MPV, PDW, AND PCT VALUE AS PREDICTORS OF PREECLAMPSIA

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Abstract : Preeclampsia is one of the most common complications and is a major cause of maternal and perinatal death worldwide, and is estimated to occur in 2-8% of the entire population. Various hematological abnormalities can be found in preeclampsia and one of them is. Various methods are used to measure platelet function, for example, mean platelet volume (MPV), plateletcrit (PCT) and platelet distribution width (PDW). Patients with preeclampsia sometimes has normal or elevated thrombocytes, thus the evaluation of MPV, PDW and PCT can also be helpful in these cases.
Methods. This study is an analytical study, and to analyze the value the three parameters (MPV, PDW and PCT) on the incidence of preeclampsia, a Diagnostic Test will be done. As for the three difference parameters (MPV, PDW and PCT) in the preeclampsia group with normal pregnancies, a case control study will be done.
Results. The mean PCT values in pregnancies with preeclampsia were lower than normal pregnancies and found to have higher difference. The high AUC MPV and PDW values were found with each cutoff value at the level of $\geq 11.3\%$ and $\geq 13.4\%$ with very good sensitivity, specificity, positive predictive value and negative predictive value. The lowest AUC PCT value was found and the cutoff value was <0.32% with sensitivity, specificity, positive predictive value and good negative predictive value. There is a significant difference between the increase in MPV and PDW values and a decrease in PCT values with the incidence of preeclampsia.

Keywords: Preeclampsia, MPV, PCT, PDW.

Introduction

Preeclampsia is one of the most common complications of pregnancy and is a major cause of maternal and perinatal mortality worldwide, and is estimated to occur in 2-8% of all pregnancies.[1] According to WHO, nearly 830 women worldwide die every day due to complications from pregnancy or childbirth in 2015.[2]

Hematological disorders can occur in preeclampsia where thrombocytopenia is the most common, which can sometimes be so severe that it can be life threatening. Thrombocytopenia in women with preeclampsia are likely to have an increase in platelet bonds at the site of a damaged vascular endothelium which results in increased consumption and secondary platelet damage. There is platelet activation along with increased degranulation which causes a decrease in platelet life span and an increase in the number of immature platelets in peripheral blood smears.[11,13] Various indices are used to measure platelet function, for example, average platelet volume (MPV), plateletcrit (PCT) and wide platelet distribution (PDW). MPV and PDW describe the average size and variation in platelet size. PCT shows platelet volume variation considered a platelet activation marker.[11,13] PDW represents platelet morphology heterogeneity due to the presence of large platelets along with normal-sized platelets. This can be clinically related to platelet activation. Large platelets are usually more reactive than small platelets due to an increase in the number and size of pseudopodia, which causes an increase in PDW values.[10] High PDW levels are believed to reflect increased inflammation, but this mechanism is unknown. The relationship between PDW and preeclampsia is still being investigated in several studies.[13]

MPV is a parameter that provides information about platelet activation and its velocity and can be examined together with a complete blood test. MPV can increase or decrease depending on the severity of an inflammatory response. MPV also indirectly reflects platelet activity, because larger platelets present an increase in aggregation, thromboxane expression and synthesis of adhesion molecules.[11,13] Plateletcrit describes total platelet mass, analogous to hematocrit for erythrocytes. It has been suggested that platelet hemostatic ability depends not only on platelet counts but also on platelet size because large platelets are more functionally active than small platelets. Plateletcrit shows more platelet hemostatic ability than platelet count alone.[9,14] There is a need for evaluation of platelet activation markers in cases of preeclampsia because it is known that platelet-related parameters are not seriously analyzed in cases of preeclampsia which have both normal platelet and platelet counts decreased. Evaluation of the values of MPV, PDW and PCT can also help assess these cases. So far, there is still no research on MPV, PDW and PCT in preeclampsia sufferers in North Sumatra. From this, researchers are interested in comparing the values of MPV, PDW and PCT between women with preeclampsia and women with normal pregnancies. Thus a clearer picture of the benefits and effectiveness of MPV, PDW and PCT will be obtained in preeclampsia patients, so that in the future, the prognosis and the course of preeclampsia can be predicted better by the clinician.

Methods

This type of research is analytical research. To analyze the diagnostic value of the three parameters (MPV, PDW and PCT) on the incidence of preeclampsia, it will be adopted with a Diagnostic Test. Whereas to determine the differences in the three parameters (MPV, PDW and PCT) in the preeclampsia group with normal pregnancy, it will be adopted with Case Control. The study was conducted at the Obstetrics and Gynecology Department of Haji Adam Malik General Hospital, Medan. The study was conducted

from April 2019. The study population was all medical record data on pregnant women suffering from preeclampsia with a platelet value of .000 150,000 / mm3 who came to the obstetric emergency room at the H. Adam Malik General Hospital in Medan.

Results

      The following are the characteristics of the subjects based on age, parity, gestational age, infant birth weight, infant outcome, mode of delivery, and days of treatment.

Table 1. Characteristics of the subjects

Characteristics	Normal Pregnancy N = 200	Preeclampsia N = 197	P value
Age			
< 20 years old	2 (1)	6 (3)	1.000
20-35 tahun	138 (69)	135 (68.1)	
>35 years old	60 (30)	56 (28.2)	
Parity			
Primigravida	57 (28.5)	41 (20.8)	0.100
Secundigravida	57 (28.5)	75 (38.1)	
Multigravida	86 (43.0)	81 (40.6)	
Gestational age			
<34 weeks	0 (0)	7 (3.6)	0.024
34-37 weeks	90 (45)	91 (46.2)	
>37 weeks	110 (55)	99 (50.3)	
Infant weight			
<2500 gr	3 (1.5)	32 (16.2)	0.000
2500-4000 gr	197 (98.5)	165 (83.8)	
>4000 gr	0 (0)	0 (0)	
Infant outcome			
Alive	200 (100)	185 (93.9)	0.000
Exitus	0 (0)	12 (6.1)	
Cara Persalinan			
Pervaginal	45 (22.5)	36 (18.3)	0.321
SC	155 (77.5)	161 (81.7)	
Lama Rawatan			
<4 days	176 (88)	38 (19.2)	0.001
>4 days	24 (12)	156 (80.3)	

      At table 1, the frequency of pregnancy characteristics with preeclampsia and normal pregnancy is explained. From both groups of normal pregnancies, and pregnancies with preeclampsia, it was found that most of the subjects came from the age group of 20-35 years with 138 people (69%) and 135 (68.1%) with p = 1,000. Based on parity, most of the research subjects from the two groups of study subjects were from multigravida with 81 people (40.6%) in the group of preeclampsia and 86 people (43%) from the normal pregnancy group with p= 0.100. Based on gestational age, subjects with gestational age of> 37 weeks ie 110 people (55%) from the normal pregnancy group and 99 people (50.3%) from the pregnancy group with preeclampsia with p = 0.024 . Based on the birth weight most of the babies from the two study groups were born weighing 2500-4000 grams, 197 people (98.5%) from the normal pregnancy group and 165 people (83.8%) from the pregnancy group with preeclampsia with a value of p = 0.000 . Based

on the outcome of the baby, the majority of babies from both study groups were born alive with 185 infants (93.3%) in the group of pregnancies with preeclampsia and 200 infants (100%) from the normal pregnancy group. While the number of babies who died was as many as 12 people (6.1%) from the preeclampsia group and no babies died in the group with normal pregnancy. Value p = 0.000. Based on the mode of delivery, most of the babies were born with the method of cesarean section as many as 161 people (81.7) in the group of pregnancies with preeclampsia and as many as 155 people (77.5%) in the normal pregnancy group with p = 0.321. Based on length of stay, most subjects from the normal pregnancy group were treated for <4 days with 176 subjects (88%). While from the group of subjects with preeclampsia the subjects were treated> 4 days with 156 subjects (80.3%). Value p = 0.000.

Table 2. Difference between MPV, PCT dan PDW Value in Preeclampsia and Normal Pregnancy

Variabel	Preeklampsia			Kehamilan Normal			P value*
	Mean	Median	SD	Mean	Median	SD	
MPV	12.66	12.64	0.85	9.82	9.80	1.0	< 0.001
PCT	0.22	0.22	0.03	0.42	0.40	0.09	< 0.001
PDW	18.53	18.54	0.96	10.69	10.55	1.52	< 0.001

* Mann Whitney Test

Based on table 2, the average platelet index value in preeclamptic pregnancies was: MPV value of $12.15 \pm 0.85\%$, PDW value of $14.40 \pm 0.96\%$ and PCT value of $0.28 \pm 0.03\%$. Where MPV and PDW values in preeclamptic pregnancies are higher than MPV and PDW values in normal pregnancies. While the value of PCT in pregnancies with preeclampsia has a lower value compared to the value of PCT in a normal pregnancy. The platelet index value in a normal pregnancy is as follows: the MPV value is $9.82 \pm 1.00\%$, the PDW value is $10.69 \pm 1.52\%$ and the PCT value is $0.43 \pm 0.09\%$ and the Mann Whitney test shows a significant difference ($p < 0.001$).

Table 3. AUC value from ROC Method of MPV Value in Preeclampsia

Area	Std Error[a]	Asymptotic Sig[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.989	0.001	0.000	0.000	1.000

Table 3 is the output of the AUC value where there is an ROC curve which indicates that the MPV value has a very good diagnostic value because the curve is far from the 50% line and approaches 100%. The AUC value obtained from the ROC method is 0.989 with p <0.001. Statistically, the AUC value of 0.989 is classified as very strong. Where the AUC value of 0.989 means that if the platelet index value is used to diagnose preeclampsia in 100 patients, then the right results will be found in 98 people. The cut off point is between 31 - 41 which means that there is a level of ≥ 11.3% with a sensitivity value of 89.3% and a specificity value of 99%. This means that if patients with pregnancy have MPV levels kadar 11.3%, then patients can be predicted to suffer from pregnancy with preeclampsia with a sensitivity value of 89.3% and a specificity value of 99%.

Table 4. AUC Value from ROC Method of PDW Value in Preeclampsia

Area	Std Error[a]	Asymptotic Sig[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
1.000	0.000	0.000	1.000	1.000

Table 4. shows that the PDW value has a very good diagnostic value because the curve is far from the 50% line and approaches 100%. The AUC value obtained from the ROC method is 1,000 with p <0.001. Statistically, the AUC value of 1,000 is very strong. Where the AUC value of 1,000 means that if the PDW value is used to diagnose preeclampsia in 100 patients, then the right results will be found in 100 people. The cut off point fot PDW value is point between 56-67 which means that there is a level of ≥ 13.4% with a sensitivity value of 81.2% and a specificity value of 96.5%. This means that if the patient with pregnancy has a PDW level of .4 13.4%, then the patient can be predicted to suffer from pregnancy with preeclampsia with a sensitivity value of 81.2% and a specificity value of 96.5%.

Table 5. AUC Value from ROC Method of PCT Value in Preeclampsia

Area	Std Error[a]	Asymptotic Sig[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.010	0.006	0.000	0.000	0.029

Table 5 show the output of the AUC value where there is an ROC curve which shows that the PCT value has a very good diagnostic value because the curve is far below the 50% line and very far from the 100% line. The AUC value obtained from the ROC method is 0.010 with p <0.0001. Statistically, the AUC value of 0.010% is classified as not strong. Where the AUC value of 0.010% means that if the platelet index value is used to diagnose preeclampsia in 100 patients, then the right results will be found in 10 people. The cut off point of PCT is between 13-17 which means there is a level of <0.32% with a sensitivity value of 96.9% and a specificity value of 94%. This means that if patients with pregnancy have PCT levels> 0.32%, then patients can be predicted to suffer preeclampsia with a sensitivity value of 96.9% and a specificity value of 94%.

Table 6. *Positive Predictive Value* **and** *Negative Predictive Value* **of MPV as a Predictor of Preeclampsia**

	MPV Value	Preeklampsia	Kehamilan Normal
Uji Diagnostik	**≥ 11.3%**	176	2
	< 11.3%	21	198

From table 6. The values of: sensitivity 89.3%; specificity is 99%; Positive Suspect Value is 98.8%; and Negative Predictive Value is 90.4%.

Table 7. *Positive Predictive Value* **and** *Negative Predictive Value* **of PDW as a Predictor of Preeclampsia**

	Nilai PDW	Preeklampsia	Kehamilan Normal
Uji Diagnostik	**≥ 13.4%**	160	7
	< 13.4%	37	193

Table 7. shows that sensitivity is 81.2%; specificity 96.5%, positive predictive value is 95.8 %; and negative predictive value is 83.9%

Table 8. *Positive Predictive Value* **and** *Negative Predictive Value* **of PCT as a Predictor of Preeclampsia**

	Nilai PCT	Preeklampsia	Kehamilan Normal
Uji Diagnostik	< 0.32%	191	12
	>0.32%	6	188

Tabel 8 shows that sensitivity is 96.4%; specificity is 94%; positive predictive value is 94.1%; and negative predictive value is 96.9%.

Discussion

This study examined groups of normal pregnancies and pregnances with preeclampsia by assessing blood platelet index levels (MPV, PDW and PCT) using a sample of 397 people. Age has an important influence on the incidence of hypertensive disorders in pregnancy. In this study, most subjects with preeclampsia were obtained, coming from the age group of 20-35 years. This is in line with the research carried out by Thalor et al (2019) where the age of the two research subjects ranged in age from 20 to 35 years, with an average age of the pregnancy group with preeclampsia being 26 years. However, the research conducted by Onisai et al (2009) observed a higher average age compared to this study. However, the number of subjects with preeclampsia aged> 35 years was still found to be quite large, around 56 people (28.2%).

Based on parity, most subjects with preeclampsia came from the multigravida group. Nuliparity is one of the risk factors for preeclampsia that has been studied previously.[20] This study is similar to the Kortuglu et al (2016) study where the parity examined in the two study groups was multiparity. Based on gestational age, most subjects with preeclampsia had a gestational age of> 37 weeks. Kortoglu et al (2016) also found gestational age in the normal pregnancy group to be 38 weeks while for the pregnancy group with preeclampsia it was 36 weeks. Based on the birth weight of the baby, the majority of babies from the pregnancy group with preeclampsia and normal pregnancy were weighing 2500-4000 grams. However, the number of babies born with a weight of <2500 grams is more in the group of pregnancies with preeclampsia compared to the normal pregnancy group. Uzan et al (2011), stated that preeclampsia can increase the risk of low birth weight compared to the control group.[20] In this study, low birth weight was caused by the number of preterm births in the preeclampsia group. Most of the research subjects with preeclampsia in this study gave birth to cesarean secsies. It can be seen that the rate of cesarean section in the preeclampsia group is greater than for pregnancies

without preeclampsia. This can be caused by various factors such as: worsening fetal or maternal conditions, eclampsia, HELLP Syndrome, or other obstetric conditions that require permanent termination. The number of subjects who need treatment> 4 days is more common in the group with preeclampsia. The duration of treatment> 4 days can be caused by the method of cesarean section delivery which is more commonly found in the group of preeclampsia, as well as the complication conditions in preeclampsia that require intensive care, or other accompanying medical conditions.

In this study the mean MPV value was higher in pregnancies with preeclampsia compared to normal pregnancies. The mean MPV value in the pregnancy group with preeclampsia in this study was 12.15 ± 0.85% higher than the normal MPV value of the pregnancy group which was 9.82 ± 1.00%. Dakre at (2018) stated that in this study the MPV that could be used as a predictor of the incidence of preeclampsia was 9.26%. Where in this study 54% of subjects had MPV values of 10-11%. This study is also in line with the research conducted by Giles et al who obtained an MPV value of 9.9%.[30] Obtained the cutoff value in this study was ± 11.3% with significant differences found (p = <0.001). Kurtoglu et al (2016) obtained the results of the study which showed that the MPV and PDW values increased significantly and showed a difference in the preeclampsia group (p = 0.006) with the cutoff value referring to the value 8.35. This study states that the optimal cut-off point for MPV is calculated as 8.65 to distinguish between early and late onset preeclampsia cases, with a sensitivity of 63,% and specificity of 60%. An MPV of more than 8.[65] was identified as a predictor for late-onset preeclampsia. Also found positive predictive value and negative predictive value showed good results (PPV 83.9%; NPV 33.3%). [37] However, there are different research results shown in a study by Chintesun (2018) where the mean MPV value in the preeclampsia group was lower than the control group with an average value of 7.82% with variations in the MPV values obtained between (5.23 - 10.7) in the group pregnancies with preeclampsia vs. 8.85% with variations in MPV values were between 6.5 - 12.7%.[50] In this study the AUC MPV value was found to be 0.989. In the study of Nooh and Hussein (2015), ROC curve analysis of changes in MPV values at 24-28 weeks gestation was found, resulting in MPV> 9.5 as the optimal cut-off for predicting the development of preeclampsia. This cut-off level has AUC 0.940, sensitivity of 92.6% and specificity of 87.0% for predictions of the development of preeclampsia. Women with MPV> 9.5 fL at 24-28 weeks gestation are more than eight times at risk of developing preeclampsia. There is some evidence that an increase in MPV can precede the symptoms of preeclampsia by around 4.6 weeks and the increase in the odds ratio to predict preeclampsia is 2.83 times. In addition, a longitudinal study revealed that MPV gradually increases in preeclampsia compared with normotensive pregnancies, suggesting that periodic MPV monitoring can help doctors predict the incidence of preeclampsia.[43] Differences between these studies may be explained by the measurement method. Some researchers found no difference in this index value between preeclampsia and control, while others showed higher MPV and PDW in preeclampsia. It is recommended that the main reason for inconsistency between these studies is probably the method of measuring the platelet index. Measurements made in EDTA change depending on time. Also, various systems used in measurements can produce different results, and this difference can reach up to 40%.[30,43]

PDW reflects anisocytosis (difference in size) of platelets, which can occur due to increased platelet production due to inflammation in the bone marrow that produces large platelets. The mean PDW values in the group of preeclampsia in this study were 14.40 ± 0.96% higher than the PDW value of the normal pregnancy group which was 10.69 ± 1.52% and there were differences in the decline in PDW values in both groups (p = <0.001). In this study the AUC PDW value was found to be 1,000. As well as having a sensitivity value of 81.2% and specificity of 96.5% with a positive predictive value of 95.8% and a negative predictive value of 83.9%. Research by Ammar et al (2014) showed a significant increase in PDW in 100 preeclamptic women (p = <0.05). The intersection value found was 10.3% with a sensitivity value of 87.5% and a specificity of 85.3% and an average value of 10.9 ± 0.91% in preeclamptic women with a good prognosis. In this study it was also considered to include MPV values in preeclamptic women who had a poor prognosis, namely the cutoff value of 12.1%, with a sensitivity value of 92.3% and a specificity of 94.7% and an average value of 12.9 ± 0.64%. [51] Yang et al (2013) obtained PDW values that showed a significant increase above the normal range in the preeclampsia group were heavier than the increase in MPV (PDW value 14.6 compared to the normal range 9-14; MPV 11.2 value compared to the normal range of 8-12%). The study also obtained a p value at PDW of <0.001 comparing the group of normal pregnancies, mild preeclampsia and severe preeclampsia. Analysis of platelet index ROC curves in the PE group identified PDW values> 13.5fL as the optimal cutoff point to predict the incidence and severity of preeclampsia. This value has AUC of 0.74, sensitivity of 72%, specificity of 71%, positive predictive value of 70%, and negative predictive value of 71%. Also, they reported that only PDWs had a statistically significant correlation with MAP (r = 0.231, p = 0.011) and, therefore, they concluded that PDW was the best marker of preeclampsia. In addition, in women with severe preeclampsia, only the PDW value increases significantly compared to the normal range of values. Through this study, we can conclude that PDW is a suitable marker for the severity of PE.[13]

PDW values, however, increase significantly above the normal range in preeclampsia. These results reveal continuous platelet consumption during the development of preeclampsia and platelet activation which compensates for the decrease in platelet count. Therefore, PDW values can act as predictors and markers of the severity of preeclampsia before low platelet counts are examined. PDW measurements may be useful in detecting pregnancies that are at risk for preeclampsia. Both test (MPV and PDW) can be done simply, quickly and are cost effective procedures.

Plateletkrit describes a total platelet. PCT shows more platelet hemostatic ability than platelet counts alone.[9,14] PCT and MPV indicate platelet volume variation is considered a marker of platelet activation. PCT was calculated by platelet count multiplied by MPV and divided by 10,000.[50] Chintesun et al (2019) presented a study by Yücel et al (2017) which found that PCT and MPV were associated with the presence of preeclampsia by classifying patients with severe preeclampsia and mild preeclampsia. [50] The mean value of PCT in the pregnancy group with preeclampsia in this study was 0.28 ± 0.03% lower than the PCT value of the normal pregnancy group which was equal to 0.43 ± 0.09% and there was a difference in the decrease in PCT values in both groups (p = <0.001). In this study, the AUC PCT value was 0.010. And has a sensitivity value of 96.4% and a specificity of 94% with a positive predictive value of 94.1% and a negative predictive value of 96.9%. There are several studies that support this study, including the study conducted by Karateke et al (2015) which found that PCT levels were significantly lower in the preeclampsia group compared to the normal pregnancy group.[50] The study by Singh and Varma (2017) showed a difference significant decrease in PCT value (p = <0.0001) was seen in preeclampsia and eclampsia. It was found that PCT values were below normal in both groups. Where the average PCT value obtained was 0.17 ± 0.07% and the cutoff point was 0.14% with a sensitivity of 5% and specificity of 83%. In addition, a decrease in PCT was also seen in 63.9% of preeclampsia patients and 81.9% of eclampsia patients made this parameter very important to assess the severity of preeclampsia. A number of studies also show similar results. The

decrease in PCT average can be attributed to the normal low value of platelet size / or the increase in MPV in this study.[18] However, the results of the study by Chintesun et al (2015) stated that PCT values did not have a significant difference between the three studied groups (p = 0.994) where the average PCT value for the normal pregnancy group, pregnancy with mild preeclampsia and the weight of each is the same, namely 0.18.[50]

Conclusion
1. Based on age, most of the subjects of both groups came from the age group of 20-35 years.
2. Based on parity, the majority of the subjects of the two groups were from the multigravida group.
3. Based on gestational age, most of the study subjects had a gestational age of> 37 weeks.
4. Based on the birth weight of the baby, most of the babies from the two study groups were born weighing 2500-4000 grams, but more infants born weighing <2500 grams were found in the preeclampsia group.
5. Based on the outcome of the baby, the majority of the subjects of the two output groups of babies born were live infants, but there were several outbreaks of infants who died in the preeclampsia group.
6. Based on the mode of delivery, most of the two groups gave birth by cesarean section.
7. Based on the length of treatment, most subjects in the preeclampsia group were treated for> 4 days, while those in the normal pregnancy group were treated <4 days.
8. The mean MPV and PDW values in pregnancies with preeclampsia were higher than normal pregnancies and found specific meaningful differences.
9. The mean value of PCT in pregnancies with preeclampsia is lower than normal pregnancies and found specifically meaningful differences.
10. The high AUC MPV and PDW values were found with each intersection value at levels ≥ 11.3% and ≥ 13.4% with excellent sensitivity, specificity, positive predictive value and negative predictive value.
11. A low PCT AUC value was found and the cutoff value was <0.32% with sensitivity, specificity, positive predictive value and good negative predictive value.
12. There were significant differences between the increase in MPV and PDW values and a decrease in PCT values with the incidence of preeclampsia.

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