

Study of Some Hematological Markers of Systemic Inflammatory Response in Preeclampsia

Abstract

Background: Preeclampsia is one of the major health problems during pregnancy, which is characterized by hypertension, proteinuria, and features of multi-organ disease, and it complicates about 2 to 8% of pregnancies with increased maternal and neonatal morbidity and mortality, aim of this study was to evaluate the following blood markers in preeclampsia; neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, red cell distribution width, mean platelet volume and platelet value. **Subjects and methods:** This was diagnostic research, observational method and cross-sectional design that was conducted at Obstetrics and Gynecology Department, Tanta University Hospitals, from 1-7-2020 to 1-11-2021. After fulfilling the Research and Ethics Committee guidelines, pregnant women were counseled to be enrolled in this study. **Results:** There was significant decrease in PLR in severe preeclampsia group compared to control group ($P<0.001$) as well as mild preeclampsia group ($P<0.001$); while there was no statistically significant difference between control group and mild preeclampsia group ($P>0.05$). There was significant elevation in RDW in severe preeclampsia group compared to control group ($P=0.005$) as well as mild preeclampsia group ($P<0.001$); There was significant reduction in MPV in severe preeclampsia group compared to mild preeclampsia group ($P<0.001$) as well as control group ($P<0.001$); while there was no statistically significant difference between mild preeclampsia group and control group ($P>0.05$). There was significant decrease in PCT in severe preeclampsia group compared to control group ($P=0.034$) as well as mild preeclampsia group ($P=0.009$); while there was no statistically significant difference between control group and mild preeclampsia group ($P>0.05$).

Conclusion In differentiation of preeclampsia, the highest sensitivity was achieved with MPV, while the highest specificity was achieved with PLR. In the differentiation of severe preeclamptic cases, the highest sensitivity was achieved with lymphocytes and MPV, while the highest specificity was achieved with PLR.

Keywords: preeclampsia, markers, systemic inflammatory response.

Introduction:

Hypertensive disorders are among the most common problem encountered during pregnancy. They affect 5-10% of all the pregnancies. They are the leading cause of maternal morbidity and mortality. (1) 16 percent of maternal deaths were attributed to hypertensive disorders. Hypertensive disorders in pregnancy are classified into chronic hypertension, pre-eclampsia, eclampsia, superimposed pre-eclampsia – eclampsia and gestational hypertension. (2)

Pre-eclampsia: Hypertension that occurs after 20 weeks of gestation in a woman with previously normal blood pressure together with proteinuria. Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least 6 hours apart. (3) Proteinuria, defined as urinary excretion of 0.3 g protein or higher in a 24-hour urine specimen. This finding usually correlates with a finding of 1+ or greater on dipstick. (4)

Preeclampsia is one of the major health problems during pregnancy, which is characterized by hypertension, proteinuria, and features of multi-organ disease, and it

complicates about 2 to 8% of pregnancies with increased maternal and neonatal morbidity and mortality. (5) The onset and progression of preeclampsia are unpredictable and the exact etiology remains unknown. (6) However, certain factors have been attributed to it, which include deficient trophoblastic invasion of the maternal vascular bed with subsequent reduction of the placental blood flow. (7) Placental under-perfusion initiates widespread systemic maternal endothelial dysfunction and increased vascular permeability. (8)

This systemic inflammatory response can be measured by using a variety of biochemical and hematological markers. Recent findings indicate that measuring blood cell subtypes ratio; such as the neutrophil to lymphocyte and platelet to lymphocyte, ratios might provide a prognostic and diagnostic clue to the chronic low-grade inflammation. (9) Platelet indices include mean platelet volume (MPV) and plateletcrit (PCT) are other examples of non-invasive biomarkers that can be tested. (10)

Patients and Methods

This was diagnostic research, observational method and cross-sectional design study that was conducted at Obstetrics and Gynecology Department, Tanta University Hospitals, from 1-7-2020 to 1-11-2021. After fulfilling the Research and Ethics Committee guidelines, pregnant women were counselled to be enrolled in this study.

One hundred pregnant women were included in this study. Cases were classified as: Group A: 20 cases as control group (normal pregnancy), Group B: 40 cases having mild preeclampsia and Group C: 40 cases having preeclampsia of severe features.

Inclusion criteria: Maternal age from 18 - 35 years old, singleton pregnancy and gestational age from 28 weeks until 37 weeks.

Exclusion criteria: Chronic systemic disease during pregnancy (chronic hypertension, diabetes mellitus, systemic lupus erythematosus, renal dysfunction, hepatic dysfunction and hematological disorders), local or systemic infection, chorioamnionitis and any medication such as corticosteroids or other categories related to inflammatory condition.

Diagnosis of preeclampsia is based on ACOG criteria (11): Blood pressure ≥ 140 mmHg systolic or 90 mmHg diastolic on two occasions at least 4 h apart after 20 weeks of gestation with a previously normal blood pressure. Proteinuria (Protein/creatinine ratio ≥ 0.3 or dipstick reading of 1+), in the absence of proteinuria, new-onset hypertension with the new onset of any of the following: Thrombocytopenia (Platelet count $\leq 100,000$ /microliter), renal insufficiency (Serum creatinine ≥ 1.1 mg/dl), and elevated levels of liver transaminases to twice normal concentration, pulmonary edema, cerebral or visual symptoms.

Diagnosis of severe preeclampsia if the patient had one or more of the following criteria (18): Blood pressure or blood pressure ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic, thrombocytopenia, renal insufficiency, elevated liver transaminases, pulmonary edema, cerebral and visual symptoms.

Methods: All patients in this study were subjected to

1) History taking: Personal history:-include name, age, marital status, parity, address, occupation and special habits Complaint: was taken in patients' own words; however, normal cases as well as mild preeclampsia may have no complaint, other than coming for routine antenatal care. Present history:-analysis of the complaint and patient was asked for other complaints related to preeclampsia such as headache, blurring of vision, epigastria pain, edema and fits. Obstetric history: include details of every delivery and abortion. Menstrual history: include age of menarche, length of the cycle, duration, amount and the first day of the last menstrual period. Past history:-

patients was asked for the presence of medical disease especially chronic hypertension, diabetes mellitus, systemic lupus erythematosus, renal dysfunction, hepatic dysfunction, hematological disorders, local or systemic infection and chorioamnionitis. Cases were asked also for past surgical interference and any taken medications.

2) Clinical examination: General examination: This was done to assess the vitals including the pulse, blood pressure, temperature and respiratory rate. General look and body areas were examined including face, neck, chest, back and limbs.

BP measurement (12): The patient was placed in a comfortable chair in the sitting position, feet flat on the floor, body relaxed and his arm was supported on a side desk or table. We used Mercury sphygmomanometer with appropriate cuff size (at least 1.5 times the circumference of the arm) and bladder (located inside the cuff) should at least be 80 percent of the circumference of the arm. The cuff was placed on the patient's arm with the center of the bladder 2 to 3 cm above the artery to prevent the stethoscope from touching the cuff. The cuff was inflated while palpating the radial artery until pulsations was no longer felt and the pressure reading was noted. The stethoscope was placed over the brachial artery; the cuff was inflated 30mmHg higher than the pressure at which radial pulsations become absent. Then, the cuff was deflated at no more than 2 to 3 mmHg per second and the pressure was read to the nearest 2 mmHg. The first Korotkoff sound and the fifth was noted for systolic and diastolic pressures. The process was repeated in the opposite arm. The highest pressure is recorded and used.

3) Investigation: Complete blood picture with the systemic inflammatory response markers: Samples for complete blood count with differentials including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), red cell distribution width, (RDW), mean platelet volume (MPV), plateletcrit value (PCT) were obtained at the admission of the patients to the department, before the initiation of any medical treatment. Other routine investigations in preeclampsia: Prothrombin time, partial thromboplastin time and international normalized ratio, Liver functions including SGOT and SGPT, Renal functions including urea and creatinine, urine analysis for presence of albumin and routine ultrasound for assessment of fetal growth, and amniotic fluid.

Ethical Consideration: An informed consent was obtained from women after adequate provision of information regarding the study requirements, purpose and risks. There was adequate provision to maintain privacy of participants and confidentiality of the data. The study was approved by the Ethics Committee of the Faculty of Medicine, Tanta University.

Statistical Methods: The collected data will be, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016. Descriptive statistics were done for numerical data as mean \pm SD (standard deviation), median and range; while they were done for categorical data as number and percentage.

Results

There was no statistically significant difference between the studied groups regarding age (p-value >0.05). **Table (1)**

Regarding neutrophils/lymphocytes ratio (NLR), there was significant decrease in NLR in severe preeclampsia group compared to control group ($P < 0.001$) as well as mild preeclampsia group ($P < 0.001$); while there was no statistically significant difference between control group and mild preeclampsia group ($P > 0.05$). Regarding platelets/lymphocytes ratio (PLR), there was significant decrease in PLR in severe

preeclampsia group compared to control group ($P < 0.001$) as well as mild preeclampsia group ($P < 0.001$); while there was no statistically significant difference between control group and mild preeclampsia group ($P > 0.05$). Regarding plateletcrit (PCT), there was significant decrease in PCT in severe preeclampsia group compared to control group ($P = 0.034$) as well as mild preeclampsia group ($P = 0.009$); while there was no statistically significant difference between control group and mild preeclampsia group ($P > 0.05$). **Table (2)**

It was done for all markers. The AUC was significant in only five (5) markers, which are lymphocytes, NLR, PLR, MPV and PCT. The highest significant sensitivity found between markers was MPV that had sensitivity of 66.2% ($p < 0.001$) while the highest significant specificity found between markers was lymphocytes and PLR that had specificity of 100% ($p < 0.001$ & 0.001 respectively). **Table (3)**

The ROC curve allowed us to detect three cutoff values for each blood parameter. The different cutoffs were one with the highest sensitivity (a screening level), one with the highest specificity (a diagnostic level), and one with a balanced sensitivity and specificity. **Table (4)**

It was done for all markers. The AUC was significant in only seven (7) markers, which are lymphocytes, neutrophils, NLR, RDW, PLR, MPV and PCT. The highest significant sensitivity was found in lymphocyte and MPV (sensitivity of 100%) ($p < 0.001$) while the highest significant specificity found between markers was lymphocytes and PLR that had specificity of 90% and 87.5% ($p < 0.001$ & 0.001 respectively). **Table (5)**

Table 1: Age distribution among the studied groups

Groups Age (years)	Group A (Control group) (n=20)	Group B (mild PE group) (n=40)	Group C (Severe PE group) (n=40)	Test	P-value*
Mean± SD	26.43±5.04	25.92± 5.07	27.05± 4.75	0.676	0.713
Median	26.5	27.0	27.0 0.676		
Range	18- 35 years	18- 35 years	18- 35 years		

Table 2: Comparison between the study groups regarding laboratory investigations

	Group A (Control group) (n=20)		Group B (Mild PE group) (n=40)		Group C (Severe PE group) (n=40)		Test -value	P value*
	Mean (±SD)	Median	Mean (±SD)	Median	Mean (±SD)	Median		
Hemoglobin	12.43 (2.36)	12.00	11.90 (2.2)	12.00	13.23 (2.22)	13.00	KW= 4.80	0.091
Lymphocyte	2.33 (.75)	2.32	2.39 (.79)	2.57	5.02 (1.48)	5.40	KW= 45.73	<0.001 P1-2 =0.831 P1-3<0.001 P2-3<0.001
Neutrophils	9.71 (4.39)	9.24	11.46 (4.73)	12.59	12.53 (5.33)	13.48	KW= 5.49	0.064

Platelets	280.33 (106.9)	291.0	256 (91.85)	253.50	222.7 (65.18)	239.50	KW= 6.83	0.033 P1-2= 0.184 P1-3=0.009 P2-3 =0.428
NLR	4.75 (3.25)	3.87	5.68 (3.75)	4.25	2.48 (1.52)	2.50	KW= 19.08	<0.001 P1-2 =0.552 P1-3<0.001 P2-3<0.001
PLR	138.46 (83.15)	112.9	118.94 (66.35)	113.57	55.39 (42.1)	45.75	KW= 43.25	<0.001 P1-2 =0.796 P1-3<0.001 P2-3<0.001
PDW	18.05 (.85)	18.00	17.91 (.94)	17.80	18.02 (1.61)	18.00	KW= 0.669	0.716
PDW	18.05 (.85)	18.00	17.91 (.94)	17.80	18.02 (1.61)	18.00	KW= 0.669	0.716
RDW	16.42 (2.43)	17.00	17 (4.21)	16.50	20.50 (4.86)	19.00	KW= 15.57	<0.001 P1-2 =0.861 P1-3=0.005 P2-3<0.001
MPV	9.13 (1.93)	8.60	6.81 (1.04)	6.65	5.81 (2.91)	5.70	KW= 25.26	<0.001 P1-2=0.096 P1-3<0.001 P2-3 <0.001
PCT	.24 (.08)	.26	.22 (.07)	.22	.18 (.07)	.18	KW= 8.23	0.016 P1-2=0.372 P1-3=0.034 P2-3 =0.009

Table 3: Validity of blood markers in Preeclampsia detection, as shown by the area under curve (AUC), Sensitivity, specificity and predictive values

	AUC	Cut Point	off	p- value	Sensitivity	Specificity	PPV	NPV
Hemoglobin	0.613	>14		0.097	36.2%	85.0%	70.7%	57.1%
Lymphocyte	0.686	>3.43		<0.001	48.7%	100%	100%	66.1%
Neutrophils	0.519	≤9.4		0.789	46.2%	70.0%	60.6%	56.5%
Platelets	0.521	≤300		0.773	73.7%	45.0%	57.3%	63.0%
NLR	0.668	≤3.52		0.014	63.7%	75.0%	71.8%	67.4%
PLR	0.678	≤58.14		0.001	47.5%	100.0%	100%	65.5%
PDW	0.534	>17.8		0.641	62.5%	55.0%	58.0%	59.5%
RDW	0.605	>14.0		0.155	83.7%	35.0%	56.3%	68.2%
MPV	0.844	≤7.0		<0.001	66.2%	95.0%	93.0%	73.8%
PCT	0.640	≤0.2		0.047	52.5%	75%	67.7%	61.2%

Table 4: Validity of blood markers in differentiating mild and severe Preeclampsia as shown by the AUC, Sensitivity, specificity and predictive values

	AUC	Cut	off	Sensitivity	Specificity	PPV	NPV	p- value
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		Point					
Hemoglobin	0.596	>12	60%	65.0%	63.16%	61.9%	0.137
Lymphocyte	0.900	>3.54	100%	90%	91%	100%	<0.001
Neutrophils	0.644	≤12.56	77.5%	57.5%	64.6%	71.9%	0.021
Platelets	0.521	≤300	73.7%	45.0%	57.3%	63.0%	0.773
NLR	0.750	≤3.42	65.0%	85.0%	81.0%	71.0%	<0.001
PLR	0.879	≤60.78	90%	87.5%	87.8%	89.7%	<0.001
PDW	0.539	>16.0	100%	20.0%	55.6%	100%	0.555
RDW	0.742	>18.0	80.0%	62.5%	68.0%	75.8%	<0.001
MPV	0.645	≤5.0	100.0%	37.5%	61.5%	100%	0.031
PCT	0.642	≤0.13	40.0%	85.0%	72.7%	58.6%	0.022

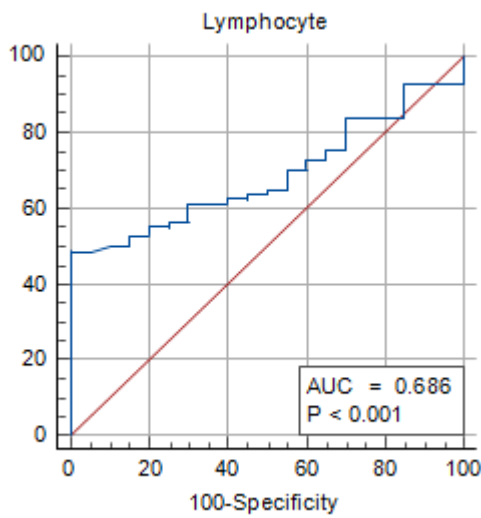


Figure (1): ROC curve of lymphocyte

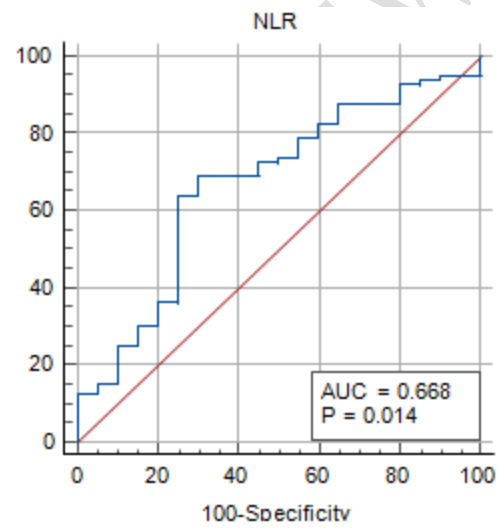


Figure (2): ROC curve of NLR

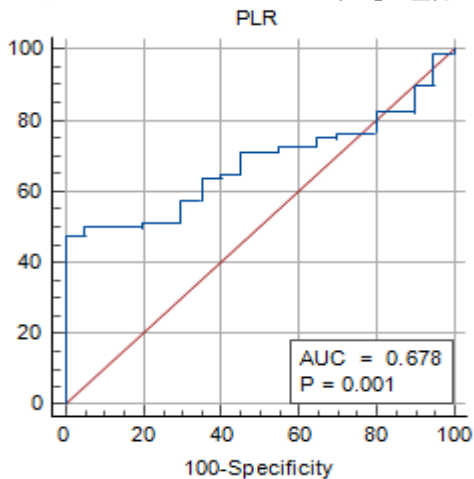


Figure (3): ROC curve of PLR

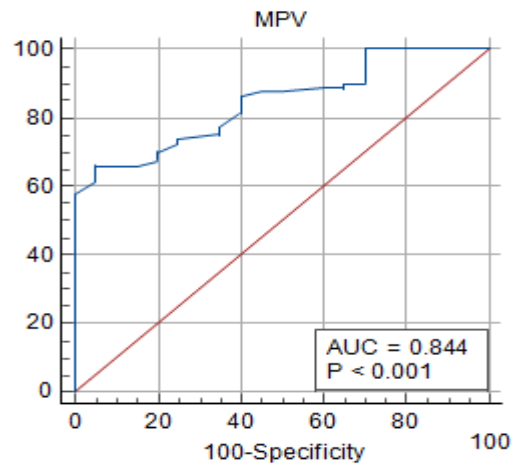


Figure (4): ROC curve of MPV

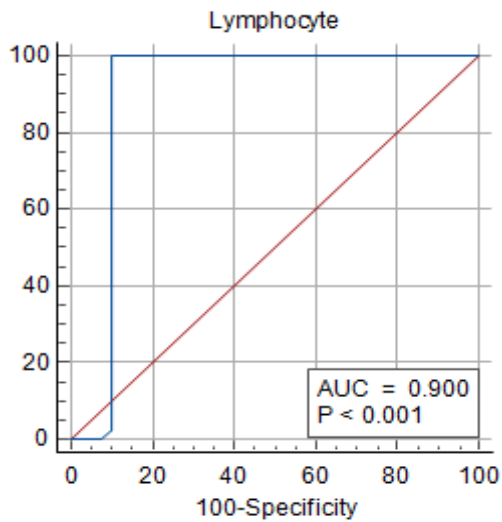


Figure (5): ROC curve of lymphocyte

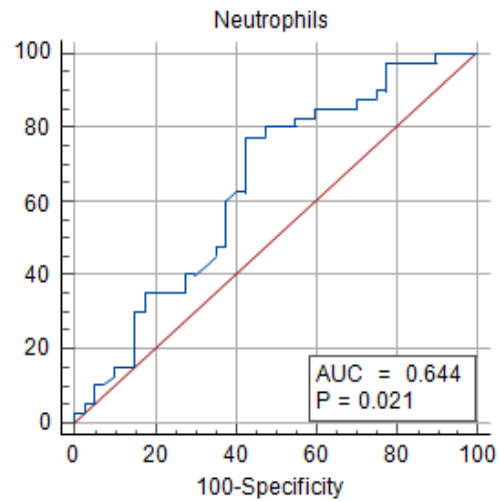


Figure (6): ROC curve of neutrophils

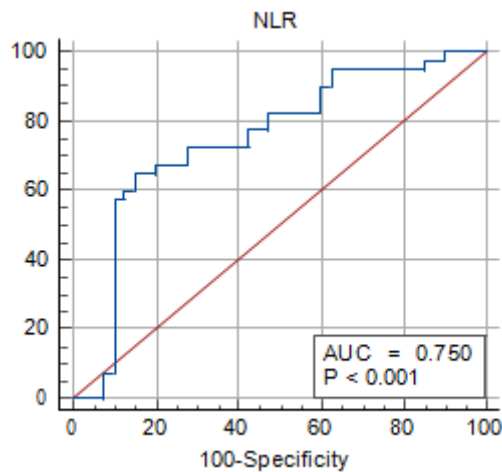


Figure (7): ROC curve of NLR

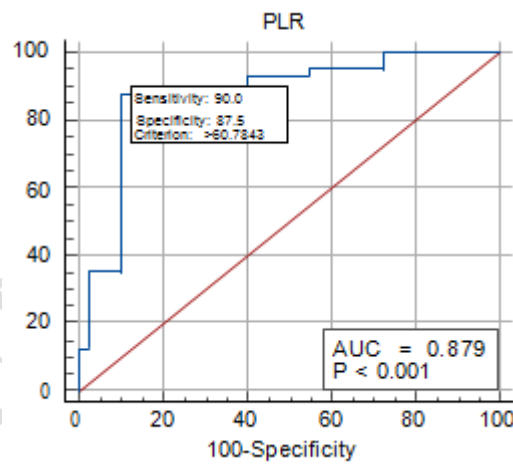


Figure (8): ROC curve of PLR

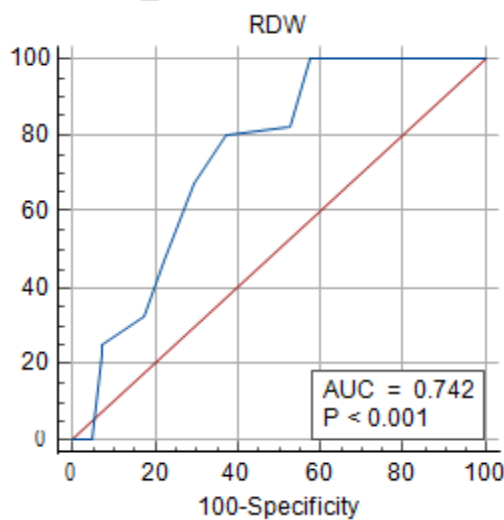


Figure (9): ROC curve of RDW

Table (5): The utility of different cutoff values in our study in the prediction of severe preeclampsia

Parameter	Balanced as presented in the results	Utility if we changed the cutoff values	
		Screening value (highest sensitivity)	Diagnostic value (highest specificity)
Lymphocyte	>3.54	>3.54	>3.54
Neutrophils	≤12.56	≤16.63	≤6.14
NLR	≤3.42	≤7.34	≤1.89
PLR	≤60.78	≤149.78	≤58.13
RDW	>18.0	>20.0	>14.0
MPV	≤5.0	≤5.0	≤8.0
PCT	≤0.13	≤0.27	≤0.11

The cutoff values in prediction of severe preeclampsia were evaluated as presented in table (5). The ROC curve allowed us to detect three cutoff values for each blood parameter. The different cutoffs were one with the highest sensitivity (a screening level), one with the highest specificity (a diagnostic level), and one with a balanced sensitivity and specificity

Discussion

Regarding the haematological markers in our study, there was no statistically significant difference between the three groups in HB level ($p>0.05$). There was significant elevation in lymphocytes level in severe preeclampsia group compared to control group ($P<0.001$) while there was no statistically significant difference between control group and mild preeclampsia group ($P>0.05$). Regarding red cell distribution width (RDW), there was significant elevation in RDW in severe preeclampsia group compared to control group ($P=0.005$) while there was no statistically significant difference between control group and mild preeclampsia group ($P>0.05$).

Regarding neutrophils, there was no statistically significant difference between the three groups ($p>0.05$). Regarding neutrophils/lymphocytes ratio (NLR), there was significant decrease in NLR in severe preeclampsia group compared to control group ($P<0.001$); while there was no statistically significant difference between control group and mild preeclampsia group ($P>0.05$).

There was significant reduction in platelets count in severe preeclampsia group compared to control group ($P=0.009$); while there was no statistically significant difference between mild preeclampsia group in comparison with control group ($p>0.05$). The platelets/lymphocytes ratio (PLR), was significantly reduced in severe preeclampsia group compared to control group ($P<0.001$) while there was no statistically significant difference between control group and mild preeclampsia group ($P>0.05$). Regarding platelets distribution width (PDW), there was no statistically significant difference between the three groups ($p>0.05$).

The mean platelets volume (MPV), there was significant reduction in MPV in severe preeclampsia group compared to control group ($P<0.001$); while there was no statistically significant difference between mild preeclampsia group and control group ($P>0.05$). Regarding plateletcrit (PCT), there was significant decrease in PCT in

severe preeclampsia group compared to control group ($P=0.034$); while there was no statistically significant difference between control group and mild preeclampsia group ($P>0.05$).

The following authors studied the same idea with different study designs, different number of cases and variable list of blood markers. These studies proved a comparative initial data at the case inclusion without significant difference. Hereby, these studies will be summarized to understand their settings and help us in our analysis and comparison.

Yücel et al. (13), they reported that there was no a statistically significant difference in NLR between the groups ($p=0.901$). Both PLR and PCT were lower in the patients with severe PE than in the control group, and these differences showed a statistical significance ($p=0.007$ and $p<0.001$). On the other hand, both RDW and MPV were statistically higher in the patients with severe PE compared to the control group ($p=0.011$ and $p<0.001$).

Boada et al. (14), they found that the Leukocyte count was found significantly different among the three groups. Severe PE group had the highest median leukocyte count ($12,100 \times 1000 / \mu\text{L}$). Neutrophil and lymphocyte counts were found significantly different among the control and PE groups. However, there was no statistically significant difference between the three studied groups as regard Hemoglobin, Lymphocyte, neutrophils, platelets, NLR and PLR.

Similar to our study, **Çintesun et al. (15)**, they revealed that MPV value was statistically higher in the control group compared to both mild and severe PE ($P < 0.001$).

The hematological markers between preeclampsia groups in our study, showed that, there was no significant difference in HB level ($p=1.00$). No statistically significant difference neutrophils level ($p>0.05$). There was no statistically significant difference in platelets count ($P>0.05$). The PDW, showed also no statistically significant difference ($p>0.05$). On the other hand, there were many parameters, which showed statistically significant difference in comparing severe with mild preeclamptic cases. There was significant elevation in RDW ($P<0.001$), significant reduction in NLR, ($P<0.001$), significant decrease in PLR, ($P<0.001$), significant reduction in MPV ($P<0.001$) and there was significant decrease in PCT ($P=0.009$).

Boada et al. (14), reported that leukocyte count was found significantly different among the three groups. Severe PE group had the highest leukocyte count ($12,100 \times 1000 / \mu\text{L}$). However, there was no statistically significant difference between the two mild and severe preeclampsia groups as regard Hemoglobin, Lymphocyte, neutrophils, platelets, NLR and PLR.

Saad et al. (15) reported that there was significant difference between the preeclampsia groups as regard PDW while there was no significant difference between the groups as regard NLR, platelet count. ⁽¹⁷⁰⁾

As well, **Sachan et al.(16)**, reported that neutrophil was significantly high in Severe PE group in comparison to the mild group. However, there was no statistically significant difference between the two preeclampsia groups as regard Hemoglobin, Lymphocyte, platelets, MPV and RDW. ⁽¹⁷¹⁾

For discrimination of preeclampsia, the area under curve (AUC) was significant in only five (5) blood markers, which were the lymphocytes, NLR, PLR, MPV and PCT. The highest significant sensitivity was achieved by MPV that had sensitivity of 66.2% ($p<0.001$), while the highest specificity was achieved by the lymphocytes and PLR that had specificity of 100% ($p<0.001$ & 0.001 respectively). For discrimination of

severe preeclamptic cases, the AUC was significant in seven (7) markers, which were lymphocytes, neutrophils, NLR, RDW, PLR, MPV and PCT. The highest significant sensitivity was found in lymphocyte and MPV (sensitivity of 100%) ($p < 0.001$) while the highest significant specificity found between markers was lymphocytes and PLR that had specificity of 90% and 87.5% ($p < 0.001$ & 0.001 respectively).

Yücel et al. (13), reported that the values of AUC for NLR, PLR and RDW were not statistically significant ($p = 0.636$, 0.104 and 0.36 , respectively). For MPV and PCT, AUC values were 0.641 and 0.712 , and the p values were statistically significant ($p = 0.028$ and $p = 0.001$). The best cut-off value for MPV was 8.04 with a sensitivity of 74.39% , a specificity of 33.33% . The best cut-off value for PCT was 0.25 with a sensitivity of 80.49% , a specificity of 22.22% .

Boada et al. (14), reported that the leukocyte count had a poor predictive value for severe preeclampsia with an AUC of 0.696 ($p = 0.0001$). The sensitivity and specificity were 65.9% and 65.5% , respectively. The maximum sensitivity and specificity were obtained at cut-off number of leukocytes $10,890/\mu\text{L}$. AUC of the neutrophil, MPV, NLR and PLR for severe preeclampsia were 0.632 , 0.564 , 0.534 and 0.588 , with p -value 0.001 , 0.064 , 0.689 and 0.19 respectively.

Saad et al. (17) had used ROC curve analysis. For predicting of preeclampsia, it showed reliable diagnostic significance of RDW with area under the curve AUC 0.89 and P -value < 0.001 at cut-off value 14.8 , with sensitivity 78.07% and specificity 88.67% . Also, PDW with AUC of 0.74 ($p < 0.001$), at cut-off value of 13.5fL had a sensitivity of 72% , a specificity of 71% . For predicting severity of preeclampsia RDW had AUC 0.829 ($p < 0.001$) at cut-off value 46.3 , RDW had a sensitivity 68.42% and sensitivity 86% . NLR showed a non-significance with AUC 0.557 P -value 0.097 at cut-off value 5.05 .

While **Sachan et al. (16)**, reported that the best predictor of PE was MPV with AUC 0.643 and P -value 0.002 at a cutoff value of $\geq 9.05\text{ fl}$ with 50.0% sensitivity and 82.4% specificity. While RDW, at a cut-off value of $\geq 11.5\%$ had AUC 0.751 and P -value 0.001 with 85.3% sensitivity and 49.0% specificity. As regarding predicting the severity of preeclampsia MPV had AUC 0.636 and P -value 0.009 at a cut off value of $\geq 9.05\text{ fl}$, with a sensitivity of 50% and specificity of 82.4% . While RDW had AUC 0.808 and P -value 0.009 at a cut-off value ≥ 12.8 with a sensitivity of 93.8% and specificity of 44.1% .

The receiver operating characteristic (ROC) curve demonstrated to what extent we can depend on the blood markers as predictors or discriminators or classifiers. It was done for all markers. For discrimination of preeclampsia, the area under curve (AUC) was significant in only five (5) blood markers, which were the lymphocytes, NLR, PLR, MPV and PCT. The highest significant sensitivity was achieved by MPV that had sensitivity of 66.2% ($p < 0.001$), while the highest specificity was achieved by the lymphocytes and PLR that had specificity of 100% ($p < 0.001$ & 0.001 respectively). For discrimination of severe preeclamptic cases, the AUC was significant in seven (7) markers, which were lymphocytes, neutrophils, NLR, RDW, PLR, MPV and PCT. The highest significant sensitivity was found in lymphocyte and MPV (sensitivity of 100%) ($p < 0.001$) while the highest significant specificity found between markers was lymphocytes and PLR that had specificity of 90% and 87.5% ($p < 0.001$ & 0.001 respectively).

Yücel et al. (13) reported that the values of AUC for NLR, PLR and RDW were not statistically significant ($p = 0.636$, 0.104 and 0.36 , respectively). For MPV and PCT, AUC values were 0.641 and 0.712 , and the p values were statistically significant

($p=0.028$ and $p=0.001$). The best cut-off value for MPV was 8.04 with a sensitivity of 74.39%, a specificity of 33.33%. The best cut-off value for PCT was 0.25 with a sensitivity of 80.49%, a specificity of 22.22%.

Bozda et al. (14), reported that the leukocyte count had a poor predictive value for severe preeclampsia with an AUC of 0.696 ($p= 0.0001$). The sensitivity and specificity were 65.9% and 65.5%, respectively. The maximum sensitivity and specificity were obtained at cut-off number of leukocytes 10,890/ μ L. AUC of the neutrophil, MPV, NLR and PLR for severe preeclampsia were 0.632, 0.564, 0.534 and 0.588, with p -value 0.001, 0.064, 0.689 and 0.19 respectively.

Moreover, **Kim et al., (18)** reported that, the best predictor for PE was PLR with an AUC of 0.759, P -value > 0.001 at an optimal cutoff value of 116 and PLR had a sensitivity of 60.1% and specificity of 82.9%. The AUC of platelet counts was 0.653, P -value >0.001 with a cutoff value of 161, along with a 29.7% sensitivity, 94.1% specificity. In that order, the AUC of MPV and PDW was 0.638 and 0.621 and P -value $>0.001, >0.001$ respectively. MPV had a sensitivity of 37.2% and specificity of 80.5% while PDW a sensitivity of 73.9% and specificity of 59.9%.

Furthermore, **Kholief et al., (19)** used ROC curve to evaluate PLR and CRP and determine the best cutoff point to predict PE. It was ≤ 77.5 for PLR and > 0.5 for CRP. The significant AUC was reported with CRP. Its AUC value was 0.905, (P -value >0.001) with 75.71% sensitivity and 100% specificity. In predicting severe PE cases, the best cutoff point of PLR was ≤ 101.364 and > 1 for CRP. PLR had AUC value 0.651, P -value 0.030 with 65.71% sensitivity and 62.86% specificity, whereas CRP had AUC value 0.611, P -value 0.109 with 62.86% sensitivity and 65.71% specificity.

Conclusion

The five hematological indices; lymphocytes, NLR, PLR, MPV and PCT had a significant area under curve in the differentiation of preeclampsia from normal pregnancy cases. In differentiation of preeclampsia, the highest sensitivity was achieved with MPV, while the highest specificity was achieved with PLR. The seven hematological indices; lymphocytes, neutrophils, NLR, RDW, PLR, MPV and PCT had a significant area under curve in the differentiation of severe preeclamptic cases. In the differentiation of severe preeclamptic cases, the highest sensitivity was achieved with lymphocytes and MPV, while the highest specificity was achieved with PLR.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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