

Evaluation of Neutrophil to Lymphocyte Ratio and Serum Uric Acid to Creatinine Ratio in Hypertensive Disorders of Pregnancy: A Cross-Sectional Study

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ABSTRACT

Background: Hypertensive disorders of pregnancy (HDP) significantly contribute to maternal and perinatal morbidity and mortality, making early identification essential. Oxidative stress and endothelial dysfunction play key roles in the pathophysiology of HDP, leading to impaired placental perfusion, systemic inflammation, hypertension, and proteinuria. Serum uric acid, an oxidative stress marker, when interpreted in relation to serum creatinine as the uric acid-creatinine ratio (UACR), may overcome limitations of isolated measurements. The Neutrophil-lymphocyte ratio (NLR) reflects systemic inflammation. Both UACR and NLR have emerged as simple, inexpensive biomarkers.

Objectives: To evaluate the utility of UACR and NLR as accessible biomarkers for early detection and risk stratification of complications in hypertensive disorders of pregnancy.

Methodology: This cross-sectional study included 82 pregnant women attending a tertiary care center between April and September 2023: 30 normotensive controls, 27 with gestational hypertension, and 25 with preeclampsia. Serum uric acid and creatinine were measured using enzymatic uricase and Jaffe's methods, respectively. NLR was calculated from complete blood counts. Statistical analysis comprised ANOVA, correlation analysis, and receiver operating characteristic (ROC) curves.

Results: Both UACR and NLR were significantly higher in gestational hypertension and preeclampsia compared with controls ($p < 0.001$), with the highest levels observed in preeclampsia. UACR showed strong positive correlations with systolic blood pressure ($r = 0.68$) and proteinuria ($r = 0.59$), while NLR demonstrated similar associations. ROC analysis showed good discriminatory ability for preeclampsia (AUC: 0.82 for UACR; 0.88 for NLR).

Conclusions: UACR and NLR are simple, cost-effective biomarkers reflecting oxidative stress and inflammation in HDP. Their combined use may enhance early detection, risk stratification, and timely clinical intervention.

Keywords: Hypertensive disorders of pregnancy, Preeclampsia, Uric acid-creatinine ratio, Neutrophil-lymphocyte ratio, Oxidative stress

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INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are a major contributor to maternal morbidity and mortality globally, accounting for nearly 14% of maternal deaths in developing countries.[1] In India, the prevalence of HDP ranges from 7-10%, with preeclampsia affecting about 2-5% of pregnancies.[2] Although hypertension itself is alarming during pregnancy, adverse effects from progression to pre-eclampsia or eclampsia present the main concern. Early detection and referral to a tertiary care centre to minimize complications is of crucial importance. Early diagnostic biomarkers of pre-eclampsia such as soluble endoglin (sEng), soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PIGF), vascular endothelial growth factor (VEGF), though resourceful are impractical for large scale screening.[3-7]

Recently, neutrophil-to-lymphocyte ratio (NLR) has emerged as an inflammatory marker that reflects the balance between innate immune activation and adaptive immune suppression, and it also aids in disease prediction in systemic inflammatory conditions including preeclampsia.[8-11] Hyperuricemia in preeclampsia is linked with endothelial injury, oxidative stress, and reduced nitric oxide bioavailability.[12] Uric acid interacts with proinflammatory cytokines directly and contributes to the pathophysiology of preeclampsia.[13-17]

Studies have reported that serum uric acid-to-creatinine ratio (UACR) is elevated in women with HDP.[18] UACR, adjusts uric acid levels for renal function further improving its diagnostic and prognostic value.[19,20] UACR and NLR may serve as cost-effective tools in resource-limited settings. Despite emerging evidence, few studies have employed UACR and NLR in segregating the spectrum of HDP. This dual-biomarker approach could aid in early risk stratification, guide clinical monitoring, and improve feto-maternal outcomes.

This study was designed to evaluate and compare serum UACR and NLR in normotensive pregnant women, women with gestational hypertension, and women with preeclampsia, and to explore their potential role as markers of disease severity.

MATERIALS AND METHODS

This was a hospital-based cross-sectional observational study conducted at the Departments of Obstetrics & Gynaecology and Biochemistry, a tertiary care centre and teaching hospital, from April 2023 to September 2023.

The sample size was calculated to detect a clinically meaningful difference of 1.0 in mean serum uric acid-to-creatinine ratio (UACR) between the gestational hypertension and preeclampsia groups. Based on a standard deviation (σ) of 1.2, two-tailed $\alpha = 0.05$, and power $(1-\beta) = 0.80$, the sample size for each group was estimated using the formula for two independent means, $N = (2(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2) / \Delta^2$

Substituting $Z_{1-\alpha/2} = 1.96$; $Z_{1-\beta} = 0.84$; $\Delta = 1.0$, the required sample size was 24 per group. To accommodate attrition (~10%), 27 women with gestational hypertension and 25 with preeclampsia were recruited. For feasibility, incidence rates from local hospital records (gestational hypertension 8-10%, preeclampsia 3-5% among antenatal attendees) indicated that ~1,000 third-trimester women would need to be screened during the six-month period to achieve this target.

This cross-sectional study enrolled 82 pregnant women 30 normotensive controls, 27 with gestational hypertension (GH), and 25 with preeclampsia (PE) women in their third trimester (28-40 weeks) were recruited and categorized into three groups: **1) Control group** - 30 normotensive, healthy pregnant women with no proteinuria. **2) Gestational hypertension group** - 27 women with blood pressure $\geq 140/90$ mmHg on two occasions at least 4 hours apart, after 20 weeks of gestation, without proteinuria [2]. **3) Preeclampsia group** - 25 women with gestational hypertension plus proteinuria (≥ 300 mg in 24 hours) or other systemic features as per ACOG 2020 guidelines [2].

Exclusion criteria included chronic hypertension, pre-existing renal disease, diabetes mellitus, autoimmune disease, active infection, and multiple gestations.

Demographic and obstetric history were recorded using a structured proforma. Blood pressure was measured in the seated position using a calibrated sphygmomanometer. Venous blood samples were obtained after an overnight fast. Complete blood counts were analyzed using an automated hematology analyzer. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Serum uric acid was estimated by enzymatic uricase method and serum creatinine by Jaffe's kinetic method on a fully automated chemistry analyzer. UACR was computed as serum uric acid (mg/dL) divided by serum creatinine (mg/dL). Proteinuria was assessed by dipstick and confirmed by 24-hour urine protein when indicated.

Statistical Analysis: Data were analysed using SPSS v21.0. Normality was tested with the Kolmogorov Smirnov test. Continuous variables were expressed as mean \pm standard deviation (SD) or median (interquartile range, IQR). Categorical variables were presented as frequencies and percentages. One-way ANOVA with post hoc Tukey's test (for parametric data) or Kruskal Wallis test (for nonparametric data) for group comparison. Pearson's correlation coefficient for linear associations between biomarkers and clinical parameters. Receiver operating characteristic (ROC) curve analysis with calculation of area under the curve (AUC), sensitivity, and specificity. A two-tailed $p < 0.05$ was considered statistically significant.

Ethical Approval: The Institutional Ethics Committee approved the study (IEC Approval No. ECR/1365/Inst/TN/2020, dated 18/02/2023). Written informed consent was obtained from all participants.

RESULTS

This study found that neutrophil-to-lymphocyte ratio (NLR) and urine albumin-to-creatinine ratio (UACR) are significantly elevated in women with preeclampsia and gestational hypertension compared to normotensive controls. Both NLR and UACR demonstrated strong diagnostic performance for preeclampsia, with NLR showing a marginally better area under the curve (AUC). The control, gestational hypertension (GHTN), and preeclampsia (PE) groups were comparable in age ($p=0.23$) and gestational age ($p = 0.65$). Systolic and diastolic blood pressure were significantly higher in the GHTN & PE groups compared to controls ($p <0.001$ for all comparisons). Proteinuria also showed a significant

difference across the groups ($p <0.001$) (Table 1).

Serum uric acid, serum creatinine, UACR, and NLR were all significantly different across the three groups (Table 2). The highest values for these biomarkers were observed in the preeclampsia group, followed by the gestational hypertension group, and then the control group. The p-values were as follows Serum Uric Acid ($p <0.001$), Serum Creatinine ($p = 0.004$), UACR ($p <0.001$), and NLR ($p <0.001$). Platelet count didn't show statistically significant difference among the groups ($p = 0.12$).

UACR and NLR were both strongly correlated with systolic blood pressure, diastolic blood pressure, and semi-quantitative proteinuria (Table 3). All correlations were highly significant, with $p <0.001$.

Table 1: Demographic and Clinical Characteristics of study participants

Parameter	Control (n=30)	Gestational HTN (n=27)	Preeclampsia (n=25)	p-Value
Age (years)	24.3 ± 3.5	24.8 ± 3.1	25.5 ± 3.3	0.23
Gestational Age (weeks)	34.5 ± 2.8	35.2 ± 3.0	34.7 ± 2.9	0.65
Systolic BP (mmHg)	112 ± 8	138 ± 10	160 ± 12	< 0.001*
Diastolic BP (mmHg)	74 ± 6	90 ± 7	102 ± 8	< 0.001*
Proteinuria (dipstick +/−)	Negative	Trace/1+	2+ / 3+	< 0.001*

Values are in mean ± SD. Proteinuria graded by dipstick. Statistical significance tested using one-way ANOVA with Tukey's post hoc test. * $p < 0.05$ considered significant.

Table 2: Biomarker Comparisons in the groups

Parameter	Control (n=30)	Gestational HTN (n=27)	Preeclampsia (n=25)	p-Value
Serum Uric Acid (mg/dL)	4.1 ± 0.5	4.85 ± 0.62	6.23 ± 0.88	< 0.001*
Serum Creatinine (mg/dL)	0.66 ± 0.09	0.72 ± 0.11	0.81 ± 0.15	0.004*
UACR (ratio)	6.21 ± 0.98	6.75 ± 1.10	7.95 ± 1.30	< 0.001*
NLR	2.5 ± 0.7	3.20 ± 0.89	4.80 ± 1.20	< 0.001*
Platelet Count ($\times 10^3/\text{mm}^3$)	215 ± 40	202 ± 45.5	185 ± 50.7	0.12

Values are in mean ± SD. UACR = uric acid-to-creatinine ratio; NLR = neutrophil-to-lymphocyte ratio. One-way ANOVA with Tukey's post hoc test used. * $p < 0.05$ considered significant.

Table 3: Correlations of UACR and NLR with Clinical Parameters

Biomarker	Clinical parameter	Correlation Coefficient (r)	p-value
UACR (uric acid-to-creatinine ratio)	Systolic Blood Pressure (mm Hg)	0.68	< 0.001
UACR (uric acid-to-creatinine ratio)	Diastolic Blood Pressure (mm Hg)	0.64	< 0.001
UACR (uric acid-to-creatinine ratio)	Proteinuria (Semi quantitative)	0.59	< 0.001
NLR (neutrophil-to-lymphocyte ratio)	Systolic Blood Pressure (mm Hg)	0.62	< 0.001
NLR (neutrophil-to-lymphocyte ratio)	Diastolic Blood Pressure (mm Hg)	0.57	< 0.001
NLR (neutrophil-to-lymphocyte ratio)	Proteinuria (Semi quantitative)	0.54	< 0.001

Correlation analysis of urine albumin-to-creatinine ratio (UACR) and neutrophil-to-lymphocyte ratio (NLR) with systolic blood pressure, diastolic blood pressure, and semi-quantitative proteinuria in gestational hypertension and preeclampsia groups. Pearson's correlation coefficient (r) used. Statistical significance set at $p < 0.05$.

The diagnostic performance of UACR and NLR for preeclampsia was evaluated using ROC curves (Table 4). The AUC for UACR was 0.82 (95% CI: 0.73 0.91), with a sensitivity of 78% and a specificity of 75%. The AUC for NLR was 0.88 (95% CI: 0.80 0.94), with a sensitivity of 84% and a specificity of 80%. NLR demonstrated a slightly better diagnostic performance compared to UACR. The ROC curves for UACR and NLR are shown in Figure 1. Bar chart depicting mean UACR and NLR levels in Control, Gestational Hypertension, and Preeclampsia groups, demonstrating a progressive rise from Control

to GH to PE are shown in Figure 2.

Figure 1 and table 4 shows ROC curves for UACR and NLR discriminating preeclampsia from normotensive controls. NLR demonstrated marginally better diagnostic performance.

Figure 2 shows comparison of mean UACR and NLR values across control, gestational hypertension, and preeclampsia groups. Error bars represent SD. One-way ANOVA applied; $p < 0.05$ considered significant.

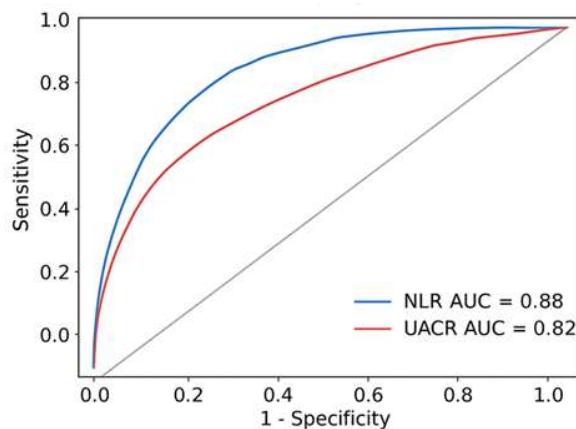


Figure 1: ROC curves for UACR and NLR

Table 4: ROC Curve Analysis

Marker	AUC	95% CI	Sensitivity (%)	Specificity (%)
UACR	0.82	0.73 0.91	78	75
NLR	0.88	0.80 0.94	84	80

Values shown as area under the curve (AUC) with 95% CI, sensitivity, and specificity. ROC analysis performed using SPSS v21.0.

Our study reinforces the finding that both UACR and NLR are significantly elevated in pregnant women with hypertensive disorders, with the highest values observed in those with preeclampsia. These results are consistent with existing literature that links oxidative stress and systemic inflammation to the pathogenesis of preeclampsia. The strong positive correlation we ob-

served between UACR and clinical parameters like blood pressure and proteinuria suggests its utility as a comprehensive marker of renal dysfunction and oxidative stress. Similarly, the elevated NLR reflects the systemic inflammatory state characteristic of preeclampsia.

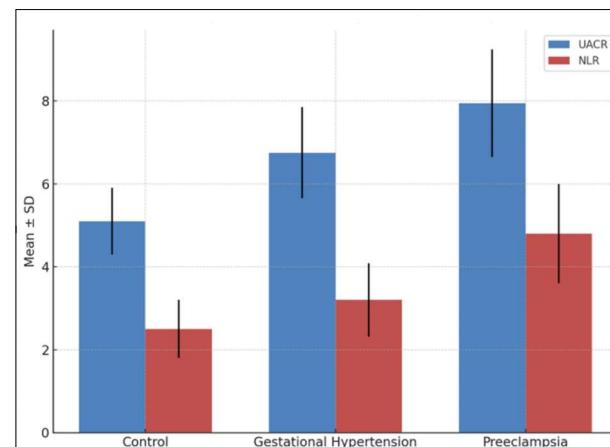


Figure 2: Bar chart showing mean UACR and NLR values across the study population

DISCUSSION

Elevated serum uric acid is a common feature of preeclampsia and is linked to endothelial dysfunction, oxidative stress, and diminished nitric oxide availability [12], as illustrated in Figure 3.

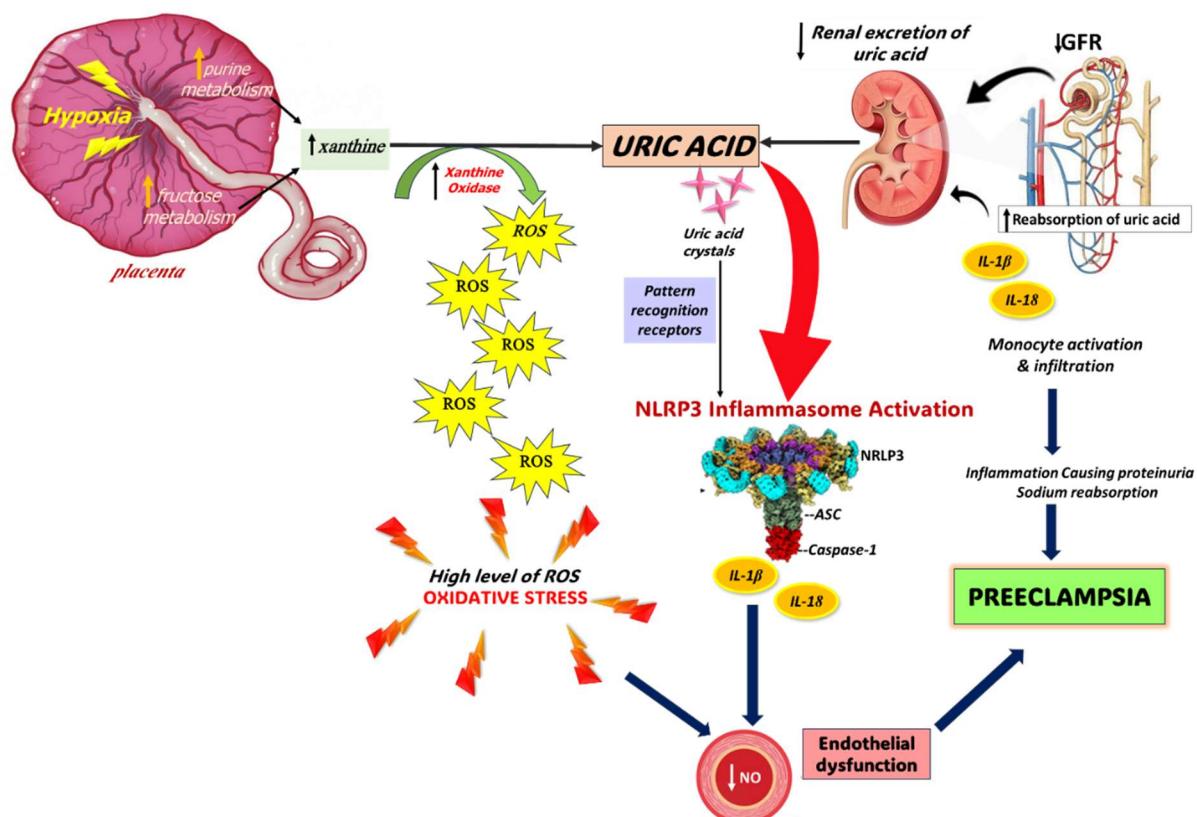


Figure 3: Pathophysiological role of Uric acid in the development of preeclampsia

Figure 3 depict Pathophysiological role of Uric acid in the development of preeclampsia. The schematic overview demonstrates how elevated Uric acid (UA) contributes to the development of preeclampsia. During pregnancy, hyperuricemia arises from increased placental debris production and enhanced fructose metabolism under hypoxic conditions, which ultimately stimulate Xanthine oxidase (XO) activity and generate excess reactive oxygen species (ROS). Reduced renal clearance caused by impaired glomerular filtration and increased tubular reabsorption further elevates UA levels, which along with other damage-associated molecular patterns (DAMPs) activates the NLRP3 inflammasome, leading to increased production of pro-inflammatory cytokines like IL-1 β and IL-18. Together, inflammation and oxidative stress further drive endothelial dysfunction and renal impairment, causing reduced glomerular filtration rate, increased sodium retention, and proteinuria, eventually contributing to the clinical presentation of preeclampsia. (Figure prepared by Author 1).

The present study demonstrated that both UACR and NLR were significantly higher in women with gestational hypertension and preeclampsia compared with normotensive pregnant women, and that values were highest in the preeclampsia group. These findings are consistent with the growing body of literature suggesting that metabolic dysregulation and systemic inflammation play central roles in the pathogenesis of HDP.

The elevated NLR observed in our study aligns with previous reports by Yücel B et al [9] and Serin S et al [10], who noted that increased neutrophil counts reflect heightened innate immune activity, while decreased lymphocyte counts indicate suppression of adaptive immunity during preeclampsia. This imbalance may contribute to exaggerated inflammatory responses and endothelial dysfunction [21].

Similarly, our finding of elevated UACR supports earlier work by Bellomo G et al [19] and Ananth CV et al [20], who highlighted that adjusting uric acid for creatinine improves its predictive value by accounting for individual variations in renal function. Elevated UACR may indicate both increased uric acid production (due to tissue ischemia and oxidative stress) and impaired renal clearance, which are hallmarks of preeclampsia [22].

An interesting observation was that both markers showed a graded increase from controls to gestational hypertension and preeclampsia, suggesting a potential role in disease stratification. This agrees with the findings of Mohammed RA et al [18], who reported that combining metabolic and inflammatory markers improved early prediction of preeclampsia severity.

From a clinical perspective, both UACR and NLR have advantages: they are inexpensive, easily measurable with standard laboratory equipment, and do not require specialized assays. This makes them particularly valuable in low-resource settings, where advanced predictive tests such as angiogenic factors may not be readily available.

LIMITATIONS

Limitations of the present study include its cross-sectional design, which precludes causal inference, and the relatively small sample size, which may limit generalizability. Longitudinal studies are needed to evaluate the predictive ability of these markers earlier in pregnancy. Additionally, while we excluded participants with overt infections or chronic inflammatory diseases, subclinical inflammation could not be entirely ruled out.

CONCLUSION

Our study suggests that serum UACR and NLR are significantly elevated in gestational hypertension and preeclampsia compared with normotensive pregnancies, with the highest levels seen in preeclampsia. The progressive rise across groups supports their potential role in assessing disease severity. Given their simplicity and low cost, these markers may serve as useful adjuncts for early risk stratification in hypertensive disorders of pregnancy, particularly in resource-limited settings.

Individual Author's Contribution: DPG contributed to every stage of the study, including conception, design, data collection, analysis, and manuscript preparation. GP and SJM both participated in study conception, data analysis, and manuscript writing.

Availability of data: The data that support the findings of this study are available from the corresponding author on reasonable request.

Declaration of Non-use of generative AI Tools: This article was prepared without the use of generative AI tools for content creation, analysis, or data generation. All findings and interpretations are based solely on the authors' independent work and expertise.

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