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ORIGINAL RESEARCH

The Association of Peripheral Blood Immunoinflammatory Markers with PE and Adverse Outcomes in Preeclampsia: A Retrospective Study

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Background: Preeclampsia (PE) is a syndrome exclusive to pregnancy, presenting substantial risks to maternal and fetal health. Systemic immune-inflammatory response is a prominent feature of PE.

Methods: A retrospective study was conducted involving 749 pregnant women in Guangzhou, China from September 2018 to September 2024. Three hundred and seventy participants were diagnosed with PE, 166 of which had adverse pregnancy outcomes (APOs). Immuno-inflammatory markers expressed in peripheral blood were evaluated during the second-trimester. APOs included postpartum haemorrhage (PPH), premature rupture of membranes (PROM), placental abruption, fetal growth restriction, neonatal intensive care unit (NICU) transfer, and fetal distress. The relationship between immune-inflammatory markers and PE and APOs was analyzed.

Results: Women with PE were at higher risk of APOs and had higher levels of neutrophil-to-lymphocyte ratio (NLR), systemic immunoinflammatory index (SII) and systemic inflammatory response index (SIRI). The AUC values for NLR, SII, and SIRI with PE were 0.594, 0.649, and 0.646 ($P < 0.001$), with cut-off values of 4.389, 994.863, and 2.406, respectively. For APOs in PE, the AUC values were 0.632, 0.627 and 0.669, with cut-off values of 4.959, 1070.408 and 3.346, respectively. Analysis indicated higher SII levels with increased incidences of fetal growth restriction, NICU transfer and fetal distress, and SIRI levels with NICU transfer and fetal distress ($P < 0.05$).

Conclusion: Elevated levels of immune-inflammatory markers including NLR, SII, and SIRI are associated with PE and APOs. Our findings underscored the different optimal cut-off values of immune-inflammatory markers in the pregnant women between PE and the APOs.

Keywords: preeclampsia, NLR, SII, SIRI, adverse pregnancy outcomes, inflammation

Introduction

Preeclampsia (PE) is a pregnancy-specific syndrome that typically manifests after the 20th week of gestation, characterized by new-onset hypertension and proteinuria.[1] It can lead to damage in multiple maternal organ systems and, in the severe cases, may progress to eclampsia. The global incidence of PE is approximately 2% to 8%[2] with regional variations. In China, the incidence is estimated at 5.6% to 9.4%.[3] PE significantly affects outcomes for both the mother and the fetus, such as cardiovascular and cerebrovascular accidents, renal insufficiency, fetal growth restriction and placental abruption,[4–6] all of which pose severe threats to fetal health and survival. Furthermore, women who have experienced PE are at an increased long-term risk of developing cardiovascular disease.[7,8] This highlights the necessity for specialized care for high-risk pregnant patients with PE.

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Recent studies have identified a systemic inflammatory response associated with PE, which has been shown to trigger the release of inflammatory mediators that negatively impact maternal vascular endothelial function.[9,10] Studies have demonstrated that women with PE exhibit elevated leukocyte and neutrophil counts compare to healthy pregnant women,[11,12] indicating the crucial role of inflammation in the pathogenesis of PE. Immune inflammatory markers have shown potential clinical utility in the prediction of PE. Notably, NLR and platelet-to-lymphocyte ratio (PLR) has been suggested in recent years as a potential marker to determine inflammation.[13,14] Besides, the SII and SIRI are two indicators of immune inflammation reflecting the equilibrium between pro-inflammatory and anti-inflammatory responses.[15,16] However, research on the association of these inflammatory biomarkers with PE, especially the APOs of PE, is limited.

Therefore, our study aimed to clarify the association between systemic immune-inflammatory markers and PE as well as the APOs of patients.

Materials and Method

Study Design and Participants

From September 2018 to September 2024, a total of 370 PE patients based on established diagnostic criteria were included at a tertiary hospital in Guangzhou, China. Among them, 166 women had adverse outcomes while 204 women not. Exclusion criteria included: (1) age under 18 years, (2) acute or chronic blood diseases, (3) multiple pregnancies, (4) chronic hypertension and (5) incomplete clinical data. Three hundred and seventy-nine healthy pregnant women were recruited from the hospital as controls. Laboratory assessments of blood samples were conducted during 14rd to 20th gestation weeks of the participants.

Definitions

The definition of PE was adhered to the guidelines from the American College of Obstetrics and Gynecology (ACOG) and the International Society for the Study of Hypertension in Pregnancy (ISSHP).[17,18] Adverse Pregnancy Outcomes (APOs) encompassed postpartum hemorrhage, premature rupture of membranes (PROM), placental abruption, fetal growth restriction, neonatal intensive care unit (NICU) transfer, and fetal distress.

NLR, PLR, SII and SIRI are indicators of the body's inflammatory response and immune status.[13–16] The NLR (Neutrophil-to-Lymphocyte Ratio) is calculated as the neutrophil count divided by the lymphocyte count, while the PLR (Platelet-to-Lymphocyte Ratio) is the platelet count divided by the lymphocyte count. The Systemic Immune-Inflammation Index (SII) is calculated as platelet count multiplied by neutrophil count divided by lymphocyte count. The Systemic Inflammation Response Index (SIRI) is calculated as neutrophil count multiplied by monocyte count divided by lymphocyte count.

Gestational diabetes mellitus (GDM) was diagnosed by the 75 g, 2-hour Oral Glucose Tolerance Test (OGTT).[19] The risk of Down syndrome pertains to screening results showing high or borderline risk, not a confirmed diagnosis. Adverse maternal history is defined by three or more spontaneous or induced abortions, or pregnancy terminations. An abnormal placenta involves irregularities in its shape or number. Additional detailed information from medical records includes postpartum hemorrhage (PPH, defined as an estimated blood loss exceeding 500 mL after vaginal delivery or greater than 1000 mL following cesarean delivery).[20] Fetal growth restriction (FGR) was used to describe fetuses with an estimated fetal weight that is less than the 10th percentile for gestational age.[21]

Statistical Analysis

Data analyses were conducted utilizing IBM SPSS Statistics for Windows version 27.0 (IBM, NY, USA). Graphical representations were generated using the GraphPad Prism 8 software. The Kolmogorov–Smirnov test for normality was employed to assess the distribution of the data. Continuous non-parametric variables were expressed as counts and percentages (%), whereas continuous parametric variables were reported as the mean ± standard deviation (SD). Based on the characteristics of the variables, a *t*-test was used for parametric variables, while chi-square tests and Fisher's exact tests were employed to compare demographic characteristics. The Mann–Whitney *U*-test was used to conduct pairwise

comparisons of data exhibiting a skewed distribution across the specified groups. The area under the receiver operating characteristic curve (AUC) was calculated to evaluate the predictive efficacy of blood biomarkers. In addition, Spearman's rank correlation coefficient was also used to determine the relationship between peripheral blood biomarkers and maternal-neonatal outcomes.[22] Statistical significance was established at $P < 0.05$ with all tests being two-tailed.

Result

Maternal Characteristics of the PE Group and the NO PE Group

The study group comprised 749 pregnancies, with 370 women diagnosed with preeclampsia. The maternal characteristics were analyzed in Table 1. The PE group was characterized by a higher mean age, body mass index (BMI), and a greater prevalence of assisted reproduction, GDM, and autoimmune disease ($P < 0.05$). Statistical analysis revealed that there were significant differences in NLR, SII, and SIRI between the two groups ($P<0.05$). The groups did not differ significantly from other measured variables.

Maternal-Neonatal Outcomes of the PE and the NO PE Groups

Maternal-neonatal complications and outcomes of the two groups were summarized in Table 2. In comparison to the NO PE group, pregnant women with PE were admitted and delivered at an earlier gestational week ($P < 0.001$). The systolic and diastolic blood pressure at hospitalization were higher in the PE group ($P < 0.001$). The Incidence rates of cesarean section, postpartum hemorrhage, PROM, and placental abruption were significantly higher among women with PE ($P < 0.05$). Newborns in the PE group exhibited shorter lengths and lower weights, as well as a higher incidence of fetal distress, fetal growth restriction, and NICU transfer ($P < 0.001$). Furthermore, statistically significant differences were observed in placental area, weight, and morphology ($P < 0.05$).

Clinical Characteristics of the APOs Group and NO APOs Group in PE

APOs in PE were showed in Table 2. The study group comprised 370 pregnancies, 166 of which resulted in adverse outcomes. The clinical characteristics of pregnant women with preeclampsia with and without APOs were analyzed in Table 3. Statistical analysis revealed that there were significant differences in NLR, SII, and SIRI between the two groups ($P < 0.05$). No significant differences were observed between the two groups concerning the other measured variables.

Table 1 Clinical Characteristics of the PE Group and the NO PE Group

	NO PE (379)	PE (370)	*P*
Age(years)	29.80±12.41	31.31±5.245	<0.001
Menstruation(days)	5.70±0.98	5.60±1.23	0.272
Primipara (%)	164 (43.3)	143 (38.6)	0.198
Primigravid (%)	220 (58.0)	202 (54.6)	0.341
Down's syndrome risk (%)	4 (1.1)	9 (2.4)	0.171
Assisted reproduction (%)	20 (5.3)	61 (16.5)	<0.001
Prenatal BMI (kg/ m^2)	26.34±4.86	28.95±4.11	<0.001
Gestation intervals>10 years (%)	4 (1.1)	11 (3.0)	0.071
Adverse maternal history (%)	29 (7.7)	42 (11.4)	0.084
GDM (%)	30 (7.9)	86 (23.2)	<0.001
Renal disease (%)	2 (0.5)	6 (1.6)	0.173
Autoimmune disease (%)	5 (1.3)	15 (4.1)	0.023
Hepatitis (%)	18 (4.7)	28 (7.6)	0.108
NLR	3.99±1.47	5.16±3.23	<0.001
PLR	138.66±44.46	135.79±59.94	0.214
SII	877.98±356.45	1165.64±802.78	<0.001
SIRI	2.64±3.66	3.51±3.42	0.041

Note: Data expressed as mean ± standard deviation or n (%).
Abbreviations: BMI, Body Mass Index; GDM, Gestational diabetes mellitus.

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Table 2 Maternal-Neonatal Outcomes of the PE Group and the NO PE Group

	NC (379)	PE (370)	*P*
Admission(weeks)	38.95±1.51	36.33±3.38	<0.001
Systolic BP (mmHg)	116.49±9.38	141.24±20.19	<0.001
Diastolic BP (mmHg)	73.38±7.89	87.63±14.41	<0.001
Delivery(weeks)	39.07±1.52	36.71±3.26	<0.001
Cesarean section (%)	162 (42.7)	290 (78.4)	<0.001
Postpartum hemorrhage (%)	6 (1.6)	19 (5.1)	0.007
PROM (%)	15 (4.0)	47 (12.7)	<0.001
Placental abruption (%)	3 (0.8)	18 (4.9)	0.034
Liver impairment (%)	3 (0.8)	8 (2.2)	0.139
Renal impairment (%)	6 (1.6)	12 (3.2)	0.078
Cardiovascular impairment (%)	4 (1.1)	8 (2.2)	0.228
Puerperal infection (%)	2 (0.5)	7 (1.9)	0.087
Shock (%)	0 (0)	2 (0.5)	0.244
Placenta area(cm^2)	431.22±75.55	388.99±124.50	<0.001
Placenta weight(g)	548.26±69.27	507.34±113.48	<0.001
Abnormal placental	11 (2.9)	22 (5.9)	*0.042*
Birth weight (kg)	3.17±0.44	2.61±0.72	<0.001
Birth length (cm)	49.86±1.89	47.03±4.74	<0.001
Fetal distress (%)	6 (1.6)	29 (7.8)	<0.001
Fetal growth restriction (%)	20 (5.2)	84 (22.7)	<0.001
NICU transfer (%)	42 (11.1)	155 (41.9)	<0.001
Induced labor/stillbirth (%)	0 (0)	2 (0.5)	0.244

Note: Data expressed as mean ± standard deviation or n (%).
Abbreviations: BP, Blood pressure; PROM, Premature rupture of membranes; NICU, Neonatal intensive care unit.

Table 3 Clinical Characteristics of the APOs Group and NO APOs Group in PE

	NO APOs (204)	APOs (166)	*P*
Age(years)	31.34±5.21	31.31±5.32	0.409
Menstruation(days)	5.66±1.26	5.54±1.20	0.666
Assisted reproduction (%)	27 (13.2)	34 (20.5)	0.062
Prenatal BMI(kg/m^2)	29.09±3.97	28.79±4.31	0.569
Gestation intervals>10years (%)	7 (3.4)	4 (2.4)	0.565
Adverse maternal history (%)	20 (9.8)	22 (13.3)	0.298
GDM (%)	40 (19.6)	46 (27.7)	0.066
Renal disease (%)	3 (1.5)	3 (1.8)	0.799
Autoimmune disease (%)	5 (2.5)	10 (6.0)	0.083
Hepatitis (%)	11 (5.4)	17 (10.2)	0.079
NLR	4.78±2.97	6.62±4.64	<0.001
PLR	129.03±51.54	139.28±63.76	0.101
SII	1016.39±601.66	1406.79±1016.58	<0.001
SIRI	3.10±2.78	4.62±4.77	<0.001

Note: Data expressed as mean ± SD (range) or n (%).
Abbreviations: BMI, Body Mass Index; GDM, Gestational diabetes mellitus.

The Association Between Systemic Immune-Inflammatory Markers and PE or APOs

The AUC for the prediction of PE based on NLR, SII, and SIRI levels was 0.594, 0.649 and 0.646 ($p < 0.001$), respectively. The optimal cut-off values were 4.389, 994.863 and 2.406 (Figure 1). The AUC of NLR, SII, and SIRI levels for predicting adverse pregnancy outcomes were 0.632, 0.627, and 0.669, respectively, with optimal cut-off values

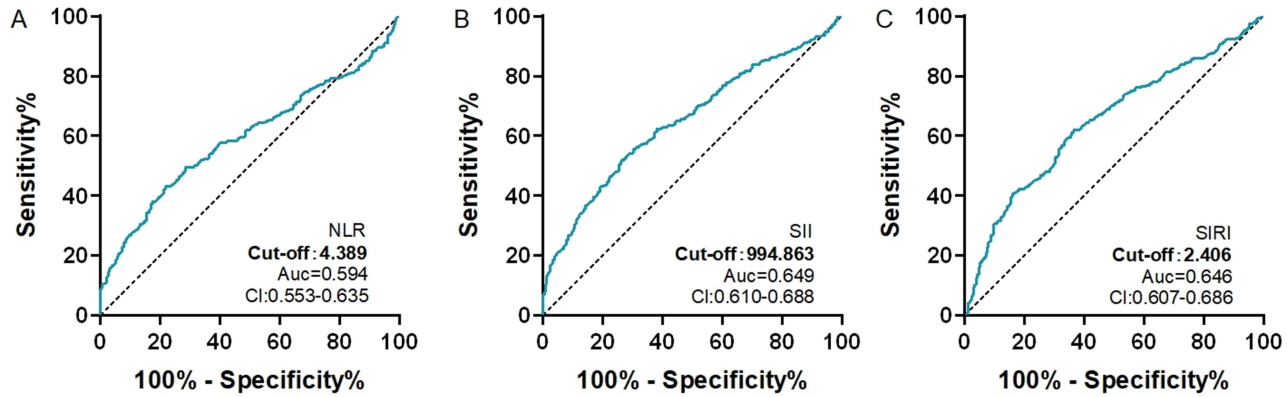

Figure 1 Risk association of NLR, SII, and SIRI with PE(**A**) NLR level; (**B**) SII level; (**C**)SIRI level.
Abbreviations: AUC, the area under the ROC curve; CI, confidence interval.

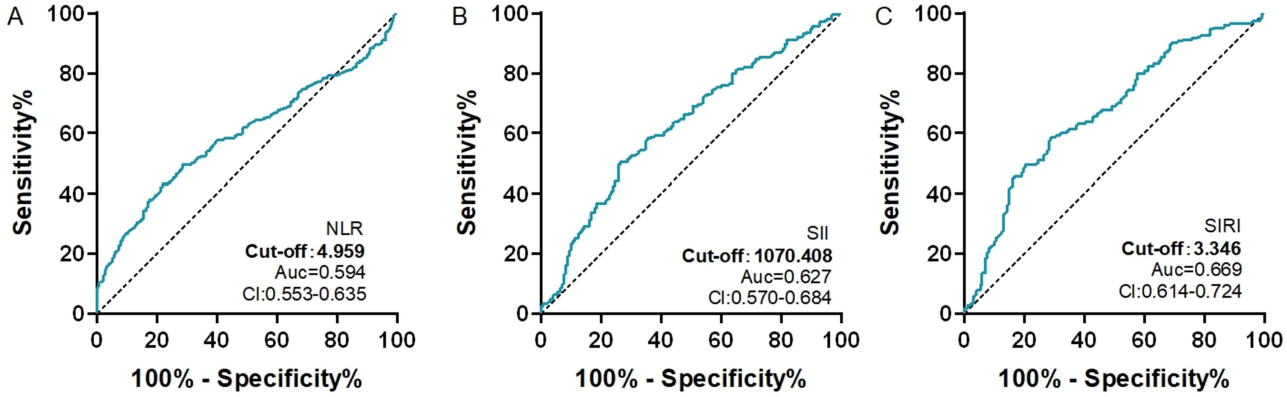

Figure 2 Risk association of NLR, SII, and SIRI with APOs in PE (**A**) NLR level; (**B**) SII level; (**C**) SIRI level.
Abbreviations: AUC, the area under the ROC curve; CI, confidence interval.

of 4.959, 1070.408 and 3.346 (Figure 2). The critical values of NLR, SII, and SIRI for the prevention of adverse maternal and infant outcomes were higher than those for the prevention of PE.

The Relationships Between the Markers and Maternal-Neonatal Outcomes

Table 4 highlighted the relationships between immune-inflammatory markers (NLR, SII, and SIRI) and maternal-neonatal outcomes. A positive correlation was observed between fetal growth restriction and SII ($r = 0.166$, $P < 0.001$). Furthermore, elevated SII and SIRI levels were associated with NICU transfer ($r = 0.140$, $P < 0.001$; $r = 0.072$, $P = 0.049$) and fetal distress ($r = 0.082$, $P = 0.023$; $r = 0.090$, $P = 0.014$).

Discussion

PE remains a major obstetric complication with significant risks to both maternal and fetal health. The systemic inflammatory response is increasingly recognised as a critical component in the pathogenesis of PE. The inflammatory response is not only associated with PE but also with its APOs. Studies have shown that in addition to PE, elevated inflammatory factors in maternal blood and amniotic fluid in women with fetal growth restriction and premature membrane rupture.[23–25] Recently, peripheral blood markers of inflammation have become a research hotspot for disease prediction during pregnancy due to their easy accessibility and stability.[26] For instance, studies have shown that SIRI might be a useful biomarker for predicting bronchopulmonary dysplasia in the preterm infants.[27] Our findings found that elevated levels of NLR, SII and SIRI were observed in women with PE compared to healthy controls, suggesting a pro-inflammatory state that may contribute to the

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Table 4 Relationships Between the Markers and Maternal-Neonatal Outcomes

	P/R	NLR	SII	SIRI
Postpartum hemorrhage	r	0.009	0.017	0.029
	P	0.799	0.649	0.426
PROM	r	0.038	0.060	0.058
	P	0.290	0.100	0.112
Placental abruption	r	0.052	0.054	0.029
	P	0.151	0.134	0.426
Fetal growth restriction	r	0.059	0.166	0.069
	P	0.105	<0.001	0.056
NICU transfer	r	0.048	0.140	0.072
	P	0.194	<0.001	0.049
Fetal distress	r	0.067	0.082	0.090
	P	0.065	0.023	0.014

Note: Analysis performed using Spearman's rank correlation analysis.
Abbreviation: PROM, Premature rupture of membranes.

pathogenesis of the condition. Notably, these markers were even more elevated in women who experienced APOs such as FGR, NICU transfer and fetal distress. This finding highlights the potential utility of these markers not only in predicting PE, but also in identifying pregnancies at higher risk of adverse outcomes.

Optimal cut-off value can improve diagnostic accuracy. Evidence indicates that an NLR cut-off of 4.47 is predictive of PE,[13,28,29] aligning with our findings of 4.389 approximately. Few studies have explored the relationship between PE and SII or SIRI[30–33], with Seyhanli's study finding a notable difference in SIRI.[31] Haiying Chen's[33] study identified SIRI ≥ 2.315 as an independent risk factor for preeclampsia, similar to our cut-off level of 2.406. The study by Akdulum[30] demonstrated that SII levels were markedly elevated in the PE group to healthy patients, with a cut-off value of 836.83. This is lower than the cut-off level of 994.863 observed in our results. These differences may be attributed to variations in study populations, timing of blood collection, and other confounding factors such as medication use. For instance, a study emphasized the necessity of considering age and found that the SII level for predicting PE was significant only in the age range from 26 to 35.[32] Gokcen's[34] study showed increased NLR and SII values after magnesium sulfate administration, the preferred drug for preventing and treating eclampsia.

Our study's strengths include a larger sample size, a precise blood collection timeline, and robust statistical methods. However, its retrospective design may introduce biases in data collection and patient selection. Aside from this, the study's focus on a single tertiary hospital in Guangzhou, China, may restrict the generalizability of the findings. Future research should include more diverse populations and prospective designs to validate these results and better understand the inflammatory mechanisms in PE.

Conclusion

In conclusion, our study highlights the potential of NLR, SII, and SIRI as predictive markers for PE and its adverse outcomes. These markers, which are easily obtainable, could be integrated into clinical practice to facilitate early identification of high-risk pregnancies. Early intervention based on these markers may improve maternal and fetal outcomes, although large prospective studies is needed to confirm their clinical utility and establish standardized cut-off values across different populations.

Data Sharing Statement

The data analyzed for the current study is available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was conducted according to the guidelines of the Declaration of Helsinki and received approval from the medical ethics committee of Nan Fang Hospital, Southern Medical University (NFEC-2016-006). Participants were informed of the utilization of their medical records for research purposes and were provided with the option to withdraw their consent.

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Disclosure

The authors declared no competing interests. The funding body was not involved in the study design; collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

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