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ORIGINAL RESEARCH ARTICLE

Integrated evaluation of uric acid, hs-CRP, and leukocyte count across preeclampsia severity among pregnant women in Al-Ahsa, Saudi Arabia: A cross-sectional study

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Abstract

Introduction: Preeclampsia (PE), a hypertensive disorder unique to pregnancy, is linked to systemic inflammation, endothelial dysfunction, and poor maternal and fetal outcomes.

Objectives: This study assessed serum uric acid, high-sensitivity C-reactive protein (hs-CRP), and total leukocyte count (TLC) in relation to preeclampsia severity, examining how well each marker discriminates individually and in combination—an analysis not previously undertaken in pregnant women from the Al-Ahsa region of Saudi Arabia.

Methods: This cross-sectional study included 58 pregnant women recruited in Al-Ahsa, Saudi Arabia: normotensive controls ($n = 28$), women with mild PE ($n = 18$), and women with severe PE ($n = 12$). Serum uric acid, hs-CRP, and TLC concentrations were determined for all participants and compared across groups using analysis of variance (ANOVA), the Kruskal–Wallis test, the Mann–Whitney *U* test, multivariate ANOVA, analysis of covariance, and receiver operating characteristic curve (ROC) analysis.

Results: Serum uric acid, hs-CRP, and TLC levels differed significantly across study groups (all $p < 0.001$), peaking in severe PE (uric acid: 343 ± 61 μmol/L; hs-CRP: 15 ± 3 mg/L; TLC: 11 ± 2 $\times 10^9$/L). A significant overall effect of disease severity on the combined biomarker profile emerged on multivariate analysis, independent of maternal and gestational age, while ROC analysis indicated excellent-to-moderate accuracy for uric acid (area under the curve [AUC] = 0.92), hs-CRP (AUC = 0.88), and TLC (AUC = 0.75) in separating preeclampsia from normotensive pregnancy (all $p < 0.001$).

Conclusion: Serum uric acid, hs-CRP, and TLC are significantly associated with increasing PE severity and individually showed strong discriminatory performance, suggesting their potential value as adjunctive markers for inflammatory assessment in antenatal care, pending prospective validation.

Keywords: Preeclampsia; Uric acid; High-sensitivity C-reactive protein; Total leukocyte count; Inflammation; Biomarkers

1. Introduction

Preeclampsia (PE) is a multisystem complication unique to pregnancy, defined by the onset of new hypertension beyond the 20th week of gestation, and it remains among the foremost drivers of maternal and perinatal illness and death globally.[1-4] It complicates an estimated 2–8% of pregnancies worldwide and carries a substantial burden of maternal harm, including renal impairment, hepatic dysfunction, eclampsia, and placental abruption, together with fetal risks such as growth restriction, preterm delivery, and fetal mortality.[1,3-5] Within Saudi Arabia and neighboring Middle Eastern countries, hypertensive pregnancy disorders remain a pressing public health issue, yet region-specific biomarker data from localities such as Al-Ahsa remain scarce.[2,6-8]

The precise cause of PE remains unknown, but abnormal placentation, endothelial injury, oxidative stress, and an exaggerated systemic inflammatory response are widely regarded as key drivers of the disease process.[9-12] A growing body of evidence points to inflammatory activation and immune dysregulation as central to disease progression, contributing to vascular damage, placental ischemia, and disrupted maternal-fetal blood flow.[13,14]

A range of inflammatory and metabolic markers has been explored as tools for identifying PE early and gauging its severity. High-sensitivity C-reactive protein (hs-CRP), a liver-derived acute-phase protein, has been linked in earlier work to endothelial damage and systemic inflammation among women with PE.[15-18] Similarly, elevated serum uric acid has been tied to oxidative stress, reduced placental perfusion, renal impairment, and worsening maternal complications.[19,20] Hematological shifts, including a rise in total leukocyte count (TLC), likewise signal inflammatory activation and immune imbalance in PE and may offer additional diagnostic and prognostic value.[21-24]

Earlier studies and meta-analyses have reported meaningful links between hs-CRP, serum uric acid, leukocyte indices, and PE severity, yet findings vary across populations, and few studies have examined all three markers together within one severity-stratified cohort.[25,26] As far as we are aware, no prior work has jointly assessed how well hs-CRP, serum uric acid, and TLC individually discriminate across PE severity grades among pregnant women in Saudi Arabia, and specifically within the Al-Ahsa region.[2,6,7] To address this gap, the present study set out to examine the inflammatory and clinical relevance of hs-CRP, serum uric acid, and TLC across PE severity levels among pregnant women in Al-Ahsa, Saudi Arabia, and to establish their individual diagnostic accuracy through receiver operating characteristic (ROC) analysis, complemented by univariate and multivariate statistical methods examining their combined association with PE severity.

2. Methods

2.1. Ethics statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Local Committee for Research Ethics at King Fahad Hospital-Hofuf, Al-Ahsa Health Cluster (IRB KFHH No. H-05-HS-065; IRB Log No. 119-EP-2023; approved November 16, 2023). Written informed consent was obtained from all participants before enrollment, and confidentiality of participant data was maintained throughout the study.

2.2. Study design and setting

This descriptive cross-sectional study enrolled pregnant women attending the Obstetrics and Gynecology Department of King Faisal Hospital and Maternity and Children Hospital, Al-Ahsa, Eastern Province, Saudi Arabia, between December 16, 2023, and November 18, 2024. Laboratory analyses were carried out at King Faisal Hospital's clinical laboratory, Al-Ahsa, which holds College of American Pathologists accreditation. The number of participants enrolled reflected how many eligible women were available and recruitable during the study window. A formal, a priori sample-size calculation for the PE groups ($n = p(1-p)z^2/E^2$) indicated a target of 36 cases; however, since recruitment was capped by a fixed study window (December 2023 to November 2024), only 30 PE cases were ultimately enrolled (18 mild, 12 severe). This shortfall against the calculated target, particularly within the severe PE subgroup, is noted as a limitation. A non-probability convenience sampling approach was used to recruit participants. Because the sample was drawn by convenience from women attending only these two facilities, the cohort may not be fully representative of the wider population of pregnant women in Al-Ahsa, and selection bias cannot be ruled out.

2.3. Participants and grouping

A total of 58 pregnant women were enrolled and categorized

into three groups: normotensive pregnant women (n = 28), women with mild PE (n = 18), and women with severe PE (n = 12). PE was defined as new-onset hypertension after 20 weeks of gestation accompanied by proteinuria or related clinical manifestations. Mild PE was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg with proteinuria. Severe PE was defined by systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 110 mmHg on two occasions, or the presence of severe clinical manifestations regardless of blood pressure level, including headache, visual disturbances, upper abdominal pain, oliguria, convulsions, elevated serum creatinine, thrombocytopenia, or markedly elevated liver enzymes, consistent with current American College of Obstetricians and Gynecologists criteria.[27]

2.4. Inclusion and exclusion criteria

Normotensive controls were healthy pregnant women with singleton pregnancy, gestational age ≥ 20 weeks, age ≥ 18 years, normal blood pressure throughout pregnancy, absence of proteinuria or signs of PE, and willingness to provide informed consent.

Women with PE were diagnosed after 20 weeks of gestation with blood pressure ≥ 140/90 mmHg measured on at least two occasions four hours apart and proteinuria ≥ 300 mg/24 h or a urine protein/creatinine ratio ≥ 0.3. Participants were excluded if they had pre-existing chronic hypertension, renal disease, diabetes mellitus, autoimmune disease, acute infection, multiple pregnancy, smoking history, inflammatory disorders, use of anti-inflammatory or immunosuppressive medications, fetal anomalies, intrauterine fetal death, or refusal to participate.

2.5. Blood sample collection and biomarker analysis

Venous blood (5 mL) was collected aseptically from each participant. Part of it (2 mL) was transferred into potassium ethylenediaminetetraacetic acid tubes for complete blood count analysis, including TLC. The remaining 3 mL was collected in serum tubes for measurement of serum uric acid and hs-CRP.

Total leukocyte count was measured using a hematology analyzer (Alinity HQ, Abbott Laboratories, USA), whereas serum uric acid and hs-CRP concentrations were determined using a clinical chemistry analyzer (Alinity c System, Abbott Laboratories, USA). Serum uric acid was measured using an enzymatic uricase-based method and hs-CRP via a high-sensitivity immunoturbidimetric assay. All samples were analyzed on the day of collection according to laboratory standard operating procedures and manufacturer instructions.

2.6. Statistical analysis

All data were entered into Excel (Microsoft 365, Microsoft Corporation, USA) and subsequently analyzed using Statistical Package for the Social Sciences (SPSS 20.0, IBM, United States). Continuous variables are reported as mean ± standard deviation; categorical variables are reported as frequency counts and percentages. The Shapiro–Wilk test, together with skewness values, was used to check whether each variable followed a normal distribution.

Group differences across the three cohorts were tested with one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, selected according to each variable's distribution. Where ANOVA indicated an overall difference, Tukey's honestly significant difference (HSD) test was applied for post hoc pairwise comparisons, and the Mann-Whitney U test was additionally used to compare groups pairwise.

To evaluate the combined effect of PE severity on the biomarker profile as a set, multivariate ANOVA (MANOVA) was performed using Pillai's trace criterion. Analysis of covariance (ANCOVA) was then used to check whether maternal age or gestational age confounded the biomarker levels observed. Parametric, non-parametric, and multivariate methods were combined deliberately to verify findings from several complementary angles given the modest sample size, rather than to inflate the count of statistically significant results. Statistical significance was set at a p-value below 0.05 throughout.

3. Results

3.1. Participant characteristics

The final cohort comprised 58 pregnant women across three groups: 28 normotensive controls (Normal, 48%), 18 with mild PE (Mild PE, 31%), and 12 with severe PE (Severe PE, 21%) (Figure 1). Mean age was similar across the three groups (31 ± 6, 32 ± 9, and 32 ± 7 years, respectively), with no significant between-group difference (p > 0.05) (Table 1). Gestational age at enrollment was somewhat lower in the Severe PE group (36 weeks) than in the Normal (38 ± 0.8 weeks) and Mild PE (38 ± 1 weeks) groups, though this difference fell short of statistical significance (p > 0.05) (Table 1), indicating that the groups were demographically comparable and that the biomarker differences reported below are unlikely to be explained by age or gestational-age confounding.

Serum uric acid levels progressively and significantly increased with PE severity: Normal 199 ± 45 µmol/L, Mild PE 211 ± 37 µmol/L, and Severe PE 343 ± 61 µmol/L (p < 0.001). hs-CRP was markedly and significantly elevated in

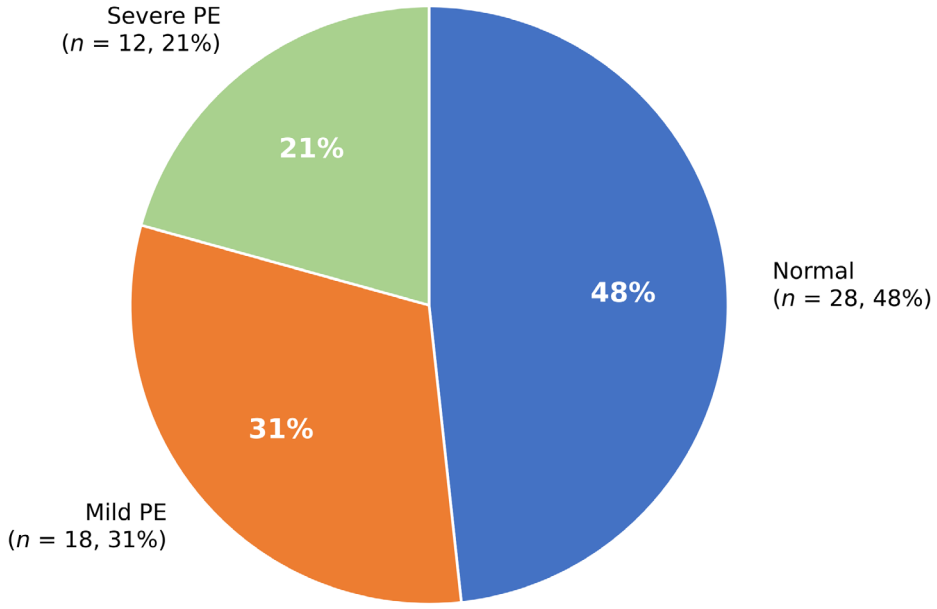


Figure 1. Distribution of study participants across groups: Normal (n = 28, 48%), Mild PE (n = 18, 31%), and Severe PE (n = 12, 21%). Patient age (p > 0.05) and gestational age (p > 0.05) did not differ significantly across groups, confirming comparable baseline demographics.

Table 1. Participant characteristics: Patient age and gestational age across study groups

Group	*n*	Patient age (years)			Gestational age (weeks)		
		Min	Max	Mean ± SD	Min	Max	Mean ± SD
Normal	28	18	42	31 ± 6	36	39	38 ± 0.8
Mild PE	18	17	47	32 ± 9	36	40	38 ± 1
Severe PE	12	21	45	32 ± 7	36	37	36

Abbreviations: PE: Preeclampsia; SD: Standard deviation.

Severe PE (15 ± 3 mg/L) compared with Mild PE (1 ± 0.9 mg/L) and Normal groups (0.9 ± 0.7 mg/L) (p < 0.001). TLC demonstrated significant elevation in Severe PE (11 ± 2 × 10^9/L) compared with Normal (7 ± 3×10^9/L) and Mild PE (5 ± 1 × 10^9/L) groups (p < 0.001) (Table 2). These severity-dependent elevations directly support the study hypothesis.

3.2. Normality assessment of study variables

To justify the choice of tests, the Shapiro–Wilk test was used to check the distribution of each variable (Table 3). Patient age was normally distributed in all groups (Normal: p = 0.295; Mild PE: p = 0.180; Severe PE: p = 0.939; all p > 0.05). Gestational age showed significant non-normality in the Normal (p < 0.001) and Severe PE groups (p < 0.001), with mild departure in the Mild PE group (p = 0.028).

Among inflammatory biomarkers, uric acid demonstrated near-normal distribution in the Normal group (p = 0.734, skewness = −0.073) but significant non-normality in the Mild PE group (p = 0.034, skewness = −1.149), while remaining normally distributed in the Severe PE group (p = 0.488). hs-CRP showed significant non-normality in both the Normal (p < 0.001, skewness = 1.234) and Mild PE groups (p < 0.001, skewness = 2.783), while showing a normal distribution in Severe PE (p = 0.190). TLC was significantly non-normal in the Normal

Table 2. Biomarker levels across study groups: Uric acid, hs-CRP, and TLC

Variable	Normal group (n = 28)			Mild PE (n = 18)			Severe PE (n = 12)		
	Min	Max	Mean ± SD	Min	Max	Mean ± SD	Min	Max	Mean ± SD
Uric acid (μmol/L)	118	295	199 ± 45	120	254	211 ± 37	250	438	343 ± 61
hs-CRP (mg/L)	0.4	3	0.9 ± 0.7	0.4	4	1 ± 0.9	9	18	15 ± 3
TLC (10^9/L)	5	13	7 ± 3	3	7	5 ± 1	7	16	11 ± 2

Abbreviations: hs-CRP: High-sensitivity C-reactive protein; PE: Preeclampsia; SD: Standard deviation; TLC: Total leukocyte count.

Table 3. Normality assessment: Shapiro–Wilk test and skewness for all variables

Variable	Shapiro–Wilk p-value			Skewness		
	Normal	Mild PE	Severe PE	Normal	Mild PE	Severe PE
Patient age (years)	0.295	0.180	0.939	−0.372	−0.435	0.120
Gestational age (weeks)	<0.001	0.028	<0.001	−1.039	−0.528	0.388
Uric acid (μmol/L)	0.734	0.034	0.488	−0.073	−1.149	0.017
hs-CRP (mg/L)	<0.001	<0.001	0.190	1.234	2.783	−1.098
TLC (10^9/L)	0.002	0.682	0.873	1.502	0.139	0.523

Note: $p < 0.05$ indicates significant departure from normality.
Abbreviations: hs-CRP: High-sensitivity C-reactive protein; PE: Preeclampsia; TLC: Total leukocyte count.

group (p = 0.002, skewness = 1.502), while normally distributed in Mild and Severe PE groups (p = 0.682 and p = 0.873, respectively). On this basis, ANOVA and the Kruskal–Wallis test were applied in parallel, as appropriate to each variable.

3.3. Comparison of inflammatory biomarkers among study groups

One-way ANOVA and Kruskal–Wallis testing showed highly significant between-group differences for all three biomarkers: Uric acid (F = 42, $p < 0.001$), hs-CRP (F = 473, $p < 0.001$), and TLC (F = 31, $p < 0.001$), with both tests concordant (Table 4), confirming that PE severity has a statistically significant impact on all three biomarker levels. Post hoc Tukey's HSD testing found no significant difference in uric acid levels between the Normal and Mild PE groups (mean difference = 12.55 μmol/L, 95% confidence interval [CI]: −21.63 to 46.74, t = 0.88, p = 0.652). The Severe PE group showed highly significant elevations compared with both the Normal group (mean difference = 144.25 μmol/L, 95% CI: 105.20–183.29, t = 8.90, $p < 0.001$) and the Mild PE group (mean difference = 131.69 μmol/L, 95% CI: 89.52–173.86, t = 7.52, $p < 0.001$) (Table 5; Figure 2).

Table 4. Overall group comparison: ANOVA and Kruskal–Wallis test results

Variable	F	ANOVA p-value	Kruskal–Wallis p-value
Uric acid (μmol/L)	42	<0.001	<0.001
hs-CRP (mg/L)	473	<0.001	<0.001
TLC (10^9/L)	31	<0.001	<0.001

Abbreviations: ANOVA: Analysis of variance; hs-CRP: High-sensitivity C-reactive protein; TLC: Total leukocyte count.

Likewise for hs-CRP, the Normal and Mild PE groups did not differ significantly (mean difference = 0.01 mg/L, 95% CI: −0.99 to 1.01, t = 0.02, p = 1.000). Severe

Table 5. Post-hoc comparisons: Tukey's HSD test for all biomarkers

Variable	Group comparison	Mean difference	95% CI lower	95% CI upper	SE	*t*	*p* (Tukey HSD)
	Mild PE vs. Normal	12.55	−21.63	46.74	14.19	0.88	0.652
Uric acid (μmol/L)	Mild PE vs. Severe PE	−131.69	−173.86	−89.52	17.50	−7.52	<0.001
	Normal vs. Severe PE	−144.25	−183.29	−105.20	16.20	−8.90	<0.001
	Mild PE vs. Normal	0.01	−0.99	1.01	0.41	0.02	1.000
hs-CRP (mg/L)	Mild PE vs. Severe PE	−13.74	−14.98	−12.51	0.51	−26.76	<0.001
	Normal vs. Severe PE	−13.75	−14.90	−12.61	0.47	−28.92	<0.001
	Mild PE vs. Normal	−1.550	–	–	0.573	−2.704	<0.020
TLC (10^9/L)	Mild PE vs. Severe PE	−5.544	–	–	0.707	−7.838	<0.001
	Normal vs. Severe PE	−3.993	–	–	0.655	−6.099	<0.001

Notes: 95% CI for the TLC comparisons could not be derived from the summary statistics available for this parametric post-hoc analysis and are therefore not presented; the corresponding non-parametric pairwise comparisons for TLC, with exact *p*-values for all three group contrasts, are reported in full in Table 6; *p*-values < 0.05 indicate statistically significant differences.
Abbreviations: CI: Confidence interval; hs-CRP: High-sensitivity C-reactive protein; HSD: Honestly significant difference; PE: Preeclampsia; SE: Standard error; TLC: Total leukocyte count.

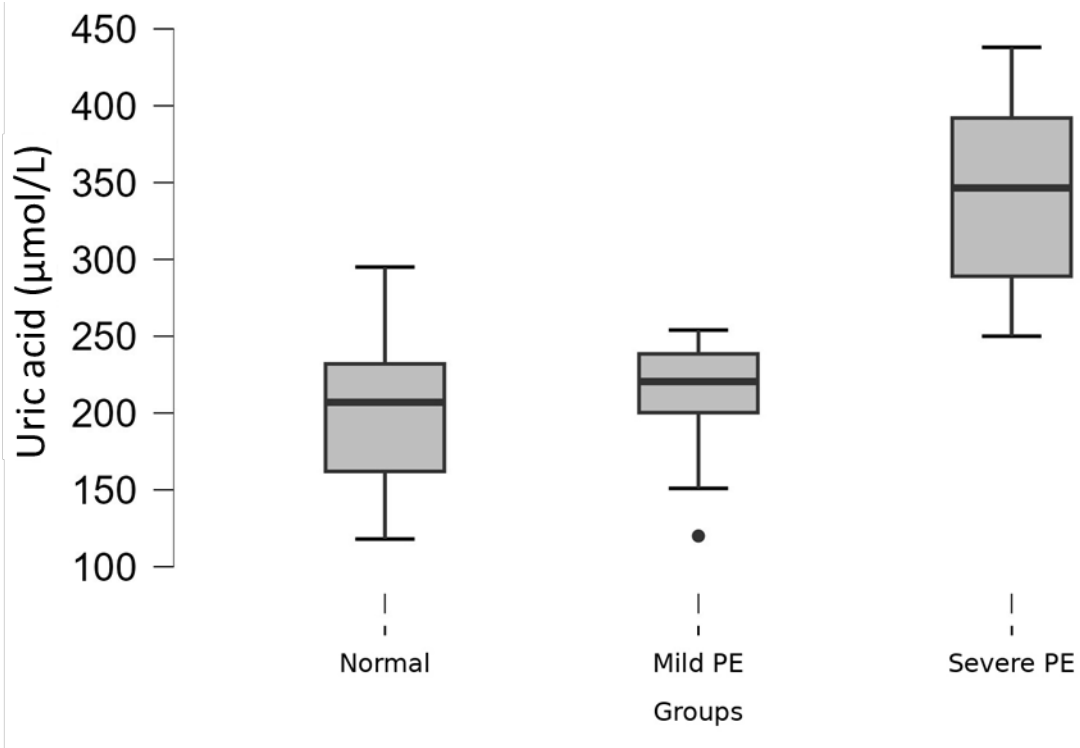


Figure 2. Box plot of serum uric acid levels (μmol/L) across study groups. Severe PE demonstrated markedly elevated uric acid levels compared with both the Normal group (mean difference = 144.25 μmol/L, $p < 0.001$) and the Mild PE group (mean difference = 131.69 μmol/L, $p < 0.001$). Normal vs. Mild PE: not significant ($p = 0.652$). Overall: ANOVA $F = 42$, $p < 0.001$; Kruskal–Wallis $p < 0.001$.
Abbreviations: ANOVA: Analysis of variance; PE: Preeclampsia.

PE patients demonstrated markedly elevated hs-CRP compared with both the Normal group (mean difference = 13.75 mg/L, 95% CI: 12.61–14.90, $t = 28.92$, $p < 0.001$) and the Mild PE group (mean difference = 13.74 mg/L, 95% CI: 12.51–14.98, $t = 26.76$, $p < 0.001$) (Table 5; Figure 3).

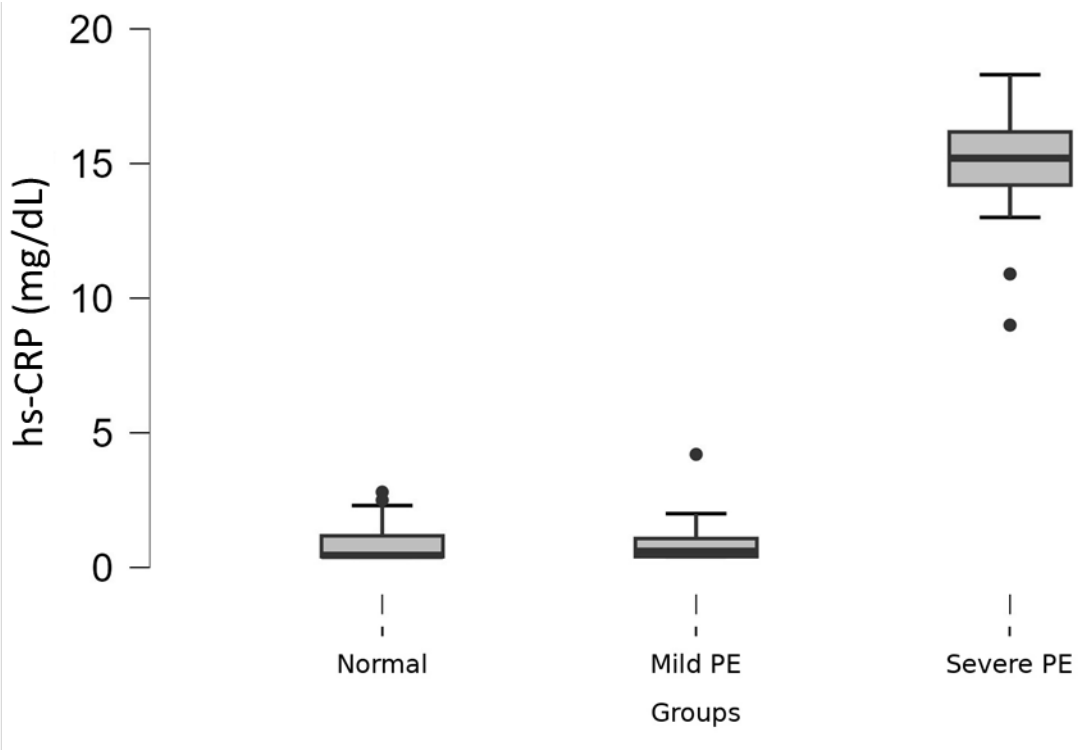


Figure 3. Box plot of hs-CRP levels (mg/L) across study groups. Severe PE demonstrated significantly elevated hs-CRP compared to both the Normal group (mean difference = 13.75 mg/L, $p < 0.001$) and the Mild PE group (mean difference = 13.74 mg/L, $p < 0.001$). Normal vs. Mild PE: not significant ($p = 1.000$). Overall: ANOVA $F = 473$, $p < 0.001$; Kruskal–Wallis $p < 0.001$.
Abbreviations: ANOVA: Analysis of variance; hs-CRP: High-sensitivity C-reactive protein; PE: Preeclampsia.

Total leukocyte content showed statistically significant differences across all group comparisons. Mild PE patients demonstrated significantly lower TLC compared with the Normal group (mean difference = 1.55×10^9/L, $t = 2.704$, $p < 0.02$). Severe PE exhibited significantly elevated TLC compared with both the Normal group (mean difference = 3.99×10^9/L, $t = 6.099$, $p < 0.001$) and the Mild PE group (mean difference = 5.54×10^9/L, $t = 7.838$, $p < 0.001$) (Table 5; Figure 4). Significant TLC differences across all three group pairs confirm that leukocyte levels are significantly associated with PE severity.

3.4. Pairwise group comparisons using Mann–Whitney *U* test

Mann–Whitney *U* pairwise comparisons corroborated the Tukey HSD findings (Table 6). Between Normal and Mild PE groups, only TLC differed significantly ($U = 129$, $p = 0.006$), while uric acid ($U = 297$, $p = 0.31$) and hs-CRP ($U = 255$, $p = 0.95$) did not, confirming that these biomarkers are specifically sensitive to severe rather than mild disease. Between Normal and Severe PE groups, all three biomarkers demonstrated highly statistically significant elevations: uric acid ($U = 6$, $p < 0.001$), hs-CRP ($U = 0.00$, $p < 0.001$), and TLC ($U = 32$, $p < 0.001$) (Table 6), confirming profound inflammatory and metabolic derangement in Severe PE compared with normotensive pregnancy.

Comparison between Mild and Severe PE groups demonstrated highly statistically significant differences for all three biomarkers: uric acid ($U = 1.5$, $p < 0.001$), hs-CRP ($U = 0.00$, $p < 0.001$), and TLC ($U = 2$, $p < 0.001$) (Table 6). The extremely low U-values for hs-CRP and uric acid indicate near-complete group separation, reflecting the magnitude of inflammatory dysregulation as PE progresses from mild to severe disease.

3.5. Correlation analysis of inflammatory biomarkers

Spearman's partial correlation analysis demonstrated statistically significant positive correlations among all three biomarkers. Uric acid showed a statistically significant moderate positive correlation with hs-CRP ($rho = 0.529$, $p < 0.001$) and with TLC ($rho = 0.430$, $p < 0.001$). hs-CRP demonstrated a statistically significant positive correlation with TLC ($rho = 0.432$, $p < 0.001$). All three correlations were significant at $p < 0.001$, indicating

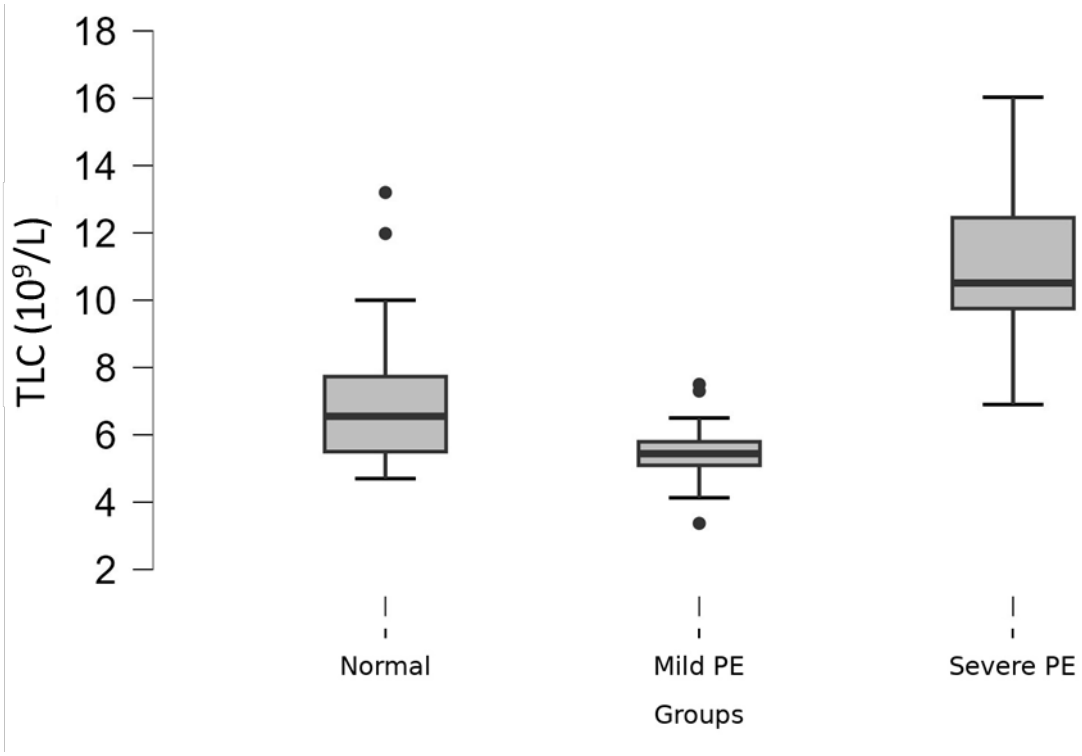


Figure 4. Box plot of total leukocyte count (TLC, 10^9/L) across study groups. Severe PE demonstrated significantly elevated TLC compared with both Normal (mean difference = 3.99 × 10^9/L, $p < 0.001$) and Mild PE groups (mean difference = 5.54 × 10^9/L, $p < 0.001$). Mild PE showed significantly lower TLC than the Normal group (mean difference = 1.55 × 10^9/L, $p < 0.02$). Overall: ANOVA $F = 31$, $p < 0.001$; Kruskal–Wallis $p < 0.001$.
Abbreviations: ANOVA: Analysis of variance; PE: Preeclampsia; TLC: Total leukocyte count.

Table 6. Pairwise group comparisons: Mann–Whitney *U* test for all biomarkers

Variable	Normal vs. Mild PE		Normal vs. Severe PE		Mild PE vs. Severe PE	
	U	*p*-value	*U*	*p*-value	*U*	*p*-value
Uric acid (μmol/L)	297	0.31	6	<0.001	1.5	<0.001
hs-CRP (mg/L)	255	0.95	0.00	<0.001	0.00	<0.001
TLC (10^9/L)	129	0.006	32	<0.001	2	<0.001

Abbreviations: hs-CRP: High-sensitivity C-reactive protein; PE: Preeclampsia; TLC: Total leukocyte count.

that uric acid, hs-CRP, and TLC rise in parallel with increasing PE severity, reflecting integrated systemic inflammatory activation (Figure 5). Spearman's partial correlation coefficients were adjusted for patient age and gestational age, consistent with the covariates examined in the ANCOVA analyses. Because these correlations were calculated across the pooled sample spanning all three severity groups, they may partly reflect the between-group separation in biomarker levels rather than within-group biomarker-to-biomarker relationships alone, and should not be interpreted as evidence of a specific biological or mechanistic connection between the markers.

3.6. Multivariate analysis

Multivariate ANOVA using Pillai's Trace demonstrated a statistically significant overall effect of PE severity on the combined biomarker profile (Pillai's Trace = 1.10, approximate $F = 22$, $p < 0.001$) (Tables 7 and 8), confirming that the collective effect of PE severity on uric acid, hs-CRP, and TLC together is statistically significant, providing multivariate support for the study hypothesis.

The ANCOVA indicated that neither patient age (uric acid: $F = 0.59$, $p = 0.44$; hs-CRP: $F = 2.68$, $p = 0.10$; TLC:

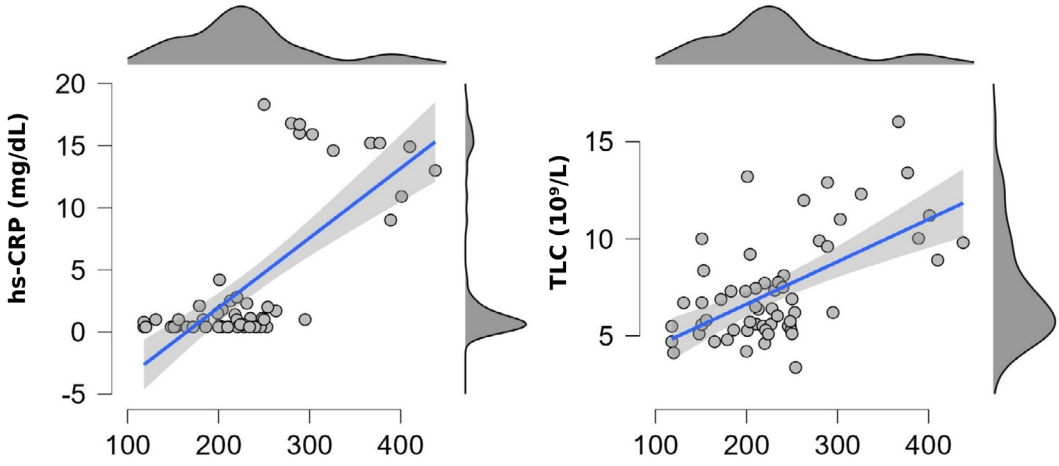


Figure 5. Scatter plots with regression lines and marginal density distributions illustrating statistically significant positive correlations among inflammatory biomarkers. Left panel: Uric acid vs. hs-CRP (*rho* = 0.529, $p < 0.001$). Right panel: Uric acid vs. TLC (*rho* = 0.430, $p < 0.001$). Both correlations are significant at $p < 0.001$. The hs-CRP–TLC correlation reported in the Results (*rho* = 0.432, $p < 0.001$) is not displayed as a separate panel here for figure clarity. Abbreviations: hs-CRP: High-sensitivity C-reactive protein; TLC: Total leukocyte count.

Table 7. Multivariate analysis: Multivariate analysis of variance (MANOVA) (Pillai Test)

MANOVA (Pillai Test)	Approximate *F*	Trace Pillai	*p*-value
Intercept	960	0.98	<0.001
Groups	22	1.10	<0.001

Table 8. Multivariate analysis: ANCOVA results—effect of covariates on biomarker levels

ANCOVA covariate	Uric acid (µmol/L)		hs-CRP (mg/L)		TLC (10^9/L)	
	F	*p*-value	*F*	*p*-value	*F*	*p*-value
Patient Age (years)	0.59	0.44	2.68	0.10	0.01	0.91
Gestational Age (weeks)	0.71	0.40	0.59	0.44	2.75	0.10

Note: ANCOVA assessed patient age and gestational age as covariates; all ANCOVA *p*-values > 0.05 indicate these covariates did not significantly affect the biomarker levels after adjusting for group differences.
Abbreviations: ANCOVA: Analysis of covariance; hs-CRP: High-sensitivity C-reactive protein; TLC: Total leukocyte count.

$F = 0.01$, $p = 0.91$) nor gestational age (uric acid: $F = 0.71$, $p = 0.40$; hs-CRP: $F = 0.59$, $p = 0.44$; TLC: $F = 2.75$, $p = 0.10$) significantly influenced any biomarker (all $p > 0.05$) (Tables 7 and 8); these covariates therefore did not appear to confound the observed associations between biomarker levels and PE severity, although the modest sample size limits power to detect smaller confounding effects.

3.7. Receiver operating characteristic analysis

The ROC curve analysis evaluated the diagnostic performance of each biomarker in distinguishing PE patients from normotensive pregnant women. Uric acid demonstrated the highest and statistically significant diagnostic accuracy with an area under the curve (AUC) of 0.92 ($p < 0.001$), indicating excellent discriminatory performance and identifying it as the strongest individual discriminator of PE severity among the three biomarkers evaluated.

The hs-CRP demonstrated strong and statistically significant diagnostic utility with an AUC of 0.88 (*p*

< 0.001), while TLC showed moderate yet statistically significant diagnostic performance with an AUC of 0.75 (p < 0.001). All three AUC values exceeded 0.70, confirming that each biomarker individually provides statistically significant diagnostic value for PE detection.

Collectively, the statistically significant AUC values for uric acid (0.92), hs-CRP (0.88), and TLC (0.75) indicate that all three inflammatory biomarkers discriminate PE from normotensive pregnancy with reasonable accuracy, consistent with the study hypothesis; these AUC values reflect PE detection and should not be interpreted as evidence of severity prediction.

4. Discussion

This study examined the inflammatory and diagnostic value of serum uric acid, hs-CRP, and TLC in normotensive pregnant women compared with women who had mild or severe PE in Al-Ahsa, Saudi Arabia. The central hypothesis—that these three biomarkers track increasing PE severity and mirror underlying systemic inflammatory and metabolic dysregulation—was borne out by the data. Every biomarker showed a statistically significant, severity-dependent rise (all $p < 0.001$), significant pairwise differences between Severe PE and both other groups (all $p < 0.001$), significant positive intercorrelations (all $rho > 0.43$, $p < 0.001$), and a highly significant combined multivariate effect of disease severity (MANOVA: Pillai's Trace = 1.10, $F = 22$, $p < 0.001$). Taken together, these results echo the well-established contribution of systemic inflammation, endothelial dysfunction, oxidative stress, and immune dysregulation to PE pathophysiology.[11-13,25]

Serum uric acid rose progressively with PE severity, with the elevation concentrated in the Severe PE group; levels did not differ significantly between the Normal and Mild PE groups. This pattern aligns with published work linking hyperuricemia in PE to impaired renal clearance, oxidative stress, placental ischemia, and endothelial dysfunction.[19,20,28] Elevated uric acid levels have been associated with adverse maternal and fetal outcomes, including preterm delivery and fetal growth restriction[29], and meta-analytic evidence further supports its role as a marker of PE severity and pregnancy complications.[30] Uric acid is thought to promote oxidative stress and endothelial injury through several mechanisms, including inhibition of nitric oxide synthesis, stimulation of pro-inflammatory cytokine release, and activation of the renin-angiotensin system, all of which are implicated in the vascular pathology of severe PE.[20,30] The absence of a significant elevation in Mild PE relative to normotensive pregnancy suggests that hyperuricemia becomes clinically detectable only once systemic endothelial and renal dysfunction reaches a threshold characteristic of severe disease, consistent with previous meta-analyses.[25,30] Uric acid also showed the highest individual diagnostic accuracy among the three biomarkers evaluated, discussed further below.

High-sensitivity C-reactive protein likewise rose with PE severity, with by far the largest and most statistically significant elevation seen in the Severe PE group; Normal and Mild PE did not differ significantly. Acute infection and other overt inflammatory conditions were pre-specified exclusion criteria (Section 2), which reduces but does not entirely eliminate the possibility that subclinical infection or another unmeasured inflammatory process contributed to this magnitude of elevation; the timing of blood sampling relative to any antihypertensive or other treatment was not systematically recorded and is noted as an additional limitation. This pattern mirrors earlier investigations and systematic reviews documenting elevated hs-CRP in PE, attributed to a hepatic acute-phase response driven by placental ischemia and pro-inflammatory cytokine release.[16-18,26,28] The pronounced elevation specifically in Severe PE is consistent with the concept that hs-CRP acts as a marker of established systemic inflammatory activation rather than early endothelial dysfunction, which may explain its limited utility as an early screening marker in mild disease.[15,28] This finding further supports incorporating hs-CRP within a multi-marker inflammatory panel rather than as a standalone early predictor, as proposed in the literature.[26]

Total leukocyte count was the only one of the three biomarkers to differ significantly across all three pairwise group comparisons, including Normal versus Mild PE, where levels were lower rather than higher; Severe PE, in contrast, showed the expected marked elevation, consistent with the leukocytosis reported in advanced PE and attributed predominantly to neutrophil activation, endothelial injury, and systemic inflammatory escalation.[23,31] This is in line with prior studies reporting raised leukocyte counts in severe hypertensive pregnancy disorders within Saudi and regional populations[24], as well as work supporting TLC's value in severe PE.[22] Some earlier studies, in contrast, reported limited prognostic significance for TLC in PE[32], which may be attributable to differences in disease-severity classification, study populations, and the use of differential rather than TLCs; the present study's use of standardized automated hematology analysis (Alinity HQ) addresses some of these methodological limitations.

All three biomarkers correlated significantly and positively with one another (Spearman's partial correlation, adjusted for age and gestational age), suggesting they are not independent but may reflect overlapping and interrelated inflammatory, oxidative, and immune activation pathways

in PE pathogenesis.[11,25,26] The correlation between uric acid and hs-CRP suggests that hyperuricemia and systemic acute-phase inflammation are mechanistically linked in PE, possibly through shared pathways of oxidative stress, xanthine oxidase activation, and cytokine-driven hepatic CRP synthesis.[13,20] Similarly, the correlations of both markers with TLC reflect an integrated immune response—as placental ischemia and endothelial injury intensify with disease progression, both the inflammatory marker cascade and leukocyte mobilization occur in parallel.[13,31] These intercorrelations provide a biological rationale for further evaluating a combined multi-marker assessment approach for PE severity, consistent with suggestions in recent systematic reviews.[25,26]

The combined multivariate effect of PE severity on the biomarker profile was highly significant, confirming that the association extends beyond any single biomarker to the constellation as a whole. ANCOVA indicated that neither patient age nor gestational age significantly influenced any of the three biomarker levels, suggesting these demographic variables were not significant confounders in this sample, although the modest sample size limits power to rule out smaller effects. This is particularly relevant given that the Severe PE group had a slightly lower mean gestational age than the other groups, yet this difference did not significantly influence biomarker levels after covariate adjustment—consistent with PE severity itself, rather than the demographic characteristics examined, driving the observed inflammatory and metabolic differences.[13,25]

Receiver operating characteristic analysis confirmed statistically significant individual diagnostic utility for all three biomarkers, with uric acid showing the strongest discriminatory performance (AUC = 0.92), followed by hs-CRP (AUC = 0.88) and TLC (AUC = 0.75). Uric acid's excellent discrimination is consistent with meta-analytic data highlighting its potential relevance for distinguishing PE from normotensive pregnancy[30,32], and suggests that, pending external validation, it could serve as a cost-effective and accessible biomarker for PE detection in clinical settings, particularly in resource-limited environments such as regional hospitals in Al-Ahsa. The strong performance of hs-CRP is consistent with systematic reviews describing its association with PE and severity[26,28], while the more moderate performance of TLC is consistent with prior studies reporting it as a supportive rather than primary diagnostic marker.[22,23] Taken together, this pattern suggests that a combined multi-marker panel may warrant future evaluation, as the joint assessment of inflammatory, metabolic, and hematological markers could capture complementary biological dimensions of PE pathophysiology.[25,26]

The findings of the present study carry particular relevance for clinical practice in Al-Ahsa and the broader Eastern Province of Saudi Arabia, a region where PE-related biomarker data remain limited.[2,6,7] The observed biomarker profiles are broadly consistent with those reported in international studies, suggesting that the inflammatory and metabolic derangements associated with PE are not population-specific but reflect universal pathophysiological mechanisms. Nevertheless, establishing regional reference data for uric acid, hs-CRP, and TLC in pregnant women from Al-Ahsa contributes meaningfully to the local clinical evidence base and supports the potential integration of these markers into antenatal monitoring protocols in Saudi Arabia.[6-8] Several strengths merit note. Assessing three biologically distinct markers together—a metabolic/oxidative-stress marker (uric acid), an acute-phase inflammatory protein (hs-CRP), and a hematological immune-activation marker (TLC)—using standardized, accredited laboratory methods gives a multi-dimensional picture of inflammatory burden across PE severity. Combining parametric (ANOVA, Tukey HSD) with non-parametric (Kruskal–Wallis, Mann–Whitney *U*) tests, and confirming distributional assumptions via Shapiro–Wilk testing beforehand, adds robustness to the statistical conclusions. The application of MANOVA and ANCOVA further strengthens the analysis by characterizing the combined biomarker effect and assessing potential demographic confounding. Finally, the study contributes regional biomarker data from Al-Ahsa, Saudi Arabia, an area where PE-specific biomarker research remains limited.[2,6,7]

This study is not without limitations. First, the comparatively small and unevenly sized sample (n = 58; Normal = 28, Mild PE = 18, Severe PE = 12), combined with recruitment from only two centers in a single region, may limit power to detect smaller effects and restricts how far these findings can be generalized to wider Saudi or international populations; Although the observed between-group differences were large in this sample (e.g., Mann–Whitney *U* values approaching 0 between Severe PE and comparator groups), this does not eliminate the risk of imprecise effect estimates in the smaller subgroups, and confirmatory studies with larger, multicenter cohorts are needed before these findings can be generalized. The comparatively high proportion of Severe PE cases relative to Mild PE in this cohort may also reflect selection bias inherent to recruitment at tertiary-care referral hospitals, where more complex or severe cases are disproportionately managed. The ROC-derived AUC values and cut-offs were not subjected to internal cross-validation (e.g., bootstrapping) or external validation in an independent cohort and should therefore be regarded as exploratory

rather than clinically validated diagnostic thresholds. Because the same dataset was used both to derive and to evaluate these ROC curves, the reported AUC values may be optimistically biased relative to their true performance in an independent sample. In addition, the use of multiple parametric, non-parametric, and multivariate tests across the three biomarkers was intended to cross-check findings through complementary analytical approaches rather than to maximize significant results. To address the risk of Type I error from the nine pairwise Mann–Whitney comparisons (Table 6), a Holm–Bonferroni correction was applied; every comparison that was significant before correction remained significant afterward, including the Normal-versus-Mild PE difference in TLC (adjusted $p = 0.018$), while the non-significant uric acid and hs-CRP differences between the Normal and Mild PE groups remained non-significant. Formal checks of the homogeneity-of-variance, linearity, and homogeneity-of-regression-slopes assumptions underlying the ANOVA and ANCOVA models were not reported and are noted as an additional limitation. Second, the cross-sectional study design precludes the assessment of longitudinal biomarker trajectories, causal directionality, and temporal changes during disease progression or following clinical intervention. Third, although ANCOVA confirmed that patient age and gestational age were not significant confounders, beyond these two variables, the original data collection for this study did not capture body mass index, parity, gravidity, blood pressure, proteinuria, renal or liver function, platelet count, medication use, or other relevant obstetric history, any of which may have influenced biomarker levels; these variables could not be reported retroactively, and we recommend that future prospective studies in this population capture them systematically. Fourth, the study evaluated TLC rather than differential leukocyte subpopulations; future studies incorporating neutrophil-to-lymphocyte ratio and other differential indices may provide additional mechanistic insight. Finally, without longitudinal follow-up data, this study cannot assess how well these biomarkers might predict PE progression or maternal and fetal outcomes over time.

5. Conclusion

In summary, this study shows that serum uric acid, hs-CRP, and TLC are significantly linked to PE severity, and each shows promise as an adjunctive marker of inflammation in pregnant women with PE, pending prospective, multicenter validation. Serum uric acid emerged as the strongest individual discriminator among the three. These results support pursuing multi-marker inflammatory assessment further, as a possible adjunct to clinical evaluation and management of PE in antenatal care.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Local Committee for Research Ethics at King Fahad Hospital-Hofuf, Al-Ahsa Health Cluster (IRB KFHH No. H-05-HS-065; IRB Log No. 119-EP-2023; approved November 16, 2023). Written informed consent was obtained from all participants before enrollment, and confidentiality of participant data was maintained throughout the study.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data, images, or identifying details. General written informed consent for study participation was obtained from all participants.

Availability of data

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

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