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ORIGINAL RESEARCH

Correlation Between Immune-Inflammatory Biomarkers During Pregnancy and Postpartum and Adverse Outcomes of Preeclampsia: A Longitudinal Retrospective Analysis

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Background: Preeclampsia (PE) is a pregnancy-specific hypertensive disorder linked to systemic inflammation. The systemic immune-inflammation index (SII), calculated from neutrophil, lymphocyte, and platelet counts, has emerged as a novel immune activation marker. Its longitudinal changes in pregnancy and predictive performance for adverse outcomes in PE are not well established.

Methods: This retrospective cohort study included 692 clinical records of women with PE who delivered at Shanghai First Maternity and Infant Hospital between January 2019 and June 2024, representing 685 unique patients, 7 of whom delivered twice. SII, systemic inflammatory response index (SIRI), other inflammatory indices, and biochemical parameters were measured at four time points: the first, second, and third trimesters, and the postpartum. Linear mixed-effects models evaluated longitudinal trends, and random intercepts were used as predictors in logistic regression models assessing adverse pregnancy outcomes. All two-and three-biomarker combinations were evaluated, and DeLong's test ($\alpha = 0.05$) was used to compare the area under the Receiver Operating Characteristic (ROC) curves and AUC values of each combination with that of the best single-biomarker model.

Results: Among the 692 records of women with PE, 204 (29.5%) experienced adverse pregnancy outcomes. SII showed an overall increasing trend during pregnancy and demonstrated moderate predictive performance (AUC = 0.666). The combination model including SII, alanine transaminase (ALT), and creatinine (Cr) achieved the highest predictive performance (AUC = 0.712, 95% CI: 0.669−0.755, $P = 0.011$), outperforming each single-biomarker.

Conclusion: SII followed an overall increasing trend during pregnancy in patients with PE and was associated with adverse pregnancy outcomes. Combining SII with ALT and Cr improved predictive performance and may be a practical tool for clinical monitoring and early intervention.

Keywords: preeclampsia, systemic immune-inflammation index, adverse pregnancy outcomes, inflammation

Introduction

Preeclampsia (PE) is a pregnancy-specific multisystem disorder that usually develops after 20 weeks of gestation and is characterized by hypertension and proteinuria.[1] The pathogenesis of PE is complex and involves various factors, including placental insufficiency, immune dysregulation, and endothelial damage.[2] In recent years, an increasing number

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of studies have focused on the role of inflammation in the onset of PE, suggesting that the inflammatory response plays a key role in the pathophysiology of PE.[3] Studies have shown elevated levels of several inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), in patients with PE. Elevated levels of these inflammatory factors may be associated with placental ischemia, oxidative stress, and endothelial dysfunction, further exacerbating disease progression.[4,5] In addition, increased monocyte and neutrophil activity in the peripheral blood of patients with PE suggests the presence of a systemic inflammatory response.[6] Recent studies have also demonstrated inflammatory cell infiltration in placental tissue of patients with PE, particularly increases in macrophages and T-lymphocytes. Activation of these cells may inhibit placental angiogenesis and affect normal fetal development.[7] Furthermore, overexpression of inflammatory factors in the placenta may exacerbate local and systemic inflammatory responses through autocrine and paracrine pathways.[3]

The detection of inflammatory markers is potentially valuable in the early diagnosis and prognostic assessment of PE. For example, elevated serum CRP levels may predict the risk of PE onset.[8] However, further investigation into the specificity and sensitivity of these inflammatory markers are required to determine their clinical value. Recent studies[9,10] have introduced more comprehensive inflammation indices, namely the systemic immune-inflammation index (SII) and the systemic inflammatory response index (SIRI), which are calculated from complete blood counts and have been increasingly used for disease diagnosis and prognostic prediction.[11–13] Some studies have confirmed the value of SII in predicting the onset of PE and in classifying the severity of PE.[14,15] However, among women diagnosed with PE, no study to date has collected longitudinal repeated measures of these indices throughout gestation to confirm the relationship between laboratory parameters and end-organ damage. This study aimed to assess the prognostic value of longitudinal repeated measurements of maternal serum SII in women diagnosed with PE. We compared its predictive performance for adverse pregnancy outcomes with that of routine laboratory assessments and evaluated the additional benefit of using repeated measurements.

Materials and Methods

Study Population

The study population comprised pregnant women who delivered at Shanghai First Maternity and Infant Hospital between January 2019 and June 2024. Inclusion criteria were a singleton pregnancy with a confirmed diagnosis of PE and available data from at least two of the following time points: the first, second and third trimesters, and postpartum. Exclusion criteria were pre-existing cardiac disease, chronic kidney disease, chronic liver disease, intrahepatic cholestasis of pregnancy (ICP), previous fetal aneuploidy, or fetal genetic disorders. A total of 692 clinical records of women diagnosed with PE corresponded to 685 unique patients, because 7 women had two separate admissions after delivering twice during the study period. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Shanghai First Maternity and Infant Hospital with a waiver of informed consent (Approval No. KS2502), as it involved retrospective data collection with patient identifiers removed and replaced by coded information to ensure strict confidentiality.

Data Collection

Baseline pregnancy characteristics and laboratory results were retrospectively collected from the hospital's electronic medical records. These data included maternal age, height, body mass index (BMI), past medical history, hospitalization and delivery records, neonatal outcomes, and laboratory test results. Complete blood counts (CBC) were performed using an automated hematology analyzer (Sysmex XN-9000; Sysmex, Kobe, Japan), and biochemical parameters were measured using a fully automated biochemical analyzer (AU5800; Beckman Coulter, Brea, CA, USA).

Inflammation-related indicators were obtained from the CBC, including monocytes (M), neutrophils (N), lymphocytes (L), and platelets (P). Specifically, SII was calculated as $P \times N / L$, and SIRI was calculated as $N \times M / L$. In addition to SII and SIRI, three traditional inflammatory indicators were calculated: neutrophil-to-lymphocyte ratio ($NLR = N / L$), platelet-to-lymphocyte ratio ($PLR = P / L$), and lymphocyte-to-monocyte ratio ($LMR = L / M$). Biochemical indices including aspartate transaminase (AST), ALT, Cr, and lactate dehydrogenase (LDH) were also recorded.

Adverse pregnancy outcomes attributable to PE were defined according to the guidelines of the American College of Obstetricians and Gynecologists (ACOG) and the International Society for the Study of Hypertension in Pregnancy (ISSHP).[16,17] These outcomes included: maternal admission to the intensive care unit (ICU) due to severe hypertension requiring continuous monitoring and blood pressure control or due to hepatic/renal function abnormalities; hepatic dysfunction (transaminase levels ≥2 × the upper normal limit); acute kidney injury (Cr > 88.4 μmol/L); eclamptic seizure; perinatal admission to the neonatal ICU (NICU); severe fetal growth restriction; and fetal distress; maternal or perinatal deaths.

Statistical Analysis

All statistical analyses were performed using R (version 4.4.1). Continuous variables were tested for normality. Normally distributed data were presented as mean ± standard deviation and were compared using the Student's *t*-test (for equal variances) or Welch's *t*-test (for unequal variances). Non-normally distributed data were presented as median (interquartile range) and were compared using the Mann–Whitney *U*-test. Categorical variables were expressed as counts (percentages) and compared using the Chi-square test.

Longitudinal biomarker data were analyzed using linear mixed-effects models. For each biomarker (SII, SIRI, NLR, PLR, LMR, AST, ALT, Cr, LDH), a model was fitted with a random intercept for each participant and time (trimester/postpartum) as a fixed effect, to account for correlations in repeated measures. The models were fitted using the "lmer()" function in R, which automatically removed data with missing values. Diagnostic checks were performed to assess residual normality, homoscedasticity, and to identify any high-leverage observations; the normality of random effects was also evaluated.

To further explore predictors of adverse pregnancy outcomes, the random intercept for each biomarker's model (denoted with a "rand_" prefix, eg, rand_ALT for ALT) was extracted as a patient-specific summary value. We then systematically evaluated all possible combinations of two and three such biomarkers in logistic regression models to predict adverse outcomes. Predictive performance were assessed using ROC curves and AUC values. We focused on combinations that improved AUC significantly over individual markers. DeLong's test was used to compare each combination model's AUC with that of the best single-biomarker model. An improved prediction was considered significant only if (1) the combination's AUC exceeded the AUC of each constituent marker, and (2) DeLong's test found a statistically significant difference ($\alpha = 0.05$).

Results

Overall, 2,193 routine blood count measurements were obtained from 692 clinical records of women diagnosed with PE. Figure 1 illustrates the longitudinal changes in the laboratory indices for participants who experienced adverse pregnancy outcomes.

Differences in demographic and outcome characteristics were observed between women who did and did not experience adverse pregnancy outcomes (Table 1). No significant difference was found between the groups in mean maternal age (31.6 vs 32.2 years, *P = 0.096*). However, significantly more women in the adverse outcome group were of advanced maternal age (≥35 years) compared to the no adverse group (27.0% vs 19.9%, *P = 0.040*). The maternal prenatal body weight (mean 75.7 vs 73.7 kg, *P = 0.042*) and BMI (median 28.6 vs 27.7, *P = 0.038*) were also higher in the adverse outcome group.

Regarding pregnancy outcomes, gestational duration was significantly shorter in the adverse outcome group (mean 251.2 vs 268.0 days, *P < 0.001*). Neonates in the adverse outcome group were smaller, with a mean length of 46.6 vs 49.5 cm and mean weight of 2,406.9 vs 3,057.8 g (both *P < 0.001*). Their 1-minute and 5-minute Apgar scores were also lower (both *P < 0.001*). However, there were no significant differences between the groups in infant sex or NICU admission rates (*P = 0.300* and *P = 0.116*, respectively).

In terms of clinical complications, severe PE was more common in the adverse outcome group (39.2% vs 11.3%, *P < 0.001*). Common symptoms during pregnancy, including dyspnea, jaundice, and edema of the lower extremities, did not differ significantly between the groups (all *P > 0.05*). The use of assisted reproductive technology was more frequent in the adverse outcome group (13.9% vs 7.4%, *P = 0.015*).

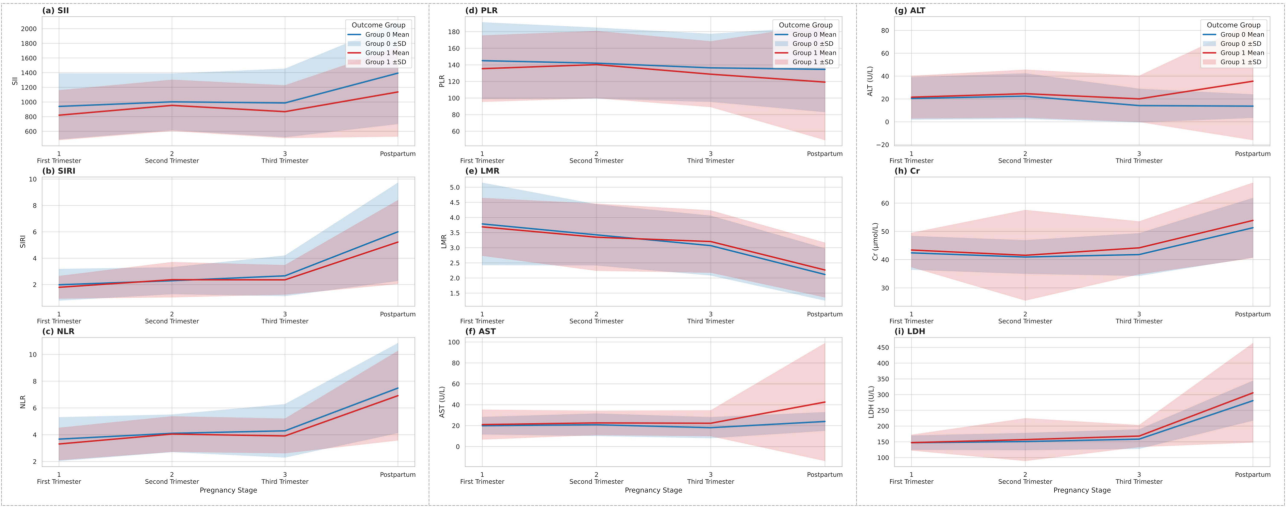

Figure 1 Line charts showing the longitudinal changes of each indicator from pregnancy to the postpartum period.
Notes: (**a**) SII; (**b**) SIRI; (**c**) NLR; (**d**) PLR; (**e**) LMR; (**f**) AST; (**g**) ALT; (**h**) Cr; (**i**) LDH. The vertical axis represents the value of each indicator, while the horizontal axis represents different time points during pregnancy and postpartum: 1, first trimester (1st–13th weeks of pregnancy); 2, second trimester (14th–27th weeks); 3, third trimester (28th week until delivery); postpartum, within six weeks after delivery. All data are expressed as mean ± standard deviation (SD). Solid thick lines represent the mean, and shaded areas represent ±SD. Group 0: no composite adverse pregnancy outcomes; Group 1: composite adverse pregnancy outcomes.
Abbreviations: SII, Systemic immune-inflammation index; SIRI, Systemic inflammatory response index; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; Cr, Serum creatinine; LDH, Lactate dehydrogenase.

We first fit separate linear mixed-effects models for each biomarker (SII, SIRI, NLR, PLR, LMR, AST, ALT, Cr, LDH). Supplemental Table S1 presents the regression results for each biomarker's association with adverse outcomes. The random-effects outputs (intercept variance, residual variance, etc.) were examined, and intraclass correlation coefficients were calculated to assess within-subject variability. Model fit was evaluated using marginal and conditional R^2 values.

Supplementary Figure S1 displays diagnostic plots for the mixed-effects models of the nine biomarkers (SII, SIRI, NLR, PLR, LMR, AST, ALT, Cr, LDH). For each biomarker model (subfigures a-i), seven diagnostic panels are shown: (1) a posterior predictive check comparing observed values with model predictions; (2) a residuals-versus-fitted plot to assess linearity; (3) a residuals-versus-fitted plot to check homoscedasticity; (4) a leverage plot to identify influential observations; (5) a variance inflation factor (VIF) plot to evaluate multicollinearity; (6) a Q-Q plot of residuals to examine normality of residuals; (7) a Q-Q plot of random effects to assess the normality of the random intercepts. These diagnostics indicate that the models adequately captured the data patterns for each index.

To further assess the biomarkers' predictive performance for adverse outcomes, we extracted each model's random intercept (eg, rand_SII, rand_ALT). We then screened all combinations of two and three biomarkers in logistic regression models. Table 2 and Figure 2a show the top 10 biomarker combinations ranked by predictive performance (ROC curves (AUCs)), and Table 3 and Figure 2b show the combinations ranked 11–20. All the top 10 combinations had significantly higher AUCs than the best single-biomarker (MaxSingleAUC). Notably, SII appeared in many of these top combinations. The three-biomarker model rand_SII + rand_ALT + rand_Cr achieved an AUC (0.712, 95% CI:0.669−0.755), an improvement of 0.046 over the MaxSingleAUC of 0.666. This suggests that combining SII, ALT, and Cr significantly improves the ability to predict adverse pregnancy outcomes. Similarly, the combinations rand_SII + rand_AST + rand_ALT and rand_SII + rand_PLR + rand_ALT yielded AUCs of 0.708 (95% CI:0.665−0.751) and 0.707 (95% CI:0.665−0.750), respectively—improvements of 0.042 and 0.041 over the MaxSingleAUC.

In the combinations ranked 11–20 (Table 3), SII remained a key contributor, and significant AUC improvements were observed. For instance, the combination rand_SII + rand_SIRI + rand_AST had an AUC of 0.699 (95% CI:0.655−0.742), which was 0.043 higher than the MaxSingleAUC of 0.656 for that set of markers. The combinations rand_SII + rand_NLR + rand_AST and rand_SII + rand_AST + rand_LDH showed AUC gains of 0.043 and 0.042, respectively, compared to their MaxSingleAUC values. These results underscore the importance of SII in multi-marker models for enhancing predictive performance.

Table 1 Baseline and Disease Characteristics of 692 Clinical Records of Women with Preeclampsia (PE), with or Without Composite Adverse Pregnancy Outcomes

Parameter	No Composite Adverse Pregnancy Outcomes (n = 488)	Composite Adverse Pregnancy Outcomes (n = 204)	Statistic	*P*
Age (years), mean ± SD	31.6±3.7	32.2±4.0	t = −1.666	*0.096*
≥ 35, n (%)			χ^2 = 4.212	***0.040***
No	391 (80.1)	149 (73.0)		
Yes	97 (19.9)	55 (27.0)		
Prenatal body weight (kg), mean ± SD	75.7±11.5	73.7±12.8	t = 2.034	***0.042***
Prenatal BMI, M (Q_2, Q_3)	28.6 (26.0,31.2)	27.7 (25.1,31.1)	z = −2.074	***0.038***
Days of pregnancy, mean ± SD	268.0±12.9	251.2±20.2	t = 13.085	***<0.001***
Severity of PE, n (%)			χ^2 =71.545	***<0.001***
Mild	433 (88.7)	124 (60.8)		
Severe	55 (11.3)	80 (39.2)		
Whether received assisted reproduction, n (%)			χ^2 = 5.903	***0.015***
No	420 (86.1)	189 (92.6)		
Yes	68 (13.9)	15 (7.4)		
Comorbid symptoms during pregnancy				
Dyspnea, n (%)			χ^2 = 0.000	*1.000*
No	483 (99.0)	202 (99.0)		
Yes	5 (1.0)	2 (1.0)		
Jaundice of skin and mucous membranes, n (%)			χ^2 = 0.238	*0.626*
No	485 (99.4)	204 (100.0)		
Yes	3 (0.6)	0 (0.0)		
Edema of bilateral lower extremities, n (%)			χ^2 = 0.388	*0.533*
No	483 (99.0)	200 (98.0)		
Yes	5 (1.0)	4 (2.0)		
Onset of the HELLP syndrome, n (%)			χ^2 = 8.873	***0.003***
No	488 (100.0)	199 (97.5)		
Yes	0 (0.0)	5 (2.5)		
Postpartum blood pressure (systolic pressure, mmHg), mean ± SD	135.40±12.2	136.5±13.4	t = −0.996	*0.320*
Postpartum blood pressure (diastolic pressure, mmHg), mean ± SD	85.0±10.2	86.0±10.7	t = −1.137	*0.256*
Whether the mother was admitted to the ICU, n (%)			χ^2 =17.398	***<0.001***
No	487 (99.8)	194 (95.1)		
Yes	1 (0.2)	10 (4.9)		
Birth length (cm), mean ± SD	49.5±1.9	46.6±4.4	t = 8.835	***<0.001***
Birth weight (g), mean ± SD	3057.8±578.6	2406.9±792.7	t = 10.605	***<0.001***
Infant sex, n (%)			χ^2 = 0.014	*0.905*
Male	232 (47.5)	98 (48.0)		
Female	256 (52.5)	106 (52.0)		
Perinatal admission to NICU, n (%)			χ^2=228.703	***<0.001***
No	488 (100.0)	120 (58.8)		
Yes	0 (0.0)	84 (41.2)		
Severe respiratory distress of perinatal infants, n (%)			χ^2 =157.156	***<0.001***
No	488 (0.0)	144 (70.6)		
Yes	0 (0.0)	60 (29.4)		
Severe fetal growth restriction (FGR), n (%)			χ^2=186.296	***<0.001***
No	488 (0.0)	134 (65.7)		
Yes	0 (0.0)	70 (34.3)		

(*Continued*)

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Table 1 (Continued).

Parameter	No Composite Adverse Pregnancy Outcomes (n = 488)	Composite Adverse Pregnancy Outcomes (n = 204)	Statistic	*P*
***Apgar1, mean±SD**	9.1±0.6	8.6±1.0	t = 5.717	***<0.001***
***Apgar5, mean±SD**	9.7±0.5	9.3±0.7	t = 7.725	***<0.0001***
Eclamptic seizures	0 (0.0)	0 (0.0)	/	/
Maternal or perinatal deaths	0 (0.0)	0 (0.0)	/	/

Notes:Data are expressed as mean ± standard deviation (SD), median (25th and 75th percentiles), or percentage; *Apgar1 means Apgar score at one minute of birth, *Apgar5 means Apgar score at five minutes of birth; Bolded *P* values denote statistical significance at $P < 0.050$.

Table 2 The Biomarker Combinations with the Top 10 Prediction Capacity

CombinationType	Variables	CombAUC	95% CI	MaxSingleAUC	AUCImprovement	*Delong_pvalue*
Three variables	rand_SII+rand_ALT+rand_Cr	0.712	0.669–0.755	0.666	0.046	***0.011***
Three variables	rand_SII+rand_AST+rand_ALT	0.708	0.665–0.751	0.666	0.042	***0.024***
Three variables	rand_SII+rand_PLR+rand_ALT	0.707	0.665–0.750	0.666	0.041	***0.017***
Three variables	rand_SII+rand_ALT+rand_LDH	0.706	0.663–0.749	0.666	0.040	***0.026***
Three variables	rand_SII+rand_LMR+rand_ALT	0.706	0.663–0.748	0.666	0.040	***0.025***
Three variables	rand_SII+rand_AST+rand_Cr	0.705	0.662–0.748	0.656	0.050	***0.003***
Three variables	rand_SII+rand_NLR+rand_ALT	0.705	0.662–0.747	0.666	0.039	***0.029***
Three variables	rand_SII+rand_SIRI+rand_ALT	0.704	0.661–0.747	0.666	0.039	***0.028***
Two variables	rand_SII+rand_ALT	0.704	0.661–0.747	0.666	0.038	***0.028***
Three variables	rand_SII+rand_LMR+rand_AST	0.700	0.656–0.743	0.656	0.044	***0.008***

Notes: Bolded *P* values denote statistical significance at $P < 0.050$.
Abbreviations: CombAUC, AUC for combinations of two and three biomarkers; MaxSingleAUC, AUC for the best single-biomarker.

DeLong's test confirmed that all these combinations had significantly better AUCs than the single-marker models ($P < 0.050$ for each). For example, the combination rand_SII + rand_ALT + rand_Cr (AUC = 0.712) had a significantly higher AUC than SII alone (AUC = 0.666, $P = 0.011$). The DeLong's test results are provided in Table 2 and Table 3.

Furthermore, combinations of four to nine biomarkers were analyzed to ensure no promising model was overlooked. Supplemental Table S2 lists the top 50 models from these analyses, which can inform future research.

Discussion

In this longitudinal retrospective cohort study, we characterized the temporal dynamics of SII across pregnancy in women with PE and evaluated its prognostic value for adverse pregnancy outcomes. SII showed an overall increasing trend during pregnancy and had moderate predictive performance (AUC = 0.666) for adverse outcomes on its own. The combination of SII with ALT and Cr achieved the highest predictive performance (AUC = 0.712, 95% CI: 0.669−0.755, $P = 0.011$), outperforming any single marker.

PE is increasingly recognized as a multisystem disorder involving immunological maladaptation, endothelial dysfunction, and placental ischemia. Inflammation plays a pivotal role in its pathogenesis, particularly through neutrophil activation, increased platelet aggregation, and lymphocyte suppression—all integral components of SII.[18] Elevated SII, calculated as platelet count × neutrophil count / lymphocyte count, may serve as a surrogate marker for the immune-inflammatory burden, especially in conditions with endothelial activation such as PE.

In the present study, we found that SII exhibited an overall increasing trend during pregnancy. Moreover, the clinical manifestations and progression of PE tend to worsen with advancing gestational age. Dimitriadis et al[19] reported that the perinatal risk of preeclampsia is highest before term. As pregnancy advances, blood flow to the placenta may become further restricted, exacerbating placental hypoxia and leading to the release of greater amounts of deleterious factors such

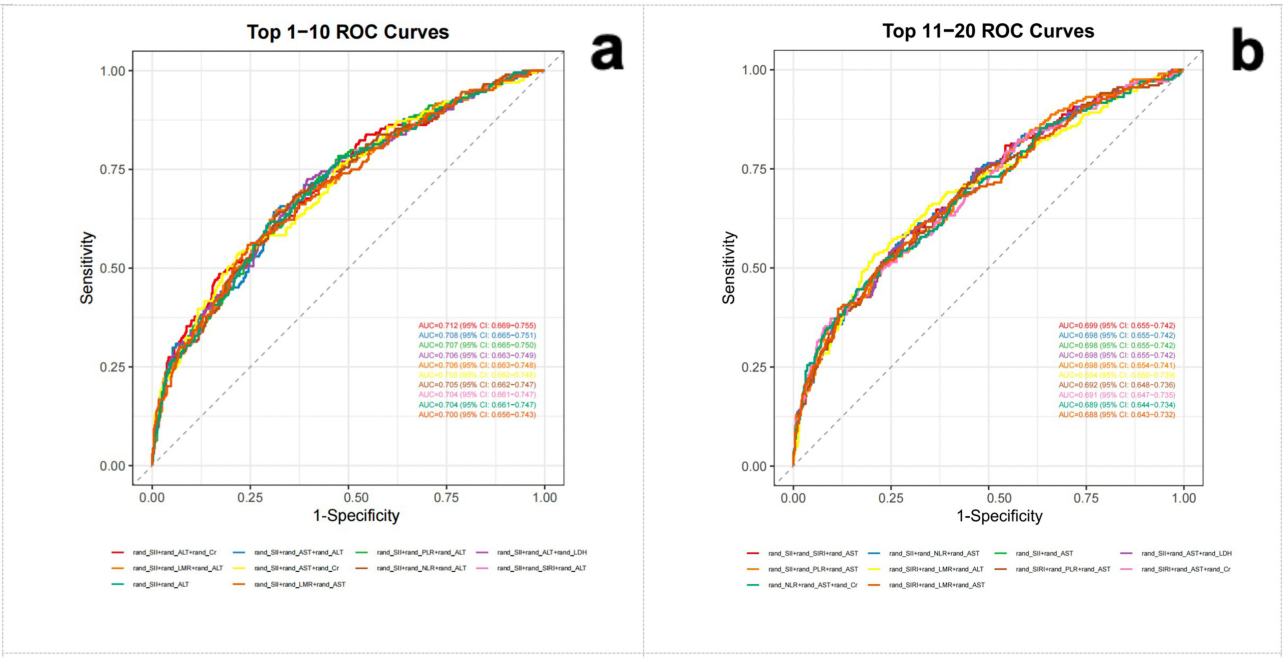

Figure 2 (A) ROC curves for the top 1–10 biomarker combinations predicting adverse outcomes in patients with PE. **(B)** ROC curves for the top 11–20 biomarker combinations predicting adverse outcomes in patients with PE.

Table 3 The Biomarker Combinations with the Top 11–20 Prediction Capacity

CombinationType	Variables	CombAUC	95% CI	MaxSingleAUC	AUCImprovement	Delong_pvalue
Three variables	rand_SII+rand_SIRI+rand_AST	0.699	0.655–0.742	0.656	0.043	***0.010***
Three variables	rand_SII+rand_NLR+rand_AST	0.698	0.655–0.742	0.656	0.043	***0.010***
Two variables	rand_SII+rand_AST	0.698	0.655–0.742	0.656	0.043	***0.010***
Three variables	rand_SII+rand_AST+rand_LDH	0.698	0.655–0.742	0.656	0.043	***0.010***
Three variables	rand_SII+rand_PLR+rand_AST	0.698	0.654–0.741	0.656	0.042	***0.011***
Three variables	rand_SIRI+rand_LMR+rand_ALT	0.694	0.650–0.739	0.666	0.029	***0.046***
Three variables	rand_SIRI+rand_PLR+rand_AST	0.692	0.648–0.736	0.656	0.036	***0.022***
Three variables	rand_SIRI+rand_AST+rand_Cr	0.691	0.647–0.735	0.656	0.035	***0.021***
Three variables	rand_NLR+rand_AST+rand_Cr	0.689	0.644–0.734	0.656	0.033	***0.035***
Three variables	rand_SIRI+rand_LMR+rand_AST	0.688	0.643–0.732	0.656	0.032	***0.023***

Notes: Bolded *P* values denote statistical significance at *P < 0.050*; Bolded *P* values denote statistical significance at P < 0.050.
Abbreviations: CombAUC, AUC for combinations of two and three biomarkers; MaxSingleAUC, AUC for the best single-biomarker.

as soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). Soluble Flt-1 is a circulating anti-angiogenic protein (the soluble form of VEGF receptor-1) that binds and neutralizes key pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Soluble endoglin is the shed form of an endothelial glycoprotein co-receptor for transforming growth factor-β (TGF-β) that likewise impairs angiogenic signaling. These anti-angiogenic factors inhibit the activity of VEGF and PlGF, promote vasoconstriction and endothelial dysfunction, and thereby exacerbate hypertension and related symptoms. In addition, placental hypoxia and injury provoke an augmented immune response, promoting the release of inflammatory cytokines such as IL-6 and TNF-α. These inflammatory mediators further aggravate endothelial damage and contribute to the development of hypertension. Furthermore, changes in maternal hormone levels may influence vascular reactivity, causing pre-existing vascular problems to become more severe in the perinatal period.[20]

While conventional monitoring of PE focuses on blood pressure, proteinuria, and single-point laboratory values, these often fail to capture dynamic changes in maternal immune status. In our analysis, SII alone provided only moderate predictive performance (AUC = 0.666) for adverse outcomes. However, when combined with ALT and Cr—markers of hepatic and renal stress—the predictive performance increased significantly (AUC = 0.712, 95% CI:0.669−0.755, $P = 0.011$), suggesting a synergistic interaction between systemic inflammation and end-organ dysfunction. SII proved to be a crucial component in many of the top multi-marker models. For instance, adding SII to combinations such as ALT + Cr or AST + ALT markedly improved the AUC compared to any combination without SII. This consistency highlights SII's central role in boosting the efficacy of predictive models.

Our findings align with emerging evidence supporting composite inflammatory scores in obstetric care. For example, the pan-immune-inflammation value, a related index, was shown to be a robust predictor of PE severity in a recent retrospective study.[18] Similarly, in autoimmune diseases, an elevated SII reflects ongoing systemic immune activation, although its correlation with clinical disease activity can be modest.[21]

Importantly, our study suggests that a rising SII trajectory is not merely an epiphenomenon but may serve as an early warning signal for poor prognosis in PE. We observed that higher SII values were significantly associated with worse maternal and perinatal outcomes. This mirrors trends in other composite biomarker studies, where indices combining neutrophilia and lymphopenia reflect systemic stress and immunological imbalance.[22]

PE continues to be a major public health concern that places a substantial economic burden on healthcare systems.[23] There is an imperative need for inexpensive, convenient, and rapid monitoring tools. SII meets these criteria: it is derived from routine CBCs—one of the most common and cost-effective tests—and can be easily calculated during regular prenatal visits.[9,24] In contrast, angiogenic or placental biomarkers (such as sFlt-1/PlGF) can be expensive and less accessible. One study reported that in the Netherlands, the net cost per patient for an sFlt-1/PlGF ratio test was $514, whereas in Switzerland it was $11,598.[25,]

Likewise, ALT and Cr are standard lab tests that are routinely measured in patients with PE. Therefore, our findings support incorporating SII, ALT, and Cr as a combined metric in routine pregnancy monitoring to improve the prediction of adverse outcomes. Notably, combining immune-inflammatory markers with liver function tests has shown promise in other contexts. For example, in pregnant women with a prothrombotic tendency, a model combining SII, SIRI, and LDH achieved an AUC of 0.805, outperforming any single indicator.[26,]

Integrating these indices into standard prenatal care could facilitate early identification of high-risk pregnancies, allowing for closer monitoring or timely interventions to improve maternal and neonatal outcomes.

Our results also resonate with other studies on inflammation in PE. In PE, elevated neutrophil counts and reduced lymphocyte counts have each been associated with poor placentation and increased oxidative stress.[27] Preeclamptic women exhibit exaggerated systemic inflammation, evidenced by heightened levels of TNF-α, IL-6, and reactive oxygen species, supporting the biological plausibility of elevated SII as a pathogenic marker.[28] These lines of evidence reinforce the utility of SII as an integrative biomarker in PE surveillance.

Similarly, the dynamic pattern of SII in our cohort is reminiscent of observations in non-pregnant populations. In various chronic conditions, disease progression often corresponds with rising SII values: as diseases such as cancer or cardiovascular disorders advance, neutrophil and platelet counts tend to increase and lymphocyte counts decrease, elevating the SII.[29] For instance, in a study of 573 patients with alpha-fetoprotein (AFP)-positive gastric cancer, Zhang et al[30] found that SII and SIRI increased progressively over time, and higher values were associated with greater one-year mortality risk in patients with elevated AFP. Similar trends are seen in cardiovascular disease. Inflammatory cell infiltration in ischemic myocardium can promote tissue repair when properly regulated, but excessive inflammation contributes to myocardial injury and fibrosis, impairing cardiac function.[18,21,31] In a study of 2,910 patients with cardiovascular-kidney-metabolic (CKM) syndrome, Huang et al[32] noted that both SII and SIRI trended upward from disease onset to just before death, underscoring the prognostic importance of systemic inflammation in CKM syndrome. The predictive performance of SII and related indices has also been documented in other conditions, including thrombotic diseases, rheumatic disorders, and postoperative outcomes.[8,10,13,21]

In our study, women aged ≥35 years were more common in the adverse outcome group (27.0% vs 19.9%, *P = 0.040*), aligning with evidence that advanced maternal age increases obstetric risk and highlighting the need for comprehensive monitoring in PE pregnancies.

Strengths of our study include the large single-center cohort, which provided a sizable sample with consistent clinical management, and the longitudinal design with repeated biomarker measurements that allowed us to model within-subject trajectories. The use of linear mixed-effects models enabled robust analysis of temporal trends while accounting for individual variability.

The study has several limitations. Its retrospective nature and single-center design may limit generalizability. We did not have data on certain molecular markers (eg, IL-6, CRP, PlGF, sFlt-1) that could further elucidate the biological mechanisms. Additionally, although we excluded patients with active infections, we could not control for all potential confounders such as subclinical infections, stress, or medications that might influence inflammatory markers. We also observed that adding four or more biomarkers into the models yielded only marginal AUC gains while increasing model complexity; many of these high-order combinations included overlapping information, which can reduce clinical utility. Future studies might employ techniques like LASSO regression to select the most informative biomarkers and avoid overfitting.

Future prospective studies in diverse populations are needed to validate our findings and determine optimal timing for measuring SII and related indices during pregnancy. Advanced approaches, including multi-marker algorithms and machine learning models that incorporate longitudinal patterns of SII and other biomarkers, hold promise for improving risk stratification in PE. Such tools could pave the way for personalized antenatal care, where patients at high risk for complications are identified early and managed more aggressively.

Conclusion

SII followed an overall increasing trend during pregnancy in patients with PE and was associated with adverse pregnancy outcomes. A combined assessment of SII, ALT, and Cr enhanced predictive performance and may offer a practical approach for clinical monitoring and early intervention. Notably, SII played a central role in multiple biomarker combinations. These findings support the integration of SII into routine surveillance protocols for high-risk pregnancies.

Data Sharing Statement

The data are available from the corresponding author (Zhendong Xu) upon reasonable request.

Ethics Approval and Informed Consent

The study protocol was approved by the Institutional Review Board of Shanghai First Maternity and Infant Hospital with a waiver of informed consent (Approval No. KS2502), as it involved retrospective data collection with patient identifiers removed and replaced by coded information to ensure strict confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article was submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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