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Original Article

Platelet to Lymphocyte Ratio (PLR) Value in Normotency, Preeclampsia and Severe Preeclampsia

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Abstract

Background : Hyperactivation of the inflammatory response in preeclampsia causes a significant increase in the number of leukocytes. Platelet to Lymphocyte Ratio (PLR) has been known as a marker of systemic inflammatory response. In preeclampsia, the role of PLR markers is still uncertain regarding the ability of clinical evaluation, differential diagnosis and evaluation of patient prognosis. The aims of this study was to analyze differences in platelet to lymphocyte ratio (PLR) values in normotensive, preeclampsia, and severe preeclampsia pregnancies
Methods : Analytical observational study with cross sectional design with 90 samples consisting of 30 normotensive, 30 preeclampsia and 30 severe preeclampsia pregnancies. Evaluation was carried out on the platelet to lymphocyte ratio (PLR) value. Analysis was carried out using the SPSS 32 edition application. Results are significant if $p<0.05$.
Results : Comparison between the normotensive versus preeclampsia versus severe preeclampsia group showed that platelet levels decreased but not significantly ($p=0.081$), lymphocyte levels increased significantly ($p<0.001$) and PLR values decreased significantly ($p<0.001$) as the degree of severity increased preeclampsia. In the severe preeclampsia group, the lowest platelet levels, the highest lymphocyte levels and the lowest PLR values were obtained. Patients with a PLR value of < 104.62 have an 8.43x (OR 8.43; CI95% 3.12–22.78) higher risk of experiencing severe preeclampsia compared to subjects with a PLR value > 104.62.
Conclusion : The PLR value was significantly lowest in the severe preeclampsia group.

Keywords : preeclampsia, severe preeclampsia, platelet to lymphocyte ratio

INTRODUCTION

One form of hypertension during pregnancy that is dangerous is preeclampsia (PE). Preeclampsia (PE) affects approximately 2–8% of all pregnancies worldwide and remains one of the leading causes of maternal morbidity and mortality.[1] In severe cases, preeclampsia can lead to maternal organ dysfunction, systemic diseases such as HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), poor maternal clinical outcomes, and poor perinatal clinical outcomes such as early and late intrauterine growth retardation.[2]

Studies show that hyper-reactivation of inflammatory cells and immunological response of neutrophils and lymphocytes occurs by releasing inflammatory cytokines and autoantibodies that cause endothelial dysfunction. The clinical manifestations of PE are associated with widespread endothelial dysfunction, leading to vasoconstriction and end-organ ischemia.[2] The enhancement of inflammatory and immune responses that occurs in preeclampsia significantly increases white blood cell count and modulates white blood cell function, leading to the production of more superoxide than nitric oxide, leading to damage and dysfunction. endothelium.[3]

Platelet to Lymphocyte Ratio (PLR) has been known as a marker of systemic inflammatory response. It is considered to have diagnostic significance in many systemic and local inflammatory diseases. In PE, abnormal changes are also observed in leukocytes. However, the role of these systemic inflammatory markers remains unclear in the clinical assessment, differential diagnosis, and prognostic assessment of PE. This study was conducted to analyze the differences in platelet to lymphocyte ratio (PLR) values as predictors of normotensive pregnancies, preeclampsia and severe preeclampsia.

METHODS

Analytical observational study with cross sectional design of 90 samples consisting of 30 normotensive 30 preeclampsia and 30 severe preeclampsia pregnancies. Evaluation was carried out on the platelet to lymphocyte ratio (PLR) value. Sampling was carried out using consecutive sampling, namely selecting research subjects based on research criteria and subjects signing an agreement to participate in the research.

The study was conducted from May to November 2023 in RSUP dr. Kariadi Semarang. Inclusion criteria include 1) pregnant women with gestational age >20 weeks, 2) singleton pregnancies, 3) patients diagnosed with normotensive pregnancy (Systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg) or preeclampsia (SBP ≥140 mmHg and/or DPB ≥90 mmHg with target organ damage) or severe preeclampsia (SBP ≥160 mmHg and/or DPB ≥110 mmHg with target organ damage). Exclusion criteria include 1) pregnant women with platelet disorders such as ITP, HELLP syndrome, 2) premature rupture of membranes, 3) multiple pregnancies, and 4) patients with uncontrolled comorbidities.

1) Individuals who met the inclusion and exclusion criteria and agreed to take part in the research were used as research subjects. Explanations were given directly by researchers, medical personnel or residents who were on duty in the Polyclinic or in the emergency installation.

2) Anamnesis was performed on the research subjects. Their name, age, address, parity, first day of last menstruation, gestational age, current complaints, general condition and vital signs were checked.

3) Every pregnant woman studied continued to undergo pregnancy checks according to the specified schedule. At each routine visit, blood pressure measurements, obstetric examinations (uterine fundal height, gestational age, fetal heart rate) and laboratory examinations (routine blood and proteinuria) were carried out.

4) The research subjects had 3 mL of venous blood drawn. For patients who were planned to receive antenatal corticosteroids, samples were taken before administration of antenatal corticosteroids.

5) Blood samples were sent to the laboratory of RSUP Dr. Kariadi for routine blood and absolute lymphocyte tests. Blood samples from the community health center were taken by midwives/ nurses, then the blood samples along with the research sample form were submitted to the laboratory section of RSUP Dr. Kariadi. Blood samples could be sent directly or stored in a cool box at a temperature of 40oC for a maximum of 12 hours before being sent to the laboratory at RSUP Dr. Kariadi.

6) Absolute platelet and lymphocyte values were collected and recorded from prints of the hematoanalyzer results of research samples. The PLR value was obtained from the platelet count divided by the absolute lymphocyte count, then the data was analyzed statistically

Tests for differences in platelet levels and PLR values between the three research groups were carried out using Kruskal Wallis because the data had an abnormal distribution. The test for differences in lymphocyte levels between the three research groups was carried out using one way ANOVA because it has a normal data distribution. ROC curve analysis was carried out to determine the best cut off value in estimating the incidence of severe preeclampsia in research subjects. Analysis of the risk of preeclampsia based on the PLR value was carried out using the Chi-Square test. Analysis was carried out using the SPSS 32 edition application. Results were said to be significant if the p value <0.05. Ethical approval was obtained from The Health Research Ethics Committee RSUP Dr. Kariadi Semarang no.

1465/EC/KEPK-RSDK/2023.

RESULTS

Analysis of platelet levels, lymphocyte levels and PLR values was carried out in the three research groups so that the following results were obtained.

There was no significant difference in the distribution of platelet levels between study groups (p=0.081). There was a significant difference in the distribution of lymphocyte levels between the study groups (p<0.001), where the highest lymphocyte levels were found in the severe preeclampsia group. There was a significant difference in the distribution of PLR values between study groups (p<0.001), where the lowest PLR value was found in the severe preeclampsia group.

There were significant differences in the distribution of PLR values between study groups, where the lowest PLR values were found in the severe preeclampsia group. There is a correlation between the PLR value and preeclampsia status with a moderate and inverse correlation level. This means that the more severe the preeclampsia status will be correlated with a decrease in the PLR value.

The PLR value (AUC: 0.826) with a cut off <104.62 had a sensitivity of 78.3% and a specificity of 70% in assessing the incidence of severe preeclampsia in research subjects.

Subjects with a PLR value ≤104.62, were 21 subjects with PEB and 13 subjects with PE-normal. Subjects with PLR values > 104.62, were 9 subjects with PEB and 47 subjects with PE-normal. There was a relationship between the PLR value and the incidence of PEB (p<0.001) where subjects with a PLR value ≤104.62 had an 8.43x (OR 8.43; CI95% 3.12–22.78) higher risk of experiencing PEB than subjects with a PLR value > 104.62.

The analysis found a correlation between platelet levels and systolic blood pressure (p=0.035) and diastolic blood pressure (p=0.031) with a weak and inverse correlation level, a correlation between lymphocyte levels and systolic blood pressure (p<0.001) and diastolic blood pressure (p<0.001) with a moderate and unidirectional

TABLE 1
Platelet to Lymphocyte Ratio based on the blood pressure status of pregnant women

Variable	Normotensive (n=30)	Preeclampsia (n=30)	Severe Preeclampsia (n=30)	*P*
Platelet	309.300 ± 53.138; 308.000 (203.000–395.000)	222.100 ± 55.103; 227.000 (109.000–358.000)	199.866 ± 86.260; 217.000 (12.000–326.000)	0.081‡
Lymphocyte	1.703 ± 457.76; 1.665 (1.000–2.910)	2.305.33 ± 641.01; 2.305 (1.040–3.950)	2.373.73 ± 713.78; 2.295 (1.140–3.910)	<0.001†
PLR	195.31 ± 63.32; 185.76 (102–310)	106.53 ± 44.35; 104.76 (37.45–191.34)	84.98 ± 33.45; 88.45 (9.23-133.33)	<0.001‡

†One-way ANOVA; ‡Kruskal wallis; significant p<0.05

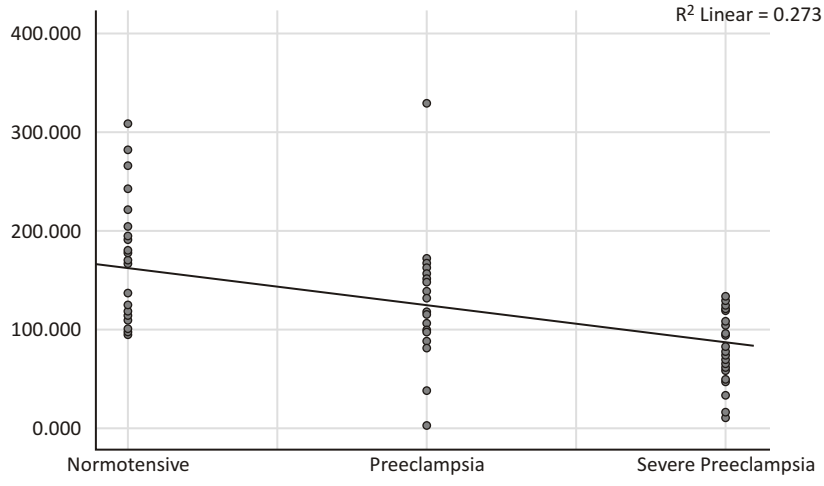

Figure 1. Scatter plot curve of platelet levels based on preeclampsia status

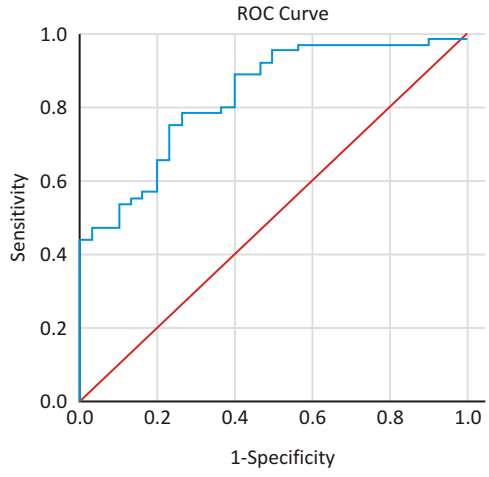

Figure 2. ROC curve analysis of PLR values on the incidence of severe preeclampsia (severe preeclampsia vs preeclampsia–normal)

TABLE 2
The risk of preeclampsia based on the PLR value

Variable		Preeclampsia		*p*	OR (CI95%)
		Severe Preeclampsia	Preeclampsia-Normal		
PLR	≤ 104.62	21	13	<0.001	8.43 (3.12–22.78)
	> 104.62	9	47		

Chi-Square; significant $p<0.05$

TABLE 3
Correlation test between PLR and systolic and diastolic blood pressure

Variable	Systolic Blood Pressure		Dystolic Blood Pressure	
	p	r	*p*	r
Platelet	0.035	-0.222	0.031	-0.227
Lymphocyte	<0.001	0.408	<0.001	0.441
PLR	<0.001	-0.522	<0.001	-0.564

Spearman; significant $p<0.05$

correlation level and a correlation between PLR values and systolic blood pressure ($p<0.001$) and diastolic blood pressure ($p<0.001$) with a moderate and inverse correlation level. This means that higher systolic blood pressure or diastolic blood pressure will correlate with decreased platelet levels, increased lymphocyte levels and decreased PLR values.

DISCUSSION

Cui H. found that PLR values were lower in PEB cases than in controls.[4] Toptas *et al*. also found that PLR values were comparable between PE pregnancies and normal pregnant women. In addition, patients with PEB had lower PLR values compared with PE.[5]

Melekoglu R *et al*. grouped preeclampsia cases as PE and PEB and reported that the sensitivity, specificity and AUC of PLR for diagnosing PEB were 45.9%, 78.1% and 0.573, respectively.[6] In two trials, the accuracy of PLR in identifying PEB reported the sensitivity, specificity and AUC of 49.6%, 74.7%, 0.639 and 55%, 50%, 0.554.[7,8] Mahmoud AGE, *et al* stated that the PLR value with a cut off 8.07 can be used as a predictor of preeclampsia with a sensitivity of 81.1%, specificity of 95.1%, PPV 28.6% and NPV 64.6%.[9] This study has a higher PLR cut-off value compared to other studies, allegedly caused by the

research subjects who had a gestational age of >20 weeks, while in the study of Mahmoud AGE, *et al* used subjects with a gestational age of 7–14 weeks and then followed until delivery. Research by Cha HH, *et al* has shown that the PLR value increases with increasing gestational age. So it is not surprising that the PLR cut-off value of this study is higher than the study of Mahmoud AGE, *et al* because of the difference in maternal gestational age.[10]

Severe preeclampsia shows hyperinflammatory activation which causes a decrease in PLR, compared with normal pregnancy. Preeclampsia develops due to defects in placentation, excessive innate/adaptive immune activation, and inflammation at the maternal-fetal interface. In preeclamptic patients, there is a shift from Th2 to Th1 lymphocytes, with reduced immune tolerance.[11] In severe preeclampsia the coagulation system is directly attacked, and the number of platelets reaches a much lower level than in normal pregnancy.[12]

Fluid retention occurs during pregnancy due to sodium and water retention caused by the effects of the estrogen and progesterone, which causes hemodilution or pseudo-thrombocytopenia. Presumably, increased vascular tone during pregnancy causes platelet destruction and coagulation defects also occur. In addition, increased serum levels of platelet-associated IgG may occur in some pregnant women suffering from hypertension. However, elevated immunoglobulins are nonspecific and do not indicate the presence of immunologically mediated thrombocytopenia.[13] Additionally, contact of platelets with damaged endothelium stimulates the coagulation cascade, which can increase platelet consumption and production in the bone marrow.[14]

Thrombocytopenia in preeclampsia is due to various causes including increased platelet consumption due to disseminated intravascular coagulopathy and/or immune mechanisms. The attachment of platelets to areas of damaged vascular endothelium can also result in secondary destruction of platelets.[15]

Prostacyclin is an important eicosanoid that has a strong inhibitory effect on platelet aggregation. Eicosanoids are continuously available in the blood vessels thereby maintaining circulating platelets in a dispersed form. Low levels of prostacyclin can cause circulating platelets to be increasingly susceptible to aggregation. Removal of platelet aggregates from the body's circulatory system is thought to be responsible for the occurrence of thrombocytopenia which often occurs in cases of hypertension during pregnancy. Platelets from patients with severe preeclampsia also showed a lower response than normal pregnancies to various aggregation agents suggesting that platelets may have undergone prior aggregation in the microcirculation.[15]

Recent studies have found that elevated plasma levels of the soluble vascular endothelial cell growth factor (VEGF) receptor sFlt1 type 1 as well as endoglin, an endothelial cell-derived member of the tumor growth factor receptor-2 (TGF-2) family, are present in patients thought to be will experience preeclampsia at the end of the first trimester. Increased levels of soluble fms-like tyrosine kinase-1 (sFlt1) and endoglin mRNA were found in the placenta of preeclamptic patients, indicating that this is the main cause of preeclampsia. sFlt1 is known to bind and inactivate VEGF and placental growth factor (PLGF), the levels of which usually increase during pregnancy, while endoglin blocks the binding of TGF-2 to endothelial cells.[16]

Preeclampsia is characterized by higher levels of superoxide and markers of systemic inflammation.[17] Lymphocytes have pro- and anti-inflammatory effects associated with pregnancy phenotypes. Anti-inflammatory T regulatory cells (Tregs) are known to suppress the maternal immune system response against fetal tissues, and T-helper 17 (Th17) cells promote inflammation , autoimmunity and transplant rejection in humans. Significant increases in Th17 cells and/or decreases in Treg numbers have been reported in severe obstetric complications. Identification of lymphocytes would be informative, but a decrease in total lymphocyte numbers in PE suggests that inflammatory features may play an important role in the maintenance of obstetric complications, such as PE.[18]

There are differences in lymphocyte levels in preeclampsia patients compared to normal pregnancies between several studies, it is suspected that one of the influencing factors is gestational age. Research that assessed the lymphocyte levels of preeclampsia patients between preterm births compared to term births found that the mean lymphocyte levels were significantly higher in preterm births (2.25 vs 2.07; $p<0.001$).[19]

This study has several limitations, including 1) the enforcement of PE and PEB criteria did not use other laboratory markers, 2) in eliminating exclusion criteria only using patient's history data and, 3) The gestational age range used as inclusion criteria was too broad (>20 weeks), but it is known that lymphocyte levels will normally change with changes in gestational age. It has been mentioned that lymphocyte levels decrease during the 1st and 2nd trimesters, then increase in the 3rd trimester.[20] Therefore, further research should conduct analysis based on the trimester of pregnancy.

CONCLUSION

The PLR value was significantly lowest in the severe preeclampsia group. Evaluation of low PLR values (<104.62) in pregnant women is at risk of developing severe preeclampsia

CONFLICTS OF INTEREST

There is no conflict of interest in this research.

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