

Diagnostic Accuracy of Platelet/Lymphocyte Ratio for Screening Complex Coronary Lesion in Different Age Group of Patients with Acute Coronary Syndrome

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ABSTRAK

Latar belakang: dengan meningkatnya angka kejadian Sindroma Koroner Akut (SKA) dengan lesi koroner kompleks dan meningkatnya kebutuhan Coronary Artery Bypass Grafting (CABG), maka diperlukan metode stratifikasi dini pasien risiko tinggi yang dapat digunakan pada praktis klinis sehari-hari, termasuk fasilitas kesehatan lini pertama sekalipun di Indonesia. Dengan melakukan stratifikasi pasien risiko tinggi, diharapkan dapat menurunkan angka morbiditas dan kematian pada kasus SKA. Tujuan penelitian ini untuk mengetahui akurasi diagnostik dan nilai titik potong platelet/lymphocyte ratio (PLR) sebagai penapis lesi koroner kompleks pada pasien kelompok usia ≤ 45 dan > 45 tahun. **Metode:** sebuah studi potong lintang retrospektif dilakukan di Intensive Cardiac Care Unit (ICCU) Rumah Sakit Cipto Mangunkusumo (RSCM). Data diambil dari rekam medis pasien SKA dewasa dan menjalani angiografi koroner dari Januari 2012 – Juli 2015. Kriteria inklusi adalah pasien dewasa (usia ≥ 18 tahun) dengan diagnosis SKA dan menjalani angiografi koroner pada saat perawatan. Akurasi diagnostik dinilai dengan menghitung sensitivitas, spesifisitas, nilai duga positif dan nilai duga negatif. Nilai titik potong ditentukan menggunakan kurva receiver operating characteristic (ROC). **Hasil:** proporsi pasien SKA dengan lesi koroner kompleks adalah 47,2%. Nilai titik potong optimal pada pasien usia ≤ 45 tahun adalah 111,06 dengan sensitivitas 91,3%, spesifisitas 91,9%, nilai duga positif 11,27 dan nilai duga negatif 0,09. Pada kelompok usia > 45 tahun, nilai titik potong optimal berada pada angka 104,78 dengan nilai sensitivitas 91,7%, spesifisitas 58,6%, nilai duga positif 2,21 dan nilai duga negatif 0,14. **Kesimpulan:** nilai titik potong PLR optimal pada kelompok usia ≤ 45 adalah 111,06 dan pada kelompok usia > 45 tahun adalah 104,78 dengan akurasi diagnostik masing-masing Area Under the Curve (AUC) 93,9% ($p < 0,001$) dan AUC 77,3% ($p < 0,001$).

Kata kunci: platelet/lymphocyte ratio (PLR), lesi koroner kompleks, skor Gensini, sindrom koroner akut.

ABSTARCT

Background: with the increasing number of patients with acute coronary syndrome (ACS) with complex coronary lesion and the increasing needs of coronary artery bypass grafting (CABG) procedures, there is an increasing need for a tool to perform early stratification in high-risk patients, which can be used in daily clinical practice, even at first-line health care facilities setting in Indonesia. It is expected that early stratification of high-risk patients can reduce morbidity and mortality rate in patients with ACS. This study aimed to identify diagnostic accuracy of platelet/lymphocyte ratio (PLR) and the optimum cut-off point of PLR as a screening tool for identifying

a complex coronary lesion in patients ≤ 45 and > 45 years old. **Methods:** this was a retrospective cross-sectional study, conducted at the ICCU of Cipto Mangunkusumo Hospital. Data was obtained from medical records of adult patients with ACS who underwent coronary angiography between January 2012 - July 2015. The inclusion criteria were adult ACS patients (aged ≥ 18 years old), diagnosed with ACS and underwent coronary angiography during hospitalization. Diagnostic accuracy was determined by calculating sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR-). The cut-off point was determined using ROC curve. **Results:** the proportion of ACS patients with complex coronary lesion in our study was 47.2%. The optimum cut-off point in patients aged ≤ 45 years was 111.06 with sensitivity, specificity, LR+ and LR of 91.3%, 91.9%, 11.27 and 0.09, respectively. The optimum cut-off points in patients aged > 45 years was 104.78 with sensitivity, specificity, LR+ and LR of 91.7%, 58.6%, 2.21 and 0.14, respectively. **Conclusion:** the optimum cut-off point for PLR in patients aged ≤ 45 years is 111.06 and for patients with age > 45 years is 104.78 with diagnostic accuracy, represented by AUC of 93.9% ($p < 0.001$) and 77.3% ($p < 0.001$), respectively for both age groups.

Keywords: PLR, complex coronary lesion, Gensini score, acute coronary syndrome.

INTRODUCTION

Cardiovascular disease is the 5th leading cause of death worldwide, both in developed and developing countries.¹ About 80% to 90% of deaths are due to cardiovascular disease are caused by coronary artery disease (CAD).^{1,2} The RISKESDAS (Baseline Health Research), an Indonesian national research program issued in 2013, showed that the prevalence of CAD was increased from 0.9% in 2007 to 1.5%.³ The prevalence was also increasing respectively with age. Acute coronary syndrome (ACS) has caused high hospitalization rate and mortality rate. In Indonesia, 1009 patients had been admitted to ICCU Cipto Mangunkusumo National Referral Hospital within a 3 year period since 2010 with a mortality rate of 17.5%.⁴ Acute coronary syndrome increases the risk of death through various mechanisms that somehow relate to the complexity of lesion involved. A preliminary study in 2015 showed that there was an increasing need for performing early percutaneous coronary intervention (PCI) each year and there is also an increasing need for coronary artery bypass grafting (CABG). The study also showed that there were more patients with complex lesions that were admitted to the ICCU unit.⁵ Age is a non-modifiable factor in ACS and the incidence of ACS has increased in men who are > 45 years and in women who are > 55 years.⁶ Trip et al⁷ suggested that there was increased incidence of death in patients aged > 60 years (28.9% RR 1.5). The incidence of ACS in young adults is

lower; however, it seems to be increasing lately. In Indonesia, several studies had shown that there was a high proportion of young adults with ACS compared to previous studies.⁸⁻¹¹ Spectrum of ACS itself has been changing in young adults from unstable angina pectoris (UAP) to ST elevation myocardial infarction (STEMI).

The role of inflammation in predicting bad outcomes in ACS patient is related to more complex lesion that increases mortality risk and major adverse cardiac event (MACE).¹²⁻¹⁴ Thus, increased complexity of the lesion may also be related to high risk of MACE.¹⁵ Inflammatory markers that has been investigated is less applicable due to lack of funding. As an alternative, platelet lymphocyte ratio (PLR) is more accessible. It may describe inflammatory process and can be used for cardiovascular cases.¹⁶ Changes of platelets and lymphocytes during acute stress give a simple picture of the inflammatory process involved. PLR may become an easy and applicable tool of examination in clinical practice as it may serves as an inflammatory marker that provides prognostic value for cardiovascular patients.¹⁶⁻²¹

Over the past several years, there has been an increasing need for PCI and an early stratification tool such as inflammatory markers to identify high-risk patients. The tool is not only determined by patient's clinical condition, but also can be use to assist decision making. Many inflammatory markers has been studied in their relation to severity of coronary lesion, yet cannot be used

in daily practice due to high cost especially in developing countries. The cheapest inflammatory markers that can be used was PLR. Many studies have shown the relation of PLR and coronary lesion and mortality in ACS patients.^{16,18-21} The PLR of Indonesian patients may not be similar to other countries due to different geographic, individual and genetic characteristics as well as different habits and different pattern of chronic infection. The role of inflammation in each age group is also different.

Previous studies have demonstrated the use of PLR in mortality and severity coronary lesion;²²⁻²⁷ however, they only used a single cut-off point of PLR for patients of all ages. However, since the spectrum of ACS in young adults is changing, further evaluation is necessary to find the optimum cut-off point based on age groups so that PLR can be used more accurately in daily practice. Early identification followed by early revascularization of high risk patient can reduce the mortality and morbidity in ACS. This study aimed to identify diagnostic accuracy of platelet/lymphocyte ratio (PLR) and the optimum cut-off point of PLR as a screening tool for identifying a complex coronary lesion in patients who are ≤ 45 years and >45 years old.

METHODS

Our study was a cross-sectional diagnostic study using secondary data. Data was obtained from medical records of adult patients with ACS who underwent coronary angiography at the ICCU of Cipto Mangunkusumo Hospital between January 2012 and July 2015. The data was collected at the end of 2015 by using total population sampling. The inclusion criteria were (1) patients aged >18 years old; (2) patients who were diagnosed with ACS and who underwent coronary angiography during hospitalization. The exclusion criteria were (1) incomplete data, particularly about leukocytes count, leukocyte differential count, platelet counts, urinalysis, chest X-ray and results of angiography; (2) patients with onset of less than 1 hour or more than 48 hours; (3) patients with hematological abnormalities such as aplastic anemia, leukemia, thrombocytopenia (platelets counts $<150,000/\text{mm}^3$) or polycythemia vera; (4) patients with

malignancy or autoimmune diseases such as systemic lupus erythematosus (SLE), Idiopathic thrombocytopenia purpura (ITP), Autoimmune Hemolytic Anemia (AIHA), rheumatoid arthritis, and scleroderma with or without steroids; (5) patients who were using systemic steroids; (6) patients with active infection, tuberculosis, sepsis and chronic infection such as HBV, HCV, and HIV; (7) patients with history of CABG. Data analysis was performed using SPSS version 21.0. PLR was calculated by equation value and was compared to Gensini score presented as area under curve (AUC) based on receiver operating characteristic (ROC) and cut-off points. Gensini score was used to describe the severity of the coronary lesion found during angiography.^{22,23} The results were subsequently represented as sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV). The protocol of our study has been approved by the Ethical Committee, Faculty of Medicine, University of Indonesia with a registration number of 921/UN2.F1/ETIK/2015 on October 19th, 2015.

RESULTS

Our study included 996 patients with ACS who were admitted to ICCU. About 871 patients were excluded from the study due to infection (274 patients), malignancy (98 patients), autoimmune and hematology abnormalities (99 patients), the incorrect onset of illness (154 patients) and history of CABG (46 patients). In total, there were 125 patients participated in our study.

Among 125 study subjects, we found that the proportion of patients having complex coronary lesion and Gensini score of >53 was 47.2%; while the proportion of those with Gensini score of ≤ 53 was 52.8%. Baseline characteristics of our study subjects are shown in **Table 1**. There were 48% of subjects who were ≤ 45 years old and 52% of subjects aged over 45 years. Among subjects in the ≤ 45 -year-old group, there were 38.3% patients with high Gensini score; while in the >45 -year-old group, there were 55.4 % patients with high Gensini score. (**Table 1**)

The mean of PLR among patients with high Gensini score was different for both groups.

Table 1. Baseline characteristics of study subjects based on age group

Characteristics	≤45 years old (n=60)		>45 years old (n=65)	
	Gensini >53 (n=23)	Gensini ≤53 (n=37)	Gensini >53 (n=36)	Gensini ≤53 (n=29)
Gender, n (%)				
- Male	20 (87)	22 (59.5)	28 (77.8)	21 (72.4)
- Female	3 (13)	15 (40.5)	8 (22.2)	8 (27.6)
Age, mean (SD)	42 (3)	42 (3)	62 (8)	62 (9)
BMI, mean (SD)	26.1 (3.9)	26.0 (3.5)	24.7 (2.7)	24.7 (4.1)
ACS type, n (%)				
- STEMI	14 (60.9)	11 (29.7)	18 (50.0)	10 (34.5)
- NSTEMI	3 (13.0)	8 (21.6)	12 (33.3)	3 (10.3)
- UAP	6 (26.1)	18 (48.6)	6 (16.7)	16 (55.2)
PLR, mean (SD)	171.08 (83.54)	88.51 (24.28)	209.91 (164.45)	133.01 (108.22)
Platelets, median (range)	225,000 (102,000-659,000)	290,000 (109,000-1,148,000)	262,500 (147,000-736,000)	242,000 (124,000-330,000)
Absolute lymphocytes count, mean (SD)	2369.6 (1241.7)	2488.5 (1115.2)	1982.1 (1270.9)	1900.8 (1083.9)
Gensini score, mean (SD)	169.3 (74.1)	18.9 (16.9)	161.0 (72.7)	25.0 (17.9)
Comorbidities, n (%)				
- DM	7 (30.4)	12 (32.4)	14 (38.9)	4 (13.8)
- Hypertension	13 (56.5)	9 (24.3)	23 (63.9)	16 (55.2)
- Dyslipidemia	18 (78.3)	29 (78.4)	25 (69.4)	23 (79.3)
Family History of CHD	5 (21.7)	5 (13.5)	9 (25.0)	13 (44.8)
Smoking, n (%)	10 (43.5)	7 (18.9)	13 (36.1)	9 (31.0)
LDL, median (range)	113 (50 – 335)	114 (48-165)	116.19 (38.44)	107.79 (36.16)
HDL, median (range)	40 (15-59)	37 (15 – 64)	41 (22 – 70)	39 (11-72)
Total cholesterol, median (range)	188 (114 – 446)	174 (58-264)	178.5 (44.82)	164.59 (39.21)
Triglycerides, median (range)	140 (56-313)	146 (58-383)	106 (52 – 390)	128 (43-353)
Uric Acid, mean (SD)	7.9 (2.3)	6.9 (3.0)	8.1 (1.9)	7.1 (2.9)
GFR, mean (SD)	82.3 (27.2)	72.6 (36.2)	56.1 (23.3)	63.1 (23.4)

*PLR = Platelet counts (cells/mm³) / absolute lymphocyte counts (cells/mm³)

Higher PLR was found in younger age group (171.08 (SD 83.54) compared to older group (209.91 (SD 164.45).

Using ROC curve analysis, we calculated the cut-off point of PLR for predicting the presence of complex coronary lesion or determining those with high Gensini score in ACS patients. The ROC analysis of patients aged ≤45 years showed that the AUC was 93.3% (95% CI: 87.4 – 100) with p value <0.001 (**Figure 1**). There were 60 cut-off points with their each sensitivity and specificity. The optimum cut-off point was found in the 37th data, i.e. a cut-off point of 111.06 for PLR with 91.3% sensitivity, 91.9% specificity, 87.5% PPV, 94.4% NPV. The

positive LR was 11.27; while the negative LR was 0.09. According to our results, the cut-off point of 111.06 had a good accuracy and it could be used as an optimum cut-off point for patients of the age group.

Based on ROC curve analysis for patients aged >45 years, we found that the AUC of PLR was 77.3% (95% CI: 65.11 – 89.5) with p value <0.001. (**Figure 1**) Out of the 65 cut-off points in our study, we found that the optimum cut-off point in this group was 104.78 with sensitivity, specificity, PPV, NPV, positive LR, and negative LR of 91.7%, 58.6%, 73.3%, 85%, 2.21 and 0.14, respectively. (**Table 2**)

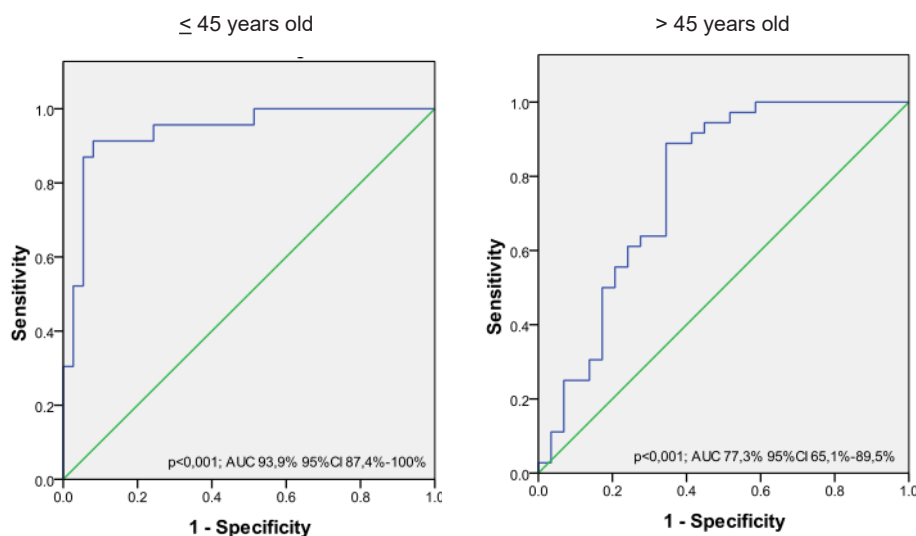


Figure 1. ROC curve and PLR cut-off point based on age groups

Table 2. Result of the study

Optimum Cut-off point	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR (+)	LR (-)	AUC	P value
≤ 45 years 111.06	91.3	91.9	87.5	94.4	11.27	0.09	93.9	<0.001
> 45 years 104.78	91.7	58.6	73.3	85	2.21	0.14	77.3	<0.001

DISCUSSION

There were 125 subjects who were eligible for analysis, which included 72.8% male and 27.2% female patients. Our data was similar with previous studies, in which higher incidence of ACS as found in men than women.¹ The median age of subjects was 48 years old with the youngest at 33 years old and the oldest at 80 years old. These findings are different from previous theory which emphasizes that high ACS incidence is found in male patients at the age of >45 years old or female patients who are >55 years old; while our study demonstrates that ACS may be found in patients as young as 33 years old. Our study also found relatively different results regarding age-related complex lesion compared to the results of previous studies that had shown non-significant correlation between age and complex lesion.²⁴⁻²⁶

Our study showed that the proportion of patients with ACS aged <45 years were 48%, which was higher than the results of other descriptive studies, i.e. the study that was

conducted in Indonesia at Cipto Mangunkusumo Hospital between 2008-2012 (22.2%) and a study conducted at Sardjito Hospital in 2014 (13.5%).¹⁰⁻¹¹ The proportion is also higher than the results of a study conducted in young adult patients with ACS of general population (2% to 10%).⁸ The higher proportion may be caused by our exclusion criteria that exclude patients with infection which was usually found as comorbidity in older patient with ACS. The shifting of onset age for this illness may be due to shifting of age distribution for risk factors of ACS in Indonesia.

The latest data from RISKEDAS has indicated that there was a shift of age distribution regarding risk factors of CAD including smoking, sedentary life style and obesity, in which the biggest proportion has been shown by subjects of 30 – 50 years old.^{8,29-30} On the contrary, previous data has demonstrated that those risk factors were found at the highest rate in subjects who were >45 years old.²⁴ The shift of age distribution for CAD risk factors may also

cause the shift of age distribution for the onset of ACS in the population. These facts should increase our awareness.

The median of PLR in subjects with high Gensini score was higher than subject on low Gensini score (146.54 vs. 89.57). This fact supports a theory on pathophysiology of ACS, which suggests that inflammatory burden is correlated to the complexity of the lesion. Several previous studies have demonstrated that there is a correlation between increased PLR and the complexity of coronary lesion; however, those studies have utilized tools that inadequately represent the complexity of coronary lesion. Moreover, the cut-off points found in those studies were different in each study indicating that different geographical characteristics may have influences to different inflammatory burden. Those differences make us difficult to use the tool for clinical practice in our region.^{24-25,27}

The number of ST elevation myocardial infarction (STEMI) cases in our study was higher in patients with high Gensini score compared to low Gensini score subjects (54.2% vs. 31.8%). Overall, the STEMI incidence in our study was higher than other types of ACS, which was 42.4%. In the younger group, STEMI was found predominantly with the rate of 60.8% compared to UAP (26.1%). Changes of ACS spectrum, which include younger age group, have become a great concern to us. Our data has supported results of previous related study that there is a changing trend of ACS spectrum from UAP to STEMI in younger patients.^{8,30} However, our data is slightly different from previous data obtained from ICCU unit of the same hospital between 2008 and 2012, which indicated that incidence UAP was still higher than STEMI/NSTEMI in young patients.¹¹ It indicates that there is a worsening of stenosis in young adults and it may correlate to vasospasm-related ischemia.

Our result demonstrated that the AUC of PLR in young ACS patients with high Gensini score was 93.3% (95%CI: 87 – 100, $p < 0.001$). There were 60 cut-off points in this age group with an optimum PLR cut-off point for subjects aged ≤ 45 years was 111.06 with sensitivity, specificity, PPV, NPV, positive LR and negative

LR of 91.9%, 87.5%, 94.4%, 11.27 and 0.09, respectively. Therefore, the cut-off point can be used as a screening tool for predicting complex coronary lesion in younger age group due to its high specificity. The pre-test probability of our study was 38.3%; while the post-test probability for positive result was 87.3%. When a patient at the age of ≤ 45 years old has a higher PLR than the cut-off point for PLR (> 111.06), it means that his/her physician can be 87.3% sure that the patient is having a complex coronary lesion. The cut-off point for PLR in our study among patients aged > 45 years was different compared that in younger group. The AUC level was 77.3% (95% CI: 65.1 – 89.5; $p < 0.001$). The optimum cut-off point in our study was 104.78 with sensitivity, specificity, PPV, NPV, positive LR, and negative LR of 91.7%, 58.6%, 73.3%, 85%, 2.21 and 0.14, respectively. The pre- test probability for this group was 55.3% and the post-test probability (for negative result) was 14.8%. When a patient who is > 45 years old present with PLR > 104.8 , it means that his/her physician can be 14.8% sure that the patient does not have any complex coronary lesion.

PLR is recommended to be used as a screening tool for predicting the presence of complex coronary lesions in patients with ACS. The tool can be used for daily practice, particularly to establish an early stratification the severity of disease in addition to the patient's clinical condition. It also can be used as stratification for elective procedure.

Limitations of the Study

Our study used a retrospective cross-sectional design which may limit us from obtaining further information since there was some similarity of history taking technique used. It may also limit us from obtaining complete supporting data, which were related to risk factors such as obesity and others factors that may affect inflammatory status such as *H. pylori* infection since such evaluation has not been routinely performed at the ICCU.

Despite some limitations, our study may still provide good evidence to increase awareness among physicians and help them to make a good stratification of ACS severity in patient who should have any intervention treatment.

CONCLUSION

The proportion of patients with ACS that had a complex coronary lesion (as indicated by high Gensini Score) was 47.2%. The optimum cut-off point for PLR in patients who were ≤ 45 years was 111.06 and in those with the age of > 45 years old was 104.78. The diagnostic accuracy of PLR based on AUC level in patients of both age groups was good enough for screening and predicting the presence of complex coronary lesion.

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