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RESEARCH

PLATELET-LYMPHOCYTE RATIO (PLR) MARKERS IN ACUTE CORONARY SYNDROME

(Platelet Lymphocyte Ratio (PLR) sebagai Petanda Sindrom Koroner Akut)

Haerani Harun, Ulung Bahrin, Darmawaty ER

ABSTRAK

Sindrom Koroner Akut (SKA) merupakan puncak manifestasi klinis aterosklerosis di arteri koroner. Inflamasi terjadi dari tahap awal pembentukan ateroma sampai ruptur plak dan trombosis. Trombosis memainkan peran penting dalam perjalanan penyakit SKA. Trombositosis dan limfopenia berhubungan dengan derajat inflamasi sistemik dan Rasio Platelet Limfosit (PLR) menjadi petanda baru yang melibatkan kedua tolok ukur hematologi tersebut. Penelitian ini merupakan penelitian retrospektif di Rumah sakit Dr. Wahidin Sudirohusodo Makassar dengan mengambil data pasien SKA UAP, STEMI, NSTEMI dan menilai PLR dari pemeriksaan darah rutin saat masuk Rumah sakit. Data PLR dibandingkan berdasarkan jenis SKA, kemudian dibandingkan dengan kontrol sehat. Hasil penelitian didapatkan 223 data pasien SKA UAP, STEMI dan NSTEMI masing-masing 89, 68, 66 data dan kontrol normal 198 data. Hasil uji statistik Kruskal wallis menunjukkan perbedaan bermakna PLR antara pasien UAP, NSTEMI dan STEMI ($p=0,011$). Hasil uji post hoc menunjukkan perbedaan bermakna antara UAP dan NSTEMI ($p=0,023$), UAP dan STEMI ($p=0,006$), tetapi tidak berbeda bermakna antara NSTEMI dan STEMI ($p=0,827$). Nilai PLR pasien SKA lebih tinggi dibandingkan dengan pembanding ($p=0,037$). Berdasarkan hasil penelitian didapatkan nilai PLR meningkat di SKA dibandingkan dengan kontrol normal. Nilai PLR di STEMI dan NSTEMI lebih tinggi dibandingkan UAP, kemungkinan berhubungan dengan pembentukan trombus dan infark miokard.

Kata kunci: Rasio platelet limfosit, trombosit, sindrom koroner akut

ABSTRACT

Acute Coronary Syndrome (ACS) is the peak of the clinical manifestations of atherosclerosis in the coronary arteries. Inflammation occurs from early stages of atheroma formation to plaque rupture and thrombosis. Thrombosis plays an important role in the pathogenesis of ACS. Thrombocytosis and lymphopenia associated with the degree of systemic inflammation and Lymphocyte Platelet Ratio (PLR) into a new marker of both hematological parameters. This is a retrospective study in Dr Wahidin Sudirohusodo hospital Makassar with retrieving data of UAP STEMI, NSTEMI patients and assess PLR from routine blood test at admission. Platelet lymphocyte ratio compared by type of ACS and then compared with the healthy controls. The results of 223 ACS patients with UAP, STEMI and NSTEMI patient data, respectively 89, 68, 66 data and 198 normal control. Kruskal-Wallis test results showed statistical significant difference PLR between patients of UAP, NSTEMI and STEMI ($p=0.011$). Post hoc test found a significant difference between UAP and NSTEMI ($p=0.023$), UAP and STEMI ($p=0.006$), but not significantly different between NSTEMI and STEMI ($p=0.827$). Platelet lymphocyte ratio in ACS patients is higher than the controls ($p=0.037$). Based on the results, PLR increased in ACS compared with normal controls. Platelet lymphocyte ratio in STEMI and NSTEMI were higher than UAP, possibly related to the formation of thrombus and myocardial infarction.

Key words: Platelet lymphocyte ratio, thrombocyte, acute coronary syndrome

INTRODUCTION

Acute Coronary Syndrome (ACS) is the culmination of clinical manifestations of atherosclerosis in coronary arteries. Acute coronary syndrome consists of Unstable

Angina Pectoris (UAP), myocardial infarction with ST elevation (*ST elevation myocardial Infarction/STEMI*) and non-ST elevation myocardial infarction (NSTEMI). According to data from the *American Heart Association* (AHA) in 2005, the number of patients with ACS

reached 1.5 million people. Meanwhile, according to *Jakarta Cardiovascular Study* in 2008, the prevalence of myocardial infarction in female patients was 4.12%, while in male patients was 7.6%.¹⁻³

Inflammation actually occurs from the earliest stages of atheroma formation to plaque rupture and thrombosis. Monocytes alter into macrophages after moving into the intima and then change the LDL particles into foam cells, playing a role in atherosclerotic lesion. Those foam cells then release cytokines, *growth factors*, *metalloproteinases* (MMP), *Reactive Oxygen Species* (ROS) and tissue factors that prolong the inflammatory response, make plaques more vulnerable to rupture, and eventually lead to the formation of thrombus.⁴⁻⁶ A previous study conducted by Mueller *et al*⁷ shows that there is a correlation between high platelet count and cardiovascular disease, but this research still cannot prove a correlation between the number of platelets and mortality in patients with ACS.⁷ Another research conducted by Kalay *et al*⁸ in Turkey, on the other hand, shows that platelet count in patients with progressive coronary atherosclerosis is high.⁸

The role of hematologic parameters on cardiovascular disease, moreover, has been examined and found. Several factors, such as *neutrophil-lymphocyte ratio* (NLR) and *Mean Platelet Volume* (MPV) can be considered as prognostic indicators. Some studies even have shown a correlation between elevated levels of platelets and decreased levels of lymphocytes with poor cardiovascular outcomes.^{7,8} Apoptosis of lymphocytes in atherosclerotic lesions can cause lymphopenia along with the burden of atherosclerosis. Therefore, decreased level of lymphocytes can also be associated with a worse prognosis. In the end, thrombocytosis and lymphopenia associated with the degree of systemic inflammation and *Platelet-Lymphocyte Ratio* (PLR) can be considered as a new marker involving both hematologic parameters.⁹

Increased PLR, furthermore, is often associated with poor prognosis for patients suffering from serious malignancy. A research conducted by Demirag and Bedir⁹ shows that the PLR value of ≥ 200 can increase risk of death 5-6 times, and decrease *survival* time in patients undergoing major vascular surgery. Similarly, a research conducted by Gary *et al*¹⁰ in Austria shows the value of PLR >150 is a risk factor of vascular disease.^{7,10}

Consequently, examination of the number of platelets and lymphocytes should be conducted in a blood test routinely performed since it is easy, non-invasive, and relatively cheap.¹⁰ Thus, PLR can be

expected as a marker that is effective and efficient for ACS cases.

METHODS

This research was a retrospective study conducted by taking the medical records of ACS patients in Dr. Wahidin Sudirohusodo Hospital, Makassar from July 2010 to July 2014. One of some inclusion criteria in sampling was that those patients had to be diagnosed with ACS, STEMI, NSTEMI or UAP by cardiologists based on medical history, physical examination and other supporting examinations. Meanwhile, one of some exclusion criteria in sampling was that ACS patients also had signs of infection or malignancy known through medical records based on their medical history and other examination results, as well as the leukocyte count of $> 25,000/\mu\text{L}$. Next, PLR values of each patient were calculated based on the absolute number of platelets and lymphocytes. Samples of ACS patients were then divided into UAP, STEMI and NSTEMI. To the control group, the data were taken from medical records of Specialist Education Program (PPDS) candidates, who were declared healthy by history, physical examination and investigations.

RESULTS AND DISCUSSION

The data of 223 patients with ACS obtained consisted of 89 UAP patients, 68 NSTEMI patients and 66 STEMI patients.

The number of male patients with ACS was greater than female ones with the largest age range of 51-60 years and the mean age of 58.65 ± 11.86 years.

Table 1. Characteristics of acute coronary syndrome patients and normal controls

Variables		Samples n=223	Controls n=198
Sex	Male	151(67.71)	84(42.42)
	Female	72(32.29)	114(57.58)
Age	≤ 30 years old	4(1.79)	142(71.72)
	31-40 years old	5(2.24)	56(0.28)
	> 41 years old	214(95.96)	
ACS	UAP	89(39.91)	
	NSTEMI	68(30.49)	
	STEMI	66(29.60)	

Primary data sources

Table 2. Number of platelets and lymphocytes in acute coronary syndrome

Variables	UAP	NSTEMI	STEMI	p*
Platelets (x10 ³ /μL)	240.72±67.01	264.60±113.94	264.23±95.59	0.215
Lymphocytes (x10 ³ /μL)	2.13±1.16	1.90±1.08	1.71±0.70	0.067
PLR	142.41±80.20	172.82±95.14	178.70±101.38	0.011

Primary data sources

The results of *Kruskal-Wallis* test in ACS showed that there was no significant difference in the number of platelets and lymphocytes among the three sample groups ($p=0.215$ and $p=0.067$). Nevertheless, there were significant differences in PRL values among the three groups ($p=0.011$). On the other hands, the results of Post hoc test, Mann-Whitney test showed that there were significant differences of PLR values between in the group of UAP and in the group of NSTEMI ($p=0.023$) as well as between in the group of UAP and in the group of STEMI ($p=0.006$). However, there was no significant difference of PLR values between in the group of NSTEMI and in the group of STEMI ($p=0.827$)

Platelet-Lymphocyte Ratio values in ACS patients (162.42 ± 92.54) were compared to healthy controls (135.56 ± 41.83). 198 data of healthy controls were obtained with a mean age of 28.93 ± 3.28 . Based on the Mann-Whitney test, there were significant differences in PLR with $p=0.037$.

ROC curves comparing ACS with the control group showed an Area Under Curve (AUC) of 0.559. The cut-off value of PLR 150 had a sensitivity of 44.4% and

Figure 1. Distribution of PLR in acute coronary syndrome patients and control group.

Note: UAP, Unstable Angina Pectoris; NSTEMI, Non-ST Elevation Myocardial Infarction; STEMI, ST Elevation Myocardial Infarction; PLR, Platelet Lymphocyte Ratio

a specificity of 78.2%, meanwhile the cut-off value of PLR 125 had a sensitivity of 59.2% and a specificity of 68%. On the other hand, ROC curves comparing UAP with NSTEMI and STEMI (myocardial infarction)

Figure 2. ROC curve in acute coronary syndrome patients. A. Acute coronary syndrome vs. healthy controls; B. UAP vs myocardial infarction.

showed an AUC of 0.618. The *cut-off* value of PLR 150 had a sensitivity of 53% and a specificity of 78.5%.

The results of this research, moreover, showed that older patients more often suffered from ACS with a mean age of 58.65 ± 11.86 . There were nine (9) patients aged ≤ 40 years old. The youngest patients were at the age of 17 years old. It means that the disease can also be found in young adults. Similarly, a research conducted by Han Yang Chun *et al*¹¹ in Korea showed that the mean age of ACS patients was 61.9 ± 12.3 . A previous study also showed that patients with ACS are dominated by men, similar to the results obtained in this research (67.71%).¹

Researches on thrombocytosis, furthermore, show that there is no clear correlation between the incidence of thrombosis and cardiovascular disease. A research conducted by Kalay *et al*⁸ in Turkey showed increased platelet counts in patients with progressive coronary atherosclerosis,⁸ but in some other studies did not show a significant correlation. Correction of how microvascular thrombocytosis provides clinical improvement and platelet function actually has been reported.¹³ The results of this research showed that there was no significant difference in the number of platelets in ACS patients ($p=0.215$). Therefore, platelet count cannot be used as a marker for ACS disease.

Decreased levels of lymphocytes in the blood actually are caused by lymphocyte activation more than a decrease in the number of lymphocytes in the body. Increased lymphocyte adhesion to endothelial cells occurs when there are inflammation and lymphocyte migration passing endothelial cells toward inflamed tissue. In other words, lymphocytes migrate more easily out of the blood vessels than neutrophils that need chemotactic stimulus and endothelial activation to migrate.¹² Lymphopenia occurs as more burden of atherosclerosis. Lymphopenia is also associated with a poor prognosis, so the heavier lymphopenia is, the more severe the clinical symptoms are.⁷

In addition, a research conducted by Kalay *et al*⁸ showed a significant difference of lymphocytes between in progressive coronary atherosclerosis and in non-progressive coronary atherosclerosis.⁸ However, the results of Kruskal-Wallis test showed that there was no significant difference of lymphocytes in patients with ACS. Thus, it cannot be used as a marker for ACS. But, in this research, the average number of lymphocytes in the group of UAP was higher (2.13 ± 1.16) than in the groups of NSTEMI and STEMI group (1.08 ± 1.90 and 1.71 ± 0.70). It indicates that lymphopenia can affect PLR. Consequently, PLR values in the group of UAP were higher.

On the other hand, the results of Kruskal-Wallis test showed that there was a significant difference of PLR in ACS patients among UAP, NSTEMI and STEMI groups ($p=0.011$). The results of *post hoc* test, Mann-Whitney test showed that there were significant differences between the group of UAP and the group of NSTEMI ($p=0.023$) and between the group of UAP and the group of STEMI ($p=0.006$). But, there was no significant differences between the group of NSTEMI and the group of STEMI ($p=0.827$). Thus, it can be said that PLR values in the group of UAP were significantly lower than in the groups of NSTEMI and STEMI.

Platelet-Lymphocyte Ratio values in patients with ACS, moreover, indicated that the group of UAP with smaller arterial occlusion and platelet aggregation had a lower value of PLR (142.41 ± 80.20) than the groups of NSTEMI and STEMI (172.82 ± 95.14 and 178 ± 101.38) with the presence of thrombus and greater occlusion. A research conducted by Gary *et al*¹⁰ research showed the *cut-off* value of PLR >150 indicates vascular disease risk. This research also showed that there was no significant difference in coronary artery disease between in patients with PLR values of ≤ 150 and in patients with PLR values of >150 . But, there was a significant difference in myocardial infarction between in patients with PLR values of ≤ 150 and in patients with PLR values of >150 .

Coronary artery occlusion in UAP due to unstable plaque had platelet aggregation, but no thrombus formation. Thrombus was found in atherosclerotic plaques of NSTEMI and STEMI groups; therefore, the greater thrombus is formed, the more severe thrombus occlusion and clinical symptoms emerge.⁶ The formation of atherosclerotic plaque in the coronary arteries can cause a partial blockage of blood vessels and can lead to symptoms of chest pain. Unstable plaque then will eventually lead to platelet activation triggering fibrin formation. As a result, thrombi can aggravate the occlusion of the coronary arteries and ultimately lead to myocardial infarction.

The results showed the values of PLR in NSTEMI and STEMI were higher than in UAP. This result is associated with thrombus atherosclerosis and myocardial infarction. Thus, PLR value can be used as a marker for progressivity of ACS, especially for thrombus atherosclerosis and myocardial infarction.

The results of Mann-Whitney test showed a significant difference of PLR ($p=0.037$) between in ACS patients (162.42 ± 92.54) and in the normal controls (135.56 ± 41.83). ROC curves comparing normal controls to patients with ACS showed PLR-150 had a sensitivity of 44.4% and a specificity of

78.2% with an AUC value of 0.559. The sensitivity and specificity values are too low to be used as a screening parameter, but can be used a marker for the diagnosis of ACS.

ROC curves comparing to UAP with STEMI and NSTEMI with AUC of 0.618 indicated PLR-150 had a sensitivity of 53.0% and a specificity of 78.5%. This PLR value had a better sensitivity and specificity than in the normal control group compared to patients with ACS. *Platelet-Lymphocyte Ratio* markers have potentials to be used as a marker for the occurrence of thrombosis and myocardial infarction.

Finally, it can be said that many factors can contribute to changes in PLR values, namely hematologic malignant disease and other inflammatory infections affecting the number of platelets and lymphocytes. However, this research as an observational study using medical records still has difficulties to avoid bias as well as some problems in the normal control group with different age ranges.

CONCLUSION AND SUGGESTION

The results of this research showed that there was a significant difference of PLR between in ACS patients and in the normal control group. PLR values in the group of UAP were significantly lower than those in the groups of NSTEMI and STEMI. *Platelet ratio lymphocyte*, consequently, has a potential as a marker for atherosclerosis thrombosis and myocardial infarction. Thus, further research is needed to eliminate the possibility of bias from other diseases and the method of sample selection had better use more number of samples.

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