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Neutrophils-Lymphocyte Ratio and Platelets Lymphocyte Ratio in Early Gestation as Predictors for the Development of Pre eclampsia

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Abstract

Purpose: Preeclampsia affects 2% to 8% of pregnancies and is a significant complication that manifests in the second or third trimester with potential adverse outcomes for both mothers and fetuses. The study aims to assess the diagnostic utility of NLR and PLR, between 12-16 weeks of POG to predict the development of preeclampsia.

Material and Methods: This prospective case- control study was conducted from January 2019 to January 2022. We included 100 pregnant women, aged between 18-40 years and at less than 16 weeks POG. CBC including hemoglobin, differential leukocyte counts and their ratio NLR and PLR for all patients at 12-16 weeks were measured. All pregnant women were followed till delivery to see development of preeclampsia. We used a receiver operating characteristic curve to evaluate the cutoff, sensitivity, and specificity values.

Results: The study enrolled 100 age and gestation matched pregnant women, out of them 30 developed preeclampsia. Mean age and gestational age were comparable within groups. The BMI (27.05±4.49, 23.96±3.5, p<0.001) and NLR (4.02±1.1, 3.13±0.8, p<0.001) were significantly more in women developing PE later while no significant difference was seen in the PLR (10.78±4.2, 10.16±3.6, p=0.475) between groups. The best predictor for preeclampsia was NLR at 12-16 weeks at an optimal cutoff value of 3.20, with a sensitivity of 70.0%and specificity of 64.0% with probability 0.74.

Conclusions: The results suggest that first trimester NLR and PLR values are useful markers in the prediction of preeclampsia. Therefore, NLR may be a part of first-trimester screening to identify high-risk women that subsequently develop PE.

Keywords: PE; Normotensive; NLR; PLR; ROC

Abbreviations

CBC: Complete Blood Count; NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; PE: Pre-Eclampsia; POG: Period of Gestation; ROC: Receiver Operator Characteristics.

Introduction

Preeclampsia (PE) constitutes a significant obstetric concern with profound implications for maternal and neonatal health globally. It is associated with increased maternal and neonatal morbidity and mortality, making it the second

most common cause of direct maternal and fetal fatalities worldwide, occurring in 5-8% of pregnancies [1]. In India, PE accounts for 6.7% of maternal deaths. According to reports from 1976 to 2015, the average incidence of eclampsia in India is 1.5%, with a range of 0.179 to 5% and the average incidence of preeclampsia is 5-15% [2]

PE manifests in a spectrum of severity, ranging from a mild, asymptomatic condition typically occurring close to term, to a severe form characterized by uncontrollably high blood pressure, usually emerging earlier in pregnancy (less than 34 weeks) [3]. The ailment is often linked to widespread endothelial dysfunction, particularly in the context of abnormal placentation. The consequences of PE involve intravascular coagulation, hemorrhage, and organ failure, particularly affecting the renal and hepatic systems, resulting from inadequate perfusion [4]. Hypertension and proteinuria constitute the fundamental clinical features of preeclampsia. The timely identification of pregnant women at a high risk of developing either preeclampsia or its severe form is crucial to prevent adverse pregnancy outcomes.

Mild systemic inflammation is a physiological state of healthy pregnancy. However, in preeclampsia, this inflammation may undergo harmful deregulation [5].Various contributors include inflammatory cells and immune responses, with neutrophils, lymphocytes, and thrombocytes actively generating inflammatory cytokines [6].Early in pregnancy, activation and increase in white blood cell countsespecially neutrophils has been seen in PE [7,8]. The arteriopathy and endothelial damage linked to preeclampsia are potentially caused by activated neutrophils [2]. The heightened inflammatory response can alter endometrial receptivity, impeding the implantation process, and ultimately lead to the development of preeclampsia due to sustained exposure to one's own activated inflammatory cells [9]. So, neutrophils and lymphocytes level could be used as predictive markers of PE.

The complete blood count (CBC), which is a common source of peripheral inflammatory markers, has the potential to be employed as a biomarker for the early detection of PE. One of the most often requested procedure in clinical laboratories is a CBC using an automated hematology analyzer. Based on fundamental blood characteristics, the neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are computed.

Pre-eclampsia is a complex syndrome with a known pathogenesis that initiates early in pregnancy, yet its clinical symptoms typically emerge in the second or third trimester. Despite this knowledge, the specific role of systemic inflammatory markers in the clinical assessment, differential diagnosis, and prognostic evaluation of pre-eclampsia (PE) remains unclear [10].

Studies by Kirbas A, et al. [11] and Gezer C, et al. [12] have reported elevated Neutrophil-to- Lymphocyte Ratio (NLR) values in early gestation, specifically at 11-13+6 weeks and 7-14 weeks respectively, with significantly higher values observed in severe preeclampsia and the preeclampsia group compared to control groups [11,12]. Notably, both of these studies were retrospective, prompting the design of our prospective study to investigate NLR and Platelet-to-Lymphocyte Ratio (PLR) as potential predictors of PE in the early diagnosis stage, between 12 and 16 weeks of Period of Gestation (POG).

Materials and Methods

In order to investigate the diagnostic utility of NLR and PLR in early gestation to predict preeclampsia, a case-control study was conducted from 2019 to 2022. The Institute Ethics Committee, AIIMS, New Delhi, granted ethical approval for the prospective data collection for this project (EC number: IEC-261/06.05.2016, OP-13/01.06.2018). The study is now underway. Population under Study: For the purpose of the study, data from 100 pregnant women, ages 18 to 40, who were less than 16 weeks along with their baby, were collected. A comparison was made between thirty pregnant women with PE and seventy age and gestation matched normotensive pregnant women. Women with a history of diabetes, chronic hypertension, ischemic heart disease, collagen vascular disease, renal illness, or numerous pregnancies were not allowed to apply.

Sample Size

Using a mean NLR of 3.75 ± 2.0 in healthy pregnant women from the study by Serin S. et al. [13], a sample size of 70 per group was required to detect a difference of 0.5 in pre-eclamptic pregnant women with 80% power and a 5% level of significance. Owing to the COVID-19 pandemic-related nationwide lockdown, outpatient services were halted and recruiting and follow-up for research were impacted. A few examine data from 70 normotensive controls and 30 preeclampsia cases.

Biochemical Measurements

Using a Beckman Coulter LH 750 Hematology analyzer for CBC, around 2 ml of venous blood was drawn and placed in EDTA-K-2 anticoagulant for analysis. Every blood sample was examined twice, and the average of the two results was applied. The cohort studies excel file contained data on the patients that were part of the investigation.

By dividing the blood neutrophil count by the lymphocyte count, NLR was computed. By dividing the platelet count by the lymphocyte count, the platelet lymphocyte ratio (PLR) was determined. According to hospital protocol, routine

prenatal testing was performed.

Outcome Measure

According to ACOG guidelines 2020, a woman with a history of normal blood pressure is eligible for preeclampsia if her blood pressure is 140 mm Hg or higher for the systolic blood pressure or 90 mm Hg or higher on two separate occasions at least four hours apart after 20 weeks of gestation.-A blood pressure measurement of at least 160 mm Hg at the systolic or 110 mm Hg at the diastolic levels. (It is possible to detect severe hypertension in a matter of minutes, allowing for prompt antihypertensive medication). proteinuria: 300 mg or more of urine per 24 hours (or this amount estimated from a timed collection) or a ratio of 0.3 mg/dL or higher for protein to creatinine, or c a dipstick reading of 2+ (used only if other quantitative methods not available).

Alternatively, new-onset hypertension accompanied by the onset of any of the following in the absence of proteinuria: Thrombocytopenia: Platelet count < 100,000 3 * 109/L Alternatively Deficit of the kidneys: more than 1.1 mg/dL serum creatinine concentrations or a doubling of the serum creatinine concentration in the absence of further renal disease or Deficiency in liver function hepatic transaminase levels in the bloods that are twice normal, together with pulmonary edema or Headache that appears suddenly, is not relieved by medicine, and cannot be explained by other medical conditions or visual symptoms [14]. Pregnant women who had a blood pressure reading of SBP ≤120 mmHg or DBP ≤80 mmHg were categorized as normotensive.

Statistical Analysis

The SPSS program version 25.0 was used to conduct descriptive and analytical statistics. To compare the data between the two groups, the independent t-test and the Mann-Whitney test were employed. Chi-square or Fisher's exact test, if applicable, was used to compare frequency data across categories. ROC analysis was used to determine the cut-off value of NLR and PLR level in predicting preeclampsia. Cut-off values were determined for the highest levels of sensitivity and specificity possible. For statistical significance, a two-sided probability of $p<0.05$ was taken into account.

Results

The study compared first trimester NLR and PLR of thirty women who developed preeclampsia later with seventy age and gestation matched normotensive pregnant women.

The mean age of the women with pre-eclampsia was 29.83±3.4 years compared with 28.43±3.3 years in the normotensive group ($P>0.05$). The PE group did, however, have a higher BMI and blood pressure, (Table 1).

Parameters	Preeclampsia (n=30)	Normotensive Controls (n=70)	Pvalue
Age (years)(Mean ± SD)	29.83±3.4	28.43±3.3	0.059
Gestational age (in weeks)	14.3±1.3	14.2±1.3	0.166
BMI (kg/m^2)(Mean ± SD)	27.05±4.49	23.96±3.5	<0.001
Gravidity Primigravida, n(%)	11 (85%)	2 (15%)	<0.001
Multigravida, n(%)	19 (22%)	68 (78%)	
SBP in mmHg, (Mean ± SD)	117.18±11.7	107.3±9.3	<0.001
DBP in mmHg, (Mean ± SD)	76.75±9.6	67.96±8.3	<0.001

Table-1: Clinical characteristics of the study participants in early gestation (12-16weeks).

Baseline values (TLC, Neutrophils, and lymphocyte, Platelets, NLR and PLR) are summarized in Table 2. Mean NLR was higher in women with pre-eclampsia compared with women in the control group (4.02±1.1 v/s 3.13±0.8; $P<0.001$). While the lymphocyte count was significantly lower in the PE group ($p<0.001$), the neutrophils percentage was significantly greater in the PE group compared to the normotensive ($p=0.001$). Although it was not statistically significant, mean PLR was greater in PE.

Parameter	Preeclampsia (n=30)	Normotensive (n=70)	Pvalue
Total leukocyte count in *10^3/ul (Mean ± SD)	9.55±2.82	8.61±2.05	0.101
Neutrophil in % (Mean ± SD)	72.40±5.2	68.30±4.7	<0.001

Lymphocyte in % (Mean ± SD)	19.07±4.1	22.63±4.2	<0.001
Platelets $\times 10^3$/ul (Mean ± SD)	204.70±68.5	223.0±60.4	0.186
NLR	4.02±1.1	3.13±0.8	<0.001
PLR	10.78±4.2	10.16±3.6	0.475

Table 2: Comparison of inflammatory parameters between PE and normotensive control.

The median SGPT, uric acid, and fasting blood sugar levels were significantly higher in women with PE compared to those without PE, hemoglobin was significantly low (p=0.010) shown in Table 3.

Blood Parameters	Preeclampsia (n=30)	Normontensive Controls (n=70)	Pvalue
Hemoglobin in g/dl (Mean ± SD)	11.30±1.2	11.91±0.9	0.01
FBS in mg/dl (Mean ± SD)	91.25±13.3	84.04±8.9	0.016
PPBS in mg/dl (Mean ± SD)	108.3±22.9	99.97±20.7	0.275
Total Protein (Mean ± SD)	7.21±0.4	7.09±0.5	0.417
Albumin in g/dl (Mean ± SD)	4.07±0.2	4.20±0.4	0.298
Globulin in g/dl (Mean ± SD)	2.92±0.5	2.86±0.4	0.717
SGOT in U/L (Median(range)	24.5(13-179)	20(8-62)	0.056
SGPTin U/L (Median(range)	26(14-202)	20(9-86)	0.001
ALPin IU/L (Median(Range)	103.5(55-388)	157(61-806)	0.016
Urea in mmol/L(Mean ± SD)	13.42±3.5	14.43±4.6	0.315
Creatinine in mg/dl (Mean ± SD)	0.27±0.4	0.28±0.4	0.953
Uric acid in mg/dl (Mean ± SD)	3.62±0.9	3.01±0.8	0.004
Fasting Insulin in mIU/L Median(range)}	10(3-69)	8.50(2-69)	0.159

Table- 3: NLR and PLR among PE and normotensive groups.

Dividing the women studied by age, only 3% of women with PE were between 18 and 25 years of age, compared to 24% of normotensive women. In the PE group, 60% of the women belonged to the age group of 26–30 years, and the NLR was also significantly higher in the PE group than in the normotensive women see (Table 4). No differences were found in age and PLR see (Table 5).

S.N.	Age (in years)	Preeclampsia (n=30), number (%)	NLR	Normotensiv e control (n=70), number (%)	NLR	Pvalue
1	18-25	1 (3%)	3.17	17 (24%)	3.29 ± 0.76	0.875
2	26-30	18 (60%)	4.21 ± 1.17	35 (50%)	3.04 ± 0.80	<0.001
3	31-40	11 (37%)	3.78 ± 1.11	18 (26%)	3.13 ± 0.86	0.087

Table 4: Distribution of NLR value according to age.

S.N.	Age (in years)	Preeclampsia (n=30), number (%)	PLR	Normotensive control (n=70), number (%)	PLR	Pvalue
1	18-25	1 (3%)	13.4	17 (24%)	10.40±4.35	0.507
2	26-30	18 (60%)	11.37±4.30	35 (50%)	10.38±3.36	0.361
3	31-40	11 (37%)	10.88±4.7	18 (26%)	9.84±3.65	0.513

Table 5: Distribution of PLR value according to age.

The relationships between PE and NLR percentages with statistically significant results are shown in Table 6. More than a third of women in the normotensive group (88%) had NLR values between 1.00 and 3.00, whereas women with preeclampsia (78%) had NLR values between 1.00 and 3.00. It was 1.00-3.00. NLR values are between 5.01 and 7.50. No statistically significant differences were observed in the distribution of women based on PLR range see (Table 7).

NLR value range	Preeclampsia, n (%)	Normontensive, n (%)	Pvalue
1.00-3.00	5 (12%)	36 (88%)	
3.01-5.00	18 (36%)	32 (64%)	<0.001
5.01-7.50	7 (78%)	2 (22%)	

Table 6: Distribution of study women according to NLR range.

PLR value range	Preeclampsia, n (%)	Normontensive, n (%)	Pvalue
4.00-9.00	9 (22%)	31 (78%)	
9.01-14.00	13 (32%)	27 (68%)	0.343
14.01-23.00	8 (40%)	12 (60%)	

Table 7: Distribution of study women according to PLR range.

ROC analysis was used to estimate the positive predictive value of NLR for preeclampsia. The most discriminate NLR value at 12–16 weeks for PE development prediction, based on the receiver operator characteristics (ROC) curve, was 3.20. This resulted in good sensitivity and specificity, at 70% and 64%, respectively, with probability 0.74, or area under the curve (AUC) = 0.743, p <0.001), as shown in Figure 1. Figure 1 shows the area under the receiver operating characteristic curve for preeclampsia prediction using NLR values. There was a 0.743 (95% confidence interval) area under the curve.

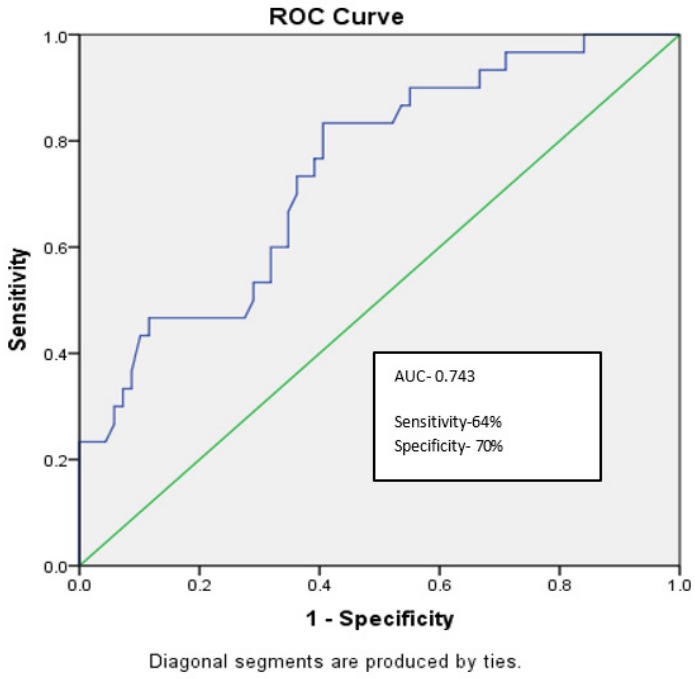

Figure 1: Area under the receiver operating characteristic curve for preeclampsia prediction using NLR values.

Discussion

PE manifests as multi-systemic illness linked to inflammatory cell activation. The antecedent event in this complex cascade is a heightened immune response, wherein inflammatory cytokines are released by neutrophils, lymphocytes, and thrombocytes. Furthermore,T cells undergo a phenotypic shift toward Th1 in PE, leading to the production of pro-inflammatory cytokines and interleukins [15,16]. This shift in T-cell behavior contributes to the overall pro-inflammatory milieu associated with preeclampsia. As a consequence, the expression of white blood cells increases, triggered by the stimulation of a systemic inflammatory response induced by these pro-inflammatory cytokines [17]. Laresgoiti-Servitje E, et al. [18]. studied that T-lymphocytes have been observed in pre-eclampsia at both normal and decreased levels, and it appears that they are not responsible for regulating the Th1/Th2 balance in this condition [18].

Our study found that, the NLR at 12–16 weeks of gestation was higher (4.02 v/s 3.13; p=<0.001) in women who were going to develop PE later in pregnancy in comparison to women who were normotensive. For the purpose of triaging pregnant women who may develop PE, NLR demonstrated good diagnostic accuracy. Although PLR levels were higher in PE women than in normotensive women, the difference did not reach statistical significance in our study.

In inflammatory responses, neutrophils, the predominant form of white blood cells in the human circulatory system, play a pivotal role [19]. The elevated Neutrophil-to-Lymphocyte Ratio (NLR) has been associated not only with various underlying inflammatory processes but also with several pregnancy-related complications. These include hyperemesis gravidarum [20], missed abortions [21], recurrent miscarriages [22], gestational diabetes [23], and premature deliveries [24].

Greer IA, et al. [25] demonstrated that in pregnancy-induced hypertension, plasma neutrophil elastase, a marker for neutrophil activation, is detectable in the mother circulation just before delivery and may contribute to vascular damage [25].

NLR serves as a cost-effective and readily accessible biomarker that could aid in the risk classification of pre-eclampsia patients. Oylumlu M, et al. [26] found that Neutrophils-to-Lymphocyte Ratio (NLR) tends to be higher in preeclampsia throughout later gestation (7.3±3.5 versus 3.1±1.1; p<0.001) [26]. Another study corroborates these findings, demonstrating that NLR in preeclampsia is elevated in later gestation (4.12 (1.81-16.50) vs. 2.33 (0.77-6.64); p<0.001) compared to healthy pregnant women. The PLR was found to be comparable between groups, with values of 109.73 (32.66-480.23) in the study group versus 98.76 (4.26-470.21) in the control group (p=0.584) [27].

In contrast, the PLR was statistically more in PE then in normotensive women (98.08 ± 18.27 v/s 85.25 ± 12.36: p<0.001) and the mean NLR was statistically significantly higher in cases (3.52 ± 1.05 and 3.22 ± 0.88: p) in later gestation. Conversely, it was discovered that there was no difference between preeclampsia and healthy pregnant women shortly before birth (p=0.423) [28].

In a study conducted by Kurtoglu E, et al. [28] which investigated the association between NLR and the clinical characteristics of preeclampsia, a retrospective analysis was performed on data from 203 women with gestational ages between 25 and 41 weeks. The preeclamptic group exhibited a significantly higher NLR (4.7 (1.1–39.6) vs. 4.1 (1.5-21.6); p<0.023) compared to the normotensive group. However,the study did not identify a correlation between the severity of the disease and the time of onset [29]. This implies that while NLR showed distinctions between preeclamptic and normotensive groups, it did not serve as an indicator for the severity.

In a study conducted by Gogoi P, et al. [29] in India, women diagnosed with pre-eclampsia exhibited higher levels of PLR and NLR. Specifically, when compared to the control group, the NLR was significantly elevated in pre-eclamptic women (6.8 ± 7.6 versus 3.0 ± 0.98; P=0.001).It's noteworthy that the evaluation of NLR and PLR has predominantly occurred in the third trimester in the majority of investigations.

Pre-eclamptic women had a much lower platelet count, though still lower [30]. Comparable findings in additional research on Indian women at a later stage of pregnancy [31,32].

A mid-gestation study, conducted in the second trimester between weeks 13 and 20, aimed to assess the diagnostic accuracy of NLR in predicting both non-severe and severe preeclampsia (PE). Statistically significant differences were observed among the three groups (p<0.01), with NLR mean values of SPE = 4.26±0.31, NSPE = 3.38±0.16, and Control = 3.14±0.16 [33]. Similarly, at 16-18 weeks, mean NLR values were found to be significantly higher in patients who later developed PE (5.55±0.81 vs. 4.55±0.66; p<0.001) [34].

In early gestation, as observed in our study at 11-13+6 weeks of gestation, NLR values were significantly higher in severe preeclampsia compared with the control group (4.54± 2.98 vs. 3.23±1.33; p<0.01) (11).

Similarly, a retrospective study conducted at 7-14 weeks of gestation revealed that both NLR (3.8 ±1.5 vs. 3.1±1.1; p <

0.001) and PLR (141.9±50.8 vs. 118.5±47.2; p<0.001) were significantly elevated in the preeclampsia group compared to the control group [12]. It was emphasized in this study that NLR could be a useful tool in determining preeclampsia in high-risk pregnancies [28]. These findings collectively support the potential of NLR as an early predictive marker for preeclampsia during the initial stages of gestation.

The ROC curve analysis demonstrated that NLR outperformed neutrophil or lymphocyte counts in the diagnostic process, effectively distinguishing PE from normotensive controls. ROC analysis reveals risk indicators for PE prediction, with the first trimester serving as the ideal cutoff point. Specifically, NLR exhibited a cutoff value of 3.20, with a 95% confidence interval (CI) of -0.64-0.87, 70% specificity, and 64% sensitivity(AUC = 0.743, P < 0.001). According to our results, women who are at risk of developing PE during the first trimester can be identified by assessing NLR values obtained between 12 and 16 weeks of gestation.

Gezer C, et al. [12] used 3.08 as the NLR cutoff value to predict preeclampsia (PE) in the first trimester, achieving a sensitivity and specificity of 74% and 70%, respectively whereas, Kirbas A, et al. [11] used an NLR cutoff value of >4.01 at 11–13 weeks gestation, with a sensitivity of 79% and specificity of 38% for predicting PE cases [11]. In a prospective case-control study by Sachan R, et al. [33] NLR demonstrated sensitivity and specificity of 53% and 65%, respectively, for predicting non-severe preeclampsia cases at a cutoff value of >3.35. Moreover, at a cutoff value of 3.42, NLR exhibited significant diagnostic accuracy in distinguishing between non- severe PE and severe PE, with a specificity of 65% and sensitivity of 81% [33]. Additionally, Singhal K, et al. [31] discovered that at a later gestational stage, pre-eclampsia cases could be differentiated from healthy pregnant controls with 68.6% sensitivity and 80% specificity at a cutoff value of 4.86 [31].

PE is a multisystem disorder and the pathogenetic steps of the disease are still unclear. Since the only treatment is delivery, timely prediction and prevention are essential to avoid the fetal and maternal consequences, especially of preterm PE. As a result, there is growing interest in the investigation of the role of novel biomarkers that would contribute in the identification of high-risk pregnant women and would shed light on the pathophysiology of the disorder. The NLR emerges as a potentially valuable tool for predicting preeclampsia (PE), demonstrating good sensitivity in distinguishing between women with normotension and those at risk of developing preeclampsia. Its predictive value holds promise for facilitating prompt referral, early diagnosis, and intervention, thereby mitigating potentially fatal complications associated with PE. The study findings provide clinicians with insights to identify women at risk for preeclampsia during the early stages of pregnancy (12–16 weeks), even before clinical symptoms manifest.

We conclude that hematological factors that are simple to measure are reliable markers of an individual's health. Systemic inflammatory response indicators can be utilized to predict PE. This study suggests that NLR may be used as a biomarker to identify women who are at risk of preeclampsia in the future. It found that women who had preeclampsia later in pregnancy had NLR levels of higher than 3.20 with 70% sensitivity and 64% specificity at 12–16 weeks of gestation.

Conflict of Interest

There is no conflict of interest among the authors.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mrs. Tarang Gupta and Dr Garima Kachhawa. The first draft of the manuscript was written by Mrs. Tarang Gupta and Dr Garima Kachhawa. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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