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Role of Neutrophil Lymphocyte Ratio and Platelet Indices as Inflammatory Indicators and Its Association with Preeclampsia

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ABSTRACT

Background: Preeclampsia (PE) is a pregnancy-specific illness that can manifest as late as 4-6 weeks after delivery and often develops after 20 weeks of gestation due to extensive endothelial dysfunction and vasospasm. PE affects between six and eight percent of pregnancies globally and is an intractable obstetric condition with substantial mortality and morbidity.

Objectives: Neutrophil to lymphocyte ratio and platelet to lymphocytic ratio measurements in pre-eclamptic women and gestationally-matched healthy controls are used to measure the systemic inflammatory markers.

Methods: In this cross-sectional study, pregnant patients with pre-eclampsia between the ages of 18 and 40 who were admitted to Department of Obstetrics and Gynaecology, Menoufia University Hospital. Two equal groups of pregnant women were created: Group (A) included 84 preeclampsia pregnant women, and group (B) included age- and gestational age-matched healthy 84 pregnant women.

Results: When comparing pre-eclamptic pregnant women to normal pregnant women, there was a statistical significant increase in both neutrophil to lymphocytic ratio (NLR) and platelet to lymphocytic ratio (PLR) (mean 4.3 vs 2.9 for NLR and 141.2 vs 113.4 for PLR, $p < 0.001$). In addition, women with severe pre-eclampsia had much higher NLR and PLR than those with mild pre-eclampsia. There were the most effective predictors of pre-eclampsia, as demonstrated by neutrophil to lymphocytic ratio and platelet to lymphocytic ratio. NLR was positively correlated with neutrophil counts, diastolic and systolic blood pressure, and gestational age at birth. The relationship between NLR and platelets was inverse. There was a positive connection between platelet to lymphocytic ratio and GA at delivery as well as platelets.

Conclusion: NLR and platelet to lymphocytic ratio were significantly higher in pre-eclampsia women, which could be used as clinical predictors of preeclampsia and its severity.

Keywords: Preeclampsia, NLR, PLR.

INTRODUCTION

After the 20th week of pregnancy, proteinuria and raised blood pressure greater than or equal to 140/90 mm Hg are used to diagnose preeclampsia (PE), a dangerous condition. It accounts for between six and eight percent of all pregnancies worldwide **(1)**.

Many researchers are working to develop a screening test that can predict the likelihood of PE and its severity because PE can lead to serious difficulties for both the mother and the fetus. In PE, variations in platelet count (PC), NLR, and platelet to lymphocytic ratio have been studied **(2)**. According to certain theories, platelets are crucial to the pathophysiology of PE. By calculating platelet indices, one can indirectly investigate platelet functioning **(3)**.

Changes to platelet parameters, such as platelet count, mean platelet volume (MPV) and platelet distribution width (PDW) have been evaluated and researched in PE. Numerous studies have shown that PE causes a sharp decline in platelet count (4). However, no relationship has been found by any researches between the platelet count and the pre-eclamptic state presence and severity **(5)**.

In healthy pregnancies, systemic inflammation happens. Pregnancy and PE both cause the activation of maternal circulating leukocytes. Studies on PE have revealed variations in the number of leukocytes, primarily neutrophils and lymphocytes **(6)**.

A novel trustworthy inflammatory marker of systemic inflammation is NLR. Neutrophils might be crucial to the pathophysiology of PE **(7)**. Autoantibodies, endothelial dysfunction, and the release of inflammatory cytokines are caused by the hyperactivation of neutrophils and lymphocytes. NLR has so been investigated as a PE marker. **(8)**.

While, some studies (6) found a statistical significance rise in NLR in PE patients, particularly in those with severe cases, others found no significant increase in NLR in patients with severe PE when compared to healthy non-pregnant individuals. **(9)**. Prior research on platelet to lymphocytic ratio as a novel inflammatory marker for PE prediction and severity assessment yielded conflicting findings **(10)**. In this study, women with PE and GA-matched healthy controls were asked to rate their levels of the systemic inflammatory markers NLR and platelet to lymphocytic ratio.

PATIENTS AND METHODS

In this cross-sectional study included 84 pregnant patients with pre-eclampsia between the ages of eighteen and forty who were admitted to the Menoufia University Hospital's Department of Obstetrics and Gynaecology to be compared to 84 healthy gestational age-matched pregnant women.

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Inclusion criteria: Pregnant women aged 18–40 years ≥ 34 weeks of pregnancy who presented with pre-eclampsia. Increased bl pressure more than140/90 mmHg measured two times 4 hours apart. Proteinuria. PE sever criteria (thrombocytopenia, injury to the liver, brain or visual abnormalities, renal failure, and pulmonary edema).

Exclusion criteria: Women who experienced fever, HELLP syndrome, anaemia, ruptured membranes, multiple pregnancies, eclampsia and infections, or concurrent morbidities (i.e., DM, hypothyroidism, chronic HTN, renal disease, collagen vascular disease, or IHD).

Control group included 84 healthy pregnant women aged eighteen to forty years ≥ 34 weeks of pregnancy with normal blood pressure, without proteinuria or any pregnancy complications.

All patients incorporated in this study were subjected to the following:

I- Full history taking including present, past, menstrual, obstetric, medical, surgical and family history.

II- Obstetric examination at admission.

III- Severity of PE including blurred vision, upper abdominal pain, nausea, vomiting, and pedal edema.

IV- Measurement of blood pressure and urine albumin is measured by dipstick test.

V- Routine investigations at admission drawn before delivery:

- **Complete blood count:** examination of CBC results encompassing WBC differential numbers, platelet counts, and haemoglobin levels. Once the absolute values were obtained, NLR and PLR were computed.
- **Random blood sugar:** measured by an automatic chemistry analyzer (AU480 system from Beckman Coulter, USA).
- **Liver and kidney functions test:** included measurements of bilirubin, urea, creatinine, ALT, and AST using an automated chemistry analyzer (AU480 system from Beckman Coulter, USA).
- **PT and INR:** by computerized coagulation analyzer.

Ethical consideration: The Ethical Scientific Committee of Menoufia University approved the study protocol, and informed consent was taken from each patient before enrollment in the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

For all of the analysis, IBM SPSS Statistics for Windows version 23.0 was utilised. The mean ± standard deviation was used to display quantitative data having a normal distribution. The interquartile range, or median, was used to display quantitative data that was not regularly distributed. The t-test was utilised to compare means for regularly distributed quantitative data, whereas the Mann-Whitney U test was utilised for non-normally distributed variables. Qualitative data were shown with numbers (percentages). The Chi square test was used to evaluate the association between the qualitative variables. To evaluate correlations between the studied data, Spearman correlation was employed. The ROC curve was used to assess the usefulness of several variables for mortality prediction. A larger AUC curve suggested better performance.

RESULTS

In comparison with normal pregnant women, pre-eclamptic pregnant women had significantly greater levels of protein in the first 24 hours of their admission. Nevertheless, there was no appreciable difference in the two groups under study with regard to maternal age or blood pressure levels, respectively [Table 1].

Table (1): Pregnant women with and without preeclampsia baseline characteristics

	Preeclampsia (N=84)	Normal pregnant (N=84)	Student's t test	P
Maternal age (years)			1.930	0.16
Mean ±SD Median (IQR) Range	26.3 ± 5 25 (23-28) (18-40)	25.2 ± 6 26 (22-29) (18-41)		
Systolic BP (mmHg)			4.361	0.31
Mean ±SD Median (IQR) Range	143 ± 25 155 (115-165) (110-175)	115 ± 10.7 125 (110-140) (105-155)		
Diastolic BP (mmHg)			1.366	0.236
Mean ±SD Median (IQR) Range	88 ± 14.3 90 (75-105) (65-110)	81.3 ± 11.1 80 (65-100) (60-110)		
Protein in 24 h (g)			6.332	< **0.001***
Mean ±SD	2.9 ± 0.8	1.6 ± 0.4		

BP: blood pressure. *= highly significant

There was a significant increase in INR and neutrophils in pregnant women with pre-eclampsia (P= 0.031, and 0.01 respectively). On the other hand, other clinical variables studied showed no significance difference [Table 2].

Table (2): Haematological characteristics of preeclamptic and non-preeclamptic pregnant women

Mean±SD	Preeclampsia(N=)	Normal pregnant(N=)	t test	P
Hemoglobin (g/dL)				
	13.2 ± 1.6	12 ± 1.2	2.1560	0.36
RDW				
	11.3 ± 1.6	12.3 ± 0.9	0.6515	0.65
Neutrophils				
	6.8 ± 1.6	4.5 ± 1.1	3.032	**0.01***
Lymphocytes				
	1.3 ± 0.31	1.8 ± 0.44	1.2662	0.095
Plts (10^3/µL)				
	225 ± 55.7	230 ± 50	1.3215	0.56
Mean plt volume				
	11 ± 2.3	10 ± 1.3	0.6615	0.56
Plt Distribution Width				
	12 ± 2.5	11.6 ± 2.1	1.6216	0.63
Plateletcrit				
	0.3 ± 0.06	0.21 ± 0.05	0.6516	0.82
TLC				
	11 ± 2.6	8 ± 1.9	2.3663	0.063

RDW: red cell distribution width; **TLC:** total leucocytic count.

NLR and PLR were considerably greater in pre-eclamptic pregnant women than in non-eclamptic pregnant women (P<0.001, < 0.001). Compared to normal pregnant women, preeclamptic pregnant women had significantly higher levels of creatine and INR (p>0.001, 0.031) (Table 3).

Table (3): NLR, platelet to lymphocytic ratio and parameters of pregnant women with preeclampsia and those without preeclampsia

Mean ±SD	Preeclampsia (N=)	Normal pregnant (N=)	t test	P-value
NLR				
	4.3 ± 1.06	2.9 ± 0.68	2.6331	< **0.001****
PLR				
	141.2 ± 34.8	113.4 ± 28.1	1.2699	< **0.001****
AST (IU/L)				
	24 ± 5.8	21.1 ± 5.1	3.6156	0.31
ALT (IU/L)				
	21.6 ± 5.3	13 ± 3.1	6.2965	0.19
Cr (mg/dL)				
	0.6 ± 0.14	0.5 ± 0.08	4.515	< **0.001****
PT				
	11.6 ± 0.9	13 ± 0.7	3.6660	0.069
INR				
	1.3 ± 0.11	1.1 ± 0.08	2.3661	**0.031***

In comparison to pregnant women with mild pre-eclampsia, those with severe pre-eclampsia had much higher protein levels in the first 24 hours, and their systolic blood pressure also was increased significantly. However, there was no appreciable difference in the mother's age or diastolic blood pressure [Table 4].

Table (4): Characteristic traits of preeclamptic pregnant patients, including severe and mild

Variables	Mild Preeclampsia (N=)	Severe Preeclampsia (N=)	Student's t Test	P
Maternal age			2.0508	0.52
Mean ± SD Median (IQR) Range	27.9 ± 4.5 28 (26-30) (18-39)	26.5 ± 4.3 27 (23-30) (18-38)		
Systolic BP			2.5023	**0.013**
Mean ± SD Median (IQR) Range	130 ± 19.7 120 (110-150) (100-160)	140.3 ± 30 150 (110-170) (100-180)		
Diastolic BP			1.3589	0.176
Mean ± SD Median (IQR) Range	83.4 ± 12.5 80 (70-100) (60-100)	86.6 ± 16.9 90 (70-100) (60-110)		
Protein in 24 h (g)			7.2415	< **0.001***
Mean ± SD	1.7 ± 0.3	2.5 ± 0.4		

BP: blood pressure; *= highly significant

When comparing the women with severe pre-eclampsia to the group with mild pre-eclampsia, there was a significant rise in TLC and neutrophils (P= 0.003 and 0.003, respectively). But, when it came to other characteristics, there were no discernible changes. When comparing the women with severe pre-eclampsia to the group with mild pre-eclampsia, there was a significant rise in INR (P= 0.011). But, when it came to other characteristics, there were no discernible changes [Table 5].

Table (5): Laboratory parameters of pregnant women with severe and mild preeclampsia

Parameter (Mean ± SD)	Mild preeclampsia	Severe preeclampsia	Student's t Test	p
Hemoglobin (g/dL)			1.3130	0.191
	11 ± 1.3	11.3 ± 1.3		
RDW			0.4615	0.645
	13.4 ± 1.2	13.5 ± 1.8		
TLC			3.0532	**0.003***
	8.1 ± 2.0	10 ± 2.4		
Neutrophils (10^3/µL)			3.0193	**0.003***
	5.5 ± 1.1	6.9 ± 1.6		
Lymphocytes (10^3/µL)			2.0269	0.44
	1.9 ± 0.45	2.1 ± 0.50		
Plt (10^3/µL)			0.4965	0.620
	225 ± 51	220 ± 54.7		
MPV (fL)			0.0552	0.956
	10 ± 1.7	10 ± 2.0		
PDW			0.8936	0.373
	12.8 ± 2.3	13 ± 2.4		
Plateletcrit			0.7535	0.452
	0.2 ± 0.05	0.2 ± 0.04		
AST			2.3457	0.20
	20.178 ± 4.9	25 ± 6.1		
ALT			2.3064	0.22
	14.7 ± 3.5	20.7 ± 4.1		
Cr			6.9987	0.76
	0.6 ± 0.14	0.7 ± 0.15		
PT			1.9260	0.056
	12.4 ± 0.7	12.6 ± 0.8		
INR			2.5808	**0.011***
	1 ± 0.07	1.1 ± 0.1		

INR: international normalized rate. *= significant

NLR and PLR in women with severe pre-eclampsia showed statistical significant increase when compared to the mild pre-eclampsia group (P= 0.01, 0.02) [Table 6].

Table (6): NLR and PLR of pregnant women with severe and mild preeclampsia

Parameter Mean ± SD	**Mild preeclampsia**	**Severe preeclampsia**	**t test**	**P**
NLR			1.5364	**0.01***
	2.7 ± 0.66	3.5 ± 0.86		
PLR			1.5307	**0.02***
	118.2 ± 29.3	136.4 ± 33.8		

*= significant.

With multi-variate analysis, NLR and PLR showed that they were the most powerful predictors of pre-eclampsia [Table 7].

Table (7): Important variables in multivariate regression analysis that predict pre-eclampsia:

Parameter	**Odds ratio**	**95% CI**	**P value**
HB	0.97	0.89 – 1.3	0.256
Neutrophil	1.09	0.96 – 1.9	0.095
Lymphocyte	1.13	0.88 – 1.63	0.198
Platelet	1.26	0.95 – 1.7	0.203
NLR	1.49	1.33 – 1.81	**0.004***
PLR	1.51	1.15 – 1.72	**0.006***

In reference to the ROC analysis, there were 95% sensitivity, 92% specificity, 86% PPV and 87% NPV [Figure 1].

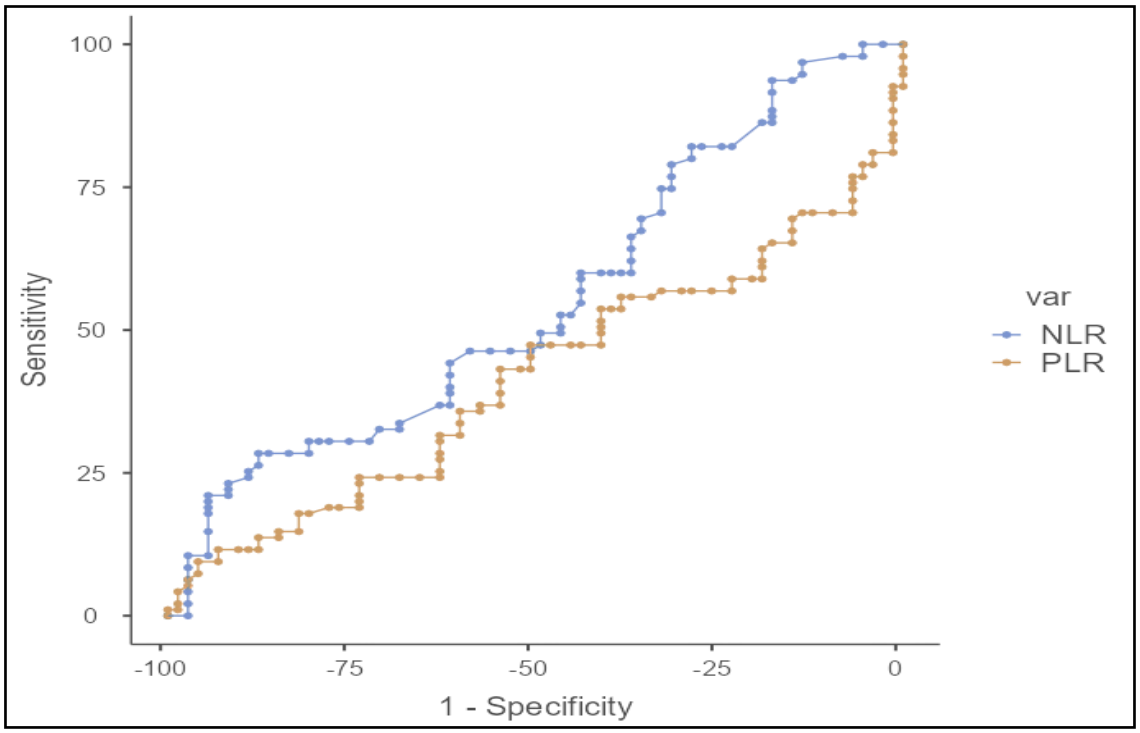

Figure (1): NLR and PLR curve.

DISCUSSION

Recent research indicates that a number of diseases, including autoimmune diseases, coronary artery disease, inflammatory diseases, gynecologic or gastrointestinal malignancies, as well as PE and autoimmune diseases. All can be predicted by systemic inflammatory markers, such as neutrophil/ lymphocytic ratio, platelet/lymphocytic ratio, red cell distribution width (RDW), MPV, and plateletcrit (PCT, which is the percentage of blood volume occupied by platelets) [11, 12].

This study compared pre-eclamptic women with gestationally age-matched healthy controls to investigate the systemic inflammatory markers NLR, PLR, and platelet indices, including MPV, PDW and plateletcrit.

The 84 pregnant women with PE who participated in this study ranged in age from eighteen to forty years old, with a mean age of twenty six. As a control group, an additional 84 seemingly healthy expectant mothers who were matched in age and gestational age were enrolled. There was no discernible difference in mother age between the two research groups. **Tessema *et al.*** [13] revealed a correlation between preeclampsia development and advanced maternal age, which is consistent with findings by **Hassen *et al.*** [14] that most pre-eclamptic patients were found to be ≥35 years old.

This study showed that, in comparison with normal pregnant women, pregnant women with pre-eclampsia had significantly higher amounts of 24-hour proteinuria, which in severe preeclampsia was significantly higher than in moderate preeclampsia. According to earlier research, there was a positive correlation between PE severity and the likelihood of unfavourable pregnancy outcomes and the level of 24-hour proteinuria. As a result, proteinuria was originally thought to be one of the essential markers for a clinical PE diagnosis [15, 16]. Proteinuria is not needed for the preeclampsia diagnosis, according to ACOG [17]. This modification to the diagnostic criteria is still present in the ACOG guidelines. It implies that some women who do not have proteinuria may develop preeclampsia **[1]**. In addition to being able for PE severity prediction, **Lei *et al.*** **[18]** study found that pregnant women with pre-eclampsia had higher levels of protein in the first 24 hours of their pregnancy when compared to normal pregnant women.

In this study, systolic blood pressure was found to be higher in PE patients in comparing to controls, however this difference was not statistical significance. On the other hand, systolic blood pressure was considerably higher in sever PE when compared to moderate PE. There was a statistically significant increase in neutrophils in PE patients compared to the control group (p=0.01). Furthermore, we discovered that TLC and neutrophils were considerably greater in severe PE compared to moderate PE. According to studies, leukocyte counts rise in PE patients, particularly those with severe PE. Additionally, the neutrophil count was higher in PE patients in comparison with healthy pregnant women [19].

Our study showed that there was a significant increase in NLR and PLR levels of PE patients compared to control group (p<0.001 & <0.001 respectively). Additionally, compared to individuals with moderate preeclampsia, they were considerably greater in patients with severe PE. Regarding NLR, the same conclusion was reached by **Kirbas *et al.*** [20] and **Kang *et al.*** [6]. NLR was also discovered by **Serin *et al.*** [21] to be able to predict the disease's severity. While, **Gogoi *et al.*** [9], **Yücel and Ustun** [12], and **Guzeltas *et al.*** [22] discovered that there were no appreciable variations in NLR among the groups. On contrary, **Kholeif *et al.*** [10], **Cui *et al.*** [7] demonstrated a marked decline in NLR. The explanation for this discrepancy in the results is that a wide range of factors, including racial characteristics, dietary characteristics, and geographic location can affect several haematological parameters in adults, including neutrophil and lymphocyte counts. Additionally, the quantity of lymphocytes and platelets can change between devices, which could affect the results. It can also be the result of different study designs and sample sizes. It is believed that PCT and MPV are indicators of platelet activation because they display variations in platelet volume. As indicated in our study, MPV showed no discernible difference between the control group and the PE patient. **Walle *et al.*** [23] reported that during PE, there is a large increase in MPV and a considerable decrease in PC, which is similar **Karateke *et al.*** **[24]** study findings. Furthermore, PCT and MPV were linked to the existence of PE, and patients with severe PE were separated from the group with mild PE, according to **Yücel and Ustun** [12]. However, **Yavuzcan *et al.*** [25] found no evidence of a significant change in MPV between the PE group and the control group. However, MPV demonstrated a substantial difference between the two groups and increased values with increase blood pressure in **Thalor *et al.*** [3] and **Gogoi *et al.*** [9]. Nevertheless, there was no discernible relationship between preeclampsia and the PC or PCT.

In our study, there was no change in RDW between the control group and PE patients. Similar results were observed by **Gogoi *et al.*** [9]. However, when **Yücel and Ustun** [12] compared patients with moderate PE to healthy pregnant controls, they found that severe PE diseased patients had considerably higher RDW levels.

The platelet counts in our study's pre-eclampsia patients inclined towards normal with no difference. Platelet counts are used to calculate the platelet indices, which could explain the discrepancy in the results. Furthermore, variations in the techniques

and tools utilized to acquire hemograms, variations in gestational age, and variations in the patient population could all be contributing factors.

The results of this study indicated statistical significant increase in INR between PE and control**,** and between moderate and severe PE. In comparison with the control group, **Bhutani *et al.*** [27] observed a rise in the coagulation profile, including INR, in the PE group and compared to mild PE, it was higher in severe PE.

Our investigation revealed no ALT and AST differences between the both groups. On the other hand, **Hassen *et al.*** [14] and **Sarmah** [28] observed that preeclamptic patients had more transaminases than controls.

We also found that serum creatine was higher in PE group than in control group ($p<0.001$) and was higher in severe PE when related to mild PE. According to **Mahmoud *et al.*** [29] the PE group's serum creatine was substantially greater than in the control group.

Furthermore, we found that NLR and PLR were among the greatest predictors of PE in our study's logistic regression analysis. The same outcomes were found by **Cui *et al.*** [7].

There were certain restrictions on this study: The sample size was modest to begin with. Second, serial marker assessment may be more beneficial because the NLR and platelet indices were only measured once upon entry. Third, since it was a single centre study, we advise conducting more multicenter research.

CONCLUSION

This study found that compared to pregnant women without pre-eclampsia, pregnant women with the disease had considerably increased NLR and PLR. Given that they were considerably higher in women with severe pre-eclampsia than in the group with mild pre-eclampsia, NLR and PLR could be used to predict the severity of preeclampsia.

RECOMMENDATIONS

Following more research, NLR and PLR might be utilised as diagnostic, prognostic, and preeclampsia severity markers. It is advised to monitor serum NLR and PLR levels on a regular basis.

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