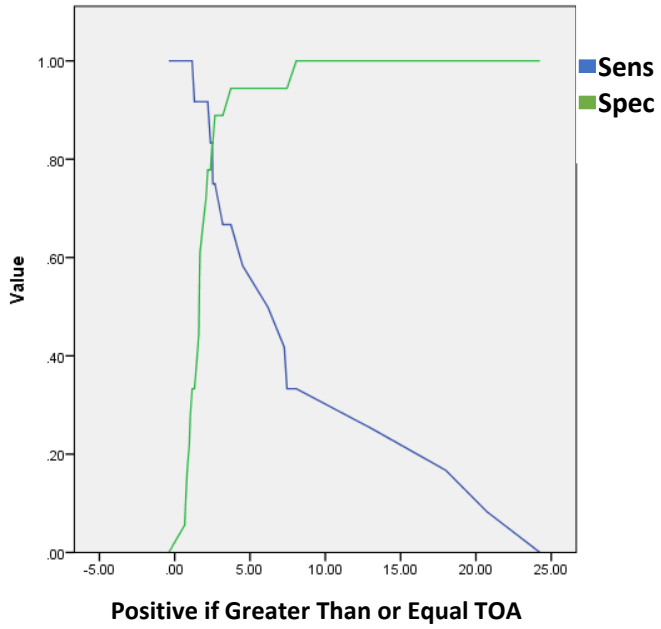

Figure 7. Sensitivity and Specificity of NLR Variables on NSTEMI (Sens: Sensitivity; Spec: Specificity)

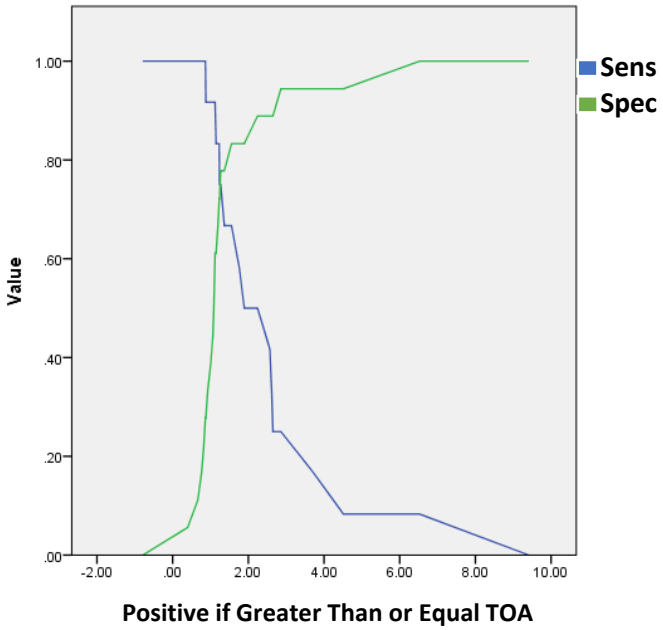

Figure 8. Sensitivity and Specificity of PLR Variables on NSTEMI (Sens: Sensitivity; Spec: Specificity)

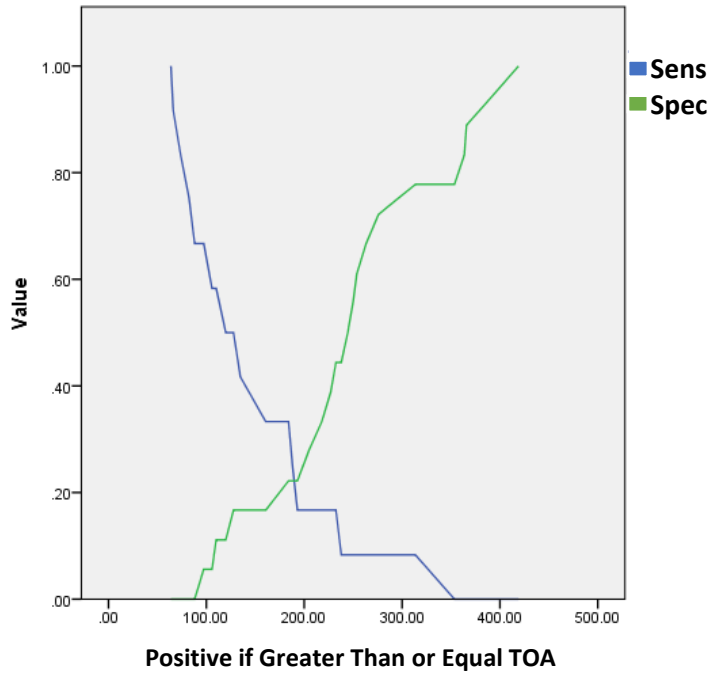

Figure 9. Sensitivity and Specificity of ALC Variables on NSTEMI (Sens: Sensitivity; Spec: Specificity)

DISCUSSION

This study shows a significant mean difference between the NSTEMI and healthy groups on the NLR variable (p-value = 0.000) with an average age of 63.33 years. Research with consistent results conducted by Guo et al. (2018) showed that elderly respondents with NSTEMI had significantly higher NLR values (p-value <0.01). Atherogenesis is an active inflammatory process with the necessary actions of functional and dysfunctional leukocytes [13]. Increased NLR values can reflect inflammatory stimulation and indicate the development and destabilization of plaque [14]. Polarization of neutrophils caused by the activation of Oxidized Calmodulin -dependent Protein Kinase II (oxCAMKII) mediated by reactive oxygen species (ROS), which is caused by changes in peroxisomal homeostasis and reduced fusion of lysosomes. 4-phenylbutyrate (4-PBA) increases neutrophil peroxisome homeostasis, reduces oxCAMKII, and balances pro-inflammatory and anti-inflammatory mediators' expression profile. Adaptive neutrophil transfer regulated by subclinical endotoxemia causes worsening of atherosclerosis [15].

The ROC analysis was carried out to see to test the ability of the trials of NSTEMI events by paying attention to the AUC to determine significance. Obtained AUC NLR value for the NSTEMI event invites (0.884, p-value 0,000, 95% CI, 0.756-1,000), and NLR cutoff value of 2.30 was found. similar results to a study conducted by Darmawan (2016), which obtained NLR sensitivity and specificity values for major adverse cardiac events, especially ACS (0.705, p <0.001, 95% CI 0.642-0.768) with NLR 3.55 dressing values. When NSTEMI occurs, the neutrophil activity will increase due to the rupture of atherosclerotic plaque, which causes an increase in the number of neutrophils recruited to perform various functions [16]. Research by de Waha et al. (2012), officially increasing the number of neutrophils associated with an increase in the area of infarction [17]. Another study by Ates et al. (2016) that examined NLR's relationship to the severity and morphology of coronary atherosclerotic plaques by computerized tomography shows that NLR was higher in patients with critical stenosis [2.40 (1.98-3.07) vs. 1.86 (1.50- 2.38), p < 0.001] [18]. Pende et al. (2016) found that Neutrophils stimulated by various mediators such as TNF-a, receptor activator of nuclear factor kappa B ligand (RANKL), and anti-ApoA-1 antibodies produce neutrophil extracellular traps (NETS) and matrix metalloprotease (MMP) promote collagen degradation and thrombus formation [19].

The Platelet-Lymphocyte ratio value created as an NSTEMI biomarker also showed significant results (p-value = 0.005). Research conducted by Azab B et al. (2012) obtained from 1,037 respondents with acute myocardial infarction had a mean platelet level in CHD patients with occlusion ≥ 70% higher than CHD patients with occlusion <70%. With the results of the agreed statistical test (p-value = 0.018). This study also found that the mean absolute lymphocyte levels in CHD patients with occlusion ≥ 70% lower when compared with CHD patients who had an occlusion <70%, were not found to find a suitable relationship (p-value = 0.327). This study also found PLR values in CHD patients with occlusion ≥ 70% higher than CHD patients with occlusion <70%, with statistically significant test results (p-value = 0.019) [20].

This study found that the mean PLR in the NSTEMI group was 264 (SD = 207) and the AUC PLR for the NSTEMI events participating (0.801, p-value 0.006, 95% CI, 0.638-0.984) with a PLR cutoff value of 1.50. Research conducted by Seyis et al. (2017), who assessed PLR relationships and coronary angiographic time in NSTEMI patients was claiming NSTEMI patients in the middle SYNTAX (SX) group over PLR values 263 (219-366) were significantly higher than 117 (82-144, 5) p <0.001. In the ROC analysis, PLR 178 or lower predicted a low SX score defined as ≤ 22 with a 91.3% sensitivity and a specificity of 100%. The advantages of PLR calculations can consider aggregation requirements and inflammation pathways and can help with the number of platelets or lymphocytes themselves in predicting atherosclerotic coronary burden [21]. Platelet-lymphocyte ratio (PLR) is an indicator of the inflammatory response previously sought concerning relationships to help prognosis for oncological abnormalities [22]. Platelets and inflammation have an essential role in the pathophysiology of CHD. In cases of acute myocardial infarction, there was a significant increase in platelet count, Mean Platelet Volume (MPV), and Platelet Distribution Width (PDW) compared to cases of stable CHD and healthy people [23].

The ALC value in this study obtained a mean value of 144.94 (SD = 82.67) with the results considered participation (p-value = 0.004). Research by Blum et al. (2003) found a decrease in T lymphocytes, CD4+ cells in patients with acute myocardial infarction [24]. Helper T cells (CD4 lymphocytes) are the primary regulator of adaptive immunity. CD4+ T cells in ACS sufferers exhibit upper-level responses to TCR stimulation and have lower T-cell threshold approval, associated with an increase in signal amplification mediated by proximal TCR. CD4+ T cells showed an increase in 70 kDa (Zap70) Zeta chain-related CD3 and protein kinase accumulation in immunologic synapses, higher initial tyrosine phosphorylation after TCR stimulation, and deactivation of the tyrosine kinase-specific lymphocyte protein [25].

Analysis of ROC on ALC for the incidence of NSTEMI found that AUC was well below 45 degrees and was significant (0.181, p 0.003, 95% CI 0.022-0.333). Lower lymphocyte values for worse cardiovascular disease, for heart disease and chronic heart failure. If chronic inflammation occurs, the number of lymphocytes will decrease due to increased lymphocyte apoptosis. Lymphocytes are a better immune response than neutrophils that cause destructive inflammatory reactions. Prolonged inflammation can be continued improvement of proliferation in megakaryocytic and relative thrombocytosis [23]. Coordination of molecular complexes in the form of positive and negative feedback loops is needed to avoid lymphocyte hyperactivity and immune tolerance inhibition [25].

CONCLUSION

This study shows a significant mean difference between the NSTEMI and healthy groups on the NLR and PLR variable. NLR and PLR have an excellent predictive ability to predict NSTEMI events. This study obtained an NLR cutoff value of patients with NSTEMI of 2.30. The PLR cutoff rate for patients with NSTEMI in this study was 1.50. There is a significant value of lymphocyte depletion for patients with NSTEMI in this study. These inexpensive markers can be essential and contribute to establishing a diagnosis that exists in patients with chest pain, especially in countries or hospitals with limited facilities and resources. Randomized controlled trial studies are needed in further research on NLR and PLR in support of the diagnosis of NSTEMI.

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ETHICAL STATEMENT

No ethical issue to be declared

COMPETING INTERESTS

No conflicts of interest

REFFERENCE

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