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Original Article

Pathology Section

# Diagnostic Value of Neutrophilic-lymphocytic Ratio, Platelet-lymphocyte Ratio, Platelet Indices in Preeclampsia: A Case-control Study

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## ABSTRACT

**Introduction:** Preeclampsia (PE) is a pregnancy-specific disorder affecting 3-14% of pregnant women characterised by endothelial dysfunction, and activation of the coagulation system. Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Mean Platelet Volume (MPV) and Plateletcrit (PCT) have all been recognised as Systemic Inflammatory Response (SIR) markers. Alteration of these parameters can have significant effect on prognosis.

**Aim:** To compare the NLR, PLR, and platelet indices between women with preeclampsia and normotensive pregnant women at Tertiary Care Centre.

**Materials and Methods:** The present case-control study was conducted from June 2022 to May 2023 at Government medical college Nizamabad, Telangana, India. The study compared 44 pregnant women aged 18-40 years with preeclampsia diagnosed at term with 44 normotensive women matched for gestational age. A 3 mL of venous blood samples were drawn and Complete Blood Count (CBC) was analysed using Sysmex XN 1000, 5-part analyser. The parameters recorded were haemoglobin, platelet count, MPV, PCT, and Platelet Distribution Width (PDW). Results were analysed using Statistical Package for Social Sciences (SPSS) software version 23. Independent sample t-test was used to compare continuous variables between cases and controls. Diagnostic accuracy was calculated from ROC curve analysis.

**Results:** A significant difference was found in NLR, MPV and PDW values between PE group and normotensive group ($p<0.05$). NLR, MPV, PDW showed an increase in mean difference of 6.76±3.76, 10.63±1.13,14.19±2.75 in PE group, respectively. However, PLR ($p=0.628$) doesn't show any statistical significance.

**Conclusion:** From the above findings of the study it is emphasised that NLR, MPV, PDW are significantly higher in PE than normotensive pregnancies and serve as cost-effective, accessible inflammatory marker in predicting preeclampsia.


**Keywords:** Gestation, Inflammatory response markers, Pregnancy disorders

## INTRODUCTION

The PE is one of the major causes of maternal mortality and morbidity affecting 3-14% of pregnancies [1]. It is a pregnancy-specific disorder characterised by a new onset of hypertension after 20 weeks of gestation in a previously normotensive pregnant woman accompanied by proteinuria and end organ dysfunction. It complicates 4-10% of all the pregnancies in India [2]. Definitive cause is not known but multiple mechanisms like inflammation, endothelial dysfunction, angiogenesis, inappropriate placentation, oxidative stress, immunological and genetic factors are thought to be associated with pathogenesis of preeclampsia [3].

The clinical consequences of PE are associated with platelet dysfunction and hypoxia leading to activation of immunological responses, including increased neutrophil counts, thrombocyte activation, and systemic inflammatory process. When endothelial damage occurs, PLTs adhere to the injured endothelium and become activated. The activated PLT secrets and releases constituents of alpha and dense granule which contribute to PLT aggregation [4]. Moreover, the damaged vascular endothelium releases tissue factor, which initiates the process of coagulation.

The activation of the coagulation system, along with PLT aggregation, leads to reduced organ perfusion and multisystem dysfunction in PE patients. The increased consumption and destruction of PLTs in PE obligated the bone marrow to produce and release young and large PLTs, resulting in increased MPV, PDW. MPV is expressed in femtolitres (fL), and increased MPV reflects the presence of larger, younger and more active platelets. PDW indicates the variability in platelet size it is derived from width of platelet volume distribution curve at 20% of peak height. Other mechanisms include Lipoprotein abnormalities in which lipids secreted by placenta activate leukocytes that are circulating through intervillous space. These activated leukocytes reenter the circulation and lead to vascular dysfunction that results in PE [1].

Thus, haematological parameters like NLR, PLR MPV, PDW, Red Cell Distribution Width (RDW), PCT are known as markers of SIR in PE [5,6]. All these markers can be obtained from simple CBC and can be used to predict the disease.

The present study aimed to compare inflammatory markers- NLR, PLR, MPV, PDW between PE and normotensive pregnancy and to assess the sensitivity and specificity of these markers in PE.

1. To compare inflammatory markers- NLR, PLR, MPV, PDW between PE and normotensive pregnancy.
2. To assess the sensitivity and specificity of these markers in PE.

## MATERIALS AND METHODS

The present case-control study conducted at Department of Pathology and Department of Obstetrics and Gynaecology (OBG) at Government Medical College, Nizamabad, Telangana, India, between 1st June 2022 to 31 May 2023 for a period one year after obtaining Institutional Ethical Committee clearance no: ECR/144/Inst/TG/2019. Diagnosis of PE was based on criteria of American College of Obstetrics and Gynaecology on hypertension in pregnancy as elevated Blood Pressure (BP) of >140/90 mmHg on two occasions at least four hours apart after 20 weeks of gestation with proteinuria>1+ in urine dipstick [7]. Normotensive pregnant women matched for age and gestation who had no co-morbidities

and were admitted to hospital for routine antenatal care or for safe institutional delivery was used as control.

**Inclusion criteria for cases:**

1. Pregnant women at ≥32 weeks gestation with new-onset hypertension after 20 weeks, defined as BP ≥140/90 mmHg on two occasions at least 4 hours apart

**Inclusion criteria for controls:**

1. Normotensive females of gestational age >32 weeks gestation without any co-morbidities or associated diseases.

**Exclusion criteria:**

1. Previous known case of hypertension;
2. Patients with multiple gestations or previous molar pregnancy or abortions;
3. On treatment for any chronic conditions like diabetes mellitus, thyroid disorders, heart diseases, renal diseases, thrombophilic disorders etc.,
4. Patients with history of any medication related to inflammatory conditions like corticosteroids are excluded.

**Sample size calculation:** Sample size was calculated by using the formula for comparing mean between two population by using expected effect size from previous study by Firdaus DY et al., which reported a mean NLR of 5.91±3.6 in preeclamptic women and 3.53±0.9 in normotensive pregnant women [3]. Using these parameters, and applying the formula for comparing two independent means with a significance level (α) of 0.05, corresponding to a Z-value of 1.96 for 95% confidence. A power (1-β) of 80%, corresponding to a Z-value of 0.84.An expected mean difference (Δ) in NLR between PE and normotensive groups of 1.3.A pooled standard deviation (σ) of 2.2, derived from prior studies minimum required sample size was calculated as 44 participants per group (total n=88).

The formula used was: $n_1=n_2=\frac{(Z_{\frac{\alpha}{2}}+Z_\beta)^2\,(\delta_2^1+\delta_2^2)}{\Delta^2}$ X2

Sample size=$\frac{(1.96+0.84)^2\,(4.4)}{(1.3)^2}$X2 =41,so approximately taken as 44.

### Study Procedure

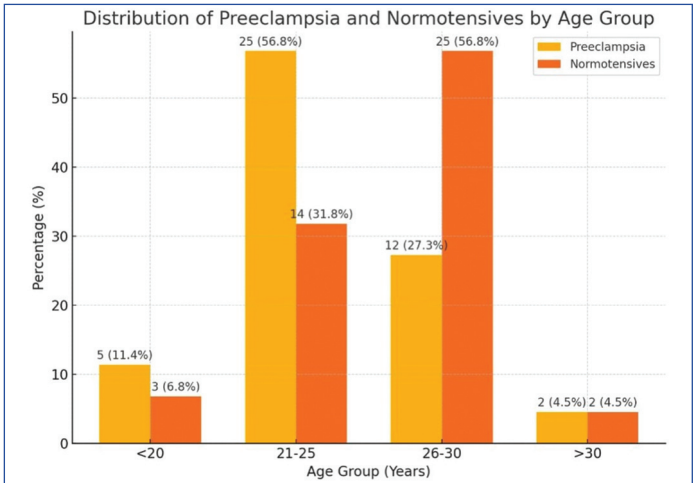
Informed consent was obtained from each study participant data related to sociodemographic characteristics such as age, residence, educational status, and occupation were collected. Clinical data including blood pressure, parity, gravidity, and gestational age were extracted from patients medical charts. A total of three milliliters of venous blood sample was collected into an Ethylene Diamine Tetra Acetic acid (EDTA) sample tube and adequately mixed. The CBC test was then performed within two hour of blood collection using a Sysmex XN-1000 automated 5-part hematology analyser (Sysmex). Haemoglobin, White Blood Cell count (WBC), neutrophil count, lymphocyte count, platelet count, RDW, MPV, PDW, and PCT values were directly obtained from analyser using impedance principle, MPV represent average size of platelets and PDW represent variability in platelet size derived from Platelet volume histogram. NLR was calculated manually by dividing absolute neutrophil count by absolute lymphocyte count. Similarly, PLR was calculated by dividing platelet count by absolute lymphocyte count and entered into excel spreadsheet. The reference ranges for NLR, PLR, MPV and PDW in normal third-trimester pregnancy which report to be NLR between 1.5-4.5, PLR between 90-200, MPV between 7.5-10.5 fL and PDW between 9-13% were derived from previously published studies [8,9].

## STATISTICAL ANALYSIS

Data analysis was done using SPSS software version 23. Independent sample t-test was used to compare continuous variables between cases and controls. The values were represented in Number (%) and Mean±SD. Statistical comparison was done between case and control groups with respect to maternal NLR, PLR, MPV, PDW values. For those parameters that showed significant differences between the PE and NT groups, ROC curve analysis was performed to determine diagnostic accuracy i.e., AUC, sensitivity, and specificity for PE diagnoses value<0.05 was considered as statistically significant.

## RESULTS

A total of 88 participants were included in the study of which 44 are PE patients as case groups and 44 patients are normotensive control groups. Study participants were divided into four categories based on age [Table/Fig-1]. Based on gravida participants were categorised as follows [Table/Fig-2]. Significant differences were observed in the following parameters: 6.76±3.76 in PE vs. 4.21±1.89 in controls (p<0.001) MPV: 10.63±1.13 fL in PE vs. 10.02±0.97 fL in controls (p=0.008) PDW: 14.19±2.75 in PE vs. 10.84±1.21 in controls (p<0.001) PLR: No significant difference (126.8±47.63 in PE vs. 121.87±47.38 in controls, p=0.628) [Table/Fig-3]. Platelet count between two groups: PE: 233.09±77.23, controls: 230.86±70. The p-value: 0.732 shows no statistical significance. Diagnostic Accuracy (ROC Curve Analysis): NLR: AUC=0.712 (95% CI: 0.60-0.81), p=0.001, cut-off=4.2, sensitivity=72%, specificity=57%, MPV: AUC=0.694 (95% CI: 0.58-0.81), p=0.002, cut-off=10.15 fL, sensitivity=70%, specificity=80%, PDW: AUC=0.886 (95% CI: 0.81-0.95), p<0.001, cut-off=12.05, sensitivity=77%, specificity=90%, PLR: AUC=0.553 (95% CI: 0.43-0.67), p=0.388, not statistically significant [Table/Fig-4].




**[Table/Fig-1]:** Classification of subjects based on age group.

| Gravida | Preeclampsia N (%) | Normotensives N (%) |
|---|---|---|
| Primi | 27 (61.36%) | 18 (40.9%) |
| Gravida-2 | 12 (27.27%) | 17 (38.6%) |
| Multigravida | 5 (11.36%) | 9 (20.4%) |

**[Table/Fig-2]:** Distribution of PE subjects based on gravida primi gravida.

| Parameters | Preeclampsia (mean±SD) | Normotensives (mean±SD) | Mean Difference (95%CI) | p-value |
|---|---|---|---|---|
| NLR | 6.76±3.76 | 4.21±1.89 | 2.54 (1.27-3.81) | 0.0001* |
| PLR | 126.8±47.63 | 121.87±47.38 | 4.92 (-15.21-25.05) | 0.628 |
| MPV (fL) | 10.63±1.13 | 10.02±0.97 | 0.6 (0.16-1.05) | 0.008* |
| PDW | 14.19±2.75 | 10.84±1.21 | 3.35 (2.44-4.26) | 0.0001* |

**[Table/Fig-3]:** Mean and Standard deviation of NLR, PLR, MPV(fl), PDW.
*Denotes a significant p-value of <0.05.

## DISCUSSION

The PE is a pregnancy specific hypertensive disorder affecting 2-8% of pregnancies globally. Definitive aetiology is not known. Maternal circulating leukocytes are activated in pregnancy and further activated in PE and are responsible for vascular dysfunction [10]. Leucocytes being important components of immune system play

| Parameters | AUC | Significance | Cut-off value | Sensitivity | Specificity |
|---|---|---|---|---|---|
| NLR | 0.712 (0.60-0.81) | 0.001* | 4.2 | 72% | 57% |
| PLR | 0.553 (0.43-0.67) | 0.388 | 120.1 | 55% | 60% |
| PDW | 0.886 (0.81-0.95) | 0.0001* | 12.05 | 77% | 90% |
| MPV(fl) | 0.694 (0.58-0.81) | 0.002* | 10.15 | 70% | 80% |

**[Table/Fig-4]:** Area under ROC curve analysis.
*Denotes a significant p-value of <0.05

## CONCLUSION(S)

From the above results of the present study its emphasised that NLR, MPV, and PDW are significantly elevated in women with PE compared to normotensive pregnant women, suggesting their potential role as accessible and cost-effective inflammatory markers. Among these, PDW exhibited the highest diagnostic accuracy. Although PLR did not show statistical significance, it may still warrant evaluation in larger populations. These findings support the use of routine haematological indices as adjunct tools in the early detection of PE. However, furthermore studies are required to verify these inflammatory markers role in assessing severity of disease.

| Parameters | Present study | Firdaus DY et al., [3] | Walle M al., [20] | Çintesun E et al., [2] | Agrawal N et al., [21] |
|---|---|---|---|---|---|
| NLR | 6.76±3.76 | 5.91+3.6 (p<0.001) | (p<0.001) | 5.37+1.21 (p=0.422) | 3.53+0.9 (p<0.001) |
| MPV | 10.63±1.13 | 8.25+0.935 (p<0.001) | 11.26+1.92 (p<0.001) | 9.1+0.8 (p<0.001) | - |
| PLR | 126.8±47.63 | 138.7+48.6 (p=0.78) | 137.1+44.9 (p<0.001) | 123.95+47.8 (p=0.27) | 151.2+48. (p<0.001) |
| PDW | 14.19±2.75 | - | 16.5+0.3 (p<0.001) | 17.8+0.6 (p=0.204) | - |
| CONCLUSION | NLR, MPV, PDW increased | NLR, PLR, MPV increased | All parameters are increased | MPV increased | NLR, PLR increased |

**[Table/Fig-5]:** Comparison of present study to various other studies [2,3,20,21].

an important role in pathogenesis of pregnancy related disorders involving decidua and placenta [11]. In women with preeclampsia, neutrophils are activated as they circulate through the intervillous space and are exposed to oxidised lipids secreted by the placenta [12]. Oxidised lipids are potent activators of neutrophils, leading to expression of COX-2 that regulates the release of thromboxane, TNF and superoxide. Thus, neutrophils obtained from preeclamptic females express significantly more COX-2 than healthy pregnant females or healthy non-pregnant females [13,14]. It was also found that there was more neutrophil endothelial adhesion and infiltration into intimal space in systemic vasculature than lymphocyte infiltration [15]. In the present study, NLR was significantly elevated in the PE group compared to the normotensive group (6.76±3.76 vs. 4.21±1.89, p<0.001), consistent with findings by Kang Q et al., who concluded that elevated NLR is associated with increased severity of PE [16].

Platelets are efficient immune modulators and effectors. Endothelial dysfunction induces vasoconstriction and platelet adhesion and aggregation, triggering coagulation and resulting in hypoxic damage to the endothelium [17]. Thrombocyte consumption in the maternal peripheral circulation stimulates bone marrow production. The platelets produced at this stage are larger than the older ones and show a strong tendency toward aggregation. Therefore, the number, volume, and function of platelets change, and platelet turnover demonstrates an increase in preeclamptic maternal vasculature [8]. Platelet count, PDW, MPV, and PCT are regarded as platelet activation markers.

However, the results are variable in different studies. Mannaerts D et al., reported that MPV of pregnancies with PE before 20 weeks and 3rd trimester is significantly higher than those normal pregnancies with optimal cut-off point of 8.15 (sensitivity 66.7% and specificity 56.3%) and 3.92 (sensitivity 84.4% and specificity 69.4%), respectively for predicting PE [6]. Previous studies conducted by Han L et al., Sitotaw C et al., and Alkholy EA et al., showed a significant increase of MPV in PE patients [9,18,19]. Comparison of present study findings with previous similar studies has been listed in [Table/Fig-5] [2,3,20,21].

The increment in the MPV value in PE patients might be due to the presence of large PLTs in the peripheral circulation. Meta-analysis conducted by Kang Q et al., concluded that NLR can be used as a laboratory marker for clinical prediction and severity of PE, with NLR values higher than in normal pregnancies [16].

### Limitation(s)

The study was conducted at a single Tertiary Care Hospital, which may not reflect population diversity. Therefore, the results may not be generalisable to broader or rural populations.

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