

Association of Platelet Lymphocyte Ratio (PLR) and Neutrophil Lymphocyte Ratio (NLR) with Global Registry of Acute Coronary Events (GRACE) Score in Acute Coronary Syndrome

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ABSTRACT

Introduction: Acute Coronary Syndrome (ACS) has morbidity and mortality significantly increase, it requires risk stratification for the assessment and selection of initial invasive strategies. The Global Registry of Acute Coronary Events (GRACE) scores recommended as risk stratification of ACS. Some of studies found that the combination of GRACE scores with other clinical and laboratory parameters can increase predictive value of ACS. Platelet Lymphocyte Ratio (PLR) and Neutrophil Lymphocyte Ratio (NLR) act as parameter of systemic inflammation in ACS. Aims of the study to determine the association between PLR and NLR with risk stratification GRACE score.

Method: This study is analytical with a cross-sectional retrospective design. This study included 70 patients with a diagnosis of ACS based on medical record data. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 22.0. P-value <0.05 was considered statistically significant.

Results: This study was found a positive correlation between PLR and NLR with the GRACE score of patients ACS ($r=0.485$, $p<0.001$; $r=0.570$, $p<0.001$). The PLR and NLR were both found the significantly higher in the high risk GRACE score respectively (188 ± 47 , $p < 0.001$; 7.9 ± 2.7 , $p<0.001$). The ROC curve analysis, cutt-off PLR of 123 and above (sensitivity of 72.7 %; specificity of 70.3), while cutt-off NLR of 4 and above (sensitivity of

78.8%; specificity of 70.3%) to detect high risk GRACE score.

Conclusion: There is a significant association between PLR and NLR with GRACE score

Keywords: Platelet Lymphocyte Ratio, Neutrophil Lymphocyte Ratio, GRACE score, Acute Coronary Syndrome

INTRODUCTION

The major cause of mortality globally is cardiovascular disease. Globally the mortality rate to cardiovascular disease reach 17.8 million, data of the American Heart Association (AHA).^[1] This mortality rates estimated increase reach 24.2 million by 2030. There are 400.000 people die every year cause of ACS.^[2] In Indonesia found 15 out of 1,000 Indonesians suffer from coronary heart disease according to basic health research data in 2018.^[3]

ACS has morbidity and mortality significantly increased, it requires risk stratification for the assessment and selection of initial invasive strategies, find the best strategy for achieving and maintaining myocardial reperfusion.^{[4][5]} GRACE score is recommended for risk stratification and assessing the prognosis of ACS.^[6] High risk stratification of GRACE score recommended for an invasive strategy, while low risk stratification of GRACE score conservative approaches for ACS patients.^[7]

Acute Coronary Syndrome is associated with rupture of atherosclerotic plaques and partial or complete thrombotic processes in arterial blood vessels. Inflammation has an important role in the initiation of atherosclerosis until rupture occurs causing ACS.^[2] Currently, neutrophil lymphocyte ratio (NLR) is accepted as parameter of systemic inflammation in ACS. High neutrophil levels, which reflect inflammation and low lymphocyte levels, which reflect physiological stress.^[8]

The increase in platelet count reflects an inflammatory response. Platelets can release thromboxane and other mediators, increase adhesion and transmigration of monocytes, which can lead to increased inflammation and weaken plaque stability, then promote the development of atherosclerosis.^[9] Platelet Lymphocyte Ratio (PLR) is reflects of inflammation and the aggregation pathway as predictor atherosclerosis in ACS.^[10]

Some of studies found that the combination of GRACE score with other clinical and laboratory parameters can increase predictive value of ACS.^[11] The Study of Zhou, found the combination of PLR and GRACE score was more effective in predicting incidence of ACS patients.^[12] Study of Acet et al, also found that high NLR was significantly with increased stratification of GRACE score.^[13] Aims of the study to determine the association and cut-off value PLR and NLR with risk stratification of GRACE score of ACS patients.

METHODS

This study is analytical with a cross-sectional retrospective design. This study included 70 patients with a diagnosis of acute coronary syndrome based on medical record of RSUP Haji Adam Malik Medan from January 2019 to December 2019.

Subject of study were included if there is following criteria: patients with a diagnosis of ACS either ST elevation acute myocardial infarction (STEMI), non-ST elevation acute myocardial infarction

(NSTEMI) or unstable angina (UA) that was clinically confirmed through presence of ischemic symptoms with ECG changes consistent with ischemia based on medical records data. There is data of neutrophils, lymphocytes and platelets examined laboratory result then calculating PLR and NLR. Data of patients were stratified according to the GRACE score into stratification low risk (< 109), intermediate-risk (109-140) and high risk (>140).

Exclusion Criteria

If the medical record data is incomplete. Patients who had a clinically active infection, malignancy, hematological disorders including all types of anemia and hematological malignancies, blood transfusion, severe liver disease, active or chronic autoimmune disease, patients on steroid therapy or chemotherapy were excluded.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 22.0 software. Numerical variables were presented as mean and standard deviation. Categorical variables were presented as percentages. Data were tested for normal distribution; differences between parametric quantitative independent groups were assessed by One way ANOVA test. The bivariate analysis using the Spearman correlation test. P-value <0.05 was considered statistically significant. Receiver Operating Characteristic (ROC) curve was used to determinate the optimal cut-off value as well as sensitivity and specificity.

RESULT

There are total 70 medical records data of ACS patients in this study. The characteristics subject of study such as age, gender, BMI, risk factors of cardiovascular, type of ACS and stratification of GRACE score are shown in (Table 1). The mean age of patient was 55.5 ± 10.8 years; this study included 65 (92.9%) male, 58(82.9%) smokers and 42 (60%) patients

hypertension. There were 47 (67.1%) patients with STEMI and 21 (30%) with NSTEMI.

The means of complete blood count parameter were compared between low, intermediate and high-risk GRACE score patients as shown in (Table 2). The mean of PLR and NLR statistically significant highest in the high-risk of GRACE score, while mean of lymphocyte count was highest in low risk of GRACE score (188 ± 47 ; 7.9 ± 2.7 ; 2.5 ± 0.7 , $p = 0.001$; respectively). There was found a positive correlation of PLR and NLR with GRACE

score ($r = 0.485$, $r = 0.570$, $p < 0.001$; respectively) (Table 3).

Table 1: Characteristic of the study

Variable	n = 70
Age, Mean±SD, years	55.5 ± 10.8
Male, n (%)	65 (92.9)
BMI, Mean±SD, kg/m ²	26.7 ± 3.9
Hypertension, n (%)	42 (60)
DM, n (%)	17 (24.3)
Dyslipidemia, n (%)	22 (31.4)
Smoke, n (%)	58(82.9)
STEMI, n (%)	47 (67.1)
NSTEMI, n (%)	21 (30)
UA, n (%)	2 (2.9)
Stratification of GRACE Score	
Low risk, n (%)	37 (52.9)
Intermediate risk, n (%)	23 (32.9)
High risk, n (%)	10 (14.3)

BMI: Body Mass Index; DM: Diabetes Mellitus; STEMI: ST Elevation Myocardial Infarction; NSTEMI: Non ST Elevation Myocardial Infarction; UA: Unstable Angina

Table 2: Comparison of the Complete Blood Count value between stratification risk of GRACE Score

Variable	Total (N= 70) X±SD	Low Risk (N=37) X±SD	Intermediate Risk (N=23) X±SD	High Risk (N=10) X±SD	P-value
WBC count, cells/mL	11743 ± 3443	12411 ± 3194	11041 ± 3676	10885 ± 3623	0.23
Platelet (10^3 sel/mm ³)	256 ± 70	271 ± 60	247 ± 83	225 ± 63	0.13
Neutrophil count	8.5 ± 2.97	8.5 ± 3.2	7.9 ± 2.7	9.5 ± 2.4	0.38
Lymphocyte count	2.1 ± 0.8	2.5 ± 0.7 ^{a,b}	1.7 ± 0.6	1.3 ± 0.4	0.001 ^{***}
PLR	136 ± 51	114.4 ± 37 ^{a,b}	148 ± 53	188 ± 47	0.001 ^{***}
NLR	4.7 ± 2.5	3.64 ± 1.7 ^{a,b}	5.23 ± 2.33 ^b	7.9 ± 2.7	0.001 ^{***}

^a P < 0.05 Significant compared with Intermediate Risk

^b P < 0.05 Significant compared with High Risk

***P < 0.001

WBC: White Blood Cell; PLR: Platelet Lymphocyte Ratio; NLR: Neutrophil Lymphocyte Ratio

Table 3: Correlation between PLR and NLR with the GRACE Score

Spearman correlation	GRACE Score	P-value
	r	
PLR	0.485	< 0.001
NLR	0.570	< 0.001

PLR: Platelet Lymphocyte Ratio; NLR: Neutrophil Lymphocyte Ratio

Table 4: ROC curve analysis showing the area under the curve for PLR and NLR with sensitivity and specificity in diagnose stratification of GRACE score

	Cutt-off value	AUC	Sensitivity (%)	Specificity (%)
PLR	123	0.751	72.7	70.3
NLR	4	0.782	78.8	70.3

PLR: Platelet Lymphocyte Ratio; NLR: Neutrophil Lymphocyte Ratio; AUC: Area Under the Curve

The ROC curve shown in (Table 4, Figure 1, Figure 2) was formed to determine sensitivity and specificity of PLR and NLR in discriminating stratification of GRACE score. The cutt-off value NLR of 4 and above had a sensitivity of 78.8% and specificity of 70.3%, while cutt-off value PLR of 123 and above had a sensitivity of 72.7 % and specificity of 70.3% to detect high risk of GRACE score.

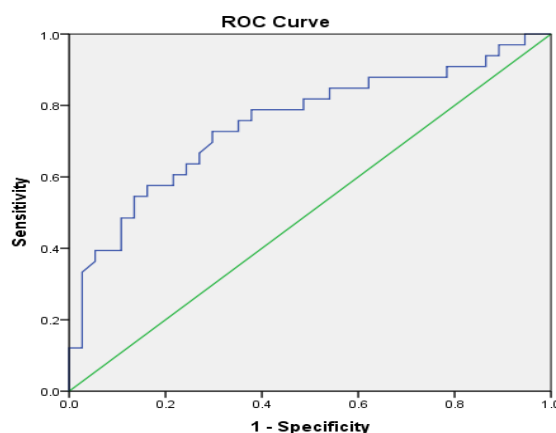


Figure 1: ROC Curve Analysis for PLR and GRACE score

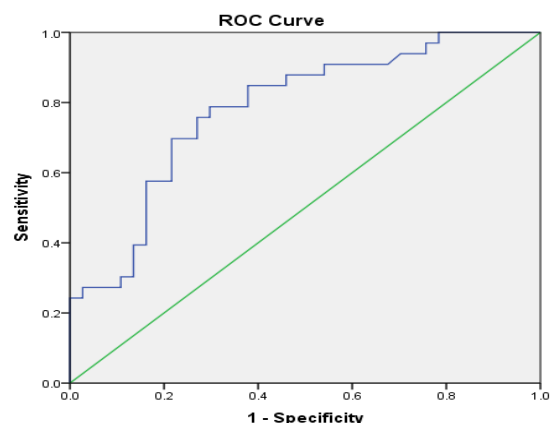


Figure 2: ROC Curve Analysis for NLR and GRACE score

DISCUSSION

Current clinical guidelines recommend the GRACE score for risk stratification and assessing the prognosis of ACS. [6] The GRACE score has good risk stratification for assessment and selection of invasive strategies early finds the best strategy for achieving and maintaining myocardial reperfusion. [5] Several studies have shown that combining the GRACE score with other clinical and laboratory parameters can improve its predictive value. [12]

In this study, we found a positive correlation between PLR and NLR with the GRACE score of ACS patients. The PLR and NLR were both found significantly higher in the high risk GRACE score. The study of Zhou, found a positive correlation between GRACE score and PLR, where the combination of GRACE score and PLR was more effective in predicting incidence in ACS patients. [12] Oncel et al. showed that the increase in NLR values had positive correlation with GRACE score. [14]

Inflammation has an important role in the initiation and progression of the atherosclerotic process. Inflammation is also known to play a role in all phases of ACS, which will affect the formation and rupture of atherosclerotic plaque. [14] Neutrophils cause atherosclerotic plaque instability. In the early stages, neutrophils invasive endothelial cells and become active when they reach the tunica intima. Induces microvascular formation, making plaque more susceptible to rupture. [15]

Thrombus formation in the ruptured atherosclerotic plaque underlying the pathophysiology of ACS. The activation of platelet adhesion and aggregation plays an important role in this process. Platelets are activated by substances released from blood vessel wall cells. Platelets can release thromboxane and other mediators, increase adhesion and transmigration of monocytes, which can lead to increased inflammation and weaken plaque stability, then promote the development of atherosclerosis. [9] Platelets have an important role in the

development, destabilization and rupture of atherosclerotic plaques, as well as in the formation of arterial fibrin-platelet thrombi that circulate on atherosclerotic plaques. [16]

Lymphocytes have been shown to modulate immunological responses at all stages of the atherosclerotic process. The systemic inflammatory response is characterized by a low lymphocyte count. [13] Lymphocytes regulate the inflammatory response and play an antiatherosclerotic role where regulatory T cells have an inhibitory effect of atherosclerosis. Low lymphocyte counts as an early marker of physiological stress and systemic inflammation of myocardial ischemia. [17]

In this study, the ROC curve analysis found the cut-off value PLR of 123 and above had a sensitivity of 72.7 % and specificity of 70.3%, while cut-off value NLR of 4 and above had a sensitivity of 78.8% and specificity of 70.3% to detect high risk GRACE score of ACS. Zhou, et al. found the combination of PLR and GRACE risk score could better predict long-term CVD events in patients with ACS. [12] Increased of PLR is associated with a worse prognosis of ACS based on the mechanism of atherosclerosis in ACS. [9] Budzianowski et al., found cut-off NLR of 4.9 and above had a sensitivity of 70% and a specificity of 65% in predicting mortality in ACS patients. [15] Neutrophils as markers of inflammation and lymphocytes as markers of regulators. NLR is an indicator of systemic inflammation in ACS, integrating both of that as predictors and mortality of ACS. [15] [18]

The limitations of the study, this was a retrospective and single-center study that included a relatively small number of patients. This study only one-time measurement of admission full blood count and calculation of PLR and NLR were included in the analysis.

CONCLUSION

There is a significant association between PLR and NLR with GRACE score. The combination of PLR and NLR with

GRACE score can provide an additional accurate predictor for ACS patients.

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