Platelet Indices Signaling in Early and Late Onset Preeclampsia

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Abstract

Pre-eclampsia (PE) is a heterogeneous disease affecting different body systems and often associated by morbimortality. Early PE prediction could reduce this accompanied morbimortality as it will give the chance for proper surveillance and utilization of prophylactic measures. This study was a cross-sectional study done to evaluate platelet indices (PI) as potential predictors for the onset and severity of preeclampsia, and it was conducted at Department of Obstetrics and Gynecology at Mansoura University Hospital from July 2021 to June 2022, on 87 pregnant women divided into 3 groups: (Group I): Healthy normotensive (NT) pregnant females with a gestation period>20 weeks are included as control group, (Group II &III): early and late onset preeclampsia (before and after 34 weeks respectively). The results showed significant difference among the three studied groups in the context of Platelet crit (PCT). We concluded that PI have been demonstrated as potential markers for PE prediction and could act as diagnostic criteria for PE.

Keyword: Platelet Indices, Platelet Count, Mean Platelet Volume, Platelet Distribution Width, Preeclampsia.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) have been demonstrated to be accompanied by a high maternal mortality rates (1). PE is one of these disorders featured by hypertension (HTN) with a blood pressure (BP) of ≥140/90mmHg and proteinuria with ≥300mg/24h urine or ≥2+ dipstick following 20th week of gestation in women who had no previous HTN or proteinuria (2). It is classified as early-onset PE (EOPE) and late-onset PE (LOPE) when present prior to or after 34 weeks of gestation, correspondingly (3).

As a result, worse maternal-fetal outcomes could be developed among cases with earlier onset (4) due to presence of neurological adverse events more in EOPE than in LOPE. Many proposed theories about preeclampsia. First, defective trophoblast invasion dysfunction (5).

It has also been suggested that platelets (PLT) have an essential role in the PE pathogenesis when they are in an active state coming in contact with damaged ,activated endothelial wall (6).

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Based on the enzymatic and metabolic backgrounds, larger PLT are very active and have greater possibility for thrombotic complications compared to matched smaller ones. As a result, coagulative and fibrinolytic conditions have been considered as good predictors for the onset and degree of PE. Different indices are utilized to measure PLT functions, among them, platelet count (PC), platelet-crit (PCT), mean PLT volume (MPV), and PLT distribution width (PDW) (7).

They are a group of PLT parameters detected together in automated complete blood count (CBC); they are associated with PLTs' morphology and proliferation kinetics. Of note, PCT is the PLT equivalent of HCT. It is the volume of PLT expressed as a percentage of total blood volume and measured based on the formula PCT = PC × MPV/10,000 (normal value of PCT is ranging from 0.22% to 0.24%). PCT parallels the PC (8).

MPV, PLT volume is a marker of PLT functions and stimulation. It is a calculation of PLT volume expressed in femtoliter (Fl). Once there is a reduction in the production, immature PLT are triggered with pseudopod formation which ultimately ends in an increase in MPV. As a result, increased MPV could be utilized as a marker of production rate and platelet activation (9). Normal range of MPV is ranging from 7.2fL to 11.7fL. High MPV with thrombocytopenia indicates peripheral destruction.

PDW in a direct manner measures variability in PLT size, alterations with PLT stimulation, and reveals the heterogeneity in PLT shape (10). It is an indicator of PLT anisocytosis. The PDW differs significantly, with ranging from 8.3% to 56.6%. Higher PDW is associated with a higher MPV (11). So, the current study aimed to assess PLT indices as potential predictors for the onset and severity of PE.

Patients And Methods

This was a cross sectional study, included 87 pregnant women with a gestational age from 20 to 40 week. attending the antenatal clinic and /or admitted in maternity ward, in obstetrics and gynecology department at Mansoura University Hospital, from July 2021 to June 2022. The study was approved by the Institutional review Board (IRB), Code no MS.21.05.1499, Faculty of Medicine, Mansoura University.

The study included patients with age ranged from 18 to 40 years with hemoglobin ratio > 10gm/dl and with gestational age > 20 weeks. patients in group I had a blood pressure <140/90, without proteinuria and without any medical disorders, while patients in group II and III had a blood pressure >140/90, with proteinuria ≥300 mg/24 h urine or ≥2+ dipstick and without any medical disorders other than HTN. Patients younger than 18 years, platelet disorders as ITP, hemoglobin ratio < 10 g/dl, with Multifetal pregnancy, with diabetes mellitus, with chronic HTN, with infectious diseases, with premature rupture of membrane (PROM), with active labor, with polyhydramnios, with inflammatory diseases, with renal diseases, or with any manifestations of other associated medical adverse events were ruled out.

Methods

After getting a written consent form all participants, we documented their personal, obstetric, past, and surgical history. The patients were examined generally and by ultrasonography to exclude any pathology.

Procedure (sampling collection)

Blood Sample

Under aseptic conditions, blood sample collection (2ml) was done for all participants

via antecubital vein puncture by a qualified nurse in tubes with potassium EDTA as an anticoagulant; then analysis for PLT indices by the Sysmex Xe-2100 automated quantitative hematology analyzer (Sysmex Corp, Japan).

Urine sample

10 ml of midstream urine was collected in sterile tube for detection of proteinuria by urinary dipsticks.

Outcome Measure

Platelet indices (PI) (PC, MPV, PDW and platelet crit (PCT) had been measured; then comparing the results of the 3 groups (control group, early onset PE, late onset PE) together.

RESULTS

There was a significant difference among the three studied groups in the context of gestational age ($p<0.001$) and there was no significant difference regarding gravidity, parity, history of miscarriage and previous CS (p- value was >0.05) (Table I).

Table (I): Sociodemographic data among the studied groups.

		Normal control group (n.= 31)		Early onset preeclampsia (n.= 29)		Late onset preeclampsia (n.= 27)		Test value	P-value
		No.	%	No.	%	No.	%		
Age (years)	**Mean± SD**	28.52± 6.09		28.86± 6.74		29.37± 6.57		KW= 0.322	0.851
Gravidity	**Mean± SD**	3.06± 1.63		2.82± 1.91		2.70± 1.41		KW= 0.946	0.623
Parity	**Mean± SD**	1.61± 1.23		1.17± 1.26		1.37± 1.18		KW= 2.204	0.332
Gestational age (weeks)	**Mean± SD**	36.42± 3.15		31.90± 2.02		36.41± 1.05		KW= 41.65	**<0.001**
Abortion	**Nil miscarriage**	20	64.5%	22	75.9%	19	70.4%	X^2= 5.07	0.535
	Once	9	29.0%	3	10.3%	5	18.5%		
	Twice	2	6.5%	2	6.9%	2	7.4%		
	> 2	0	0.0%	2	6.9%	1	3.7%		
Previous CS	**Nil c.s**	7	22.6%	15	51.7%	10	37.0%	X^2= 6.80	0.339
	Once	10	32.3%	8	27.6%	6	22.2%		
	Twice	9	29.0%	4	13.8%	7	25.9%		
	> 2	5	16.1%	2	6.9%	4	14.8%		

There was a significant difference among the three studied groups in the context of platelet crit (PCT) ($p<0.001$) and was no significant difference among the three studied groups as regards Hb and PC, MPV and PDW (p- value was >0.05) (Table II).

Table (II): Comparison among the studied groups as regards CBC.

	Normal control group (n.= 31)		Early onset preeclampsia (n.= 29)		Late onset preeclampsia (n.= 27)		Test value	P-value
	Mean	± SD	Mean	± SD	Mean	± SD		
Hb (g/dl)	11.02	0.82	11.58	1.11	11.13	1.17	KW= 4.53	0.104
PC (×103/mm3)	239.16	59.27	212.17	98.83	214.56	80.44	KW= 4.482	0.106
MPV (µm3)	13.64	15.94	11.20	2.50	10.39	1.69	KW= 2.800	0.247
PDW (%)	12.74	2.44	13.91	2.70	13.22	2.42	KW= 3.144	0.208
PCT	0.23	0.07	0.13	0.07	0.18	0.09	F= 12.37	<0.001

There was a significant difference among the three studied groups as regards proteinuria, SBD, DBP and edema (p<0.001) (Table III).

Table (III): Comparison between the studied groups clinically.

		Normal control group (n.= 31)		**Early onset preeclampsia (n.= 29)**		**Late onset preeclampsia (n.= 27)**		**est value**	**P-valu**
		No.	%	No.	%	No.	%		
Blood pressure									
SBP (mm/ Hg)	**Mean± SD**	105.81± 9.92		152.41± 11.23		153.33± 18.40		W=56.52	**<0.001**
	Range	90.0- 130.0		140.0- 180.0		90.0- 180.0			
	Median	110.0		150.0		150.0			
DBP (mm/ Hg)	**Mean± SD**	67.74± 7.62		97.59± 5.77		98.52± 10.27		W=63.41	**<0.001**
	Range	60.0- 80.0		90.0- 110.0		90.0- 140.0			
	Median	70.0		100.0		100.0			
Protein-uria	**Nil**	31	100.0%	0	0.0%	0	0.0%	^{2}=88.15	**<0.001**
	1+	0	0.0%	2	6.9%	1	3.7%		
	2+	0	0.0%	17	58.6%	14	51.9%		
	3+	0	0.0%	4	13.8%	5	18.5%		
	4+	0	0.0%	6	20.7%	7	25.9%		
Edema	**Nil**	31	100.0%	3	10.3%	8	29.6%	^{2}=54.91	**<0.001**
	1+	0	0.0%	6	20.7%	4	14.8%		
	2+	0	0.0%	15	51.7%	12	44.4%		
	3+	0	0.0%	4	13.8%	3	11.1%		
	4+	0	0.0%	1	3.4%	0	0.0%		

Table (IV): Comparison among the studied groups as regards basic investigation.

	Normal control group (n.= 31)				Early onset preeclampsia (n.= 29)				Late onset preeclampsia (n.= 27)				Test value	P-value
	Mean ± SD	Median	Min.	Max.	Mean ± SD	Median	Min.	Max.	Mean ± SD	Median	Min.	Max.		
S. Creatinine (mg/dl)	.55± .15	0.60	0.20	0.80	0.68 ±0.17	0.70	0.30	1.00	0.67 ±.12	0.70	0.40	1.00	KW= 11.04	**0.004**
AST (U/L)	21.45 ± 4.11	21.00	15.00	31.00	29.9±11.47	25.00	16.00	56.00	26.45 ±12.54	25.00	15.00	82.00	KW= 10.35	**0.006**
ALT(U/L)	20.84± 4.20	20.00	15.00	30.00	26.44 ±12.96	21.80	11.00	65.00	24.60 ±8.82	23.00	15.20	58.00	KW = 3.77	0.152

PC can significantly determine early preeclampsia from healthy group at cut off 213 with the sensitivity (Sn), specificity (Sp), PPV and NPV was 69%, 67.7%, 68% and 68.5% respectively (p=0.016). PCT can significantly determine early preeclampsia from healthy group at cut off 0.19 with the sensitivity, Sp, PPV and NPV was 86.2%, 71%, 75% and 83.7% respectively (p< 0.001). PDW can insignificantly determine early preeclampsia from healthy group at cut off 13.1 with the sensitivity, Sp, PPV and NPV was 62.1%, 64.5%, 63.8% and 63% respectively (p=0.077). MPV can insignificantly determine early preeclampsia from healthy group at cut off 9 with the Sn, Sp, PPV and NPV was 79.3%, 35.5%, 55% and 63% respectively (p=0.090) (Table V).

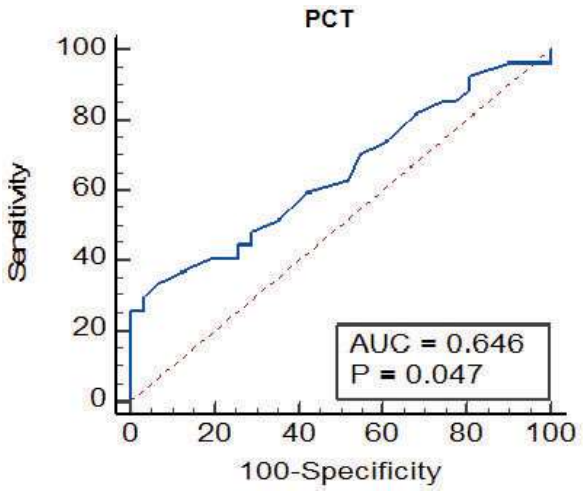

Table (V): Validity of Platelet Indices in determination of early preeclampsia from healthy group.

parameters	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV	P value
PC	≤ 213	0.674	69%	67.7%	68%	68.5%	**0.016**
PCT	≤ 0.19	0.830	86.2%	71%	75%	83.7%	**<0.001**
PDW	>13.1	0.628	62.1%	64.5%	63.8%	63%	0.077
MPV	>9.6	0.530	79.3%	35.5%	55%	63%	0.690

PC can insignificantly determine late preeclampsia from healthy group at cut off 150 with the Sn, Sp, PPV and NPV was 29.6%, 100%, 100% and 58.7% respectively (p=0.321). PCT can significantly determine late preeclampsia from healthy group at cut off 0.14 with the Sn, Sp, PPV and NPV was 33.3%, 93.5%, 83.7% and 58.5% respectively (p=0.047). PDW can insignificantly determine early preeclampsia from healthy group at cut off 11 with the Sn, Sp, PPV and NPV was 88.9%, 29%, 55.6% and 72.3% respectively (p=0.567). MPV can insignificantly determine early preeclampsia from healthy group at cut off 10 with the Sn, Sp, PPV and NPV was 66.7%, 58.1%, 61.4% and 63.6% respectively (p=0.090) (Table VI).

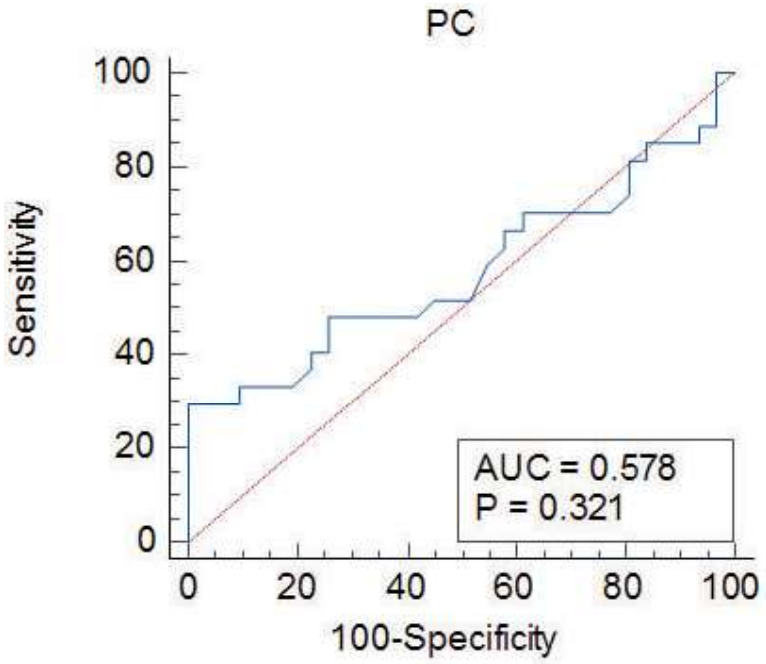

Table (VI) Validity of Platelet Indices in determination of late preeclampsia from healthy group.

parameters	Cutoff value	AUC	Sensitivity (Sn)	Specificity (Sp)	PPV	NPV	P value
PC	≤ 150	0.578	29.6%	100%	100%	58.7%	0.321
PCT	≤ 0.14	0.646	33.3%	93.5%	83.7%	58.5%	**0.047**
PDW	>11	0.544	88.9%	29%	55.6%	72.3%	0.567
MPV	≤ 10	0.590	66.7%	58.1%	61.4%	63.6%	0.233

Preeclampsia (PE) is a HDP featured by either proteinuria or end-organ dysfunction following 20th gestational week. It is due to abnormal placental vascular response, accompanied by an increase in the vascular resistance, improved PLT aggregations and stimulation of the coagulation system (12).

Platelet count (PC), PCT, MPV, and PDW are among the PI acquired from an automated CBC test. Alterations in PLT parameters have been considered as common hematologic changes in PE. In addition, such parameters are recognized as promising candidates in the context of PE pathogenesis and diagnosis (13).

In the current study, we found that there was a significant difference among the three studied groups as regards PCT ($p<0.001$) as early preeclampsia group reported significant lower platelet crit compared to healthy controls ($p<0.001$) and late preeclampsia group ($p=0.036$). There was no significant difference among the three studied groups with regard to Hb, PC, MVP and PDW (p- value was >0.05). Also, Karateke et al., reported that preeclampsia group had a significant lower platelet crit levels compared to control group ($p<0.001$)(14). Freitas et al., displayed that PCT levels were lower in severely preeclamptic cases compared to non-pregnant controls. Their study included only women with severe preeclampsia. However, we evaluated early and late onset preeclampsia (6).

On the other hand, in a study by Walle et al., PCT didn't demonstrate a significant difference among their studied groups. By using ROC-curve analysis in our study, PC can significantly determine early preeclampsia from healthy group at cut off 213 with the Sn, Sp, PPV and NPV was 69%, 67.7%, 68% and 68.5% respectively ($p=0.016$). Our results were in accordance with Walle et al., (15) as the ROC curve in the study displayed that PC had the 2nd-largest AUC (0.79), allowing it to differentiate PE cases from normotensive (NT) pregnant females at a cutoff value 176.5 × 109 /L with a Sn of 65.1%, Sp of 87.3%, and test accuracy of 76.19%.

Bawore et al., also demonstrated that there were significant differences among the NT and non-severe PE group, and severe PE groups in terms of PC and PCT that displayed significantly decreasing value with the disease severity (16).

Also, our study showed that PCT can significantly determine early preeclampsia from healthy group at cut off 0.19 with the Sn, Sp, PPV and NPV were 86.2%, 71%, 75% and 83.7% correspondingly ($p<0.001$). However, While PDW and MPV can insignificantly determine early preeclampsia from healthy group. Moreover, PCT was the only parameter that can significantly determine late preeclampsia from healthy group at cut off 0.14 with the Sn, Sp, PPV and NPV was 33.3%, 93.5%, 83.7% and 58.5% respectively ($p=0.047$). This recommends that PCT could be used as a marker for PE prediction.

Such value came in the same line with the findings of researches conducted at several studies (11, 17, 18). However, the authors of these studies didn't compare between Platelets indices as regard to early and late preeclampsia

In contrast, the ROC analysis in recent study displayed that PDW had the smallest AUC (0.68). In spite of having the shortest AUC, PDW could differentiate PE cases from NT pre. gnant females with 42.9% Sn, 93.7% Sp, and 68.2% test accuracy at a cutoff value of ≥16.75 fl (15).

According to Bawore et al., outcomes, PCT could differentiate NT pregnant females from preeclamptic pregnant ones, at a cutoff value of 0.1915% with a Sn of 68.3% and Sp of 69.2% has an AUC of 0.776 ($p=0.001$). Hence, it is considered as a good predictor of PE (16).

CONCLUSION

The current study demonstrated that; PI are potential candidate markers for PE prediction. PCT could act as diagnostic criteria for PE. Our results showed that PCT is the best parameter for predicting both Early and Late PE. In addition, PI could be used more extensively as they are a simple, effortless and cost-effective tool.

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