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Association of first trimester clinical and laboratory findings as an early predictor of preeclampsia

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Abstract

This study aimed to evaluate whether clinical and laboratory findings obtained during the first trimester of pregnancy can serve as early predictors for the development of preeclampsia (PE). This retrospective case-control study included 50 women who developed PE and 50 healthy controls. Demographic characteristics, first-trimester blood pressure, biochemical parameters (thyroid-stimulating hormone [TSH], calcium, uric acid, aspartate aminotransferase [AST], lactate dehydrogenase [LDH]), and inflammatory markers (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], AST-to-platelet ratio index [APRI], systemic immune-inflammation index [SII]) were analyzed. Women who developed PE were significantly older (33.02±5.73 vs. 29.12±5.94 years, p=0.001) and had higher body mass index (32.95±5.71 vs. 29.17±4.68 kg/m^2, p=0.001) than controls. First-trimester blood pressures were significantly higher in the PE group: systolic (120.20±18.13 vs. 104±11.43 mmHg) and diastolic (76.80±13.32 vs. 63.20±7.13 mmHg) (both p<0.001). Inflammatory markers showed significantly elevated levels: NLR (4.09±1.24 vs. 3.20±0.81), APRI (7.84±3.05 vs. 6.17±2.75), and SII (1036.73±530.05 vs. 722.62±264.20) (all p≤0.005). ROC analysis revealed area under the curve values of 0.724 for NLR, 0.706 for SII, and 0.683 for APRI. Optimal cut-off values were: NLR ≥3.59 (sensitivity 66.0%, specificity 74.0%, positive predictive value [PPV] 69.5%, negative predictive value [NPV] 70.5%), APRI ≥6.33 (sensitivity 68.0%, specificity 70.0%, PPV 69.4%, NPV 68.6%), and SII ≥936.12 (sensitivity 52.0%, specificity 86.0%, PPV 78.8%, NPV 64.2%). Multivariate analysis identified maternal age (adjusted odds ratio [OR]=1.618, p=0.026), diastolic blood pressure (adjusted OR=1.276, p=0.044), low serum calcium (p=0.023), and elevated TSH (adjusted OR=6.640, p=0.049) as independent predictors. First-trimester maternal age, diastolic blood pressure, calcium, and TSH levels are independent predictors of PE development. Inflammatory markers demonstrated promising predictive ability. These parameters could potentially improve early risk stratification for PE, allowing for closer monitoring and interventions in high-risk women.

Keywords: Biological markers, first trimester pregnancy, inflammatory mediators, pregnancy complications, preeclampsia

Introduction

Preeclampsia (PE), characterized by hypertension, proteinuria or multiple organ disease, occurs in 4.6% of pregnancies and can cause maternal and neonatal mortality and morbidity [1]. The risk of developing PE during pregnancy is significantly increased by pre-existing conditions, such as chronic hypertension, pregestational diabetes, kidney disease, prior PE episodes, and certain autoimmune disorders (like antiphospholipid syndrome and systemic lupus erythematosus) [2].

The pathogenesis of PE is now understood to be a complex, multifactorial process involving intricate interactions between maternal, fetal, and placental factors. Recent advances in understanding have revealed that PE results from a two-stage pathophysiological cascade. Stage 1 involves defective placentation occurring between 6–18 weeks of gestation, characterized by insufficient trophoblast invasion and inadequate remodeling of maternal spiral arteries. This leads to reduced uteroplacental perfusion and relative placental ischemia. Stage 2, typically manifesting after 20 weeks of gestation, involves the maternal systemic response to placental dysfunction, including widespread endothelial dysfunction, exaggerated inflammatory responses, and altered angiogenic balance [3].

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Contemporary research has identified several key molecular mechanisms underlying PE pathogenesis. Angiogenic imbalance plays a central role, with elevated levels of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), alongside decreased pro-angiogenic factors including vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). This imbalance contributes to widespread endothelial dysfunction and the characteristic clinical manifestations of PE. Oxidative stress and metabolic dysfunction have emerged as critical components of PE pathogenesis, with the ischemic placenta generating excessive reactive oxygen species (ROS), leading to lipid peroxidation, protein modification, and DNA damage [4].

Systemic inflammation is a complex physiologic response in which the immune system is activated following various stimuli such as stress and infections, leading to the production of inflammatory mediators [5]. Measurement of blood cell subtype ratios such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), AST-to-platelet ratio index (APRI) and systemic immune-inflammation index (SII), which are thought to reflect underlying inflammatory processes in the pathogenesis of PE, may provide prognostic and diagnostic clues for diseases related to systemic inflammation [6]. Recent studies [7] increasingly support the association between maternal systemic inflammation and susceptibility to pre-eclampsia and suggest that these easily available inflammatory indices may serve as early indicators of disease development. The advantage of these markers lies in the fact that they are derived from standard laboratory assessments, do not require additional specialized testing and thus allow cost-effective risk stratification in a variety of healthcare settings.

Routine laboratory parameters assessed during standard prenatal care, such as first trimester Thyroid-Stimulating Hormone (TSH), serum proteins (albumin), markers of electrolyte metabolism (calcium, uric acid) and liver enzymes (AST, LDH), may change weeks or months before the development of pre-eclampsia and studies are ongoing to determine whether these changes predict pre-eclampsia [8]. This may be explained by early pathophysiologic changes associated with endothelial stress, placental dysfunction and altered metabolic adaptation to pregnancy, which are reflected in these biochemical parameters. Recent mechanistic insights suggest that abnormal TSH levels may influence trophoblast invasion and spiral artery remodeling through thyroid hormone receptor pathways, while elevated liver enzymes may reflect subclinical hepatocellular stress induced by circulating anti-angiogenic factors [9]. Similarly, elevated uric acid may indicate early oxidative stress and purine metabolism dysregulation, while hypocalcemia has been linked to altered calcium homeostasis and increased vascular reactivity [10].

Pre-eclampsia and gestational hypertension have been associated with abnormal liver function, particularly elevated liver enzymes (AST, ALT). According to multicenter cohort studies, abnormal AST and ALT levels during pregnancy increase the risk of PE by 1.12 to 3-fold, which may indicate early hepatocellular damage before symptoms appear [11]. Contemporary understanding suggests that liver dysfunction in PE results from both direct hepatocellular injury due to oxidative stress and indirect effects of hemodynamic changes and complement activation [12]. The pathophysiologic mechanisms behind pre-eclampsia can also be demonstrated by serum uric acid levels. Recent research has revealed that hyperuricemia in PE results not only from decreased glomerular filtration but also from increased xanthine oxidase activity in placental tissues and altered transporters in renal tubules [13]. Studies examining calcium supplementation for the prevention of pre-eclampsia have shown that calcium metabolism is also important, with recent meta-analyses demonstrating significant protective effects particularly in populations with low baseline calcium intake [14].

Given the complex interactions between multiple clinical and laboratory parameters in PE pathogenesis and the pressing need for early prediction tools, the primary aim of our study was to evaluate whether first-trimester clinical and laboratory findings could serve as early predictors of PE development. Our specific objectives were to: identify independent risk factors from routinely collected data that could enhance PE risk stratification without requiring additional specialized testing; assess the predictive value of demographic characteristics, maternal blood pressure, liver enzymes, thyroid function, and inflammatory markers (NLR, PLR, APRI, SII) from first-trimester screening; establish optimal cut-off values for inflammatory markers with significant predictive ability; and develop a practical approach for early PE risk assessment that could be readily implemented across diverse healthcare settings. Through this comprehensive approach, we aimed to identify clinically accessible predictors that could potentially enable timely preventive interventions and improve maternal and fetal outcomes.

Material and Methods

Study Design and Setting

This retrospective case-control study was conducted between January 2020 and January 2024 in patients who gave birth due to PE in the Perinatology Service of Istanbul Haseki Training and Research Hospital and whose medical records between 10–14 weeks of gestation were available. All procedures were performed in accordance with the ethical guidelines of the 1964 Declaration of Helsinki and its subsequent amendments, and the study protocol was approved by the Human Ethics Committee of Haseki Training and Research Hospital on May 23, 2024 (Decision number 41–2024). The ethics committee waived the requirement for informed consent due to the retrospective nature of the study.

Participants

Inclusion criteria comprised women diagnosed with PE (n=50) according to ACOG criteria: hypertension with systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg after 20 weeks of gestation, accompanied by either proteinuria ≥0.3 g in 24-hour urine collection (or urine dipstick protein ≥2+) or evidence of end-organ damage (including elevated liver enzymes >2× upper normal limit, thrombocytopenia <100,000/μL, renal insufficiency with serum creatinine >1.1 mg/dL, pulmonary

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edema, or new-onset cerebral or visual symptoms). The control group (n=50) consisted of healthy pregnant women without systemic disease who experienced no hypertensive complications throughout pregnancy and delivered at term without maternal or neonatal complications.

From a total of 138 pregnant women initially screened, 38 patients were excluded based on the following criteria: inadequate ultrasound quality (n=10), laboratory evidence of acute inflammation with elevated WBC count >12,000 cells/μL or CRP levels >10 mg/L (n=8), multiple pregnancies (n=5), pregnancy-related conditions affecting liver enzymes such as intrahepatic cholestasis or pancreatitis (n=5), use of medications affecting hematologic measurements including anticoagulants, corticosteroids, or immunosuppressive agents (n=4), history of hematologic or inflammatory diseases or thrombosis (n=4), and fetal abnormalities or placental pathologies (n=2). These WBC and CRP thresholds represent pregnancy-specific upper limits for detecting subclinical inflammation that could confound inflammatory marker analyses. Additional exclusion criteria included kidney diseases, infectious conditions that might affect inflammatory markers, and pregnancies in women younger than 18 years. The final study population comprised 100 participants (50 PE cases and 50 controls) who had complete blood count parameters available from their first-trimester antenatal visits (Figure 1).

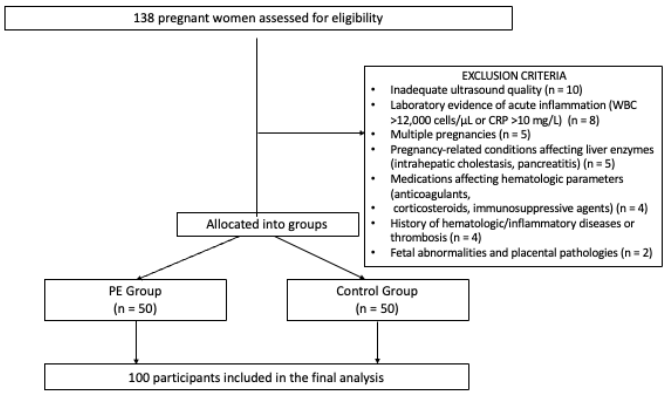

Figure 1. Patient selection flow diagram; Flow diagram showing patient selection process; Of 138 pregnant women screened, 38 were excluded based on predefined criteria; Final study population: 100 participants (50 preeclampsia cases, 50 controls)

Laboratory Analyses

Blood samples were collected from the antecubital vein during routine antenatal visits between 10-14 weeks of gestation for both groups. Samples were collected during normal clinic hours (8:00 am to 5:00 pm) as part of standard clinical practice, without specific timing requirements or fasting conditions. Samples were collected in tubes containing ethylenediaminetetraacetic acid (K3EDTA). CBC was analyzed using an automated Cell-Dyn 3700 hematology analyzer (Abbott Laboratories, Chicago, IL, USA).

Laboratory parameters were categorized as follows:

Hematological Parameters: Platelet count (×10³/μL), Neutrophil count (×10³/μL), and Lymphocyte count (×10³/μL).

Biochemical Parameters: AST (U/L), ALT (U/L), LDH (U/L), TSH (mIU/L), Albumin (g/L), Creatinine (mg/dL), Uric acid (mg/dL), and Calcium (mg/dL).

Inflammatory Markers: Several inflammatory indices were calculated from the CBC:

- NLR=Neutrophil count/lymphocyte count
- PLR=Platelet count/lymphocyte count
- APRI=(AST/Platelet count)x100
- SII=Platelet count×neutrophil count/lymphocyte count

Statistical Analysis

IBM SPSS Statistics version 25.0 was used to conduct the statistical analysis. The normality of the data was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test or Student's t-test, as appropriate, was used to compare continuous variables, which were displayed as mean±standard deviation. Fisher's exact or chi-squared tests were used to compare categorical variables. Using forward stepwise selection, variables exhibiting significant differences in univariate analysis ($p<0.05$) were added to multivariate logistic regression analysis. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were used to display the results. The ability of inflammatory markers to discriminate in the prediction of PE was assessed using ROC curve analysis. Youden's index was used to determine the ideal cut-off values. Model calibration was evaluated using the Hosmer-Lemeshow test. Statistical significance was defined as a p-value <0.05.

Sample size (n=50 per group) was calculated to provide 80% power to detect a clinically meaningful effect size (Cohen's d=0.8) with α=0.05 (two-tailed), using G*Power 3.1.9.7 software. Post-hoc analysis revealed adequate power (>80%) for primary inflammatory markers: NLR achieved 94% power (effect size=0.89), TSH achieved 93% power (effect size=0.88), calcium achieved >99% power (effect size=1.21), and diastolic BP achieved >99% power (effect size=1.33). With 50 cases and 5 predictors in multivariate logistic regression, we achieved a 10:1 events-per-variable ratio, meeting recommended statistical guidelines.

Results

Table 1 presents the demographic and clinical characteristics of the study population. Women with PE were significantly older than women without PE (33.02±5.73 vs. 29.12±5.94 years, p=0.001). Maternal weight was higher in the PE group (84.98±14.51 vs. 76.54±11.81 kg, p=0.002), while height did not differ significantly between groups (p=0.168). Consequently, body mass index (BMI) was significantly higher in women who developed PE (32.95±5.71 vs. 29.17±4.68 kg/m², p=0.001). The prevalence of smoking was lower in the PE group compared to the control group (2% vs. 12%, p=0.05).

Regarding obstetric history, there were no significant differences in gravidity (p=0.724), parity (p=0.933), or nulliparity status

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(p=0.812) between the groups. However, women with PE had a significantly higher rate of previous cesarean sections (54% vs. 24%, p=0.002) and a lower rate of previous normal spontaneous deliveries (30% vs. 56%, p=0.009) compared to the control group. A history of PE in previous pregnancies was substantially more common in the PE group than in controls (48% vs. 4%, p<0.001), highlighting the recurrent nature of this condition. The number of previous abortions was comparable between groups (p=0.144), as was the gestational age at screening (p=0.213).

Blood pressure measurements showed marked differences between the groups. Both systolic (120.20±18.13 vs. 104±11.43 mmHg, p<0.001) and diastolic (76.80±13.32 vs. 63.20±7.13 mmHg, p<0.001) blood pressure values were significantly higher in the PE group even in the first trimester. Notably, 40% of women in the PE group had chronic hypertension, while none of the control subjects had hypertension (p<0.001). Similarly, 30% of women in the PE group were receiving antihypertensive treatment at the time of screening, compared to none in the control group (p<0.001).

Table 1. Demographic and clinical characteristics

	PE (n=50)	Non-PE (n=50)	p-value
Demographic characteristics			
Maternal age (years)	33.02±5.73	29.12±5.94	0.001*
Weight (kg)	84.98±14.51	76.54±11.81	0.002*
Height (cm)	160.68±5.04	162.14±5.46	0.168
BMI (kg/m²)	32.95±5.71	29.17±4.68	0.001*
Smoking status, n (%)			
Yes	1 (2)	6 (12)	0.05*
No	49 (98)	44 (88)	
Obstetric history			
Gravidity	2.88±1.29	2.78±1.53	0.724
Parity	1.54±1.13	1.52±1.23	0.933
Nulliparity, n (%)			
Yes	11 (22)	12 (24)	0.812
No	39 (78)	38 (76)	
Number of abortions	0.40±0.73	0.22±0.47	0.144
Normal spontaneous delivery, n (%)			
Yes	15 (30)	28 (56)	0.009*
No	35 (70)	22 (44)	
Cesarean section, n (%)			
Yes	27 (54)	12 (24)	0.002*
No	23 (46)	38 (76)	
History of PE, n (%)			
Yes	24 (48)	2 (4)	<0.001*
No	26 (52)	48 (96)	
Gestational age at screening (weeks)	12.90±1.06	13.16±1.02	0.213
Vital signs at screening			
Systolic blood pressure (mmHg)	120.20±18.13	104±11.43	<0.001*
Diastolic blood pressure (mmHg)	76.80±13.32	63.20±7.13	<0.001*
Chronic hypertension, n (%)			
Yes	20 (40)	0 (0)	<0.001*
No	30 (60)	50 (100)	
Antihypertensive treatment, n (%)			
Yes	15 (30)	0 (0)	<0.001*
No	35 (70)	50 (100)	

*Values are presented as mean±standard deviation or number (percentage); *Statistical significance is defined as p<0.05; PE: preeclampsia, BMI: body mass index

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Table 2 presents a comprehensive analysis of laboratory parameters in women with and without PE. Regarding hematological parameters, there was no significant difference in platelet counts between the PE and control groups (246.06±68.60 vs. 226.60±50.41×10³/μL, p=0.109). However, neutrophil counts were significantly elevated in women who developed PE [7.17 (6.46–8.36) vs. 6.05 (4.76–6.60)×10³/μL, p<0.001]. Lymphocyte counts were comparable between groups with no significant difference observed (1.90±0.55 vs. 1.93±0.48 ×10³/μL, p=0.761).

Analysis of biochemical parameters revealed several significant differences. Liver function tests showed that AST (17.90±5.42 vs. 13.44±5.32 U/L, p<0.001) and LDH (191.84±46.01 vs. 165.36±15.15 U/L, p<0.001) were significantly higher in the PE group, while ALT levels did not differ significantly [16.00 (12.00–19.00) vs. 14.00 (10.75–17.00) U/L, p=0.197]. TSH levels were markedly higher in women who developed PE [2.23 (1.67–2.65) vs. 1.34 (0.98–1.71) mIU/L, p<0.001]. Serum albumin was significantly lower in the PE group [39.50 (37.00–41.75) vs. 42.50 (38.00–45.00) g/L, p=0.045]. No significant difference was observed in creatinine levels [0.48 (0.43–0.56) vs. 0.52 (0.45–0.57) mg/dL, p=0.128]. Uric acid was significantly elevated in the PE group (3.76±0.90 vs. 3.10±0.48 mg/dL, p<0.001), while calcium levels were significantly lower [8.90 (8.70–9.10) vs. 9.40 (9.00–9.50) mg/dL, p<0.001].

Inflammatory markers demonstrated a pattern of increased inflammation in women who developed PE. The NLR was significantly higher in the PE group [3.66 (3.17–4.26) vs. 2.90 (2.51–3.57), p<0.001]. The APRI showed significantly higher values in women with PE [7.32 (5.90–9.02) vs. 5.44 (4.33–6.38), p=0.002]. Similarly, the SII was significantly elevated in the PE group (1036.73±530.05 vs. 722.62±264.20, p=0.005). The PLR showed a trend toward higher values in women with PE, but this difference did not reach statistical significance [122.80 (92.08–155.40) vs. 118.93 (97.48–134.49), p=0.142].

Table 2. Laboratory parameters

	PE (n=50)	Non-PE (n=50)	p-value
Hematological parameters			
Platelet count (×10³/μL)	246.06±68.60	226.60±50.41	0.109
Neutrophil count (×10³/μL)°	7.17 (6.46–8.36)	6.05 (4.76–6.60)	<0.001*
Lymphocyte count (×10³/μL)	1.90±0.55	1.93±0.48	0.761
Biochemical parameters			
AST (U/L)	17.90±5.42	13.44±5.32	<0.001*
ALT (U/L)°	16.00 (12.00–19.00)	14.00 (10.75–17.00)	0.197
LDH (U/L)	191.84±46.01	165.36±15.15	<0.001*
TSH (mIU/L)°	2.23 (1.67–2.65)	1.34 (0.98–1.71)	<0.001*
Albumin (g/L)°	39.50 (37.00–41.75)	42.50 (38.00–45.00)	0.045*
Creatinine (mg/dL)°	0.48 (0.43–0.56)	0.52 (0.45–0.57)	0.128
Uric acid (mg/dL)	3.76±0.90	3.10±0.48	<0.001*
Calcium (mg/dL)°	8.90 (8.70–9.10)	9.40 (9.00–9.50)	<0.001*
Inflammatory markers			
NLR°	3.66 (3.17–4.26)	2.90 (2.51–3.57)	<0.001*
PLR°	122.80 (92.08–155.40)	118.93 (97.48–134.49)	0.142
APRI°	7.32 (5.90– 9.02)	5.44 (4.33–6.38)	0.002*
SII	1036.73±530.05	722.62±264.20	0.005*

*Statistical significance is defined as p<0.05, °Values are presented as median (25th-75th percentile) based on non-parametric analysis, Other values are presented as mean±standard deviation; AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, TSH: thyroid-stimulating hormone, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, APRI: AST to platelet ratio index, SII: systemic immune-inflammation index

Table 3 presents the analysis of first trimester screening markers in a subset of the study population (24 women who developed PE and 21 controls). The serum concentration of β-hCG, expressed as MoM, was slightly elevated in women who later developed PE compared to controls (1.38±0.47 vs. 1.24±0.38 MoM); however, this difference did not reach statistical significance (p=0.270). Conversely, PAPP-A levels were marginally lower in the PE group compared to the control group (1.18±0.48 vs. 1.33±0.53 MoM), though this difference was also not statistically significant (p=0.313).

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Table 3. First trimester screening markers

Parameter	PE (n=24)	Non-PE (n=21)	p-value
β-hCG (MoM)	1.38±0.47	1.24±0.38	0.270
PAPP-A (MoM)	1.18±0.48	1.33±0.53	0.313

*Values are presented as mean±standard deviation, *Statistical significance is defined as p<0.05; β-hCG: Beta-human chorionic gonadotropin, PAPP-A: pregnancy-associated plasma protein A, MoM: multiple of the median

Table 4 illustrates the significant impact of PE on delivery parameters and neonatal outcomes. Blood pressure values at the time of delivery were markedly elevated in women with PE compared to controls, with systolic blood pressure (150.91±18.78 vs. 111.80±6.29 mmHg, p<0.001) and diastolic blood pressure (93.86±9.94 vs. 67.80±6.16 mmHg, p<0.001) both significantly higher in the PE group, consistent with the diagnostic criteria for the condition.

Women with PE delivered at significantly earlier gestational ages compared to controls (35.62±3.10 vs. 38.88±1.31 weeks, p<0.001), highlighting the association between PE and preterm birth. Mode of delivery differed significantly between groups, with a substantially higher rate of cesarean sections among women with PE (93.3% vs. 44%, p<0.001) and correspondingly lower rate of vaginal deliveries (6.7% vs. 56%). The distribution of newborn gender did not differ significantly between the groups (p=0.341). Although birth pH was lower in the PE group, this difference did not reach statistical significance (7.13±1.12 vs. 7.33±0.06, p=0.202).

Perinatal outcomes were notably poorer in the PE group. Birth weight was significantly lower in neonates born to mothers with PE (2562.76±782.82 vs. 3217.20±498.27 g, p<0.001), which may be attributed to both the earlier gestational age at delivery and the placental dysfunction associated with PE. Apgar scores were significantly lower in the PE group at both 1 minute (7.20±2.04 vs. 8.68±0.74, p<0.001) and 5 minutes (8.20±1.92 vs. 9.80±0.50, p<0.001), indicating poorer immediate neonatal adaptation.

Most strikingly, neonates born to mothers with PE had a substantially higher requirement for intensive care admission compared to those born to mothers without PE (45.5% vs. 2%, p<0.001). This more than twenty-fold increase in NICU admission rates underscores the significant impact of PE on neonatal morbidity and healthcare resource utilization.

Table 4. Delivery parameters and perinatal outcomes

	PE (n=50)	Non-PE (n=50)	p-value
Systolic BP at delivery (mmHg)	150.91±18.78	111.80±6.29	<0.001*
Diastolic BP at delivery (mmHg)	93.86±9.94	67.80±6.16	<0.001*
Gestational age at delivery (weeks)	35.62±3.10	38.88±1.31	<0.001*
Mode of delivery, n (%)			
Cesarean section	42 (93.3)	22 (44)	<0.001*
Vaginal delivery	3 (6.7)	28 (56)	
Newborn gender, n (%)			
Female	19 (42.2)	26 (52)	0.341
Male	26 (57.8)	24 (48)	
Birth pH	7.13±1.12	7.33±0.06	0.202
Birth weight (g)	2562.76±782.82	3217.20±498.27	<0.001*
Apgar score at 1 minute	7.20±2.04	8.68±0.74	<0.001*
Apgar score at 5 minutes	8.20±1.92	9.80±0.50	<0.001*
NICU, n (%)			
Yes	20 (45.5)	1 (2)	<0.001*
No	24 (54.5)	49 (98)	

*Values are presented as mean±standard deviation or number (percentage), *Statistical significance is defined as p<0.05; BP: blood pressure, NICU: neonatal intensive care unit

Figure 2 illustrates the ROC curves for inflammatory markers in predicting PE. All markers demonstrated diagnostic capability significantly better than chance, as evidenced by curves positioned above the reference line. The NLR exhibited the strongest predictive performance (AUC=0.724, 95% CI: 0.622–0.826, p<0.001), followed by the SII (AUC=0.706, 95% CI: 0.603–0.808, p<0.001) and APRI (AUC=0.683, 95% CI: 0.577–0.788, p=0.002). Optimal cut-off values determined

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by Youden's index were: NLR≥3.59 (sensitivity 66.0%, specificity 74.0%, PPV 69.5%, NPV 70.5%), APRI≥6.33 (sensitivity 68.0%, specificity 70.0%, PPV 69.4%, NPV 68.6%), and SII≥936.12 (sensitivity 52.0%, specificity 86.0%, PPV 78.8%, NPV 64.2%). Among the inflammatory markers, SII demonstrated the highest specificity and PPV, while NLR showed the best balance between sensitivity and specificity.

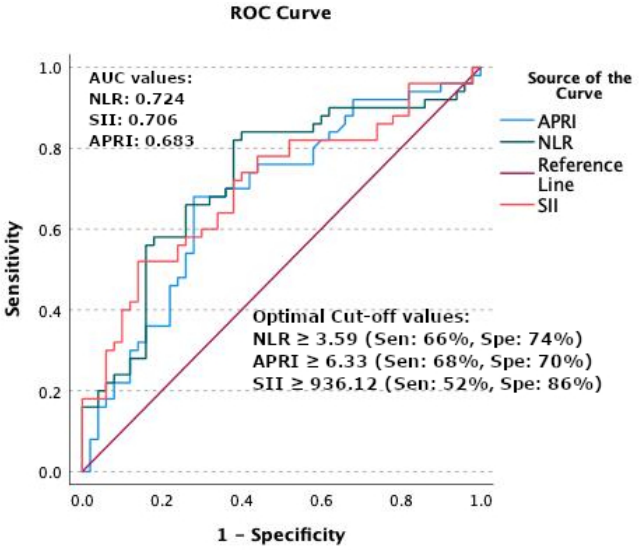

Figure 2. ROC curves for inflammatory markers in predicting preeclampsia; ROC curves demonstrating the diagnostic performance of NLR (AUC=0.724), SII (AUC=0.706), and APRI (AUC=0.683) in predicting preeclampsia; Optimal cut-off values: NLR≥3.59, APRI≥6.33, and SII≥936.12

To identify independent predictors of PE, multivariate logistic regression analysis was performed using variables that showed significant differences in univariate analysis ($p<0.05$). A forward stepwise selection method was utilized with entry and removal criteria of $p<0.05$ and $p>0.10$, respectively. Variables showing significant association with PE in univariate analysis included maternal age, BMI, diastolic blood pressure, calcium, TSH, and inflammatory markers (NLR, APRI, SII).

The multivariate logistic regression model identified maternal age (adjusted OR=1.618, 95% CI: 1.059–2.471, p=0.026), diastolic blood pressure (adjusted OR=1.276, 95% CI: 1.006–1.619, p=0.044), low serum calcium levels (p=0.023), and elevated TSH (adjusted OR=6.640, 95% CI: 1.009–43.706, p=0.049) as independent predictors of PE. The NLR showed a trend toward significance (adjusted OR=5.223, 95% CI: 0.776–35.165, p=0.089).

The model showed good calibration according to the Hosmer-Lemeshow test (χ^2=1.754, df=8, p=0.988). The Nagelkerke R^2 value of 0.895 and overall prediction accuracy of 93.5% (sensitivity 95.8%, specificity 92.1%) suggest promising predictive capability. However, it is important to note that these performance metrics may be optimistic given our limited sample size, and external validation in larger, independent cohorts is needed to confirm the generalizability of these findings.

Table 5 presents the detailed results of the multivariate logistic regression analysis, including regression coefficients, standard errors, Wald statistics, p-values, adjusted odds ratios, and their 95% confidence intervals for each independent predictor.

Table 5. Multivariate logistic regression analysis for PE prediction

Variable	β Coefficient	Standard error	Wald	p-value	Adjusted OR	95% CI for OR
Maternal age (years)	0.481	0.217	4.931	0.026*	1.618	1.059–2.471
Diastolic blood pressure (mmHg)	0.244	0.121	4.055	0.044*	1.276	1.006–1.619
Calcium (mg/dL)	-7.930	3.490	5.163	0.023*	<0.001∞	-
TSH (mIU/L)	1.893	0.962	3.869	0.049*	6.640	1.009–43.706
NLR	1.653	0.973	2.888	0.089	5.223	0.776–35.165
Constant	30.381	21.748	1.952	0.162	-	-

*Statistically significant ($p<0.05$); ∞Extremely small value (less than 0.001); OR: odds ratio, CI: confidence Interval, TSH: thyroid-stimulating hormone, NLR: neutrophil-to-lymphocyte ratio; Model characteristics: Nagelkerke R^2=0.895, Hosmer-Lemeshow test: χ^2=1.754, df=8, p=0.988, Overall classification accuracy: 93.5%, Sensitivity: 95.8%, Specificity: 92.1%

Discussion

In this study, we investigated whether first trimester clinical and laboratory findings can serve as early predictors of PE. Our findings demonstrate that several maternal characteristics and biochemical markers are significantly associated with the subsequent development of PE, highlighting their potential utility in early risk stratification.

Maternal age and BMI were significantly higher in women who developed PE, consistent with previous studies [15-18] that identify advanced maternal age and obesity as established risk factors for PE. Women with increased maternal age and elevated BMI face higher risks of developing PE, attributable in part to the greater prevalence of chronic hypertension and previous preeclamptic episodes in this population.

First-trimester diastolic blood pressure was much higher in women who subsequently developed PE in our study than in those who stayed normotensive. With each 1 mmHg increase linked with a 28% higher risk of developing the condition, more importantly multivariate logistic regression analysis confirmed diastolic blood pressure as an independent predictor of PE (adjusted OR=1.276,

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95% CI: 1.006–1.619, p=0.044). This result consistency with several earlier studies. First reporting sBP, dBP, and MAP measured by automatic blood pressure devices at 11–13 weeks of gestation predicted PE, Pooon et al. [19] Miller et al. [20] also found that pre-eclampsia risk was higher in first trimester high blood pressure sufferers. This association implies that even modest increases in early gestational blood pressure may reflect underlying endothelial abnormalities that predispose women to acquire pre-eclampsia and that vascular dysfunction may be present long before the clinical manifestation of the disease.

Our multivariate analysis revealed that elevated TSH was a significant independent predictor of pre-eclampsia (adjusted OR=6.640, 95% CI: 1.009–43.706, p=0.049) and that first trimester TSH levels were significantly higher in women who later developed pre-eclampsia compared to controls [2.23 (1.67–2.65) vs. 1.34 (0.98–1.71) mIU/L, p<0.001]. This finding is consistent with several previous studies. In a meta-analysis examining the relationship between thyroid function abnormalities and PE by Hajifoghaha et al. [21]. They found that TSH was significantly higher in preeclamptic women. Similarly, subclinical hypothyroidism during pregnancy was associated with a higher risk of PE compared with euthyroidism in the meta-analysis by Toloza et al. [22]. These findings suggest that thyroid function assessment in early pregnancy may provide valuable information for PE risk stratification and emphasize the potential importance of closer monitoring of women with elevated TSH throughout pregnancy.

Our study demonstrated strong correlations between first trimester inflammatory markers and the onset of pre-eclampsia. With AUC values of 0.724, 0.706 and 0.683, respectively, ROC curve analysis revealed that NLR, SII and APRI exhibited significant discriminative ability for the prediction of pre-eclampsia. Furthermore, NLR showed statistical relevance as an independent predictor in multivariate analysis. These results complement several previous research projects proving that a good predictor of pre-eclampsia is the first trimester NLR [23]. In our study, using an optimal NLR cut-off of 3.59, we found a sensitivity of 66.0% and a specificity of 74.0%. This is quite different from the results published by Oğlak et al. [24] who found a higher optimal cut-off of 4.12, thus producing increased sensitivity (82.1%) but decreased specificity (62.0%). Such differences are likely to reflect differences in laboratory techniques, sample collection timing or study population between research settings. Although our results support the growing body of data showing that NLR is a useful predictive marker, it is crucial to acknowledge the conflicting results in the body of knowledge. According to some studies [25] first trimester NLR is neither significantly different between affected individuals and healthy controls, nor does it effectively predict pre-eclampsia.

Our analysis revealed that the APRI demonstrated moderate discriminative ability (AUC=0.683, p=0.002) with an optimal cut-off value of 6.33 (sensitivity 68.0%, specificity 70.0%) and higher values in women who later developed PE. These findings complement those of Ozkan et al. [26], who found notably higher APRI levels in women with severe PE relative to control subjects (1.41±9.36 vs. 0.23±0.09, p<0.001). On the other hand, our findings differ from those of Cendek et al. [27], who observed no statistically significant variation in first-trimester APRI levels between healthy pregnant women and women with PE.

First trimester SII values were notably higher in women who later developed pre-eclampsia compared to controls (1036.73±530.05 vs. 722.62±264.20, p=0.005), ROC analysis confirming the predictive values (AUC=0.706, 95% CI: 0.603–0.808, p=0.005) showed. These results support Cevher Akdulum's research [28] demonstrating higher SII values in preeclamptic patients, so supporting its use as a first trimester marker of PE. In PE patients between the ages of 26 and 35, Maziashvili [29] also found notably higher SII values than in healthy controls. Conversely, our findings contradict those of Seyhanli's study [25], which revealed no appreciable first trimester predictive capacity of SII.

In our study, neither difference reached statistical relevance; β-hCG was somewhat raised in women who subsequently developed PE (1.38±0.47 vs. 1.24±0.38 MoM) and PAPP-A was somewhat lower (1.18±0.48 vs. 1.33±0.53 MoM). These results run counter to Canini's study, which found much lower β-hCG in preeclamptic pregnancies, and Keikkala's study demonstrating lower %hCG-h (0.92 MoM, p=0.001) and PAPP-A (0.95 MoM, p=0.001) in early-onset PE cases. Noël discovered, meanwhile, similar performance for PE screening between PAPP-A and PlGF.

These conflicting findings highlight the need for further research with larger, more diverse populations to validate optimal cut-off values and establish standardized reference intervals before these markers can be incorporated into routine clinical practice. The observed inconsistencies in inflammatory marker findings across different studies warrant further discussion beyond the previously mentioned factors of laboratory techniques, sample timing, and population differences. Additional methodological considerations that may contribute to these discrepancies include variations in exclusion criteria for detecting subclinical inflammation, differences in platelet counting methodologies and AST measurement standardization across laboratories, pre-analytical factors such as sample storage conditions and processing delays, and inadequate statistical power in smaller studies to detect clinically meaningful differences. These methodological heterogeneities underscore the critical importance of establishing standardized protocols and conducting larger multicenter validation studies before clinical implementation of these inflammatory markers as routine predictive tools for preeclampsia.

Differences in the demographics of research populations, the timing of sample collection or the techniques applied in laboratory studies may lead to inconsistencies. Until these methodological challenges are addressed through standardized

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international protocols and robust multicenter trials, clinicians should interpret inflammatory marker results with caution and consider them as supplementary rather than standalone predictive tools for preeclampsia risk assessment.

Strengths of the Study

Several noteworthy strengths of our work improve its relevance to research on PE prediction. A multifarious evaluation of possible predictors is obtained by means of a thorough investigation of several parameters clinical, biochemical, and inflammatory markers) within the same cohort. With ROC analyses determining clinically relevant cut-off values for inflammatory markers, our strong statistical approach combining univariate and multivariate analyses identified independent predictors while controlling for confounders. Novel inflammatory indices (NLR, APRI, and SII) in first-trimester prediction fills in a significant void in the literature. Significantly, the parameters we found as predictive maternal age, diastolic blood pressure, calcium, and TSH are routinely measured during normal prenatal care, so improving the clinical relevance of our results without calling for specific testing. Furthermore, by concentrating on first-trimester evaluation, our work addresses the important demand for early prediction tools able to identify high-risk women before clinical start, so possibly facilitating early preventive actions.

Study Limitations

Our study has several important methodological limitations. The retrospective design limits causal inference and introduces potential selection bias. The single-center approach, while ensuring protocol standardization, restricts generalizability to diverse populations and healthcare settings with different laboratory methods. Limited availability of first-trimester screening data (β-hCG and PAPP-A available for only 45% of participants) constrained our ability to develop comprehensive multi-marker prediction models.

A significant limitation is the imbalance in chronic hypertension between groups (40% in PE group vs. 0% in controls), which potentially confounds blood pressure measurements and limits interpretation of findings. Additionally, the potential for model overfitting exists given our relatively small sample size (n=100) and high reported accuracy (93.5%).

These design limitations underscore the need for prospective, multicenter validation studies with larger cohorts and robust internal validation techniques such as k-fold cross-validation before clinical implementation of our findings.

Practical Implications and Future Directions

The findings of our study have several important clinical implications. First, the identified predictors (maternal age, diastolic blood pressure, calcium, and TSH) are routinely measured during standard prenatal care, making implementation of risk assessment based on these parameters feasible without additional cost or specialized testing. Second, establishing optimal cut-off values for inflammatory markers provides clinicians with practical thresholds for risk stratification. Third, identifying women at high risk for PE in the first trimester allows for early implementation of preventive strategies such as low-dose aspirin, enhanced monitoring protocols, and lifestyle interventions.

Future research should focus on prospective validation of these findings in larger, more diverse populations, with particular attention to women from different ethnic backgrounds and those with varied risk profiles. The development of an integrated prediction model combining maternal characteristics, biochemical markers, and inflammatory indices would be valuable for clinical implementation. Additionally, investigating the effectiveness of early interventions based on first-trimester risk assessment would provide evidence for the clinical utility of this approach. Longitudinal studies examining the trajectory of inflammatory markers throughout pregnancy might also offer insights into the pathophysiological processes underlying PE and potentially identify therapeutic targets for prevention or treatment.

Conclusion

In conclusion, our study identifies several readily available first-trimester parameters (maternal age, diastolic blood pressure, calcium, and TSH) as independent predictors of PE. The inflammatory markers NLR, APRI, and SII also demonstrate promising predictive ability. These findings suggest that a multi-parametric approach to PE screening in the first trimester could improve risk stratification, allowing for closer monitoring and potential preventive interventions in high-risk women. While our model demonstrates impressive accuracy (93.5%), it should be emphasized that these results require validation through prospective and multicenter studies to establish external validity. Future prospective studies with larger cohorts are needed to validate these findings and develop integrated prediction models that could be implemented in routine clinical practice.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This research was performed in compliance with the principles outlined in the most recent version of the Declaration of Helsinki (Decision number: 41-2024 dated May 23, 2024) after approval by the Human Ethics Committee of Haseki Training and Research Hospital. In addition, the purpose and nature of all procedures performed were properly explained to each pregnant woman and she was asked to sign a written informed consent form to participate in this study.

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