Evaluation of platelet parameters as a marker of preeclampsia: A retrospective case-controlled study

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Abstract

Introduction: Preeclampsia (PE) is characterized by proteinuria and gestational hypertension, and is a leading global cause of maternal mortality and perinatal morbidity. This study aims to investigate the diagnostic value of platelet indices, namely platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), Platelet large cell ratio (P-LCR), platelet to lymphocyte ratio(PLR), and PC/MPV (PLM) in women with preeclampsia.

Methods: Four groups were evaluated: Case group (n=50) including Sever preeclampsia (n=23), mild preeclampsia (n=16), hellp syndrome (n=11) and healthy control group (n=50). Using the same automated blood cell count, platelet parameters were collected. Statistical analysis was conducted by analysis of the variance, t-test, and receiver operational characteristics (ROC) curve. $P \leq 0.05$ was considered significant.

Results: MPV, PDW, and RDW were significantly lower and HCT, RBC, PC, PLR, and PLM were significantly higher in the case group. Lower PLR was found in mild preeclampsia compare to severe.

Conclusion. The AUC for PC, PLR, and PLM were considered as regular. Therefore, we can suggest that the patients with cut-off values of these parameters should be carefully followed for the development of PE

Introduction

Preeclampsia (PE) is one of the main health complications of pregnancy. Preeclampsia is a multi-system disease characterized in a pre-normotensive female by new-onset hypertension and proteinuria or end-organ dysfunction after the 20th gestational week; the condition will continue for 6 weeks after delivery (Obstetricians and Gynecologists, 2013). PE involves about 3% of all pregnancy and about 5–10% of pregnancy is affected by hypertensive disorders.These women have an elevated risk of maternal and fetal mortality and significant fetal morbidity, especially when PE is severe (Hutcheon et al., 2011).

Distinguishing between mild (mPE) and severe preeclampsia (sPE) due to the intensity of symptoms is clinically essential. This condition will lead to HELLP syndrome (hemolysis, elevated liver enzyme, low platelets), eclampsia (characterized by seizures as a symptom of cerebral artery disease), or disseminated intravascular coagulation (Sibai et al., 1998, Chobanian, 2003).

Increased plasma levels of β-thromboglobulin and platelet factor-4 (Inglis et al., 1982, Konijnenberg et al., 1997) and increased expression of platelet activation markers in women with preeclampsia indicate platelet activation in this disease (Janes et al., 1995, Konijnenberg et al., 1997). The exact mechanism of PE pathogenesis and definitive preventive treatment remain unclear. A deficient trophoblastic penetration of the maternal vascular bed, restricting maternal blood supply to the placenta, is one potential pathophysiological mechanism, thereby causing a degree of ischemia (Burton et al., 2009a, Burton et al., 2009b). Angiogenic responses that induce widespread systemic and maternal endothelial dysfunction

are caused by placental under perfusion. Vascular permeability and vasoconstriction may enhance, the coagulation system may become active, and microangiopathic hemolysis may progress (Maynard and Karumanchi, 2011).The coagulation mechanism may be triggered by the interaction of platelets with the injured endothelium, enhancing the consumption and production of platelets in the bone marrow (Juan et al., 2011).

As part of the data collected from complete blood counts, platelet indices are available. They include the mean platelet volume (MPV) reflecting the function of the marrow bone, platelet distribution width (PDW) corresponding to the platelet size distribution; and Platelet large cell ratio (PLCR), representing the percentage of platelets greater than 12 fL (Lux et al., 1995, Uysal et al., 2011). In various clinical situations, elevated neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently created considerable interest as systemic indicators of inflammatory response. PLR is reported to demonstrate improved activation of platelets leading to atherosclerosis initiation and progress (Tamhane et al., 2008).

The importance of various platelet indices as predictors of preeclampsia has been previously investigated; however, findings in this regard are controversial. The purpose of this study was to investigate the diagnostic significance of platelet parameters in PE.

Material And Methods

2.1. Study design and study population:

We performed a retrospective case-control study in Imam Reza hospital, Kermanshah, Iran with the approval of our local ethics committee. The patients (n=50) consisted of 16 mPE females, 23sPE females, 11 HELLP syndrome. Healthy pregnant women (n=50) receiving antenatal treatment have been taken as controls. All infants were delivered from January 2015 to January 2020.

2.2 Ethical approval

This research was approved by the Kermanshah University of Medical Science Regional Research Ethical Committee, which deemed that formal consent was not necessary due to the retrospective nature of the study.

2.3 Data collection

In all of the cases, prior maternal medical history was standard. The gestational age was estimated using obstetric ultrasonographic data for the last menstrual cycle and/or the first trimester and validated 1 h after delivery using the new Ballard method (Ballard *et al.*, 1991). Pregnant Hypertension (blood pressure of 140/90 mmHg or higher, assessed twice at least four h apart) and consistent proteinuria (300 mg/day or more) after 20 weeks of gestation were the diagnostic criteria for mPE. Systolic blood pressure 160 mmHg, or diastolic blood pressure 110 mmHg, on two occasions greater than 4 h apart, with proteinuria (300 mg/day or more); or a protein (mg/dL)/creatinine (mg/dL) ratio 0.3 and serum creatinine 1.1 mg/

dL; or a doubling of serum creatinine level in the absence of any other renal disease were the diagnostic criteria for sPE. In addition, the severe PE category included any patient with, pulmonary edema, HELLP syndrome characterized by hemolysis, liver impairment cerebral or visual disturbance, and/or thrombocytopenia (platelet count less than 100 000/mL). Chronic hypertension, gestational diabetes, hepatic and/or cardiovascular disease, cancer, infection, and/or an inherited or acquired coagulation disorder.

2.4 Statistical analysis

The data analysis was performed using SPSS for Windows (version 20.0). Continuous variables were assessed for normality and their differences were compared between cases and controls using the Student's t-test and the Mann–Whitney U-test, where the results were normally and abnormally distributed. Diagnostic screening tests were utilized to assess the diagnostic cutoffs using the receiver operating characteristic (ROC) curve with different parameters (based on test sensitivity and specificity). $P<0.05$ was considered statistically significant.

Results

100 women comprised of four groups: severe preeclampsia (n=23), mild preeclampsia (n=16), hellp syndrome (n=11), and healthy control group (n=50). Table 1 describes the baseline characteristics of all groups. Gestational age was significantly higher in women with preeclampsia. Table 2 demonstrated that there were significant differences among case and control groups for HCT, RBC, PC, MPV, PDW, RDW, PLR, and PLM. MPV, PDW, and RDW were significantly lower and HCT, RBC, PC, PLR, and PLM were significantly higher in the case group. When the sPE and mPE were compared, lower PLR was found in mild preeclampsia compare to severe (Table 3). In addition to low PC and PLM in the Hellp syndrome group, HCT and Hb were also higher in this group than the sPE group.

AUC was calculated based on calculations of sensitivity and specificity for different variable cut-offs. The diagnostic value was also measured independently for the HCT, RBC, PC, MPV, PDW, RDW, PLR, and PLM (Table4). The best parameter is the one with the biggest AUC (Martinez *et al.*, 2003) . The AUC for PC, PLR, and PLM were considered as regular, while that one for other variables was not good (Table4, fig1).

Discussion

The identification of pregnant women with an elevated PE risk is one of the most significant priorities of obstetrics. Moreover, the concept of sensitive and specific biomarkers would not only allow for the identification of patients at risk of PE, but would also allow for close monitoring, accurate diagnosis of PE, and prompt intervention in pregnancy.

In the present study gestational age was significantly higher in women with PE, which is in line with the result of AlSheeha et.al study (AlSheeha *et al.*, 2016). In accordance with the present results, previous studies have demonstrated lower PC count, PLR, and PLM in preeclamptic women compared to the

control group (Doğan *et al.*, 2015, AlSheeha *et al.*, 2016). Some researchers showed higher values of MPV in preeclamptic women which is following our results (Trudinger, 1976, Ahmed *et al.*, 1993, Järemo *et al.*, 2000). Dogan et.al (Doğan *et al.*, 2015) also reported significantly higher MPV in women with preeclampsia than the control group which is in accordance with the result of this study.

One interesting finding is that PLM in patient groups is lower than control group. A possible explanation for this might be that increased platelet turnover due to endothelial injury reduces platelet counts, rises MPV, and (in particular) reduces the PC/MPV ratio in preeclamptic females. In accordance with the present results, previous studies have demonstrated a significantly higher level of PDW among preeclamptic women (Freitas *et al.*, 2013, Yang *et al.*, 2014, Karateke *et al.*, 2015).Our findings indicate that platelet replacement by the bone marrow is accelerated in extreme preeclamptic women, leading to platelet anisocytosis based on PDW and MPV values.(Freitas *et al.*, 2013). Another important finding is that PC and PLR in sPE are higher than mPE. This outcome is contrary to that AlSheeha et. al (AlSheeha *et al.*, 2016) who found no significant PC parameters differences in the sPE and mPe group.

We used the ROC curve to help interpret our results, which is an authoritative tool for the study of biomarker accuracy. Moreover, in logistic models, the deflection point in the ROC curve is the optimal cut-off point for the categorization of variables. The distinguishing power of the test (or the overall accuracy) can be calculated by measuring the area of the ROC curve. Medronho et al. described AUC according to diagnostic quality and this score (expressed in the terms 'Excellent, Good, Normal and Bad') is used to assess the quality of the analyzed parameters(RA *et al.*, 2009). In our research, this analysis demonstrates that PC and PLR had regular diagnostic significance. Freitas et al demonstrated that all that platelet parameters were of regular diagnostic importance, except for PCT, considered to be 'bad' for this function(Freitas *et al.*, 2013).

Conclusion

PC, PLR, and PLM appear as good candidates in this context, as they are simple and generally performed methods, with lower costs and greater accessibility in the clinical laboratory. Large-scale prospective researches from early pregnancy are required to achieve a definitive conclusion.

Declarations

Conflict of interest: None

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Tables

Table 1: Characteristics of the cases and controls

Variable	Cases (n=50)	Control (n=50)	p-value
	Mean(SD)	Mean(SD)	
Age (years)	28.16±6.91	29.92±5.86	0.1
Gestational age (weeks)	37.43±3.7	32.63±7.32	< 0.001
Parity	0.94±0.99	0.68±0.93	0.1

Table 2: Comparison of changes in hematological and platelet parameters width between healthy pregnant and preeclampsia women.

Variable	Cases (n=50)		Control (n=50)		p-value
	Mean ±SD	Median (IQR)	Mean ±SD	Median (IQR)	
HCT (%)	35.37±4.53	37.45 (37.45 -39.92)	37.74±4.23	35.75 (31.92 – 38.72)	0.01
Hb g/dl	12.20±1.81	12.6 (11.77 – 13.62)	12.6±1.64	12.35 (11.17 – 13.42)	0.4
RBC ($\times 10^6$/ µL)	4.24±1.02	4.36 (4.12 – 4.75)	4.4±0.46	4.18 (3.7 – 4.4)	0.008
WBC × 10^3/ µL	11.22±3.23	10.7 (8.85 -13.12)	11.02±3.25	10.85 (8.97 – 13.47)	0.6
PC × 10^3/µL	158.2±89.71	197 (177.5 - 229)	205.74±58.99	153.5 (92.25 – 194.5)	< 0.001
MPV fL	10.73±1.06	10.05 (9.4 – 10.1)	10.26±1.7	10.6 (10 – 11.35)	0.02
PDW fl	15.02±3.16	13.2 (12.07 – 15.27)	13.93±2.97	15 (12.8 – 16.35)	0.05
PLCR %	31.7±7.93	26.5 (21.7 – 33.1)	28.17±8.77	31.3 (26.2 – 37.7)	0.2
RDW %	14.26±1.69	13.65 (13.1 – 14.62)	14.01±1.25	13.95 (13.4 – 14.72)	0.04
neutrophil	8.36±2.90	.55 (0.41 - 074)	8.26±3.05	0.57 (0.47 – 0.80)	0.3
monocyte	0.61±0.26	7.76 (6.06 – 9.13)	0.58±0.25	7.78 (6.02 – 10.87)	0.7
lymphocyte	2.36±0.81	1.97 (1.65 – 2.78)	2.19±0.72	2.37 (1.72 – 2.88)	0.2
PLR	74.4±46.87	93.81 (75.8 – 126.26)	101.5±36.8	67.93 (38.49 – 104.42)	< 0.001
NLR	4.01±2.28	3.45 (2.71 – 4.72)	4.22±2.55	3.59 (2.6 – 4.53)	0.6
PLM	15.64±2.08	19.63 (16.03 – 23.53)	20.61±7.4	14.3 (8.05 – 18.89)	< 0.001

WBC: white blood cell; RBC; red blood cell; HCT; hematocrit; Hb: hemoglobin; PC: platelet; MPV: mean platelet volume; PDW: platelet distribution width, PLRC: Platelet large cell ratio; RDW: red blood cell distribution width; PlR: platelet to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, PLM: Pc to MPV ratio

Table 3: Comparison of hematological values in the women with mild and severe preeclampsia

Variable	HELLP (n=11)	Sever(n=23)	Mild(n=16)	P 1	P2	P3
HCT (%) Median (IQR)	31.7 (27.8 – 36.5)	36.8 (34.6 – 40.7)	35.8 (31.55 – 38.52)	0.004	0.1	0.06
Hb g/dl	9.9 (9.2 – 12.6)	12.6 (11.6 - 14)	12.7 (11.62 – 13.4)	0.006	0.5	0.2
RBC ($\times 10^6/\mu L$)	3.98 (3.29 – 4.37)	4.23 (4.05 – 4.51)	4.15 (3.66 – 4.39)	0.09	0.2	0.3
WBC $\times 10^3/\mu L$	11.1 (10 – 14.6)	11 (8.7 – 13.9)	10.5 (8.2 – 11.95)	0.7	0.4	0.3
PC $\times 10^3/\mu L$	90 (59 - 162)	166 (134 - 228)	105.5(75.75-220.25)	0.004	0.06	0.2
MPV fL	10.4 (10 – 11.9)	10.6 (10 - 12)	10.6 (9.8 – 11.6)	0.9	0.5	0.5
PDW fl	15.2 (13.2- 22.8)	14.9 (12.8 – 15.5)	15.1 (11.9 – 16.2)	0.2	0.9	0.2
PLCR %	31.5 (27.6- 39)	31.3 (25.3 – 39.3)	31.3 (24.4 – 35.4)	0.5	0.6	0.4
RDW %	14.7 (13.5 – 15.2)	14.1 (13.3 – 14.8)	13.75 (13.4 – 14.55)	0.2	0.7	0.1
neutrophil	0.63 (0.47 – 0.86)	0.54 (0.29 -0.74)	0.73 (0.51 – 0.80)	0.2	0.08	0.7
monocyte	9.8 (6.8 – 11.95)	7.96 (5.52 – 11.32)	6.99 (5.88 – 8.73)	0.2	0.3	0.02
lymphocyte	2.37 (1.42 – 2.7)	2.28 (1.7 – 2.77)	2.66 (1.83 – 3.12)	0.8	0.2	0.4
PLR	38.32(33.32 – 77.6)	84.83 (54.66 – 112.25)	58.49 (26.31 – 71.87)	0.02	0.03	0.7
NLR	3.82 (2.82 – 7.95)	3.77 (2.54 – 5.1)	3.38 (2.1 – 3.82)	0.5	0.1	0.1
PLM	6.98 (5.87 – 15.88)	14.85 (11.7- 22.4)	10 (7.96 – 21.6)	0.009	0.1	0.1

P1: comparison between hellp and sever

P2; comparison between severe and mild

P3: comparison between mild and hellp

Table 4: Diagnostic value analysis for significant different data between patients and control group.

Parameter	AUC	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-	Parameters classification according to AUC
(%)HCT	.637	36.3	62	53	54	62	1.3	0.7	Not good
($\times 10^6$/RBC µL)	.670	4.18	66	51	80	66	1.3	0.67	Not good
$\times 10^3/\mu L$PC	.702	162.500	82	55	56	82	1.8	0.33	Regular
MPV fl	.372	9.85	60	21	20.4	60	0.76	1.9	Not good
PDW fl	.399	13.55	42	38	36.7	42	0.67	1.5	Not good
RDW %	.457	13.85	48	49	48	48	0.9	1.1	Not good
PLR	.701	72.67	78	64	64.6	78	2.2	0.3	Regular
PLM	.707	15.25	84	60	61.2	84	2.1	0.27	Regular

Figures

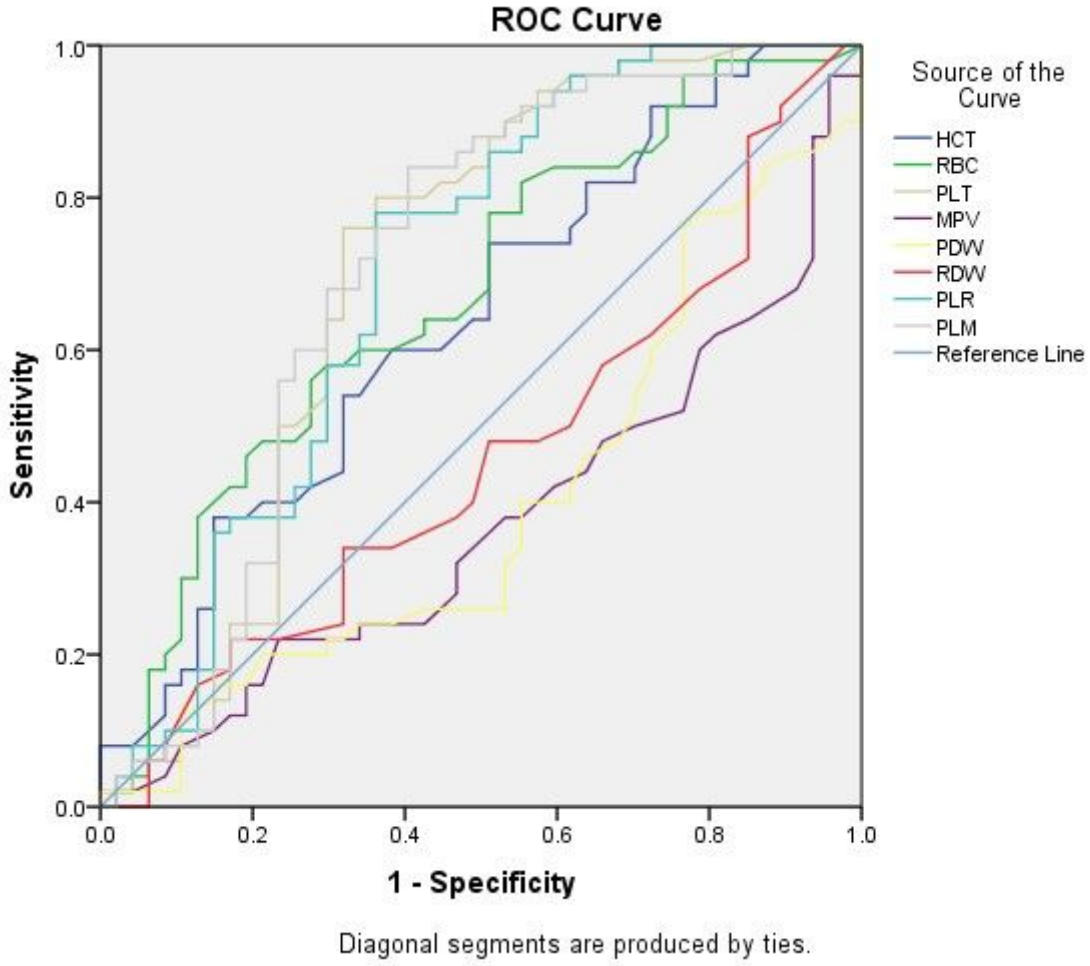

Figure 1

Receiver operating characteristic curve for predictors of cases with preeclampsia