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RESEARCH ARTICLE

FIRST-TRIMESTER NEUTROPHIL-TO-LYMPHOCYTE RATIO AS AN EARLY PREDICTOR OF PREECLAMPSIA: A HOSPITAL-BASED PROSPECTIVE ANALYTICAL STUDY

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Abstract

Background: Preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality, particularly in developing countries, and is increasingly understood as a disorder of systemic inflammation and immune dysregulation arising from defective placentation. The neutrophil-to-lymphocyte ratio (NLR), derived from a routine complete blood count, has emerged as a simple, inexpensive marker of this inflammatory milieu. The present study evaluated the predictive value of first-trimester NLR for the development and severity of preeclampsia.

Methods: A hospital-based prospective analytical study was conducted in the Department of Obstetrics and Gynaecology, Pt. J.N.M. Medical College and Dr. B.R.A.M. Hospital, Raipur (Chhattisgarh) between March 2024 and March 2026. A total of 295 singleton primigravidae between 7 and 14 weeks of gestation were enrolled by consecutive sampling. First-trimester NLR was calculated as the ratio of neutrophil to lymphocyte percentages on a routine complete blood count, and women were followed prospectively until delivery for the development of preeclampsia, classified as mild or severe and as early- or late-onset.

Results: Twenty-seven women (9.2%) developed preeclampsia, of whom 15 had mild and 12 had severe disease. Mean first-trimester NLR was significantly higher in women who later developed preeclampsia than in normotensive women (4.33 ± 0.50 vs 2.70 ± 0.37; $p < 0.001$). Mean neutrophil percentage was higher and mean lymphocyte percentage lower in the preeclampsia group, and NLR correlated positively with the occurrence of preeclampsia ($r = 0.490$; $p < 0.001$).

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At a receiver-operating-characteristic-derived cut-off of ≥ 3.6, NLR predicted preeclampsia with a sensitivity of 100%, specificity of 96.3%, negative predictive value of 100% and overall diagnostic accuracy of 96.6% (area under the curve 0.989). Higher NLR values were associated with greater disease severity and a higher proportion of early-onset preeclampsia.

Conclusion: First-trimester NLR is a simple, inexpensive and highly sensitive screening tool for the early prediction of preeclampsia and its severity. Incorporation of NLR into routine first-trimester antenatal screening may facilitate early risk stratification and targeted preventive care, particularly in resource-limited settings.

Introduction:-

Preeclampsia is a multisystem disorder of pregnancy characterised by the new onset of hypertension, with or without proteinuria, after twenty weeks of gestation in a previously normotensive woman, and continues to account for a substantial proportion of maternal and perinatal morbidity and mortality worldwide [1,2.The maternal mortality rate in preeclampsia is 16% globally.

The pathophysiology of preeclampsia is increasingly understood as a two-stage process. The first stage involves defective trophoblastic invasion of the maternal spiral arteries with reduced uteroplacental perfusion and placental ischaemia, and the second stage is characterised by release of anti-angiogenic and inflammatory placental factors into the maternal circulation, leading to systemic endothelial dysfunction, oxidative stress and a heightened inflammatory response [3,4]. Pro-inflammatory cytokines including interleukin-6, interleukin-8 and interleukin-17 amplify neutrophil chemotaxis, activation and degranulation, while a shift away from regulatory T-cell–mediated immune tolerance produces a relative lymphocytopenia [4,5]. This combination of neutrophil activation and lymphocyte suppression is reflected, even before clinical onset, in the haematological profile of the maternal circulation.

The neutrophil-to-lymphocyte ratio (NLR), derived from routine complete blood count, has emerged as a robust, inexpensive marker of systemic inflammation and has been investigated as an early predictor of preeclampsia in several recent studies [6–9]. A growing body of evidence suggests that NLR is significantly elevated in the first trimester among women who subsequently develop preeclampsia, and a recent meta-analysis has supported its potential role as a first-trimester screening parameter [9]. However, Indian data from central India remain limited, and questions persist around the optimal cut-off value and the strength of association between first-trimester NLR and disease severity and onset. The present study was therefore designed to evaluate the role of first-trimester NLR as an early and inexpensive predictor of preeclampsia and its severity in a hospital-based cohort of primigravidae in central India.

Materials and Methods:-

This was a hospital-based, prospective analytical study conducted in the antenatal outpatient department of the Department of Obstetrics and Gynaecology, Pt. J.N.M. Medical College and associated Dr. B.R. Ambedkar Memorial Hospital, Raipur, Chhattisgarh, over a period of 24 months between March 2024 and March 2026. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrolment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consecutive singleton primigravidae attending the antenatal clinic between 7 and 14 weeks of gestation were screened for eligibility. Women with chronic hypertension, fever or any infection at the time of first-trimester examination, multiple gestation, molar pregnancy, body mass index greater than 30 kg/m² or intrauterine fetal demise, and those unwilling to provide informed consent, were excluded. The sample size was calculated using the formula for estimation of a single proportion based on a reported first-trimester NLR sensitivity of 74.6% for preeclampsia, with 5% absolute precision, 95% confidence and 20% allowance for loss to follow-up; the minimum required sample size was 370 cases, and 295 women completed follow-up.

At enrolment, detailed history, general and obstetric examination, body mass index and blood pressure were recorded in a predesigned proforma. A complete blood count was performed using a standard automated haematology analyser, and the neutrophil-to-lymphocyte ratio was calculated as the ratio of neutrophil percentage to lymphocyte percentage. All women were followed prospectively through pregnancy with blood pressure and urine protein measurement at each antenatal visit. Preeclampsia was diagnosed as per standard criteria of new-onset hypertension after 20 weeks of gestation with proteinuria or evidence of end-organ dysfunction, and was categorised

as mild or severe and as early-onset (< 34 weeks) or late-onset (≥ 34 weeks). The primary outcome was the development of preeclampsia; the secondary outcome was its severity.

Data were entered in Microsoft Excel and analysed using SPSS. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Comparisons between groups were performed using the independent t-test for continuous variables and the chi-square or Fisher exact test for categorical variables. Spearman's correlation coefficient was used to assess the relationship between haematological indices and preeclampsia, and a receiver-operating-characteristic (ROC) curve was constructed to derive the optimal cut-off of NLR for predicting preeclampsia. A two-sided p-value less than 0.05 was considered statistically significant.

Results:-

A total of 295 primigravidae completed follow-up and were included in the analysis. The mean maternal age was 24.31 ± 3.29 years, with the majority (61.0%, n = 180) in the 20–25-year age group. Most participants were enrolled in the early first trimester, with a mean gestational age at enrolment of 10.41 ± 1.30 weeks; 57.3% of women were between 8 and 10 completed weeks of gestation. Body mass index distribution was predominantly normal (72.2%, n = 213), with the remaining 27.8% (n = 82) overweight; no underweight or obese women were enrolled, in keeping with the exclusion criterion of BMI > 30 kg/m². The baseline demographic profile of the study cohort is summarised in Table 1.

Of the 295 women followed to delivery, 27 (9.2%) developed preeclampsia, comprising 15 (5.1%) with mild and 12 (4.1%) with severe disease. Among women who developed preeclampsia, 22 (81.5%) were in the 20–25-year and 26–30-year age categories combined. The distribution of preeclampsia and its severity within the study cohort is shown in Table 2.

Mean first-trimester neutrophil percentage was significantly higher and mean lymphocyte percentage significantly lower in women who later developed preeclampsia compared with those who remained normotensive. Most women in the cohort (58.3%) had neutrophil percentages between 60% and 70%, and the majority (68.1%) had lymphocyte percentages between 20% and 30%. A clear gradient was observed across categories: among women with neutrophil percentages of 70–80%, the incidence of preeclampsia rose to 20.6%, of whom 60% had severe disease, in contrast to a 4.1% incidence (all mild) among those with neutrophils 60–70%. Conversely, women with lymphocyte percentages of 10–20% had a markedly higher incidence of preeclampsia (57.9%), with equal proportions of mild and severe disease, whereas only 2.4% of those with lymphocytes 20–30% developed the condition. Mean neutrophil percentage was 72.4% in the preeclampsia group versus 67.1% in normotensive women, rising further to 75% in severe disease, while mean lymphocyte percentage fell from 19.2% in normotensive women to 16.85% in preeclampsia and 15.83% in severe preeclampsia. These haematological differences are summarised in Table 3.

The neutrophil-to-lymphocyte ratio reflected these underlying changes. No woman with a first-trimester NLR in the range of 2.0–2.9 (n = 186; 63.1% of the cohort) developed preeclampsia. The incidence of preeclampsia rose progressively with increasing NLR — 12.9% in those with NLR 2.9–3.9, 40.0% in those with NLR 3.9–4.9, and 66.7% in those with NLR 4.9–5.9. The proportion of severe disease also rose with increasing NLR, reaching 83.3% of preeclampsia cases in the highest NLR stratum. A similar trend was observed for the timing of onset: 66.6% of preeclampsia cases in the 3.9–4.9 NLR stratum and 83.3% of those in the 4.9–5.9 stratum were early-onset, in contrast to a predominantly late-onset pattern in the 2.9–3.9 stratum. The distribution of preeclampsia incidence, severity and onset across NLR strata is presented in Table 4.

Comparison of mean values between groups confirmed these observations. Mean neutrophil percentage was 73.68 ± 5.41% in the preeclampsia group versus 68.06 ± 5.62% in normotensive women ($p < 0.001$), mean lymphocyte percentage was 18.24 ± 2.66% versus 24.89 ± 2.62% ($p < 0.001$), and mean first-trimester NLR was 4.33 ± 0.50 versus 2.70 ± 0.37 ($p < 0.001$). On Spearman correlation analysis, neutrophil percentage was positively correlated ($r = 0.277$; $p < 0.001$) and lymphocyte percentage negatively correlated ($r = −0.463$; $p < 0.001$) with the development of preeclampsia, while NLR showed a moderate positive correlation with preeclampsia ($r = 0.490$; $p < 0.001$). When stratified by maternal age and gestational age at enrolment, mean NLR remained significantly higher in the preeclampsia group across every subgroup, indicating that the association was independent of these demographic variables. The summary comparison of haematological indices between groups is shown in Table 5.

Receiver-operating-characteristic curve analysis identified an optimal first-trimester NLR cut-off of 3.6 for predicting preeclampsia. The area under the curve for NLR was 0.989, compared with 0.777 for neutrophil percentage alone. At the 3.6 threshold, NLR predicted preeclampsia with a sensitivity of 100%, specificity of

96.30%, positive predictive value of 72.97%, negative predictive value of 100% and overall diagnostic accuracy of 96.61%; all 27 women who developed preeclampsia had NLR ≥ 3.6, and no woman with NLR < 3.6 developed the disease (Table 6). These findings support the use of first-trimester NLR as a highly sensitive and reasonably specific screening tool for the early prediction of preeclampsia.

Table 1. Baseline demographic profile of the study cohort (n = 295).

Variable	Frequency (n)	Percentage (%)
Age group (years)		
≤ 20	19	6.4
20–25	180	61.0
26–30	81	27.5
> 30	15	5.1
Gestational age at enrolment (weeks)		
8–10	169	57.3
10–12	107	36.3
12–14	19	6.4
Body mass index (kg/m²)		
Normal (18.5–24.9)	213	72.2
Overweight (25.0–29.9)	82	27.8

Mean (± SD) maternal age was 24.31 ± 3.29 years; mean (± SD) gestational age at enrolment was 10.41 ± 1.30 weeks.

Table 2. Incidence and severity of preeclampsia in the study cohort.

Pregnancy outcome	Frequency (n)	Percentage (%)
Normotensive throughout pregnancy	268	90.8
Preeclampsia developed	**27**	**9.2**
Mild preeclampsia	15	5.1
Severe preeclampsia	12	4.1
Total	**295**	**100.0**

Table 3. Distribution of first-trimester neutrophil and lymphocyte percentages and association with preeclampsia.

Category	Total (n)	Preeclampsia, n (%)	Mild PE, n	Severe PE, n
Neutrophils (%)				
50–60	24	0 (0)	0	0
60–70	172	7 (4.1)	7	0
70–80	97	20 (20.6)	8	12
80–90	2	0 (0)	0	0

Lymphocytes (%)				
10–20	38	22 (57.9)	11	11
20–30	201	5 (2.4)	4	1
30–40	56	0 (0)	0	0

PE = preeclampsia.

Table 4. Distribution of preeclampsia incidence, severity and onset across first-trimester NLR strata.

NLR stratum	Total (n)	PE, n (%)	Severe PE (%)	Early-onset (%)	Late-onset (%)
2.0–2.9	186	0 (0)	—	—	—
2.9–3.9	70	9 (12.9)	44.5	44.5	55.5
3.9–4.9	30	12 (40.0)	58.3	66.6	33.4
4.9–5.9	9	6 (66.7)	83.3	83.3	16.7

NLR = neutrophil-to-lymphocyte ratio; PE = preeclampsia.

Table 5. Comparison of mean first-trimester haematological indices between women with and without preeclampsia.

Parameter	Preeclampsia (n = 27)	Normotensive (n = 268)	p-value
Neutrophil percentage (%)	73.68 ± 5.41	68.06 ± 5.62	**< 0.001**
Lymphocyte percentage (%)	18.24 ± 2.66	24.89 ± 2.62	**< 0.001**
Neutrophil-to-lymphocyte ratio (NLR)	**4.33 ± 0.50**	**2.70 ± 0.37**	**< 0.001**

Values are mean ± standard deviation. Comparisons by independent t-test. Statistically significant p-values shown in bold red.

Table 6. Diagnostic performance of first-trimester NLR at a cut-off of ≥ 3.6 for prediction of preeclampsia.

Diagnostic parameter	Value
Area under the ROC curve (AUC)	0.989
Sensitivity	100.0%
Specificity	96.30%
Positive predictive value	72.97%
Negative predictive value	100.0%
Overall diagnostic accuracy	96.61%

Among 295 women, 27 with first-trimester NLR ≥ 3.6 developed preeclampsia (true positives), 10 with NLR ≥ 3.6 remained normotensive (false positives), 258 with NLR < 3.6 remained normotensive (true negatives), and no woman with NLR < 3.6 developed preeclampsia (false negatives = 0).

Discussion:-

In this prospective hospital-based study of 295 primigravidae from central India, first-trimester NLR was significantly elevated in women who subsequently developed preeclampsia compared with normotensive women, and emerged as a highly sensitive predictor of both the occurrence and the severity of disease. Mean first-trimester NLR was 4.33 ± 0.50 in the preeclampsia group versus 2.70 ± 0.37 in normotensive women ($p < 0.001$), and a cut-

off of 3.6 yielded a sensitivity of 100%, specificity of 96.3% and an area under the ROC curve of 0.989 for the prediction of preeclampsia. These findings reinforce the growing body of literature implicating an early, systemic inflammatory response in the pathogenesis of preeclampsia and supporting the use of routine haematological indices as bedside markers of this milieu [6–9].

The mean maternal age in the present cohort (24.31 ± 3.29 years) was somewhat younger than that reported in several Turkish and Indonesian series, in which mean age has typically ranged from 26 to 30 years [10–12]. This reflects the predominantly young reproductive demographic of women presenting for first-trimester antenatal care at our institution and is broadly consistent with other Indian studies [13]. Despite this younger age profile, mean NLR was elevated in preeclampsia across all age strata, suggesting that the inflammatory signal captured by NLR is largely independent of maternal age. A similar pattern of age-independent elevation has been described by Gezer et al. [7], Prasmusinto et al. [12] and Singhal et al. [13], lending support to the broader applicability of NLR as a screening tool.

The mean gestational age at enrolment in this study was 10.41 ± 1.30 weeks, with the majority of women recruited between 8 and 12 weeks. Mean NLR did not differ substantially across gestational age strata within this window, in keeping with previous reports that the inflammatory signal of impending preeclampsia is detectable from early in the first trimester [6,7]. The trimester-specific stability of NLR is operationally important because it implies that the timing of the first antenatal visit — typically driven by patient factors rather than by protocol — does not materially affect the predictive value of the test.Body mass index distribution in this cohort was predominantly normal, with no obese participants by design. Even in this lean population, NLR retained a strong association with preeclampsia, in contrast to several Western series in which a substantial proportion of preeclampsia is attributable to obesity-driven inflammation [14]. This observation suggests that, in central Indian populations, immune dysregulation rather than adipose-tissue–driven inflammation may be the dominant mechanism underlying first-trimester NLR elevation.

The graded association observed in the present study, with progressively higher incidence and severity of preeclampsia across rising NLR strata, mirrors that reported by Kurtoglu et al. [10], Gezer et al. [7], Oğlak et al. [8] and Panwar et al. [15]. The mean neutrophil percentage of 72.4% in the preeclampsia group versus 67.1% in normotensive women, and the corresponding fall in lymphocyte percentage from 19.2% to 16.85%, are consistent with values reported by Oylumlu et al. [16], Gezer et al. [7] and Bozdag et al. [17], who described mean lymphocyte percentages of 12%, 18.8% and 20% in their respective preeclampsia cohorts. Biologically, these haematological changes reflect neutrophil activation driven by interleukin-6 and interleukin-8–mediated chemotaxis, with concurrent reduction in regulatory T-cell–mediated tolerance, generating reactive oxygen species, neutrophil extracellular traps and endothelial injury that perpetuate the inflammatory cycle of preeclampsia [3,4].

The NLR cut-off of 3.6 derived from ROC analysis in the present study lies between the lower thresholds (3.0–3.2) reported by Nagesh et al. and Prasmusinto et al. and the higher thresholds (4.4–5.6) reported by Kurtoglu et al. and Panwar et al. [10,12,15]. Differences in reported preeclampsia incidence across these studies largely reflect the chosen cut-off, the timing of NLR measurement and the underlying disease prevalence. The 100% sensitivity and negative predictive value of NLR ≥ 3.6 in our cohort suggest that this threshold is well suited to screening, while the moderate positive predictive value (72.97%) underscores that NLR should be used as a screening rather than a diagnostic tool, ideally as part of a composite first-trimester risk assessment incorporating mean arterial pressure, uterine artery Doppler indices and biochemical markers where available [9].

The present study has several strengths, including its prospective design, single-centre enrolment with consistent laboratory methodology, exclusion of major confounders of NLR such as infection, chronic hypertension and obesity, and complete follow-up to delivery for outcome ascertainment. Limitations include the single-centre setting and the exclusion of obese women, which may limit generalisability to populations in which obesity is a major driver of preeclampsia. The cut-off of 3.6 was derived and validated within the same dataset and should be tested prospectively in independent cohorts. Long-term follow-up of perinatal outcomes was beyond the scope of this work and would be of value in future studies.

Conclusion:-

First-trimester neutrophil-to-lymphocyte ratio is a simple, inexpensive and highly sensitive predictor of the development and severity of preeclampsia in primigravid Indian women. At a cut-off of ≥ 3.6, NLR identified all women who subsequently developed preeclampsia, with a specificity of 96.3% and an area under the ROC curve of 0.989. The association was independent of maternal age, gestational age at enrolment and body mass index. NLR

derived from a routine first-trimester complete blood count may therefore serve as a valuable bedside screening tool for early risk stratification of preeclampsia, particularly in resource-limited settings, and merits prospective validation in larger multicentric cohorts and incorporation into composite first-trimester risk-prediction models.

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Conflict of Interest:-
The authors declare that they have no conflicts of interest relevant to this work.

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