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Correlation between Neutrophil-to-Lymphocyte Ratio and Left Ventricular Ejection Fraction in ST-Elevation Myocardial Infarction Patients Receiving Primary Percutaneous Coronary Intervention

Karunia Widhi Agatin Putri[1], Firandi Saputra[2], Hendry Purnasidha Bagaswoto[2], Budi Yuli Setianto[2*]

[1]Medical Study Program, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada

ARTICLE INFO

*Corresponding author
Email:
budyuls@ugm.ac.id

Address:
Jl. Farmako Sekip Utara, Yogyakarta 55281

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ABSTRACT

Background: ST-elevation myocardial infarction (STEMI) is a very serious type of heart attack during which one of the heart's major arteries (one of the arteries that supplies oxygen and nutrient-rich blood to the heart muscle) is blocked. Furthermore, it is one of the acute coronary syndrome (ACS) spectrum with a high mortality and morbidity rate. Reperfusion therapy in the form of primary percutaneous coronary intervention (PCI) is currently recommended for STEMI patients, and the total occlusion of coronary vessels during STEMI leads to myocardial dysfunction. The left ventricular ejection fraction (LVEF) is a parameter for determining the ventricular systolic function and is known as a prognostic factor in heart disease. The neutrophil-to-lymphocyte Ratio (NLR), a simple biomarker, has been widely studied as a predictor of major adverse cardiac events in ACS patients and mortality in STEMI patients. In addition, simple biomarkers are needed to stratify the risk of STEMI patients against decreased LVEF post-primary PCI.

Aim and Objective: To investigate the correlation between NLR and LVEF in STEMI patients receiving primary PCI

Methods: This is an observational analytical study with a cross-sectional design. A total of 196 STEMI patients receiving primary PCI from August 2019—November 2020 was included in this study. The data were consecutively obtained from SCIENCE (Sardjito Cardiovascular Intensive Care) registry. Furthermore, the data were analyzed using Pearson's Correlation and Phi Correlation Tests was used to determine the correlation between NLR and LVEF. The NLR cut-off value was obtained from the analysis of the receiver characteristic curve analysis.

Results: There was no significant negative NLR and LVEF correlations in both the overall analysis (r = -0,065; p = 0,362) and in sub-group analysis (r=-0,107; p=0,133) based on the cut-off value of NLR (5,73) and LVEF (50%).

Conclusions: There was no significant negative correlation between NLR and LVEF in STEMI patients receiving primary PCI.

INTISARI

Latar Belakang: Infark miokardium akut dengan elevasi segmen ST (IMA-EST) merupakan salah satu spektrum sindrom koroner akut (SKA) yang memiliki beban mortalitas dan morbiditas yang tinggi. Terapi reperfusi berupa intervensi koroner perkutan (IKP) primer direkomendasikan untuk pasien IMA-EST. Oklusi total pembuluh darah jantung pada IMA-EST menyebabkan terjadinya disfungsi miokardium. Fraksi ejeksi ventrikel kiri

(FEVK) merupakan parameter untuk penilaian fungsi sistolik ventrikel dan berguna untuk prognosis penyakit jantung. Neutrophil-to-lymphocyte Ratio (NLR), suatu biomarka sederhana, telah banyak diteliti sebagai prediktor kejadian kardiovaskuler mayor pada pasien SKA dan mortalitas pada pasien IMA-EST. Diperlukan biomarka sederhana untuk stratifikasi risiko pasien IMA-EST terhadap kejadian penurunan FEVK setelah dilakukan IKP primer.

Tujuan: Untuk mengetahui hubungan antara NLR dengan fraksi ejeksi ventrikel kiri pada pasien IMA-EST yang menjalani IKP primer.

Metode: Penelitian ini merupakan penelitian observasional analitik dengan desain potong lintang. Subjek penelitian berjumlah 196 pasien dengan diagnosis IMA-EST yang dilakukan IKP primer pada Agustus 2019—November 2020. Data didapatkan dari registri SCIENCE (Sardjito Cardiovascular Intensive Care) secara consecutive sampling. Analisis data menggunakan uji korelasi Pearson dan uji korelasi Phi mengetahui korelasi antara NLR dengan FEVK. Nilai cut-off NLR didapatkan dari kurva receiver operating characteristic.

Hasil: Tidak terdapat korelasi negatif yang signifikan antara NLR dengan FEVK, baik secara keseluruhan (r=-0,065; p=0,362) maupun setelah dilakukan pengelompokan berdasarkan nilai cut-off NLR 5,73 dan FEVK 50% (r=-0,107; p=0,133).

Kesimpulan: Tidak terdapat korelasi negatif yang signifikan antara NLR dengan FEVK pada pasien IMA-EST yang dilakukan IKP primer.

Introduction

Ischemic heart disease is the leading cause of death worldwide, and a type, namely acute coronary syndrome (ACS), is a cardiovascular problem that causes high mortality and high treatment costs. ACS is the main cause of mortality and morbidity in the Asia-Pacific region.[1,2] In Indonesia, the incidence of coronary heart disease is about 1.5%.[3] One spectrum of ACS, acute myocardial infarction with ST segment elevation (STEMI), is a heart disease with transmural myocardial ischemia due to myocardial injury or necrosis and characterized by abnormal cardiac biomarkers and ST segment elevation on electrocardiogram (ECG) images.[4] This STEMI accounts for about 38% of all ACS cases.[5]

The neutrophil to lymphocyte ratio (NLR) is a simple biomarker that represents a balance between the levels of neutrophils and lymphocytes in the body and an indication of systemic inflammation.[6] These biomarkers are also inexpensive and easily accessible.[7] The NLR shows two immune response pathways, namely nonspecific inflammation reflected by neutrophils, and the physical response is identified from the number of lymphocytes.8 Therefore, it can be a marker for the reactive and adaptive components of the inflammatory response.

The inflammatory process plays a role in the STEMI pathogenesis, including the progression of the atherosclerotic plaque. Furthermore, it is known that neutrophils play a role in the formation of platelet aggregation in the intravascular lumen, as well as in the release of proteolytic enzymes that support the atherosclerotic plaque rupture. The NLR has been recognized as a prognostic marker of various diseases, such as cancer, acute pulmonary embolism, and hepatic fibrosis and cirrhosis.[9,10,11,12] It is also associated with cardiovascular risk due to patients with coronary artery disease and as a predictor of increased cardiovascular incidence.[13]

The total cardiac vessel occlusion in STEMI causes myocardial dysfunction. This is triggered by an imbalance between the supply and demand of oxygen in the tissues, causing myocardial death.[14] The destruction of myocardial cells during an infarction result in decreased ventricular contraction, which leads to dysfunction. Left ventricular ejection fraction (LVEF) is a parameter for assessing ventricular systolic function and has a role in the heart disease prognosis and as a predictor of mortality after STEMI. In addition, it is known that a low ejection fraction (≤30%) in post-infarct patients is correlated with the presence of various complications, such as heart failure, lethal arrythmia, etc.[14,15]

The recommended therapy in STEMI is reperfusion therapy done by primary percutaneous coronary intervention (PCI). Primary PCI is an arterial procedure associated with infarction within twelve hours after onset of symptoms without prior thrombolytic therapy.[16] This intervention was known to have a high rate of success and low rate of complications, and the post-intervention major adverse cardiovascular event (MACE) rate was 12%.[15,17] The research on the improvement of myocardial function, measured by the left ventricular ejection fraction value also showed mixed results. Approximately 42.2% of the patients experienced a reduction in LVEF during 13 months of follow-up period.[18]

A simple biomarker is required to stratify the risk of STEMI patients towards the decreased incidence of LVEF after primary PCI. This study aims to determine the correlation between NLR and LVEF in STEMI patients with primary PCI.

Methods

Research Design

This research is an observational analytical study with a cross-sectional design. The data of the patients was obtained from the SCIENCE (Sardjito Cardiovascular Intensive Care) registry in August 2019-November 2020 by consecutive sampling. The variables are the value of NLR as the independent variable and LVEF as the dependent variable. Furthermore, the two variables are on the scale of the ratio, and were analyzed as a dichotomous nominal scale with a classification based on the cut-off value.

The NLR was defined as the ratio of neutrophils to lymphocytes obtained from venous blood samples during the admission of patients to the emergency room. Blood samples were examined at the Clinical Pathology Laboratory, Dr. Sardjito Hospital Yogyakarta. The measurements of leukocytes and their components, including neutrophils and lymphocytes are taken automatically by a hemocytometer machine. NLR is expressed in numeric (ratio) and categorical (dichotomous) scales based on the cut-off value obtained from the receiver operating characteristic (ROC) curve.

The LVEF was assessed by transthoracic echocardiography (Vivid S6, GE Medical system, USA) during ICCU treatment (in less than 24 hours after the primary PCI). Furthermore, the ejection fraction was measured by the Teichholz/ M-mode method. Echocardiographic examinations are performed under the cardiologist's supervision. The echocardiography results were read by two examiners without knowledge of the ECG image, with the previous calculation of the Cohen Kappa coefficient being performed to determine the similarity between the two examiners. The results of the Kappa coefficient are 100% or very strong.[19] The LVEF is expressed in numeric (ratio) and categorical (dichotomous) scales based on the cut-off value, namely <50% and ≥50%.

Research Subject

The subjects were STEMI patients that have successfully received primary PCI reperfusion at Dr. Sardjito Hospital, Yogyakarta which met the research criteria. The inclusion criteria of the subjects were STEMI patients with onset of chest pain <12 hours, aged 30-75 that have successfully received reperfusion therapy done by primary PCI (with TIMI flow 3). The exclusion criteria for subjects, namely history of chronic renal failure stage> IV; history of chronic heart failure before heart attack; and sufferers with malignancy.

A total of 230 research subject data were obtained and the subject selection was carried out based on predetermined inclusion and exclusion criteria. A total of 34 subjects were excluded because they did not meet the criteria, and therefore 196 subjects were included in the data analysis. The research subject selection can be seen in Figure 1.

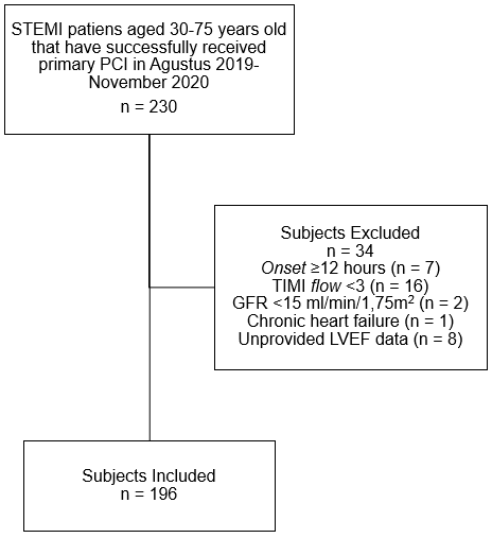

Figure 1. Research Subject Selection Process

Data Analysis

A univariate analysis in the form of descriptive statistics was carried out to identify the basic characteristics of the research subject. The normality test for numerical data was carried out by the Kolmogorov Smirnov test. The relationship between the independent (NLR) and the dependent (LVEF) variables were assessed using bivariate analysis in the form of correlative hypothesis test. The correlative analysis used is the Pearson correlation test if at least one variable is normally distributed, or the Spearman correlation test if the two variables are not normally distributed. The correlation test can be carried out if the assumption test in the form of a linearity test is fulfilled.[20] The NLR cut-off value is obtained from the receiver operating characteristic (ROC) curve analysis. The optimal cut-off value chosen is the value with the highest Youden index. After dividing based on the cut-off value, bivariate analysis between the NLR and the LVEF was carried out using the Phi correlation test. Statistical analysis using IBM SPSS Statistics 23 software with a 95% confidence interval and p value ≤ of 0.05 was considered significant.

Results

Basic Characteristics of Research Subjects

There were 196 patients as research subjects. The mean age of the subjects was 57.33 ± 8.27 years, for male of 172 subjects (87.8%) and female of 24 (12.2%). The NLR value in the subject had a median of 7.26 (0.92-57.39) and an average LVEF value after successful primary PCI was 48.28 ± 12.8%. The characteristics of the research subjects are shown on table 1.

Table 1.
Characteristics of Research Subjects

Variable	Value (n=196)
Age [years], average ± SD	57,33 ± 8,27
Gender	
Male, n (%)	172 (87,8)
Female, n (%)	24 (12,2)
NLR, median (min—max)	7,26 (0,92—57,39)
LVEF [%], average ± SD	48,28 ± 12,8
LVEF ≥50%, n (%)	90 (45,9)
LVEF <50%, n (%)	106 (54,1)
Onset [hours], average (min-max)	6 (1—11)
Wire Crossing Time	
Ideal [<120 minutes], n (%)	71 (36,2)
Not Ideal [≥120 minutes], n (%)	125 (63,8)
Total Ischemic Time [minutes], media (min—max)	484 (48—1200)
STEMI Classification	
Anterior, n (%)	88 (44,9)
Non-Anterior, n (%)	108 (55,1)
Diabetes Mellitus, n (%)	64 (32,7)
Hypertension, n (%)	119 (60,7)
Stroke History, n (%)	19 (9,7)
Smoking, n (%)	132 (67,3)

Description: NLR, neutrophil-to-lymphocyte ratio; LVEF, le ventricular ejection fraction; SD, standard deviation; n, numbe min, minimum value; max, max value

The research subjects were divided into two groups, such as high NLR (NLR ≥5.73, n = 120) and low NLR (NLR <5.73, n = 150). The value of 5.73 is the optimal cut-off obtained from the ROC curve analysis (Figure 2) with the coordinate point of the X axis (1 – specificity) of 0.556 and the Y axis (sensitivity) of 0.651, as well as Youden's index of 0.105. The area under the curve (area under the curve, AUC) is 0.527 as shown in table 2. This means that the NLR cut-off value of 5.73 indicate a decrease in LVEF with an ability of 52.7% (95%CI 44,5—60.8%).

The characteristics of the research subjects based on the cut-off NLR value are presented in table 3. There was no significant difference in subject characteristics between the two NLR groups, with the exception of variable diabetes mellitus (p-value = 0.016).

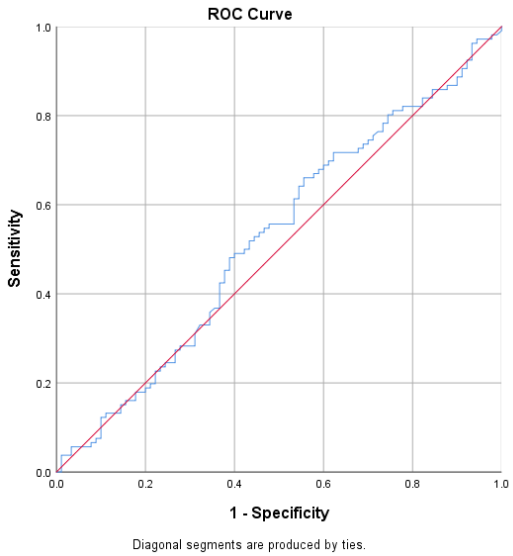

Figure 2. ROC Curve

Table 2.
Area Under the Curve (AUC)

Area Under the Curve	**P Value**	**95%CI**
0,527	0,522	0,445—0,608

Description: p, degree of significance; CI, confidence interval

Table 3.
Characteristics of Research Subjects Based on the NLR Group

Variable	**NLR ≥5,73 (n=120)**	**NLR <5,73 (n=76)**	**P Value**
Age [years], average ± SD	58,63 ± 8,08	56,50 ± 8,31	0,077
Gender			
Male, n (%)	109 (63,4)	63 (36,3)	0,153
Female, n (%)	11 (45,8)	13 (54,2)	
Onset [hours], median (min-max)	5,5 (1—11)	6 (1—11)	0,789
Wire Crossing Time			
Ideal [<120 minutes], n (%)	47 (66,2)	24 (33,8)	0,854
Not Ideal [≥120 minutes], n (%)	73 (58,4)	52 (41,6)	
Total Ischemic Time [minutes], median (min—max)	469 (186—1123)	522,50 (48—1200)	0,338
STEMI Classification			
Anterior, n (%)	58 (65,2)	31 (34,8)	0,375
Non-Anterior, n (%)	62 (57,9)	45 (42,1)	
Diabetes Mellitus, n (%)	31 (48,4)	33 (51,6)	0,016
Hypertension, n (%)	71 (59,7)	48 (40,3)	0,684
Stroke History, n (%)	10 (52,6)	9 (47,4)	0,575
Smoking, n (%)	83 (62,9)	49 (37,1)	0,599

Description: NLR, neutrophil-to-lymphocyte ratio; LVEF, left ventricular ejection fraction; SD, standard deviation; n, number; min, minimum value; max, maximum value, p, degree of significance

*significant at p value ≤ 0.05

Analysis of the correlation between NLR and LVEF

The linearity test between the two variables was carried out as a condition for the correlation analysis to be carried out. The linearity test was carried out through statistical analysis presented in table 4. Based on the table, it is known that the calculated F value is smaller than the F table and the p value> 0.05, therefore it can be concluded that the assumption of linearity between the two variables is fulfilled and correlation analysis can be carried out.

Table 4.
Linearity Test of NLR with LVEF

			dF	F tabl value	F coun value	P value
NLR * LVEF	Between groups	Deviation from Linearity	186	1,99	1,66	0,223
	In Group		8			

Description: NLR, neutrophil-to-lymphocyte ratio; LVEF, left ventricula ejection fraction; dF, degree of freedom, p, degree of significance

The results of the Kolmogorov-Smirnov normality test showed that NLR data were not normally distributed, but LVEF was normally distributed. The correlation test used is the Pearson correlation test. The correlation analysis between the numerical variables NLR and LVEF is shown in table 5.

Table 5.
Pearson Correlation Test between NLR and LVEF

	LVEF
NLR	r = -0,065
	p = 0,362
	n = 196

Description: NLR, neutrophil-to-lymphocyte ratio; LVEF, left ventricular ejection fraction; r, the correlation coefficient; p, the degree of significance

*significant at p value ≤ 0.05

Furthermore, a categorical correlation test was carried out with the Phi test to determine the relationship between NLR and LVEF based on the cut-off value. The NLR value was divided into two based on the cut-off value into NLR ≥5.73 and NLR <5.73, while LVEF was divided into two based on the limit of LVEF 50%, into LVEF <50% and LVEF ≥50%. The correlation analysis between categorical variables (dichotomous nominal) NLR and LVEF is shown in table 6.

Table 6.
Phi Correlation Test between NLR and LVEF

		LVEF				r	P Value
		<50%		≥50%			
		n	%	n	%		
NLR	**≥5,73**	70	58,3	50	41,7	-0,107	0,133
	<5,73	36	47,4	40	52,6		
Total		106	54,1	90	45,9		

Description: NLR, *neutrophil-to-lymphocyte ratio*; LVEF, left ventricular ejection fraction; n, number; r, the correlation coefficient; p, the degree of significance

*significant at p value ≤ 0.05

Pearson's correlation test results indicated that NLR did not generally correlate significantly with LVEF (r = -0.065; p = 0.362). Similar results were obtained after analysis based on the cut-off values of NLR and LVEF. Based on the Phi test, there was no statistically significant correlation between NLR and LVEF (r = -0.107; p = 0.133) after grouping based on the cut-off value of each variable. The correlation coefficient (r) is negative and indicating a negative relationship direction. This means that a high NLR value correlates with a low LVEF value and vice versa. However, the r-value indicates a very weak degree of correlation between variables. The p value in the analysis indicates an insignificant correlation. Therefore, hypothesis 1 (H1) is rejected and null hypothesis (H0) is accepted. This means that there is no significant negative correlation between the NLR and LVEF variables.

Discussion

The relationship between the NLR and the LVEF

An analysis of 196 patients that had successfully receieved primary PCI was analyzed to determine the correlation between NLR at admission and LVEF in less than 24 hours after the intervention. This study showed a very weak and insignificant negative correlation between NLR and LVEF in STEMI patients that had successfully received primary PCI. Similar results were also obtained after further analysis by categorizing the NLR and LVEF variables based on the cut-off value.

A negative correlation coefficient (r) means that a high NLR value correlates with a low LVEF and vice versa. A negative correlation between NLR and LVEF was also reported in previous studies. Chen et al. demonstrated that NLR has a statistically significant negative correlation with LVEF in STEMI patients with primary PCI and that NLR is a predictor of myocardial damage in patients with acute coronary syndrome. The inflammatory process reflected by the NLR is associated with cardiac contractility dysfunction.[21] Furthermore, Arbel et al. observed that high NLR was independently associated with low LVEF in STEMI patients with primary PCI. The underlying mechanisms are impaired epicardial and microvascular perfusion due to neutrophilia-related rheological changes, the release of pro-inflammatory cytokines, and lack of cytoskeletal flexibility.[13] Moreover, pro-inflammatory cytokines cause negative inotropic effects on the myocardium. The number of pro-inflammatory cytokines in individuals with high NLR is associated with an increase in ventricular diastolic diameter, collagen

deposition at the infarct site, impaired cardiac muscle metabolism, and trigger myocardial remodeling. This condition triggers cardiac contractility disorders, and even heart failure.[21] High levels of pro-inflammatory cytokines and proteolytic enzymes are known to cause left ventricular systolic dysfunction.[7]

In this study, it was reported that the degree of closeness of the relationship between NLR and LVEF is very small and not statistically significant. This is due to the relatively small sample size, as investigated by Karakas et al. the implementation in a single hospital could not explain the significant relationship between NLR and left ventricular function. However, in contrast to this study, after dividing the subjects into two cohort groups (LVEF <50% with LVEF ≥ 50%), it was reported that the mean NLR was significantly higher in the low LVEF group.[22]

Other studies showing a significant relationship between these two variables generally includes patients with TIMI flow <3 after the treatment, in contrast to this study, which only included patients with TIMI flow 3 or successful primary PCI. This shows that this study complements the previous findings. Furthermore, it is known that the NLR value before primary PCI can be a predictor of post-treatment no-reflow in STEMI patients because neutrophilia exacerbates myocardial ischemia with neutrophil-mediated microvascular blockage and may expand the infarct area.[23] TIMI flow 3 was also known to predict improvement in LVEF after treatment.[18]

Other factors believed to affect this study are the LVEF measurement method, some of the confounders that were not analyzed, and the one-time measurement of NLR and LVEF. First, the Teichholz/ M-mode method was used for the LVEF measurement. Ballenger et al. demonstrated a significant difference in the average LVEF between the Teichholz/ M-mode method and other methods, such as 2D Simpson echocardiography, radionuclide ventriculography, and cardiovascular magnetic resonance.[24] The M-mode method only measures circumferential contraction in one plane. Therefore, important assumptions must be made about the geometry of the left ventricular space, and therefore changes in linear measurements can serve as a substitute for changes in volume. The longitudinal contraction of LVEF also cannot be measured directly either, but with a correction factor to adjust to LVEF based on a visual assessment towards the apical contraction. The weakness of this measurement method for asymmetric contractions (for example wall motion abnormalities) such as left ventricular dysfunction is due to ischemia.[25]

Second, several possible confounders were not analyzed. NLR is a marker of systemic inflammation and has been shown to affect various diseases. Several diseases are known to be associated with NLR values, namely inflammatory diseases such as gastritis, rheumatoid arthritis, cholecystitis, and gout, as well as immune system disorders.[26,27,28] The criteria for selecting subjects in research cannot rule out these clinical conditions. In contrast, there are also several factors that affect the LVEF value in STEMI patients. The use of drugs that affect myocardial contractility was not analyzed. It is known that inotropic agents such as dobutamine or milrinone are administered to cardiogenic shock patients with decreased cardiac output.29 Angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) drugs are also known to affect the LVEF value.[30,31]

Third, the NLR and LVEF measurements were only performed once, namely NLR at admission and LVEF after primary PCI. As a result, the LVEF improvement cannot be measured optimally. Serrao et al showed that lower LVEF values have an effect on the LVEF improvement after treatment. The study also showed an LVEF reduction in patients after thirteen months of follow-up.[18] Post-treatment NLR values were are known to be associated with infarct size and MACE risk, as well as having a better role as an indicator of myocardial damage than NLR before PCI execution.[32]

In addition to an insignificant correlation, this study also showed a weak ability of the NLR to predict the reduction in LVEF by ROC analysis. Furthermore, it is known that the NLR cut-off of 5.73 can predict a decrease in LVEF with a predictive value of 52.7% (95%CI 44.5–60.8%), a sensitivity of 66.0%, and a specificity of 44.4%. Therefore, it has been shown that NLR is not a useful biomarker for determining LVEF reduction in STEMI patients that have successfully undergone primary PCI.

Research Limitations

This study only examined a one-time measurement of NLR during admission and LVEF after primary PCI, and therefore it could not describe any long-term changes in LVEF. The baseline value of LVEF before treatment as well as primary post-PCI NLR were not presented. Furthermore, the causal relationship between NLR and LVEF cannot be explained by the correlation analysis. Moreover, the study was only conducted in single location (single center), therefore patient data were limited.

Conclusions

There is no significant correlation between NLR and LVEF values in STEMI patients that have successfully received primary PCI. This study shows that the NLR value cannot be used as a risk stratification system to determine the LVEF value in STEMI patients that have successfully received primary PCI.nter. The further study is needed with larger sample size.

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Disclosure and Ethics

This research was ethically approved by the ethics commission from the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada with number KE/FK/0558/EC/2019 in May 2019 and extended in June 2020 with a number KE/FK/0629/EC/2020.

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