Platelet Count-to-platelet Distribution Width Ratio and other Platelet Indices as Cost-effective Markers of Preeclampsia: a case control study

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ABSTRACT

Background

Platelet indices, like platelet count (PC), plateletcrite, mean platelet volume (MPV) and platelet distribution width (PDW), and their ratios have shown to be cost-effective and better predictors of preeclampsia (PE). However, platelet count/platelet distribution width ratio was not studied.

Objective

To compare platelet indices and their ratios between pregnant women with and without predictors of preeclampsia.

Method

An analytical, comparative, case-control study. Two groups were compared; pregnant women with preeclampsia (case, n=24) and without preeclampsia (control, n=72). Multivariable linear regression analysis for hematological parameters was performed to assess the effect of gestational age. Logistic regression was performed to calculate odds ratio. Receiver operating characteristic curve was used to determine sensitivity, specificity and cutoff values. $P < 0.05$ was considered significant.

Result

There was statistically significant reduction in values of platelet count, plateletcrit, platelet count/mean platelet volume, and platelet count/platelet distribution width among the pregnant women with preeclampsia compared to control group, while significant increase was noticed in platelet distribution width and mean platelet volume. platelet count/platelet distribution width had the highest area under the curve (AUC) of 0.767, followed by platelet distribution width (AUC=0.752). At the cutoff of 15.1 ($p<0.001$) for platelet count/platelet distribution width, sensitivity was 70.8%, and specificity was 81.9%. The odds of diagnosing true positive cases of preeclampsia was 11.02 (95% CI =3.79-31.99, p=<0.001) times higher compared to values below it at this cutoff.

Conclusion

Platelet indices are economical tests that can act as indicators of risk of preeclampsia. Among these, platelet count/platelet distribution width has the highest sensitivity and specificity in the detection of preeclampsia at the cutoff of 15.1 and has emerged as better predictor of preeclampsia.

KEY WORDS

Platelet count, Platelet distribution width, Platelet indices, Preeclampsia

INTRODUCTION

Preeclampsia (PE) is defined by new-onset hypertension and proteinuria after the 20th gestational week.[1] The global burden of PE is 4.6%, while in Southeast Asia, it is 5.1%.[2] In Nepal, eclampsia is the second major cause of maternal mortality, contributing to 21% of cases.[3] Therefore, early identification and cost-effective sensitive markers are of great importance.

Simple laboratory tests, such as hematocrit, platelet indices, which include platelet count (PC), plateletcrite, mean platelet volume (MPV) and platelet distribution width (PDW), are considered better predictors of PE, which are widely available and cost effective. Plateletcrite denotes the volume occupied by platelet in blood, MPV denotes the analyzer-calculated measure of thrombocyte volume, and PDW is the indicator of volume variability in platelet size.[4] Among these, some studies have shown MPV, PDW or both to be better predictors of PE.[1,5-7] The ratio of PC to MPV also has been studied and have shown to be diagnostic.[8,9] On the other hand, there are studies, which have shown results that conflict with these findings.[10-12] However, these studies have not calculated PC/PDW, and the role of PC/PDW in PE is unaccounted for. Nevertheless, a few researchers have studied the role of the PDW/PC but in conditions other than PE.[13-15]

Thus, the objective of this study was to compare platelet indices along with various combinations of their ratios (PC/MPV and PC/PDW) between pregnant women with and without PE to determine if these parameters can be better predictors of PE.

METHODS

This is an analytical, single-center, observational, cross-sectional study conducted at the Patan Academy of Health Sciences, Nepal, extending from mid-January 2018 to mid-May 2019. The study population included pregnant women of 20 weeks gestation or more presenting in antenatal checkup (ANC) clinic, maternity wards, or pathological clinical laboratory. They were categorized into either case (with preeclampsia) or control (without preeclampsia) groups. The inclusion criteria for the control group were nonproteinuric and normotensive pregnant females with blood pressure less than 140/90 mmHg with a single fetus. For cases, the criteria were PE diagnosed, defined as systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure and urinary excretion of 300 mg protein or higher in a 24-hour urine specimen. Gestational age was calculated from the last menstrual period (LMP) and/or with the help of ultrasonography performed at the time of the first trimester. The exclusion criteria in both groups were twin pregnancy or more, known bleeding disorder, chronic hypertension, diabetes mellitus, renal disease, liver disease, and missing records.

The sample size calculation was performed using the mean difference value of PC in cases and controls. For this, an initial pilot study was conducted with the permission of the department chair in the maternity ward of the Obstetrics and Gynecology department for one month to establish the number of cases that were admitted in a month. During this study, five new cases of PE were admitted, and corresponding platelet values were noted. After this, using the case-to-control ratio of 1:3, controls were searched from the ANC clinic, and the platelet values of 15 controls were noted. From these values, the sample size was calculated through Open Epi software with a 95% confidence interval and 80% power, and a total sample size of 12 was obtained with 3 cases and 9 controls. With this observation, at six months, we had a total of 24 cases and 72 controls.

The formula used for sample size calculations is as follows:

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2 / \kappa)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_2 = \frac{(\kappa * \sigma_1^2 + \sigma_2^2)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

where,

n1 = sample size of group 1

n2 = sample size of group 2

σ1 = standard deviation of group 1

σ2 = standard deviation of group 2

Δ = difference in group means

k = ratio = n2/n1

$Z_{1-\alpha/2}$ = two-sided Z value (eg. Z = 1.96 for 95%CI)

$Z_{1-\beta}$ = power

The values obtained from 1 month of pilot study are as follows:

n1 = 5 - Group 1 (case)

n2 = 15 – Group 2 (control)

σ1 = 36.07

σ2 = 32.07

Δ = -74.67

K = 3

$Z_{1-\alpha/2}$ = 1.96

$Z_{1-\beta}$ = 80%

Patients meeting the above inclusion/exclusion criteria were informed about the research and were asked to sign the consent form (English or Nepali) if they agreed to have their blood samples used for the research purpose. A proforma sheet was used for data collection where a brief history of the patient was documented by the researcher along with other parameters mentioned in laboratory variables. The blood and urinary investigations that are included in this study are routinely performed during the ANC visit (for controls) and when the patent is admitted to an inpatient setting with a diagnosis of PE (cases). Thus, no extra sample collection was needed, and no financial burden was imposed on the patient. Some of the values were obtained from the patient file. The rest of the values of the hematological parameters, such as PDW, MPV and plateletcrite, were collected from the analyzer itself, as these values were not recorded anywhere else. These values are automatically generated in the machine while doing the PC.

For hematological tests, two milliliters of blood was collected in EDTA (ethylene diamine triacitic acid) tubes. All samples were processed within two hours of sample collection. Hematological tests included hematocrit (HCT), plateletcrite, PC, MPV, and PDW, which were estimated by a Sysmex XN-550 automated hematology analyzer. For screening of urinary protein, dipstick tests were used, and for confirmation of proteinuria, 24-hour urine samples were collected and estimated by Vitros 350.

Collected data were entered into SPSS (Statistical Package for the Social Sciences) V. 20.0 statistical analysis software for results and analysis. Continuous variables were expressed as the mean ± standard deviation (SD) or median and inter quartile range (IQR) depending on the distribution of the data. Numbers and percentages were provided for dichotomous and polychotomous variables. A normality test was performed for each of the parameters using the Shapiro–Wilk test. For normally distributed data, a parametric test (Student's t-test) was used to compare the differences in means between cases and controls, and for skewed graphs, a nonparametric test (Mann–Whitney U test) was used. Multivariable linear regression analysis for each of the hematological parameters was performed to assess the effects of gestational age. For dichotomous and polychotomous variables, p values were calculated according to the chi-square test or Fisher's exact test where appropriate. Binary logistic regression analysis was performed to calculate the odds ratio (OR) at the 95% confidence interval (CI). A receiver operating characteristic (ROC) curve was used to analyze the sensitivity and specificity of the different diagnostic tests and to find significant cutoff values to predict the presence of PE. A p value less than 5% was considered statistically significant while evaluating the area under the curve as well as for other statistical tests.

RESULTS

A total of 24 cases and 72 controls were enrolled in the study. Baseline demographic data are presented in table 1. No significant difference was observed between the majority of the baseline demographic characteristics, except for gestational age (31.4 vs 26.6 weeks; P < 0.05) and BMI (30.0 vs 24.5; P < 0.05), which were found to be significantly higher among cases as compared to the controls.

Table 1. Baseline demographic data

Parameters		Preeclampsia		P
Patient's information		Cases (n=24)	Control (n=72)	
Maternal Age (year)		28.6 ±4.6	27.1 ±4.7	0.166*
Gestational age(week)		31.4 ±3.1	26.6 ±1.8	<0.001*
BMI (kg/m²)		30.0 ±5.6	24.5 ±3.1	<0.001*
		n (%)	**n (%)**	
Gravida	Primigravida	14(58.3)	43(59.7)	0.904#
	Multigravida	10(41.7)	29(40.3)	
Education level	Below HS	9(37.5)	41(56.9)	0.099#
	HS and above	15(62.5)	31(43.1)	
Smoker	Yes	0(0)	1(1.4)	NA
	No	24(100)	71(98.6)	
Alcoholic	Yes	1(4.2)	7(9.7)	0.675!
	No	23(95.8)	65(90.3)	
Husband smoker	Yes	5(20.8)	16(22.2)	0.887#
	No	19(79.2)	56(77.8)	
Husband Alcoholic	Yes	8(33.3)	32(44.4)	0.339#
	No	16(66.7)	40(55.6)	

*Independent sample t-test
#Pearson Chi-square test
! Fisher's Exact Test
HS - Higher Secondary
NA – Not applicable as one cell has a value of zero
Values <0.05 were considered significant

As the gestational age was significantly different among cases and controls, it was adjusted in the multivariable linear regression analysis for each of the hematological parameters. The results showed no statistically significant difference between the cases and controls for platelet indices.

A comparison of hematological patterns between cases and controls indicated no significant difference in the median hematocrit value (36.8 vs 35.5; P=0.164). However, the remaining parameters were found to be significantly different between the two groups (Table 2). The results indicated that cases had a lower PC, plateletcrit, PC/MPV, and PC/PDW than controls, while PDW and MPV were higher among cases.

Table 2. Mean or median values of hematological parameters in cases and controls

Hematological Parameters	Cases (n=24)	Control (n=72)	p-value
	Mean ± SD or Median (Q1, Q3)	Mean ± SD Median (Q1, Q3)	
Hematocrit (%)	36.8(34.5,39.0)	35.7(34.2-36.8)	0.164#
PC (x103uL)	204.0±68.0	242.8±51.6	0.004*
Plateletcrit (%)	0.2±0.1	0.2±0.06	0.012*
PDW (fL)	15.1(12.3,17.3)	12.5(10.8,13.8)	<0.001#
MPV (fL)	10.8±1.6	10.1±1.2	0.021*
PC/MPV	19.5±7.6	24.5±6.6	0.002*
PC/PDW	14.4±7.0	19.9±5.7	<0.001*

PC – Platelet count
PDW – Platelet distribution width
MPV – Mean platelet volume
* Independent T test
# Mann–Whitney U test
A P value <0.05 was considered significant.

As most of the hematological parameters among cases were significantly different from those of the control group, an ROC curve was generated to determine the cutoff values and AUC for the different platelet indices and their ratios (Figures 1 and 2). Among the different parameters, PC/PDW had the highest AUC of 0.767, with a sensitivity of 70.8 and specificity of 81.9 at the cutoff value of 15.1 (Table 3).

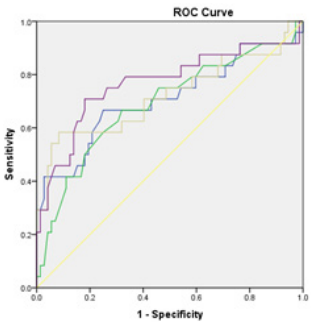

Figure 1. ROC curve of Platelet count, plateletcrite, PC/MPV and PC/PDW

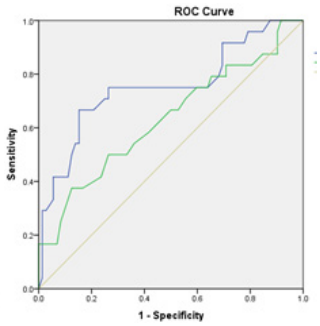

Figure 2. ROC curve of PDW and MPV

Furthermore, binary logistic regression analysis was performed to compare and determine the risk of PE diagnosis. The results indicated that the risk of having PE was 11-fold higher if the patient had a PC/PDW value less than or equal to 15.1 (OR=11.02; CI 3.79-31.99; P<0.05). Other hematologic parameters, such as PC ≤ 200.5 x 103 uL, Plateletcrite ≤ 0.215%, PDW ≥ 13.55 fL, and PC/MPV ≤ 21.86 were, all significant indicators of PE (Table 4).

DISCUSSION

PE is one of the major causes of morbidity and mortality in Nepal.[3] Early detection of the disease would help in planning proper monitoring and timely management, which is of high importance. However, there are still debates regarding appropriate screening techniques for PE.[16] Various new markers have been identified for the early detection of the diseases.[16,17] But, in a facility such as ours, all patients are not able to afford these expensive tests. Thus, simple laboratory markers can be of enormous help, and platelet indices have emerged as good predictors for PE.[5,6] In our setup, only platelet count is routinely considered for screening, and other platelet indices are ignored, which are automatically generated by the modern hematology analyzer when we run the test for PC without any financial burden to the patient.

Table 3. Sensitivity, specificity, cutoff, AUC, and level of significance of platelet indices

Parameters	Sensitivity (%)	Specificity (%)	Cutoff	AUC	95% CI AUC	Level of significance
PC (x103uL)	66.7	75	≤200.5	0.707	0.57-0.85	0.002
Plateletcrit (%)	66.7	68.1	≤0.215	0.689	0.556-0.822	0.006
PDW (fL)	75.0	73.6	≥13.55	0.752	0.627-0.877	<0.001
MPV (fL)	62.5	54.2	≥10.35	0.632	0.495-0.769	0.054
PC/MPV	70.8	59.7	≤21.86	0.720	0.580-0.859	0.001
PC/PDW	70.8	81.9	≤15.1	0.767	0.639-0.895	<0.001

PC – Platelet count
PDW – Platelet distribution width
MPV – Mean platelet volume
AUC – Area under the curve
CI: confidence interval
P < 0.05 was accepted as statistically significant.

Table 4. Logistic regression analysis of risk factors predicting preeclampsia.

Hematological Parameters	Cutoffs	Odds Ratio (95% CI)	P value
PC (x103uL)	≤200.5	6.00 (2.20, 16.35)	<0.001
	>200.5	Reference	
Plateletcrite (%)	≤0.215	4.3 (1.59-11.38)	0.004
	>0.215	Reference	
PDW (fL)	≥13.55	8.4(2.89-24.21)	<0.001
	<13.55	Reference	
MPV(fL)	≥10.35	1.9(0.76-5.08)	0.161
	<10.35	Reference	
PC/MPV	≤21.86	3.6(1.33-9.77)	0.012
	>21.86	Reference	
PC/PDW	≤15.1	11.02(3.79-31.99)	<0.001
	>15.1	Reference	

PC – Platelet count
PDW – Platelet distribution width
MPV – Mean platelet volume
P < 0.05 was accepted as statistically significant.
CI: confidence interval

Studies have shown that the values of these platelet indices may vary according to the age of gestation.[18-20] In this study, it was found that gestational age was significantly different among the case and control groups. Therefore, to minimize the bias caused by the difference in gestational age in the value of the palatelet indices, multivariate linear regression analysis for each of the hematological parameters was performed, which showed no difference.

The exact pathogenesis of PE is not known, but it has been hypothesized that due to deficient trophoblastic invasion of the maternal vascular bed, blood flow to the placenta is decreased, leading to various ischemic responses. The end result is systemic inflammation, damage to the endothelium and damage to different organs at the late stage of pregnancy.[11,20] The injured endothelium can lead to platelet accumulation, thus activating the coagulation system. The consumption of platelets at injured sites could be the reason behind the significantly low platelet count and plateletcrite among the PE cases compared to the control group in our study. As plateletcrite denotes the volume occupied by the platelet in the blood, with decreased PC, plateletcrite can also be decreased.[4] Similar findings were observed in other studies.[21,22]

Prior studies had different cutoffs, sensitivities and specificities for the hematological parameters to differentiate normotensive pregnant women from preeclamptic women, but PC/PDW was not performed in those studies.[21-23] In this study, PC/PDW was significantly decreased in PE cases compared to the control group and had the highest AUC of 0.767 (95% CI: 0.639-0.895) at the cutoff of 15.1 (sensitivity of 70.8%; specificity of 81.9%). The risk of PE was highest at this cutoff, i.e., 11-fold higher (OR= 11.02; 95% CI: 3.79-31.99; P < 0.001), thus making PC/PDW the best marker of PE.

The current study also demonstrated that MPV and PDW values were significantly higher among cases compared to the control group, which is in line with the study conducted by Eman Abdel-Moneim Alkholy et al and Shaifali Dadhich et al.[7,24] The rationale behind increased MPV and PDW could be stimulation of bone marrow for the production of new platelets due to the consumption of platelets at the injured sites. The newly produced platelets will be larger in size and more active both metabolically and enzymatically.[5,11] Moreover, some reports have shown that PDW and MPV can predict the severity of diseases. Yang et al. claimed that PDW at a cutoff of > 13.5 fL with an AUC of 0.74 (sensitivity of 72%; specificity of 71%) can predict the severity of the disease.[6] This finding is in line with the current study, where a PDW value of ≥ 13.55 fL as the optimal cutoff had an AUC of 0.752 (95% CI: 0.627-0.877) with a sensitivity of 75.05% and specificity of 73.6%. In addition, at this cutoff of ≥ 13.55 fL, pregnant women were eight times more likely to be diagnosed with PE (OR=8.4; CI: 2.89-24.21; P < 0.05). In a longitudinal study by Nooh et al. at PDW > 19.9 fL, women in gestation weeks 24-28 were 13 times at risk of developing PE, and since it positively correlated with mean arterial pressure (MAP), PDW could be the best marker for predicting the severity of hypertension.[1] Özdemirci et al., in another study, claimed that at the cutoff MPV levels of 8.65, 8.65, and 9.25 fL in the preeclamptic early-, late-, and term-birth subgroups, respectively (sensitivity of the subgroups early, late, and term were 71%, 75%, and 79%, respectively), could predict severe PE 25 and Dundar et al. stated that a rise in MPV may occur before the development of PE symptoms by approximately 4.6 weeks.[26] This can help clinicians with early diagnosis and early detection of the severity of the disease.

However, some studies have not shown any significance between PE and MPV.[10,12] One reason could be due to the different methods and/or equipment used. There are various preanalytical and analytical factors that can hinder the value of MPV.[27] Of these, a few modifiable factors, such as the venipuncture method (without stasis), adequate filling of the tube with blood, and proper mixing, were considered in this study. Additionally, MPV may increase in the presence of EDTA with increasing time. Thus, in the current study, all the samples were processed within two hours of sample collection to avoid preanalytical error.

One of the limitations of our study was that the cases were not further grouped into mild, moderate and severe categories; thus, we were unable to know if the values could predict the severity of the diseases. Another limitation is being a cross-sectional study, we are not able to understand the sequential changes in platelet indices with increasing gestational age and were unable to identifying the exact cutoff values that can be used clinically.

CONCLUSION

The present study suggests that PC, along with other platelet indices, are strong indicators of the risk of PE. In addition, from the financial perspective, it is economical, as the platelet indices are auto generated upon running the routine tests. Among all the parameters in platelet indices, PC/PDW had the highest sensitivity and specificity in the detection of PE, and at the cutoff of 15.1, the risk of PE was 11-fold higher. Thus, it is imperative that the patients are monitored carefully for the development of PE who exhibit such values and further pro spective studies would help in tracking the sequential changes in platelet indices with advancing gestational age.

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