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The Relationship between Platelet to Lymphocyte Ratio and Platelet Indices with Disease Severity Level of Systemic Lupus Erythematosus

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is an episodic, chronic autoimmune inflammatory disease characterized by remission and flare phases. Laboratory parameters required to assess the severity of disease activity in SLE include platelet count and platelet indices. Several studies regarding the Platelet to Lymphocyte Ratio (PLR) and platelet indices on the severity of SLE patients remain inconsistent. This study aimed to evaluate the relationship between PLR value and platelet index with the degree of disease severity in SLE patients. This study used a retrospective analytic observational design in SLE patients from January 2016 to December 2019 at Dr. Sardjito Central Hospital. Disease severity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. Platelet to Lymphocyte Ratio (PLR) values and platelet indices were measured with a hematology analyzer. The data were analyzed using correlation, bivariate, multiple regression tests, and the ROC curve to determine the PLR cut-off. There were 55 SLE patients with high activity (SLEDAI 11-19; n=30(54,54%)) and very high activity (SLEDAI 20; n=25(45.45%)). There was a significant correlation (p <0.05) between the PLR value, platelet count, plateletcrit, and Mean Platelet Volume (MPV) with SLEDAI scores (p <0.05), but only the MPV variable was significant as an independent variable (p=0.0357). In the ROC curve, a cut-off PLR value of 124 was obtained with a sensitivity of 68.0%, specificity of 66.7%, likelihood ratio=2.04 (AUC=0.659 with p-value=0.035) to detect very high disease activity. Based on the PLR value, platelet count and plateletcrit negatively correlated with SLEDAI score but were related to the very high degree of thrombocytopenia in disease activity. The MPV value reflected the high platelet turnover, which had a positive correlation with the SLEDAI score. Patients with a PLR value ≤ 124 were 2.04 times more likely to have a SLEDAI score of 20, indicating potential use as a predictor of disease activity. The PLR value and platelet indices were significantly related to the degree of SLE activity.

Keywords: Platelet to lymphocyte ratio, platelet indices, SLEDAI score, systemic lupus erythematosus

INTRODUCTION

Platelet to lymphocyte ratio (PLR) is a conventional inflammatory index that can be calculated from routine blood tests and has been shown to be associated with disease activity and prognosis of various inflammatory-related diseases, such as sepsis, cancer, autoimmune diseases such as SLE.[1] Multisystem involvement is found in this disease, such as mucocutaneous (malar rash), musculoskeletal (arthritis), hematological (anemia), neurologic (cerebri) and renal (nephritis) in SLE.[2] The PLR value was obtained by calculating the absolute number of platelets divided by the number of lymphocytes.

There are no clinical or laboratory manifestations of SLE that can alone represent the degree of disease activity at a time. Long-term monitoring of SLE has an essential role in determining the classification, dosage of drugs, and preventing complications. Therefore, a diagnostic device is needed that can evaluate the activity of the SLE disease course.[3]

To date, many studies have investigated the value of PLR in assessing the activity of autoimmune diseases, such as arthritis, polymyositis, and SLE itself.[2] The primary function of platelets is to form a mechanical plug during the normal hemostatic response to vascular injury. The Mean Platelet Volume (MPV) is the average number of platelets that describes the function and activity of platelets. The higher MPV indicates the number of large platelets as a sign of increased platelet turnover.[4] Some opinions suggest that the platelet index parameter is important in mediating the immune response, maintaining vascular homeostasis, and inflammation.[5]

However, the other use of PLR and other platelet indices (platelet count, plateletcrit, MPV) as functional indices in assessing SLE disease activity remains unclear. There have been no consistent

results. Previous studies have shown that PLR is increased in SLE patients compared to controls.[2] This study retrospectively evaluated PLR values and several platelet indices (platelets, plateletcrit, MPV) in SLE patients at Dr. Sardjito Hospital and explored the clinical significance of these markers.

METHODS

This study was an analytic observational retrospective study, conducted by consecutively collecting the data from the medical record, primary patient data, patient clinical data, laboratory test results, and other supporting tests of patients diagnosed with SLE at Dr. Sardjito Hospital. The research subjects were all patients diagnosed with SLE at Dr. Sardjito Hospital in January 2016 – December 2019 who performed a complete blood count, CRP, procalcitonin, complement C3-C4, ANA/ANA IF test, and Anti dsDNA test with serum samples.

Laboratory tests performed were hemoglobin, hematocrit, platelet count, leukocyte count, leukocyte count, PLR, CRP, serum albumin procalcitonin, kidney function tests (BUN, creatinine), complete urinalysis, ANA, ANA IF, Anti dsDNA test, C3, and C4. Cases with incomplete medical records were excluded from the study. Each clinical data and laboratory results were input into the SLEDAI score.

The EDTA blood samples for complete blood count were taken on the same day as serum samples. The patient's complete blood count was tested using an automatic device, Sysmex XN1000–Sysmex XN550 (flow cytometry method) or Advia 120 (optical method). Although these three devices have different test methods, they show a good correlation with the results of routine hematological tests.

The criteria commonly used for classification and diagnosis are the American Rheumatism Association (ARA) criteria. Disease activity at the time of admission was measured by the SLE disease activity index (SLEDAI). Various systems can be used to assess SLE activity that combines clinical conditions and laboratory results. A scoring system that is practical and widely used in clinical applications is the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score. The score is considered accurate and reliable. A SLEDAI score above five is associated with a greater likelihood of initial therapy. Categories of disease activity based on SLEDAI scores are as follows: no activity (SLEDAI=0), mild activity (SLEDAI= 1-5), moderate activity (SLEDAI 6-10), high activity (SLEDAI 11-19), and very high activity (SLEDAI 20).[3]

A total of 61 SLE patients were obtained at Dr. Sardjito Hospital from 2016 to 2019. However, only 55 patients met the study criteria (diagnosed with SLE based on ARA criteria and had complete medical records and supporting tests to assess SLEDAI scores). The exclusion criteria are patients with incomplete data of SLEDAI score and patients with the non-autoimmune comorbid disease.

Statistical analysis used MedCalc version 19.0. It considered significance if $p < 0.05$. Data distribution was analyzed using Shapiro-Wilk. Difference tests were carried out according to the characteristics of the data. Parametric data were presented as mean±standard deviation, non-parametric data were presented as median (minimum-maximum), and categorical data were presented as proportion table. The correlation test of the Spearman rank test was used, and multiple regression analysis was carried out on the significant variables. In addition, the ROC test was carried out to determine the cut-off variable as a predictor.

This study had received approval from the Health Research Ethics Committee of the Faculty of Medicine, Gadjah Mada University/Dr. Sardjito Hospital with number No: KE/FK0160/EC/2021

RESULTS AND DISCUSSIONS

A total of 61 SLE patients were obtained at Dr. Sardjito Hospital from 2016 to 2019. However, only 55 patients met the study criteria (diagnosed with SLE based on ARA criteria and had complete medical records and supporting tests to assess SLEDAI scores). There were three male patients (5.45%) and 52 female patients (94.54%) with a median age of 18 years (10-56 years) who were involved as research subjects. The youngest patient found in this study was at the age of 10, and the majority were females. This study was in line with several previous studies, which found that the majority of SLE patients were over ten years old and females.[3,6]

Table 1 describes the clinical characteristics of the research subjects divided into two groups based on the SLEDAI score, which describes the activity of SLE disease into categories of high activity and very high activity. There were 55 SLE patients, SLE with high activity (SLEDAI 11-19; n=30 (54.54%)) and very high activity (SLEDAI 20; n=25(45.45%)) were found. This fact was due to the limited population of the study sample, and the population was taken at the highest referral hospital, causing a tendency of more severe

disease. This finding was in line with the worsening of the patient's condition that higher number of death outcomes was found in the SLE group with a very high activity SLEDAI category as many as seven patients (28% of the total number of patients with the very high activity SLEDAI score category).

Statistical difference tests (Table 2 and Table 3) were performed on all laboratory parameters (hemoglobin, erythrocytes, hematocrit, leukocytes, platelets, NLR, PLR, CRP, procalcitonin, albumin,

Table 1. Clinical characteristics of research subjects

Parameter	Total (n= 55)	SLEDAI Score High Activity (n= 30)	SLEDAI Score Very High Activity (n= 25)	p
Age (years)	18.00 (10.00-56.00)	18.00 (10.00-56.00)	21.00 (1.00-49.00)	0.7607**
Gender				
Male, n (%)	3 (5.45%)	2 (6.67%)	1 (4.00%)	1.0000****
Female, n (%)	52 (94.54%)	28 (93.33%)	24 (96.00%)	
Patients outcome				
Survived, n (%)	47 (85.45 %)	29(96,66%)	18 (72%)	
Died, n (%)	8 (14.54%)	1(3.33%)	7 (28%)	
Autoimmune comorbid				
Yes	5 (9.09%)	3 (10.00%)	2 (8.40%)	1.0000****
None	50 (90.90%)	27 (90.00%)	23 (92.00%)	

** Mann-Whitney test: 2 unpaired numerical groups, at least one of them were data with abnormal distribution
**** Fisher test: 2 unpaired categorical groups, criteria for Chi-Square were not met

Table 2. Hematology parameters of research subjects

Parameter	Total (n=55)	SLEDAI Score High Activity (n= 30)	SLEDAI Score Very High Activity (n= 25)	p
Hemoglobin (g/dL)	10.26±1.98	10.96±1.80	9.42±1.88	1.0000*
Erythrocyte ($\times10^6$/µL)	3.80±0.82	4.05±0.80	3.50±0.76	1.0000*
Hematocrit (%)	31.12±6.07	33.16±5.64	28.68±5.76	1.0000*
Leukocyte ($\times10^3$/µL)	5.87 (0.83-5.87)	5.68 (1.46-22.22)	6.27 (1.84-29.88)	0.5428**
Platelet ($\times10^3$/µL)	133,00 (4.00-589.00)	207.00 (4.00-589.00)	110.00 (31.00-458.00)	**0.0332****
NLR (1.0-2.4)	3.68 (0.31-70.20)	3.80 (0.31-35.71)	3.46 (1.10-70.20)	0.9730**
PLR (69.32-164,78)	130.34 (0.65-864.28)	227.378 (0.651-864.286)	109.58 (26.98-803.50)	**0.0443****
MPV (7.2-11.7 fL)	10.00 (5.10-13.80)	9.70 (5.10-13.80)	10.70 (5.80-13.10)	**<0.0001****
Plateletcrit (0.22-0.24 %)	0.14 (0.002-0.55)	0.15 (0.002-0.55)	0.12 (0.03-0.38)	**0.0010****

* Unpaired T-test: 2 unpaired numerical groups, both were data with normal distribution
** Mann-Whitney test: 2 unpaired numerical groups, at least one of them were data with abnormal distribution

Table 3. Clinical chemistry and immunology parameters of research subjects

Parameter	Total (n=55)	SLEDAI Score High Activity (n= 30)	SLEDAI Score Very High Activity (n= 25)	p
CRP (mg/L) (<10 mg/L)	15.00 (5.00-150.00)	11.00 (5.00-150.00)	15.00 (5.00-89.00)	0.8187**
Procalcitonin (ng/mL) (<0.15 ng/mL)	0.86 (0.02-114.90)	0.51 (0.02-100.42)	1.00 (0.08-114.90)	0.0832**
Albumin (g/dL) (3.4-5.4 g/dL)	3.09 (1.73-5.13)	3.34 (1.93-5.13)	2.78 (1.73-4.60)	**<0.0001****
BUN (mg/dL)	12.00 (5.00-97.20)	11.30 (5.50-38.10)	15.10 (5.00-97.20)	0.1083**
Creatinine (mg/dL)	0.66 (0.29-5.76)	0.62 (0.29-2.82)	0.66 (0.34-5.76)	0.2400**
Anti dsDNA (U/mL) (<25 U/mL)	200.00 (25.40-200.00)	200.00 (25.40-200.00)	200.00 (25.40-200.00)	0.6116**
IF ANA				
Positive, n (%)	38 (69.09%)	19 (63.33%)	19 (76.00%)	0.4720***
Negative, n (%)	17 (30.90%)	11 (36.67%)	6 (24.00%)	
C3 (mg/dL) (80-160 mg/dL)	61.00 (15.00-171.00)	73.50 (15.00-171.00)	42.00 (20.00-170.00)	0.0692**
C4 (mg/dL) (16-48 mg/dL)	11.00 (1.77-43.00)	12.50 (2.00-32.52)	9.00 (1.77-43.00)	0.2332**

* Unpaired T-test: 2 unpaired numerical groups, both were data with normal distribution
** Mann-Whitney test: 2 unpaired numerical groups, at least one of them were data with abnormal distribution
*** Chi-Square test: 2 unpaired categorical groups, criteria for Chi-Square were met
**** Fisher test: 2 unpaired categorical groups, criteria for Chi-Square were not met

BUN, creatinine, anti-dsDNA, ANA IF, C3, C4), showed statistically significant differences (p <0.05) on PLR, platelet, MPV, plateletcrit and albumin variables in the high activity and very high activity groups. This finding was in line with a study by Qin *et al*., which compared PLR, MPV, and several other inflammatory markers to the SLEDAI score.[2] However, this study found no significant difference in the NLR to the SLEDAI score in the high activity and very high activity categories.

The correlation Spearman rank test (Figure 1) showed a significant correlation of the Albumin, PLR, platelets, plateletcrit, and MPV. The albumin had a significant value, a negative and weak correlation (p=0.0083, rho= -0.353 (-0.565 to -0.0962)). The PLR variable had a significant value, a negative and weak correlation (p=0.0487, rho = -0.267 (-0.497 to -0.00195)). The platelet count variable had a significant value, a negative and weak correlation (p=0.0093, r = -0.348 (-0.561 to -0.0909)). The MPV variable had a significant value, a positive and weak correlation (p=0.0068, r=0.361 (0.106 to 0.571)). In addition, the plateletcrit variable had a significant value, a negative and weak correlation (p=0.0222; r = -0.308 (-0.530 to -0.0463)).

Multiple regression analysis was performed on several significant independent variables to determine the independent variable that most influenced the SLEDAI score's output.

The ROC analysis test (Figure 2) was performed to determine the cut-off value of PLR in predicting the degree of SLE disease activity through the SLEDAI score, and the ROC/Area Under Curve (AUC) curve was described by determining the sensitivity and specificity in various cut-off levels. To predict the degree of very high activity, the optimal cut-off value obtained was PLR 124.09, sensitivity 68.0%, specificity 66.7%, Likelihood ratio = 2.04; AUC=0.659 with p-value = 0.035 (p <0.05).

Platelets play an important role in inflammation, and recent evidence has determined several additional functions for platelets in the inflammatory

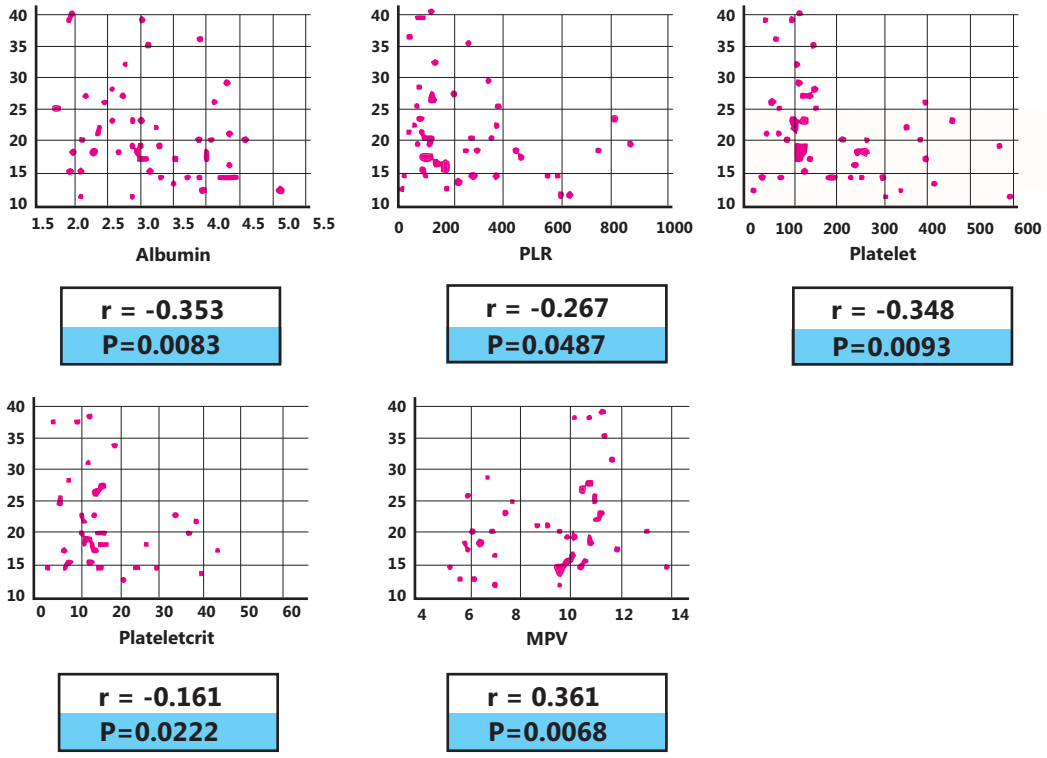

Figure 1. Correlation between various independent variables with SLEDAI score (Y-axis)

Table 4. Multiple regression analysis of various independent variables

Independent Variable	Coefficient	Partial r	t	p
Albumin	-1.9564	-0.2094	-1.483	0.1445
PLR	-0.0055	-0.1582	-1.110	0.2726
Platelet	0.0432	0.1819	1.282	0.2060
Plateletcrit	-61.9830	-0.2319	-1.652	0.1051
MPV	1.8026	0.2978	2.161	**0.0357**

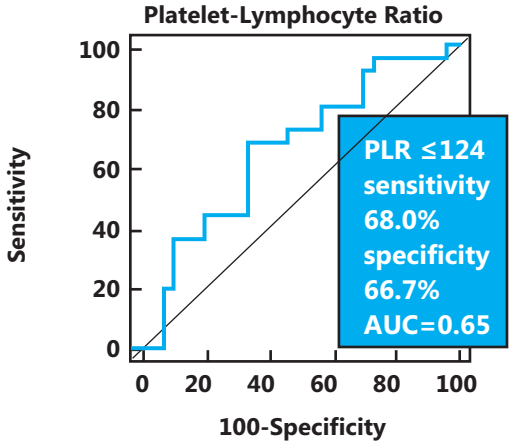

Figure 2. ROC/AUC curve of PLR variable

process. Many studies have demonstrated the important role of platelets in the pathogenesis of various inflammatory in clinical conditions in which inflammation is important. Many group studies have found associations between changes in the platelet index and activation of the coagulation system, severe infections, trauma, systemic inflammatory reaction syndrome, and thrombotic disease.[7] The platelet index has been shown to have diagnostic value in certain inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and atherosclerosis.[7] In this study, the results of the statistical difference test and significant correlations on the PLR and platelet index variables (platelet, plateletcrit, MPV) were found. This result was in line with several systematic reviews by Yasemin *et al.*, which found significant correlations from several studies on PLR and platelet index in various inflammatory diseases. This study found increased PLR value in the group of SLE patients with high activity, following a study by Qin *et al.*, which found increased PLR value compared to the normal population and the normal range of PLR. However, this study highlighted the decreased PLR value in SLE

patients with very high activity. Therefore, the correlation curve showed a negative but still weak correlation. This result was possible because the population of SLE patients with very high activity has experienced thrombocytopenia. As described in the characteristics of research subjects (Table 1), the median platelet count value of 110,000/uL (31,000-458,000/uL) was found in the group of SLE patients with very high activity. It will inevitably affect the PLR value. However, research with a wider and more diverse population is still needed to describe the PLR value at each level of SLE disease activity. From the results of the multiple regression analysis test (Table 4), MPV was found as an independent variable that affects the severity of the disease in SLE with a p-value < 0.05 (0.357). Likewise, several studies also found that the MPV and plateletcrit values tend to decrease and increase in various disease conditions associated with inflammation.[7] Mean platelet volume acts as a negative or positive acute phase reactant under different inflammatory conditions. High MPV values are associated with severe inflammation due to the presence of large circulating platelets. Mean platelet volume may decrease in severe inflammatory conditions due to ingestion and sequestration of these large platelets in the vascular segment in inflammatory conditions. Low MPV is associated with low-grade inflammation, such as rheumatoid arthritis and familial Mediterranean fever. Therefore, decreased and increased MPV can be found in acute and chronic disorders. The MPV value in this study was still in the normal range, but an increased MPV value was found in the group of SLE patients with very high activity. It can certainly be associated with the severity of inflammation in this patient population, indicated by the CRP value, which tends to have a higher median value in the SLE patient population with very high activity. This phenomenon is also related to the plateletcrit value in the population in which decreased plateletcrit value is found because the platelet count and MPV value influence it. From various analyses of correlation tests, significant results were obtained on all parameters related to platelets. The ROC/AUC test results showed a significant value of the PLR parameter to the population, which was distinguished by the SLEDAI score with the optimal cut-off value for PLR of 124.09, sensitivity 68.0%, specificity 66.7%, Likelihood ratio = 2.04 AUC=0.659 and p=0.035 (p <0.05)). Patients with PLR values < 124 were 2.04 times more likely to have a SLEDAI score of 20, suggesting a potential use as predictors of disease activity. This certainly supports the utility of platelet parameters as prognostic and diagnostic factors in inflammatory diseases, including SLE. However, due to its weak correlation, sensitivity, and specificity of the PLR value, further research is still needed on the use of PLR and other platelet indices, although statistical significance has been obtained in this study.

CONCLUSIONS AND SUGGESTIONS

There was a relationship between PLR and platelet index values to the degree of SLE disease activity to reflect the inflammatory response and disease activity in SLE patients. However, they have not been able to replace the SLEDAI score assessment.

Further research is needed on the usefulness of PLR and other platelet indices to a broader patient population based on the level of SLE disease activity due to the limitations of research in retrospective designs, making a narrower population range due to selection bias.

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