JKKI: Jurnal Kedokteran dan Kesehatan Indonesia
Indonesian Journal of Medicine and Health
Journal homepage: https://journal.uii.ac.id/JKKI
P-ISSN 2085-4145 | E-ISSN 2527-2950

Correlation between platelet indices and preeclampsia with severe features

Dzicky Rifqi Fuady*[1,3], Unggul Yudatmo[1], Muhammad Farid Ghazali[1] , Dian Rosdiana[2], Fitranto Arjadi[4]

[1]Obstetric Gynecology Department, Karawang Public Hospital, Karawang, West Java, Indonesia
[2]Clinical Pathology Department, Karawang Public Hospital, Karawang, West Java, Indonesia
[3]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[4]Faculty of Medicine, Universitas Jenderal Soedirman, Purwokerto, Central Java, Indonesia

Original Article

ARTICLE INFO

Keywords:
pre-eclampsia,
severe features,
platelet indices

***Corresponding author:**
dzicky.rifqi.fuady@gmail.com

DOI: 10.20885/JKKI.Vol15.Iss1.art6

History:
Received: April 15, 2023
Accepted: January 25, 2024
Online: April 29, 2024

Copyright @2024 Authors.

ABSTRACT

Backgrounds: Pre-eclampsia is a pregnancy-related syndrome with a 2-8% prevalence worldwide. In Indonesia, its incidence was 128,273 (5.3%) cases that caused 30-40% of maternal deaths. In 2021, at Karawang General Public Hospital, there are 43% cases of pre-eclampsia with 3% of complication. The pathophysiology is related to the inflammatory and coagulation system that includes platelets. Thus, platelet indices as indicators for platelet changes could be potential laboratory markers for pre-eclampsia.
Objective: To examine the relationship between the platelet indices and pre-eclampsia severe features at the Karawang General Public Hospital
Methods: The six months cross-sectional study was conducted at the Karawang General Public Hospital for pre-eclampsia pregnant women with at least 28 weeks of gestational age. The pre-eclampsia criteria were blood pressure higher or equal to 140/90 mmHg and qualitative proteinuria dipstick +1. The subjects were divided into two groups: pre-eclampsia with severe features and without severe features. Severe features criteria were thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, new onset headache, and visual disturbances. Pregnant women have their blood platelet indices checked in the form of platelet crit (PCT), mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR). Data were analyzed with descriptive analysis (percentage), cut-off analysis, ROC curve, AUC analysis, bivariate Chi-square analysis, and multivariate logistic regression analysis.
Results: There was a significant difference ($p < 0.05$) in the value of PCT, MPV, PDW, and P-LCR between pregnant pre-eclampsia women with severe features and pregnant pre-eclampsia women without severe features. P-LCR has the best sensitivity (52.9%) and specificity (98.9%).
Conclusions: There was a significant change in the value of the platelet indices (PCT, MPV, PDW, P-LCR) in pregnant pre-eclampsia women with severe features at the Karawang General Public Hospital.

INTRODUCTION

Pre-eclampsia is a pregnancy-related syndrome that affects all organ systems in the pregnant patient and causes 76,000 maternal deaths and 500,000 fetal deaths annually worldwide.[1,2] The prevalence in developing countries ranges from 1.8–16.7%. In Indonesia, the incidence of pre-eclampsia is 128,273 (5.3%) cases per year, which leads to 30-40% of maternal deaths.[3,4] These data show that pre-eclampsia is still a big problem in obstetrics and gynecology practice in Indonesia, including in

rural areas such as Karawang. Considering the large spectrum of problems and a high mortality rate, innovation may be needed in daily practice, which can take the form of management and diagnosis.

Early diagnosis of pre-eclampsia, especially those with severe features is needed to determine the treatment plan.[5] The method can be clinical, biopsychical, or chemical (laboratory) indicators that are highly available and affordable.[6] In rural areas, it is challenging to perform too many examinations, especially if the costs are expensive. An idea emerged that perhaps there are routinely tested laboratory examinations, but often missed or underestimated, one of which is the existence of platelet indices.[7]

The pathophysiology of pre-eclampsia was inflammation, coagulation, and hematology disturbance.[8,9] The increased inflammatory process in pre-eclampsia was accompanied by endothelial injury, vasoconstriction, and massive platelet aggregation. These will further induce coagulopathy processes. Thrombocytes are hematological components that play a role in the hemostasis and coagulopathy process.[10] Platelet examination is very simple and doable in almost all rural areas in Indonesia.[11]

Thrombocytopenia is the most common and early sign of hemostatic abnormalities and coagulopathy, including pre-eclampsia, but it hasn't always existed in all pre-eclampsia women with severe features.[12] Platelet indices are laboratory tests included in a routine complete blood count. It was markers of platelet activation that are useful in various diseases, including pre-eclampsia. The other markers such as soluble FMS–like tyrosine kinase–1 (sFlt–1),[13] soluble endoglin (sEng), placental growth factor (PIGF), and vascular endothelial growth factors (VEGF) were are relatively difficult to reach and not affordable.[14-16]

Platelet indices (PCT, MPV, PDW, and P–LCR) are part of the complete blood examination in a hematological analysis and are almost always available in every hospital but infrequently used. To our knowledge, no such studies in Indonesia, especially in Karawang, West Java. Thus, we wanted to study platelet indices in our pre-eclampsia severe features patients.

METHODS

Study design

This cross-sectional study was conducted at the Karawang Public Hospital for six months (February–July 2022).

Research subjects

The inclusion criteria are pregnant women with a gestational age of more than 28 weeks and a single living fetus. The control group (pre-eclampsia without severe feature) were pregnant women with blood pressure ≥ 140/90 mmHg, qualitative proteinuria dipstick ≥ +1 without signs of pre-eclampsia severe features. Another group (pre-eclampsia with severe features) was pregnant women with at least one of the following features: blood pressure ≥ 160/110 mmHg and qualitative proteinuria dipstick ≥ +1; thrombocytopenia < 100,000/L; impaired liver function: increase in aspartate transaminase (AST) and alanine transaminase (ALT) (twice from the normal limits); heartburn; renal insufficiency: creatinine >1.1 mg/dL (twice of the standard serum creatinine level in the absence of kidney disease); pulmonary edema: shortness of breath clinically or radiologically; new–onset frontal headache without other causes; visual disturbances without any other causes.6 The exclusion criteria were pregnant women with diabetes mellitus, chronic liver disease, chronic kidney disease, chronic hypertension, bleeding disease (leukemia, hemophilia), heart disease, and use of anticoagulants. The diagnosis of those conditions must come from the internist and or cardiologist. Incomplete data from the participants will be removed from the sample.

Data collections

Sampling was done using a consecutive technique to avoid sampling bias. Secondary data and laboratory data of subjects were taken from medical according to the arrival at the Karawang Hospital in 2022 until we met the minimal samples (65 samples per group, a total of 130 samples) according to the inclusion and exclusion criteria. The sample size was calculated using the following formula:[17]

$$n1 = n2 = \left(\frac{(\mathrm{Z}\alpha + \mathrm{Z}\beta)\mathrm{MD}}{\mathrm{X1} - \mathrm{X2}}\right)^2$$

Type I error was 5%, with a 1. 64 Zα value.

Type II error was 10%, with Zβ being 1.28. The X1 – X2 value was 4. The mean deviation (MD) was retrieved from previous Umezuluike et al. research.18 The samples were taken randomly from at least 28 weeks of gestational age without restrictions on the time between sample collection and delivery. The other collected data were the subject's age, gestational age, type of delivery, complications, AST, ALT, urea nitrogen, creatinine, and platelet count. Besides, we also analyzed parity, platelet crit, MPV, PDW, and P-LCR. Age was categorized as 35 years old as it was the cut-off for high-risk pregnancies age. The parity cut-off was twice, and the gestational age was 37 weeks (term pregnancies cut-off). Blood AST, ALT, urea nitrogen, and creatinine levels cut off was using pre-eclampsia with severe features criteria.[6] The PCT, MPV, PDW, and P-LCR cut-off was counted using the receiver operating characteristic (ROC) curve and area under the curve (AUC) value analysis. We categorized delivery modes by spontaneous, assisted delivery, and cesarean section. The pre-eclampsia complications in the participants of the studies were severe hypertension, fetal distress, partial HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and pulmonary edema.

Statistical analysis

The analysis of this study consisted of univariate, bivariate, and multivariate analyses. Bivariate analyses are using the chi-square test or Fisher's alternative test. The cut–off value of the platelet index was made based on the results of the ROC curve analysis. The AUC curve value assessed the quality and strength of the relationship between variables. Multivariate analysis was performed using a logistic regression test.

We used our own PCT, MPV, PDW, and P–LCR cut–off values based on the ROC value. There was a significant difference ($p < 0.05$) in all platelet indices between pre-eclampsia women with and without severe features. We carried out further analysis with ROC and AUC analysis.

Ethics

Ethical approval was granted by the health research ethics committee of the Universitas Jenderal Sudirman, No. 023/KEPK/PE/II/2022, February 11th, 2022.

RESULTS

Basic clinical characteristics

The total subjects were 174 patients divided into two groups that are 87 (50%) pre-eclampsia without severe features and 87 (50%) with severe features. We found an equal number of participants in pre-eclampsia with and without severe features. We also analyzed that most of the AST, ALT, blood urea nitrogen, creatinine, PCT, MPV, PDW, and P-LCR were at normal levels. Table 1 presents the baseline clinical characteristics of the subjects.

The pre-eclampsia with severe features group (n=87) has the following characteristics: severe hypertension (60%), thrombocytopenia (6%), impaired liver function (11%), impaired renal function (17%), pulmonary edema (3%), new onset headache or visual disturbances (7%), and eclampsia (20%). In this group, the number of severe features of each patient was as follows: single feature (68%), double (17%), and three features (2%).

Bivariate analysis

Table 2 presents data in numbers, percentages, p-values, and odds ratio (OR) along with the data confidence interval (95% Confidence Interval) based on the group. We can find several variables that have significant differences between preeclampsia with and without severe features group: gestational age, blood creatine levels, platelet count, PCT, MPV, PDW, and P-LCR ($p<0.05$). The variable with the highest odds ratio value is P-LCR with 96.49 (CI 95% 12.8 – 724). The odds ratio (OR) for the platelet indices was relatively large, with the smallest being PCT (3.11) and the largest being P–LCR (96.49).

ROC Curve and AUC Curve

Figure 1 presents the ROC curves. The AUC value among all platelet indices is 0.7–0.8, which means it has sufficient accuracy. Moreover, Table 3 shows that all platelet indices (PCT, MPV, PDW, and P–LCR) have similar strengths. The P–LCR has the best sensitivity and specificity (52.9% sensitivity and 98.9% specificity).

Multivariate analysis: Logistic regression

In multivariate analysis (Table 4), we found that PCT and ALT had significant values ($p < 0.05$) compared to other variables. These results

Table 1. Subjects' basic clinical characteristics

Characteristics		Number (%)
Groups	Preeclampsia with severe features	87 (50)
	Preeclampsia without severe features	87 (50)
Age	≤ 35 years	117 (76.2)
	> 35 years	57 (32.8)
Gestational age	< 37 weeks	149 (85.6)
	≥ 37 weeks	25 (14.4)
Delivery methods	Spontaneous delivery	57 (32.8)
	Assisted delivery	6 (3.4)
	Caesarean section	111 (63.8)
Complication	Severe hypertension (≥ 160/110 mmHg)	99 (56.9)
	Fetal distress	5 (2.9)
	Eclampsia	12 (6.9)
	Partial HELLP syndrome	8 (4.6)
	Pulmonary edema	3 (1.7)
Blood ast levels	Low (≤ 70 u/l)	166 (95.4)
	High (> 70 u/l)	8 (4.6)
Blood alt levels	Low (≤ 70 u/l)	168 (96.6)
	High (> 70 u/l)	6 (3.4)
Blood urea nitrogen levels	Low (≤ 100 mg/dl)	173 (99.4)
	High (> 100 mg/dl)	1 (0.6)
Blood creatinine levels	Low (≤ 1.1 mg/dl)	158 (90.8)
	High (> 1.1 mg/dl)	16 (9.2)
Platelet count (PC)	Low (≤ 100,000 /µl)	6 (3.4)
	High (> 100,000 /µl)	168 (96.6)
Platelet crit (PCT)	Low (≤ 0.295 %)	90 (51.7)
	High (> 0,295 %)	84 (48.3)
Mean platelet volume (MPV)	Low (≤ 11.25 fl)	125 (71.8)
	High (> 11.25 fl)	49 (28.2)
Platelet distribution width (PDW)	Low (≤ 13.75 fL)	124 (71.3)
	High (> 13.75 fL)	50 (28.7)
Platelet large cell ratio (P–LCR)	Low (≤ 35.95 %)	127 (73.0)
	High (> 35.95 %)	47 (27.0)

HELLP: hemolysis, elevated liver enzymes and low platelets

indicate that these two parameters have a better statistical value than the other parameters.

DISCUSSION

This study assessed the significance of platelet indices in detecting and diagnosing pre-eclampsia with severe features. We found that all these parameters had similar power. However, all platelet indices showed poor sensitivity. However, most of these platelet indices specificity values were strong, except PCT. These results indicate that the platelet indices are not good enough to detect pre-eclampsia with severe features, but the specificity values were good (> 90%). The high specificity suggests that perhaps platelet indices may be beneficial to increase the accuracy of the diagnosis in women with high suspiciousness of pre-eclampsia with severe features. Platelet indices may aid classic parameters such as AST, ALT, urea creatinine, and platelet count.

Table 2. Clinical characteristics comparison between the case and control group

Variable	Groups		p-value	OR (CI 95%)
	Preeclampsia with severe features n (%)	Preeclampsia with severe features n (%)		
Age				
≤ 35 years	53 (60.9)	64 (73.6)	0.076	0.56 (0.29–1.07)
> 35 years	34 (39.1)	23 (26.4)		
Parity				
≤ 2 times	43 (49.4)	55 (63.2)	0.067	0.57 (0.3–1.04)
> 2 times	44 (50.4)	32 (36.8)		
Gestational age				
< 37 weeks	25 (84.4)	31 (96.87)	0.023*	8.68 (1.0–75)
≥ 37 weeks	7 (15.6)	1 (3.13)		
Blood AST levels				
Low (≤ 70 U/L)	87 (100)	79 (90.8)	0.004*	-
High (> 70 U/L)	0 (0)	8 (9.2)		
Blood ALT levels				
Low (≤ 70 U/L)	87 (100)	81 (93.1)	0.013*	-
High (> 70 U/L)	0 (0)	6 (6.9)		
Blood urea nitrogen levels				
Low (≤ 100 mg/dL)	87 (100)	86 (98.9)	0.316	-
High (> 100 mg/dL)	0 (0)	1 (1.1)		
Blood creatinine levels				
Low (≤ 1.1 mg/dL)	86 (98.9)	72 (82.8)	0.001*	17.92 (2.3–138)
High (> 1.1 mg/dL)	1 (1.1)	15 (17.2)		
Platelet count (PC)				
Low (≤ 100,000 /µL)	0 (0)	6 (6.9)	0.013*	-
High (> 100,000 /µL)	87 (100)	81 (93.1)		
Platelet crit (PCT)				
Low (≤ 0.295 %)	33 (37.9)	57 (65.5)	0.001*	3.11 (1.67–5.77)
High (> 0,295 %)	54 (62.1)	30 (34.4)		
Mean platelet volume (MPV)				
Low (≤ 11.25 fL)	83 (95.4)	42 (48.3)	0.001*	22.2 (7.5–65.9)
High (> 11.25 fL)	4 (4.6)	45 (51.7)		
Platelet distribution width (PDW)				
Low (≤ 13.75 fL)	81 (93.1)	43 (49.4)	0.001*	13.8 (5.4–35)
High (> 13.75 fL)	6 (6.9)	44 (50.6)		
Platelet large cell ratio (P–LCR)				
Low (≤ 35.95 %)	86 (98.9)	41 (47.1)	0.001*	96.49 (12.8–724)
High (> 35.95 %)	1 (1.1)	46 (52.9)		

* $p < 0.05$, significant; there were several data groups that do not have p–values and 95% confidence interval because there are data in one column that has a value of zero, CI: Confidence Interval

Table 3. AUC value, sensitivity, specificity, and cut off of analysis

Variable	AUC	SD	CI 95%	Sensitivity (%)	Specificity (%)	Cut–off value	p-value
Platelet crit (PCT)	0.713	0.040	0.64–0.79	34.5	37.9	0.295 %	0.001*
Mean platelet volume (MPV)	0.744	0.038	0.69–0.82	51.7	95.4	11.25 fL	0.001*
Platelet distribution width (PDW)	0.706	0.041	0.63–0.79	50.6	93.1	13.75 fL	0.001*
Platelet large cell ratio (P–LCR)	0.735	0.039	0.66–0.81	52.9	98.9	35.95 %	0.001*

*p < 0.05, significant; AUC curve (area under the curve); SD (standard deviation), CI: confidence interval

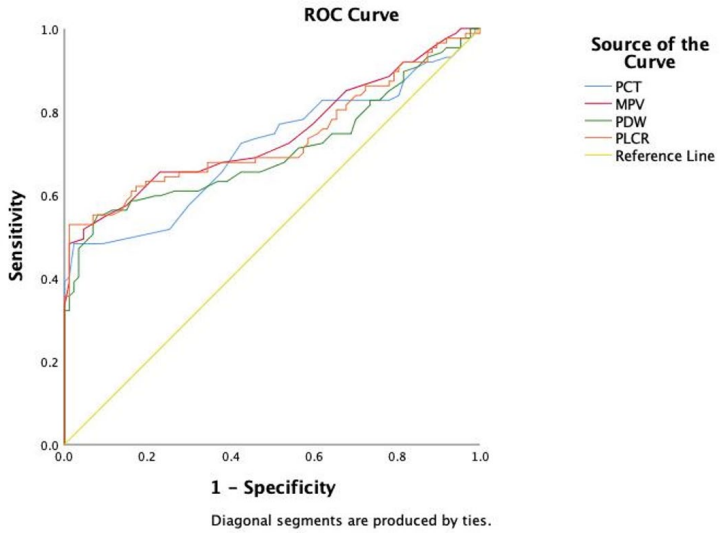

Figure 1. ROC curves of platelet crit (PCT), mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P–LCR)

Table 4. Multivariate analysis: Logistic regression of PCT, MPV, PDW and P–LCR

No	Variable	Beta value (β)	Standard Error (SE)	Wald	p-value	Adjusted OR	CI 95%
X1	PCT	-0.341	0.151	5.133	0.023*	1.003	0.529–0.955
X2	MPV	0.348	0.196	3.165	0.075	0.711	0.965–2.079
X3	PDW	0.029	0.032	0.803	0.370	1.416	0.966–1.096
X4	P–LCR	-0.030	0.029	1.042	0.307	1.029	0.916–1.028
X5	PC	0.003	0.002	2.878	0.090	0.970	1.000–1.006
X6	Creatinine	0.001	0.003	0.041	0.840	1.001	0.9951.0–06
X7	ALT	0.006	0.003	4.771	0.029*	1.006	1.001–1.011
X8	AST	0.001	0.003	0.228	0.633	1.001	0.995–1.007
	Constant	-30.329(β0)	14.487	4.383	0.036	0.000	-

* p < 0.05, significant; Beta value (β): an average amount by which the dependent variable increases when the independent variable increases one standard deviation and other independent variables are held constant; Standard error: average distance that the observed values differ from the regression line. Wald test: a test used to compare models on best fit criteria; Adjusted OR: an odds ratio that has been adjusted to account for other predictor variables in a model. Odds ratio means ratio of the odds of an event occurring in a treatment group to the odds of an event occurring in a control group; PCT: platelet crit, MPV: mean platelet volume, PDW: platelet distribution width; P-LCR: platelet large cell ratio; PC: Platelet count; AST: aspartate transaminase; ALT: alanine transaminase

Recent research found higher interest in predictive biomarkers for pre-eclampsia with severe features for several reasons, such as early diagnosis and delivery time determination. Nowadays, the best first-trimester screening for pre-eclampsia was sFlt-1 and placental growth factor with modest sensitivity and high negative predictive values. Based on pre-eclampsia's complicated pathophysiology, there is an immense effort to search for new biomarkers to improve early diagnosis and prediction of pre-eclampsia.19 However, there is a fundamental question regarding the accuracy of novel pre-eclampsia biomarkers in current worldwide guidelines for diagnosis purposes. Some concerns about the current standard diagnosis mode for pre-eclampsia, including the inability to predict pre-eclampsia in the general pregnant population and at a specific gestational age.[19]

The basis for determining new biomarkers is understanding the pathophysiology of pre-eclampsia. The origins of pre-eclampsia biomarkers are placental disorders, endothelial dysfunction, and involvement of other organs. Biomarkers originating from the placenta are called placenta-enriched molecules, including messenger RNA (mRNA), micro RNAs (miRNAs), and proteins that are valuable as biomarkers. There are differences in biomarkers specific to preeclamptic women, such as single-cell RNA originating from extravillous cytotrophoblast that can increase at 11-17 weeks of gestation and further increase at 32-34 weeks of gestation. Another example is the primate-specific chromosome 19 miRNA cluster (C19MC) found in placentas, embryonic and cancer cells. Apart from that, some studies are still trying to find potential biomarkers of pre-eclampsia originating from the placenta, for example, PIGF and the sFlt-1/PIGD ratio, and these markers have started into clinical application in several centers. Other biomarkers that begin to be studied are pregnancy-associated plasma protein A (PAPP-A) and alpha-fetoprotein (AFP). These molecules are detectable from the first trimester of pregnancy. Apart from that, growth differentiation factor 15 (GDF-15) is also starting to be widely studied. The combination of the ratios among these biomarkers posed diagnostic value, but the supporting research is still ongoing.[19]

Changes in the endothelium and endothelial dysfunction are closely related to pre-eclampsia, and there is a plausibility of biomarkers originating from this endothelium. The endothelium plays a vital role in cardiovascular function. There are at least various microRNAs associated with pre-eclampsia, namely mir-574-5p, mir-1972, and mir-4793, which increased in preeclamptic mothers compared to normotension women with a low false positive rate. Among these microRNAs, a combination of miR149 and miR363 provides high sensitivity and specificity values, 45 and 90%, respectively. The GATA2 molecule is also known to play a role in the transcription of several of these miRNA genes, and its number decreases in patients with early onset pre-eclampsia (gestational age < 34 weeks). The GATA2 levels decreased 12 weeks earlier, so it has the potential to be a biomarker for pre-eclampsia.[19]

Endothelial proteins are also known to have the potential to be biomarkers of pre-eclampsia. Nitric oxide (NO) is generally known as a messenger in the cardiovascular system, mainly as a vasodilator, leukocyte adhesion, and platelet aggregation. A known potential biomarker is asymmetric dimethylarginine (ADMA), whose levels increase at more than 20 weeks of age. Endothelin-1 (ET-1) is also an endothelial protein that acts as a vasoconstrictor secreted by the endothelium and vascular polio muscle. ET-1 levels are known to increase 2-3 times in preeclamptic compared to normotension pregnant women. There is a combination of ET-1, sFlt-1, and systolic blood pressure as a predictor of pre-eclampsia with a sensitivity of 80% and a specificity of 90% in predicting the development of pre-eclampsia. Other molecules that play a role are vascular cell adhesion molecule-1 (VCAM-1) and Endocan, whose levels increase in early-onset pre-eclampsia. In pre-eclampsia, involvement of the kidneys, liver, and brain is possible. However, research on biomarkers from these organs has not developed much and has not yet revealed potential pre-eclampsia biomarkers.[19]

Several other molecules were known to have potential as biomarkers, such as beta hCG levels, Leptin, and uric acid, which are higher in eclamptic patients compared to normotension pregnant women in the second trimester. In mothers with severe pre-eclampsia, Leptin, and uric acid levels increase significantly. However, these hormones are not usual for pre-eclampsia diagnosis, and further research on a larger

scale is still needed to support its use. A soluble endoglin, a transmembrane glycoprotein that plays a crucial role in angiogenesis and inflammation, and albumin-like glycoprotein (AFP) produced by the liver have also shown biomarker potential. However, there is no correlation between AFP and pre-eclampsia. To date, PlGF and Flt-1 are the most widely used in many places to rule out the diagnosis of pre-eclampsia when there is a suspicion of pre-eclampsia.[20]

The problem with using biomarkers is the timing of their use. Due to the multifactorial nature of pre-eclampsia pathophysiology, different onset times may result in distinctive markers. Abnormal placentation in pre-eclampsia may be a pathology in the early-onset type, and placental biomarkers may be beneficial. On the other hand, in late-onset pre-eclampsia, the pathology can originate from various organs. The initial hypothesis was that the closer to the onset of pre-eclampsia, the more significant the changes in these biomarkers. For example, soluble endoglin (sEng) increases significantly at 30-33 weeks of gestation, but there is no significant increase at gestation under 30 weeks. Additionally, the heterogeneity of patients and research methods is also one of the limitations of current pre-eclampsia biomarker research.[21]

A previous study by Reddy et al. assessed MPV and PDW of pre-eclampsia women. The MPV and PDW cut-off was 10.95 fL and 17.75, while in this study were 11.25 fL (2.7%) and 13.75 fL (22.5% difference), respectively. However, our research shows that MPV and PDW provide better performance in sensitivity and specificity.[5] These differences in cut-off, sensitivity, and specificity values indicate that perhaps different cut-off values do have sensitivity and specificity values. On the other hand, racial and genetic differences may influence the platelet index values obtained.[5] However, this research data may be the first in Indonesia, and future research on similar topics can use this research as a comparison.

Platelet crit is an indicator of the platelet volume used in the blood.[7] The pathophysiology of pre-eclampsia is increased consumption and destruction of platelets so that signs of thrombocytopenia will occur.[22] Low platelet count due to high consumption eventually reduces their relative volume in the blood compared to the other components. Platelet crit is similar to hematocrit, which decreases when the hemoglobin decreases.[7] However, previous studies showed that platelet crit differences were nonsignificant ($p > 0.05$).[23] These results indicate that platelet crit may have the potential to be a significant marker to help diagnose pre-eclampsia with severe features in the Indonesian population.[24]

Mean platelet volume is a measurement of platelet size. The MPV level elevation is associated with platelet diameter enlargement because of the accelerated platelet production and activation.[25] The platelet was ball-shaped with many pseudopodia and a higher MPV value.[7] This shape change is related to platelet activation due to inflammation and platelet consumption in pre-eclampsia. A meta-analysis showed that MPV increased in preeclamptic women compared to normotensive pregnant women.[26] Another study showed a significant MPV elevation between normotensive pregnant women, pre-eclampsia pregnant women with severe features, and those without severe features.[5] In Ethiopia, there was significant MPV elevation ($p<0.05$) between normotensive women, pre-eclampsia women with severe features, and those without, with a cut-off value of 9.45.[27] The difference in cut–off may be due to the higher number of samples in this study or the different characteristics of the respondents related to genetics, race, and lifestyle.

Platelet distribution width measured the variability of platelet size in percentage size (%). Levels of PDW directly assessed size variability, shape changes due to activation, and platelet morphological heterogeneity. The PDW elevation was due to increased production of platelets due to massive consumption of platelets and inflammation.[28] A case-control study proved that PDW increased in preeclamptic women compared to normotensive pregnant women.[23] In Ethiopia, a study concluded that there was a significant difference ($p<0.05$) in PDW levels between normotensive women, pre-eclampsia women with severe features, and those without severe features. The cut-off value used in this study was 10.85.[27] This difference in cut-off may be due to the higher number of samples in this study or the different characteristics of the respondents related to genetics, race, and lifestyle.

Platelet large cell ratio (P–LCR) is an indicator that shows the presence of platelets with a larger size (> 12 fL) in the blood circulation in percentage units. The standard P–LCR ratio was 15–35%, not

much different from the cut-off used in this study. Activation of the coagulation system elevated platelet consumption and platelet production.[29] As a result, the immature platelets released with a larger size detected P–LCR value.[27] Ethiopian study showed that there was a significant difference ($p < 0.05$) in P–LCR levels between normotensive women, pre-eclampsia women with severe features, and those without, with a cut-off value of 26.2.[27] The difference in cut-off may be due to the higher number of samples in this study or the different characteristics of the respondents related to genetics, race, and lifestyle.

However, other ratio parameters might be more beneficial for investigating the clinical use of platelet indices, for example, the PCT/MPV or the platelet count/MPV ratio. However, we decided not to continue the analysis on these ratios because the strength of each parameter (PCT, MPV, PDW, and P-LCR) was poor, with reduced significance following the calculation of all ratios. Considering that the results of this study are not very satisfactory, the classic guidelines and established parameters, such as the ACOG's guideline, should still be used so that there is international standardization of the diagnosis and management of pre-eclampsia with severe features.[30]

This study has limitations, including the cross-sectional design and limited samples with more severe feature criteria. The results of this research may not be directly applicable to daily practice, but hopefully, they can provide new insight into the benefits of platelet indices. Therefore, we suggest future studies to improve the generalizability of the results. If studied on a larger scale, platelet indices may show more real potential in obstetrics, gynecology, or other fields. A prospective longitudinal study may be helpful for further examination of platelet indices in pre-eclampsia with severe features patients. We hope that the results of this research can become an innovation for the diagnosis and early detection of pre-eclampsia with severe features in rural areas of Indonesia.

CONCLUSION

There was a significant change in the value of the platelet indices (PCT, MPV, PDW, P–LCR) in pregnant preeclampsia women with severe features at the Karawang General Public Hospital. We suggest that research on this topic be conducted on a broader scale and in deeper analysis to prove the platelet indices' role in preeclampsia with severe features detection.

CONFLICT OF INTEREST

The authors have no potential or actual conflict of interest to disclose/none of the authors disclose any future conflict of interest related to the present article. We have no relationship or sponsorship with any organization.

ACKNOWLEDGMENT

We thank Karawang General Public Hospital for its support in this research.

AUTHOR CONTRIBUTIONS

DRF: concepts or ideas, design, the definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review; UY: concepts or ideas, design, the definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review; MFG: concepts or ideas, design, manuscript editing, manuscript review; DR: concepts or ideas, design, manuscript review; FA: concepts or ideas, design, manuscript review.

Data sharing statements

The datasets used and/or analyzed during the current study are available at Mendeley Data Repository. Fuady, Dzicky Rifqi; Yudatmo, Unggul; Ghazali, Muhammad Farid; Rosdiana, Dian; Arjadi, Fitranto (2022), "Platelet Indices of Preeclampsia Pregnant Women", Mendeley Data, V3, doi: 10.17632/824ws2dmg3.3. https://data.mendeley.com/datasets/824ws2dmg3

LIST OF ABBREVIATIONS

AUC: Area under curve; HELLP: Hemolysis, elevated liver enzymes and low platelets; MPV: Mean platelet volume; OR: Odds ratio; P-LCR: Platelet large cell ratio; PCT: Platelet crit; PDW: Platelet distribution width; PIGF: Placental growth factor; ROC: Receiver operating characteristic; sFlt -1: Soluble FMS–like tyrosine kinase–1; AST: Aspartate transaminase; ALT: Alanine transaminase; VEGF: Vascular endothelial growth factors; mRNA: messenger RNA; miRNA: micro RNA; C19MC: the primate specific chromosome 19 miRNA cluster; PIGF: placental growth factor; PAPP-A: pregnancy-associated plasma protein A; AFP : Alpha fetoprotein; GDF-15: Growth Differentiation Factor 15; GATA2: GATA-binding factor 2 is a transcription factor; NO : Nitric oxide; ET-1 : Endothelin-1; VCAM-1: vascular cell adhesion molecule-1.

REFERENCES

1. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. Williams obstetrics, 25e: Mcgraw-hill New York, NY, USA; 2018. ISBN: 978-1-259-64432-0
2. Sutton AL, Harper LM, Tita AT. Hypertensive disorders in pregnancy. Obstet Gynecol Clin North Am. 2018;45(2):333-47. DOI: https://doi.org/10.1016/j.ogc.2018.01.012.
3. Legawati L, Utama NR. Analisis faktor risiko kejadian preeklampsia berat di RSUD rujukan kabupaten dan provinsi Kalimantan Tengah. JSM. 2017;3(1):19-37. DOI: https://doi.org/10.33084/jsm.v3i1.210.
4. WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia: Implications and actions. World Health Organization; 2014. DOI: https://www.who.int/publications/i/item/9789241548335.
5. Reddy SG, Prasad CSBR. Significance of platelet indices as severity marker in nonthrombocytopenic preeclampsia cases. J Lab Physicians. 2019;11(03):186-91. DOI: https://doi.org/10.4103%2FJLP.JLP_161_18.
6. ACOG. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. Obstet Gynecol. 2020;135(6):e237-e60. DOI: https://doi.org/10.1097/aog.0000000000003891
7. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: A systematic review. Biochemia Medica. 2016;26(2):178-93. DOI: https://doi.org/10.11613/bm.2016.020.
8. Youssef L, Miranda J, Blasco M, Paules C, Crovetto F, Palomo M, et al. Complement and coagulation cascades activation is the main pathophysiological pathway in early-onset severe preeclampsia revealed by maternal proteomics. Sci Rep. 2021;11(1):3048. DOI: https://doi.org/10.1038/s41598-021-82733-z.
9. Ives CW, Sinkey R, Rajapreyar I, Tita AT, Oparil S. Preeclampsia—pathophysiology and clinical presentations: JACC state-of-the-art review. J Am Coll Cardiol. 2020;76(14):1690-702. DOI: https://doi.org/10.1016/j.jacc.2020.08.014.
10. Sang Y, Roest M, de Laat B, de Groot PG, Huskens D. Interplay between platelets and coagulation. Blood Rev. 2021;46:100733. https://doi.org/10.1016/j.blre.2020.100733.
11. Pogorzelska K, Krętowska A, Krawczuk-Rybak M, Sawicka-Żukowska M. Characteristics of platelet indices and their prognostic significance in selected medical condition – A systematic review. Adv Med Sci. 2020;65(2):310-5. DOI: https://doi.org/10.1016/j.advms.2020.05.002
12. Helmo FR, Lopes AMM, Carneiro ACDM, Campos CG, Silva PB, dos Reis Monteiro MLG, et al. Angiogenic and antiangiogenic factors in preeclampsia. Pathol Res Pract. 2018;214(1):7-14. DOI: https://doi.org/10.1016/j.prp.2017.10.021.
13. Verlohren S, Brennecke SP, Galindo A, Karumanchi SA, Mirkovic LB, Schlembach D, et al. Clinical interpretation and implementation of the sFlt-1/PlGF ratio in the prediction, diagnosis and management of preeclampsia. Pregnancy Hypertens. 2022;27:42-50. DOI: https://doi.org/10.1016/j.preghy.2021.12.003.
14. Zhang L, Li X, Zhou C, You Z, Zhang J, Cao G. The diagnosis values of serum STAT4 and sEng in preeclampsia. J Clin Lab Anal. 2020;34(2):e23073. DOI: https://doi.org/10.1002/jcla.23073.
15. Vahedian-Azimi A, Karimi L, Reiner Ž, Makvandi S, Sahebkar A. Effects of statins on preeclampsia: A systematic review. Pregnancy Hypertens. 2021;23:123-30. DOI: https://doi.org/10.1016/j.preghy.2020.11.014.
16. Ukah UV, De Silva DA, Payne B, Magee LA, Hutcheon JA, Brown H, et al. Prediction of adverse maternal outcomes from pre-eclampsia and other hypertensive disorders of pregnancy: A systematic review. Pregnancy hypertens. 2018;11:115-23. DOI: https://doi.org/10.1016/j.preghy.2017.11.006.
17. Sopiyudin M. Besar sampel dan cara pengambilan sampel dalam penelitian kedokteran dan kesehatan edisi 3, penerbit Salemba Medika. Jakarta; 2010. ISBN 9786028570367.
18. Umezuluike BS, Anikwe CC, Nnachi OC, Iwe BC, Ifemelumma CC, Dimejesi IB. Correlation of platelet parameters with ad-

verse maternal and neonatal outcomes in severe preeclampsia: A case-control study. Heliyon. 2021;7(12). DOI: https://doi.org/10.1016/j.heliyon.2021.e08484.
19. MacDonald TM, Walker SP, Hannan NJ, Tong S, Kaitu'u-Lino TJ. Clinical tools and biomarkers to predict preeclampsia. EBioMedicine. 2022;75:103780. DOI: https://doi.org/10.1016/j.ebiom.2021.103780.
20. Danielli M, Thomas RC, Gillies CL, Hu J, Khunti K, Tan BK. Blood biomarkers to predict the onset of pre-eclampsia: A systematic review and meta-analysis. Heliyon. 2022;8(11):e11226. DOI: https://doi.org/10.1016/j.heliyon.2022.e11226.
21. Han L, Holland OJ, Da Silva Costa F, Perkins AV. Potential biomarkers for late-onset and term preeclampsia: A scoping review. Front Physiol. 2023;14. DOI: https://doi.org/10.3389/fphys.2023.1143543.
22. Tasleem S, Ali SI, Begum MN. A study of coagulation profile in preeclampsia compared to normal pregnancy. Natl J Physiol Phar Pharmacol. 2022;12(12):2037-41. DOI: http://dx.doi.org/10.5455/njppp.2022.12.04165202213042022.
23. Thalor N, Singh K, Pujani M, Chauhan V, Agarwal C, Ahuja R. A correlation between platelet indices and preeclampsia. Hematol Transfus Cell Ther. 2019;41(2):129-33. DOI: https://doi.org/10.1016%2Fj.htct.2018.08.008.
24. Grill S, Rusterholz C, Zanetti-Dällenbach R, Tercanli S, Holzgreve W, Hahn S, et al. Potential markers of preeclampsia-A review. Reprod Biol Endocrinol. 2009;7:70. DOI:https://doi.org/10.1186/1477-7827-7-70.
25. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): New perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm. 2019;9213074. DOI: https://doi.org/10.1155/2019/9213074.
26. Bellos I, Fitrou G, Pergialiotis V, Papantoniou N, Daskalakis G. Mean platelet volume values in preeclampsia: A systematic review and meta-analysis. Pregnancy Hypertens. 2018;13:174-80. DOI: https://doi.org/10.1016/j.preghy.2018.06.016.
27. Tesfay F, Negash M, Alemu J, Yahya M, Teklu G, Yibrah M, et al. Role of platelet parameters in early detection and prediction of severity of preeclampsia: A comparative cross-sectional study at Ayder comprehensive specialized and Mekelle general hospitals, Mekelle, Tigray, Ethiopia. PLoS ONE. 2019;14(11). DOI: https://doi.org/10.1371/journal.pone.0225536.
28. Tzur I, Barchel D, Izhakian S, Swarka M, Garach-Jehoshua O, Krutkina E, et al. Platelet distribution width: A novel prognostic marker in an internal medicine ward. J Community Hosp Intern Med Perspect. 2019;9(6):464-70. https://doi.org/10.1080/20009666.2019.1688095.
29. Bayleyegn B, Asrie F, Yalew A, Woldu B. Role of platelet indices as a potential marker for malaria severity. J Parasitol Res. 2021;2021:1-8. https://doi.org/10.1155/2021/5531091.
30. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol. 2019;133(1):1. https://doi.org/10.1097/aog.0000000000003018.