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ORIGINAL RESEARCH

Association Between Systemic Immune-Inflammation Index in Early Pregnancy and Preeclampsia: A Multicenter Cohort Study

Qiong Li[1,*], Meng Li[2,*], Chenyang Zhao[1], Xiaohu Chen[3], Chunyi Zhang[3], Ying Li[4], Yu Chen[4], Chaoyan Yue[3]

[1]Department of Obstetrics and Gynecology, The First People's Hospital of Chenzhou, Chenzhou, People's Republic of China; [2]Department of Ultrasound, Obstetrics & Gynecology Hospital of Fudan University, Shanghai Key Lab of Reproduction and Development, Shanghai Key Lab of Female Reproductive Endocrine Related Diseases, Shanghai, People's Republic of China; [3]Department of Laboratory Medicine, Obstetrics & Gynecology Hospital of Fudan University, Shanghai Key Lab of Reproduction and Development, Shanghai Key Lab of Female Reproductive Endocrine Related Diseases, Shanghai, People's Republic of China; [4]Department of Obstetrics, Women's Hospital of Jiangnan University, Wuxi Maternity and Child Health Care Hospital, Wuxi, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yu Chen, Department of Obstetrics, Women's Hospital of Jiangnan University, Wuxi Maternity and Child Health Care Hospital, Huaishu Alley, No. 48, Liangxi District, Wuxi, 214001, People's Republic of China, Email tt-seven@126.com; Chaoyan Yue, Department of Laboratory Medicine, Obstetrics and Gynecology Hospital of Fudan University, Shanghai Key Lab of Reproduction and Development, Shanghai Key Lab of Female Reproductive Endocrine Related Diseases, Fang Xie Road, No. 419, Shanghai, 200000, People's Republic of China, Email 20111250007@fudan.edu.cn

Objective: The systemic immune-inflammation index (SII) is an effective indicator for evaluating systemic immune-inflammatory responses. The development of preeclampsia (PE) may be attributed to an excessive systemic inflammatory response in pregnant women, however, the relationship between SII and PE remains unclear.

Methods: This study included 47,480 singleton pregnant women from three hospitals, comprising 2489 PE patients and 34,835 healthy controls. The gestational age for SII detection is 11.59 ± 3.98 weeks. Participants were divided into four groups based on the quartiles of SII calculated at baseline. Multivariable logistic regression and smooth fitting curves were used to analyze the relationship between SII and PE. Subgroup analyses based on age, BMI, and parity were conducted, and interaction tests were performed to assess the impact of different subgroups on the outcomes.

Results: After adjusting for relevant confounding factors, we observed that compared to SII Q1, participants in SII Q4 had a 21% increased risk of PE (OR = 1.21, 95% CI: 1.05–1.39, $P = 0.0078$) and a 12% increased risk of preterm birth (OR = 1.12, 95% CI: 1.00–1.26, $P = 0.0488$). Smooth fitting curves indicate that the risk of PE increases as SII rises. In subgroups of women aged ≥ 35 years and those with a BMI > 24, SII Q4 was significantly associated with an increased risk of PE compared to SII Q1. Interaction tests showed that BMI and parity did not significantly influence this positive correlation (interaction $P > 0.05$). Age may affect the association between SII and PE (interaction $P < 0.05$), with a more pronounced positive correlation observed in women aged ≥ 35 years.

Conclusion: The results indicate that elevated SII in early pregnancy is a potential marker associated with an increased risk of PE.

Keywords: systemic immune-inflammation index, preeclampsia, multicenter cohort study

Introduction

Preeclampsia (PE) is one of the severe complications of pregnancy, with an incidence of 5~8%, and it is a major cause of maternal and neonatal morbidity and mortality.[1] The primary clinical manifestations of PE include hypertension and proteinuria appearing after 20 weeks of gestation, and some patients may experience multi-organ dysfunction, such as hepatic and renal impairment, neurological involvement, thrombocytopenia, and fetal growth restriction.[2] Currently, the pathogenesis of PE is not fully understood, which poses significant challenges for its prevention and treatment. Previous studies have suggested that the development of PE may be attributed to an excessive systemic inflammatory response in

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pregnant women, which is caused by the overactivation of both the innate and adaptive immune systems.[3,4] This systemic immune-inflammatory response, combined with genetic and environmental factors, collectively promotes the onset and progression of PE.[5,6]

The Systemic Immune-Inflammation Index (SII), which is calculated as the product of the platelet count and the neutrophil count divided by the lymphocyte count, serves as a marker of systemic inflammation and immune response.[7] SII can be easily calculated from routine blood tests, making it a practical tool for clinical use. Studies have shown that higher SII levels are associated with an increased risk of various diseases.[8–12] This makes SII a potential biomarker for early risk stratification and prediction of the diseases. Although previous studies have indicated that increased neutrophil counts and platelet aggregation are common in PE patients,[13–15] the conclusions have been inconsistent due to differences in study design, sample size, and basic characteristics of the study population. Compared to a single immune or inflammatory index, SII provides a more comprehensive assessment of the body's inflammatory state.[11] It has been reported that SII demonstrates superior diagnostic performance for PE compared to the Neutrophil-Lymphocyte Ratio (NLR) or the Monocyte-Lymphocyte Ratio (MLR).[16] Elevated SII levels have been shown to be independently associated with increased urinary albumin excretion.[10] Moreover, individuals with higher SII levels tend to exhibit more severe clinical manifestations, including greater organ dysfunction and higher rates of adverse maternal and fetal outcomes.[16] However, previous studies have several limitations, including small sample sizes, inadequate adjustment for confounding factors, and a primary focus on the predictive value of SII for PE without comprehensive evaluation of its association with PE when measured in early pregnancy.[17,18]

To address these limitations, this study utilizes multicenter clinical data to investigate SII levels in early pregnancy. SII was further stratified based on quartiles, and potential confounding factors were carefully adjusted. Subgroup analyses were conducted based on maternal age, pre-pregnancy body mass index (BMI), and parity to assess the robustness of the association between SII and PE. These methodological improvements allow us to better assess the association between SII and the risk of PE. This research aims to contribute epidemiological evidence for identifying biomarkers predictive of PE and to offer new insights into the exploration of its underlying pathogenesis.

Methods

Design and Participants

This is a retrospective multicenter cohort study that involved a total of 47,480 singleton pregnant women who delivered between January 2018 and June 2024, comprising 2489 PE patients and 34,835 normal controls. All participants were seen and delivered at one of the three hospitals: Fudan University Obstetrics and Gynecology Hospital, Chenzhou First People's Hospital, or Wuxi Maternity and Child Health Care Hospital. Since early pregnancy data can facilitate simpler and more effective risk stratification, it allows for early warnings to high-risk populations before clinical symptoms appear. Clinical data were collected and laboratory tests were performed during the participants' first visit (before 20 weeks of gestation), and they all delivered at the hospital where they were seen. All clinical data and laboratory results were obtained from the Hospital Information System (HIS) and Laboratory Information System (LIS). The exclusion criteria for this study are as follow: First platelet, neutrophil, and lymphocyte test times exceeding 20 weeks of gestation, twin or multiple pregnancies, pre-existing hypertension diagnosed before pregnancy, patients with comorbidities such as hematological disorders, kidney disease, diabetes, autoimmune disorders, or other internal or surgical diseases, patients without complete maternal and neonatal records. This study was approved by the ethics committees of the three above hospitals. All participants provided broad informed consent at their first visit. This study adhered to the principles of the Declaration of Helsinki.

Variables and Measurements

In this study, the SII was used as the exposure factor. For all participants, venous blood was collected at their first visit, and the lymphocyte, neutrophil, and platelet counts were measured using an automated hematology analyzer, with the unit of measurement being 10^9/L. The test results from the three hospitals have all passed external quality assessment and

are thus comparable. The SII was calculated as the product of the platelet count and the neutrophil count divided by the lymphocyte count.[19,20] Participants were stratified according to the quartiles of SII.

Based on previous studies and clinical experience,[21] potential confounding factors related to SII and PE were included in the final analysis. Covariates included age, BMI, systolic blood pressure, diastolic blood pressure, aspirin use, antihypertensive medication use, history of hypertension, tobacco use, alcohol consumption, in vitro fertilization (IVF), alanine transaminase, uric acid, creatinine, total serum cholesterol, triglycerides, fasting blood glucose, gestational week at testing, and adverse pregnancy history. We further examined collinearity and found no collinearity between the included confounding factors and the exposure. Specifically, age was categorized as normal (< 35 years) and advanced (≥ 35 years); BMI was categorized as underweight or normal (< 24 kg/m²) and overweight (≥ 24 kg/m²); parity was categorized as nulliparous and multiparous.

Outcomes and Measurements

The primary outcome of this study was PE. PE was diagnosed according to the 2020 guidelines of the American College of Obstetricians and Gynecologists (ACOG),[22] using the following criteria: normal blood pressure before pregnancy, with the onset of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation, along with proteinuria of + or greater on routine urinalysis or a 24-hour urine protein level exceeding 300 mg. Alternatively, the presence of any of the following conditions in the absence of proteinuria: platelet count < 100×10^9/L, liver dysfunction (serum transaminases more than twice the normal value), renal dysfunction (serum creatinine > 1.1 mg/dL or more than twice the normal value), pulmonary edema, new-onset headache not explained by other causes, and visual disturbances.

The secondary outcomes of this study were low birth weight (birth weight < 2500 g) and preterm birth (delivery before 37 weeks of gestation). Gestational age was determined by early pregnancy ultrasound.

Statistical Analysis

Our study divided the SII into four quartiles from the lowest (Q1) to the highest (Q4). Continuous variables are presented as means and standard deviations (SD), while categorical variables are presented as percentages. To evaluate the differences in covariates among participants grouped by SII quartiles, weighted *t*-tests were used for continuous variables, and weighted chi-square tests were used for categorical variables. To examine the association between SII and PE, multivariable logistic regression analysis was conducted to build multivariate tests. Model I did not adjust for any covariates. Model II adjusted for age, BMI, systolic blood pressure, diastolic blood pressure, aspirin use, antihypertensive medication use, history of hypertension, tobacco use, alcohol consumption, IVF, alanine transaminase, uric acid, creatinine, total serum cholesterol, triglycerides, fasting blood glucose, gestational week at testing, and adverse pregnancy history. The association between SII and PE was assessed using odds ratios (OR) and 95% confidence intervals (CI). Smooth fitting curves were used to explore the dose-response relationship between SII and PE. Finally, subgroup analyses based on age, BMI, and parity were conducted to examine the impact of different subgroups on the outcomes. Interaction tests were performed to assess heterogeneity among these subgroups, with $P > 0.05$ indicating no heterogeneity.

All reported *P*-values are two-tailed. Statistical analyses were performed using IBM SPSS (version 21.0, IBM, Armonk, NY) and R statistical packages (R Foundation, https://www.r-project.org, version 4.4.1).

Results

Baseline Characteristics

Table 1 lists the baseline characteristics of participants grouped by SII quartiles. Overall, the number of participants in each group was balanced. Significant differences in baseline characteristics were observed between the four groups, except for low birth weight, history of hypertension, tobacco use, and parity. Participants with higher SII had a higher incidence of PE compared to those with lower SII.

Table 1 Baseline Characteristics of Participants

Characteristic	SII Q1 n=11870	SII Q2 n=11869	SII Q3 n=11871	SII Q4 n=11870	*P*-value
Age (years)	31.08 ± 4.00	31.17 ± 4.06	31.28 ± 4.10	31.54 ± 4.32	<0.001
BMI (kg/m2)	21.04 ± 2.81	21.46 ± 3.00	21.69 ± 3.14	21.98 ± 3.32	<0.001
Systolic blood pressure	113.46 ± 11.82	114.50 ± 12.18	115.54 ± 12.58	117.17 ± 12.97	<0.001
Diastolic blood pressure	68.37 ± 9.18	69.35 ± 9.51	69.97 ± 9.61	71.10 ± 9.89	<0.001
SII Test week	11.14 ± 3.81	11.41 ± 3.81	11.71 ± 3.98	12.04 ± 4.14	<0.001
SII	519.69 ± 95.91	744.31 ± 54.40	949.33 ± 68.67	1346.4 ± 223.70	<0.001
Platelet (× 10^9/L)	202.06 ± 42.80	228.82 ± 42.58	247.07 ± 45.50	274.41 ± 52.31	<0.001
Neutrophils (× 10^9/L)	4.74 ± 1.14	5.74 ± 1.17	6.46 ± 1.27	7.57 ± 1.58	<0.001
Lymphocytes (× 10^9/L)	1.84 ± 0.47	1.75 ± 0.43	1.67 ± 0.41	1.55 ± 0.40	<0.001
Alanine transaminase (IU/L)	17.26 ± 15.76	17.81 ± 14.89	18.41 ± 16.30	19.34 ± 17.23	<0.001
Uric acid (μmol/L)	210.00 ± 45.50	215.14 ± 46.58	218.41 ± 48.16	224.44 ± 50.25	<0.001
Creatinine	42.52 ± 8.66	41.78 ± 8.91	41.62 ± 9.05	41.19 ± 9.55	<0.001
Total cholesterol	4.46 ± 0.81	4.56 ± 0.81	4.63 ± 0.85	4.71 ± 0.86	<0.001
Triglycerides	1.24 ± 0.64	1.33 ± 0.68	1.43 ± 0.73	1.53 ± 0.77	<0.001
Fast blood glucose	4.53 ± 0.43	4.51 ± 0.48	4.51 ± 0.52	4.53 ± 0.60	0.007
Preeclampsia (%)					<0.001
No	11404 (96.07%)	11284 (95.07%)	11223 (94.54%)	11080 (93.34%)	
Yes	466 (3.93%)	585 (4.93%)	648 (5.46%)	790 (6.66%)	
Preterm birth (%)					0.003
No	7562 (92.57%)	7751 (92.08%)	7831 (91.64%)	8064 (91.08%)	
Yes	607 (7.43%)	667 (7.92%)	714 (8.36%)	790 (8.92%)	
Low birth weight (%)					0.132
No	11290 (95.17%)	11263 (94.90%)	11298 (95.19%)	11221 (94.60%)	
Yes	573 (4.83%)	605 (5.10%)	571 (4.81%)	640 (5.40%)	
Aspirin (%)					<0.001
No	9967 (98.45%)	9633 (97.96%)	9327 (97.68%)	8793 (96.85%)	
Yes	157 (1.55%)	201 (2.04%)	222 (2.32%)	286 (3.15%)	
Depressor (%)					<0.001
No	10088 (99.77%)	9770 (99.72%)	9483 (99.57%)	9002 (99.05%)	
Yes	23 (0.23%)	27 (0.28%)	41 (0.43%)	86 (0.95%)	
Hypertension history (%)					0.414
No	10261 (86.46%)	10315 (86.92%)	10228 (86.18%)	10263 (86.48%)	
Yes	1607 (13.54%)	1552 (13.08%)	1640 (13.82%)	1605 (13.52%)	
Tobacco (%)					0.634
No	9894 (98.13%)	9606 (98.34%)	9284 (98.15%)	8809 (98.14%)	
Yes	189 (1.87%)	162 (1.66%)	175 (1.85%)	167 (1.86%)	
Alcohol (%)					<0.001
No	9618 (95.39%)	9379 (96.02%)	9115 (96.36%)	8665 (96.54%)	
Yes	465 (4.61%)	389 (3.98%)	344 (3.64%)	311 (3.46%)	
Parity (%)					0.500
Primipara	8390 (72.00%)	8282 (71.24%)	8277 (71.31%)	8264 (71.23%)	
Multipara	3263 (28.00%)	3344 (28.76%)	3330 (28.69%)	3338 (28.77%)	
IVF (%)					0.035
No	10148 (94.13%)	10008 (94.50%)	9829 (94.66%)	9384 (93.78%)	
Yes	633 (5.87%)	583 (5.50%)	555 (5.34%)	622 (6.22%)	
Adverse pregnancy history (%)					0.003
No	11168 (94.09%)	11145 (93.90%)	11118 (93.66%)	11037 (92.98%)	
Yes	702 (5.91%)	724 (6.10%)	753 (6.34%)	833 (7.02%)	

Notes: Q1 < 648.88, Q2 = 648.88 ~ 1079.54, Q3 = 1079.54 ~ 2056.81, Q4 > 2056.81. Mean ± SD for continuous variables: P value was calculated by weighted linear regression model. % for categorical variables: *P* value was calculated by weighted chi-square test.
Abbreviations: SII, systemic immune-inflammation index; Q, quartile; BMI, body mass index; IVF, In Vitro Fertilization.

Table 2 Risk of Primary and Secondary Outcomes

Outcome	No. of PE (%)	Model I		Model II	
		OR (95% CI)	*P*-value	Adjust OR (95% CI)	*P*-value
Primary Outcome					
Preeclampsia					
SII Q1	466 (3.93%)	Reference		Reference	
SII Q2	585 (4.93%)	1.27 (1.12–1.44)	0.0002	1.14 (0.99–1.32)	0.0711
SII Q3	648 (5.46%)	1.41 (1.25–1.60)	<0.0001	1.14 (0.99–1.32)	0.0667
SII Q4	790 (6.66%)	1.74 (1.55–1.96)	<0.0001	1.21 (1.05–1.39)	0.0078
Secondary Outcomes					
Preterm birth					
SII Q1	607 (7.43%)	Reference		Reference	
SII Q2	667 (7.92%)	1.06 (0.94–1.19)	0.3427	1.06 (0.94–1.19)	0.3427
SII Q3	714 (8.36%)	1.00 (0.88–1.12)	0.9447	1.00 (0.88–1.12)	0.9447
SII Q4	790 (8.92%)	1.12 (1.00–1.26)	0.0480	1.12 (1.00–1.26)	0.0480
Low birth weight					
SII Q1	573 (4.83%)	Reference		Reference	
SII Q2	605 (5.10%)	1.07 (0.96–1.20)	0.2333	1.03 (0.90–1.17)	0.7064
SII Q3	571 (4.81%)	1.14 (1.01–1.27)	0.0268	0.97 (0.85–1.11)	0.6792
SII Q4	640 (5.40%)	1.22 (1.09–1.36)	0.0004	0.90 (0.78–1.03)	0.1350

Notes: Model I: No covariates were adjusted. Model II: Adjusted for age, BMI, systolic blood pressure; diastolic blood pressure, aspirin, depressor, hypertension history, tobacco, alcohol, IVF, alanine transaminase, uric acid, creatinine, total serum cholesterol, triglycerides, fast blood glucose, test week, adverse pregnancy history.
Abbreviations: SII, systemic immune-inflammation index; Q, quartile; BMI, body mass index; IVF, In Vitro Fertilization; OR, odds ratio.

Association Between SII and PE

Table 2 presents the results of the multivariable regression analysis for the association between SII and PE. This association was significant in Model I. However, in Model II, when stratified by SII quartiles, compared to SII Q1, the risk of PE increases as SII rises, with a 21% higher risk when SII is in Q4 (OR = 1.21, 95% CI: 1.05–1.39, $P = 0.0078$). Figure 1 shows the risk of PE across SII quartiles.

Similarly, in Model I, there were significant differences in the association between SII quartiles and the secondary outcomes of preterm birth and low birth weight. However, in Model II, compared to SII Q1, the risk of preterm birth increases as SII rises, with a 12% higher risk when SII is in Q4 (OR = 1.12, 95% CI: 1.00–1.26, $P = 0.0488$). Regarding low birth weight, there were no significant differences in risk between SII Q1, SII Q2, SII Q3, and SII Q4.

Smooth fitting curves demonstrated a dose-response relationship between SII and PE (Figure 2), indicating a positive correlation between SII and the risk of PE.

Subgroup Analysis

Further subgroup analysis showed that the association between SII and PE was not consistent, as shown in Table 3 and Figure 3. The relationship between SII quartiles and PE varied across subgroups stratified by age, BMI, and parity. After adjusting for covariates, in the subgroup of women aged 35 years or older, the positive correlation between SII and PE remained significant. In the subgroup of women with a BMI of 24 or higher, the risk of PE in SII Q4 was 36% higher compared to SII Q1 (OR = 1.36, 95% CI: 1.05–1.77, $P = 0.0193$). In the multiparous subgroup, the risk of PE was 79% higher in SII Q3 (OR = 1.79, 95% CI: 1.25–2.56, $P = 0.0014$) and 51% higher in SII Q4 (OR = 1.51, 95% CI: 1.05–2.17, $P = 0.0269$) compared to SII Q1, suggesting that higher SII levels are more strongly associated with PE in older women, those with a higher BMI, and multiparas. Interaction tests showed no statistically significant differences in the relationship between SII and PE across BMI and parity subgroups (interaction $P > 0.05$), indicating that BMI and parity do not significantly influence this positive correlation, while interestingly, interaction tests revealed

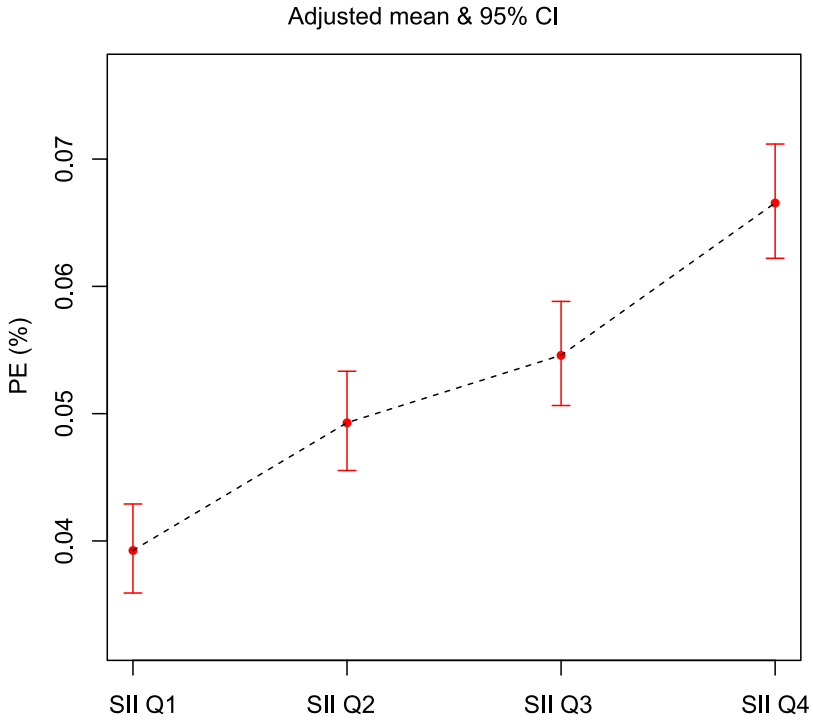

Figure 1 The overall relationship between SII and the risk of PE based on SII quartiles.
Abbreviations: PE, preeclampsia; SII, systemic immune-inflammation index; Q, quartile; CI, confidence interval.

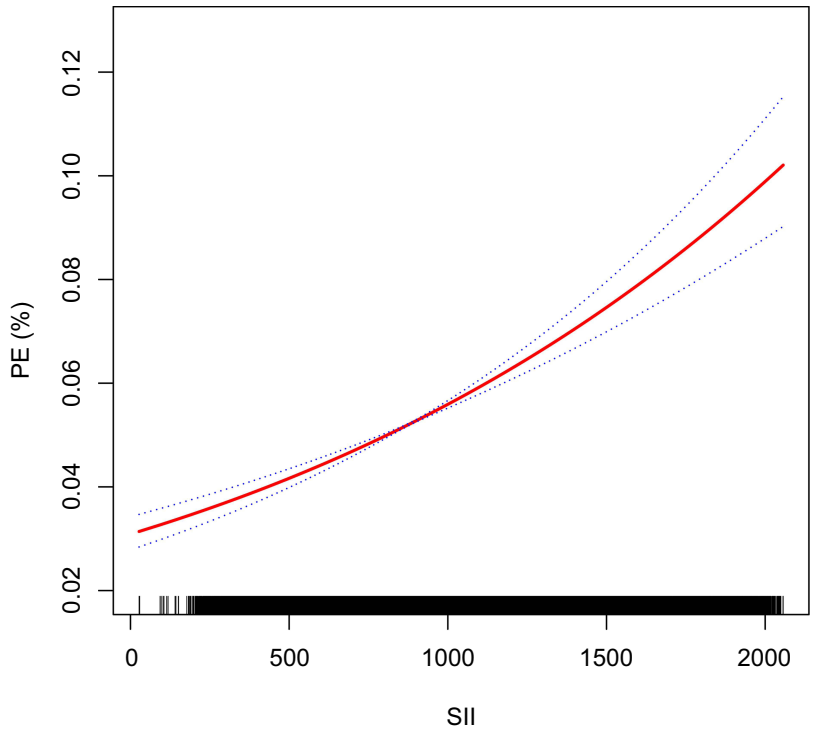

Figure 2 The dose-response relationship between SII and PE reflected by smoothed curve fitting. The redline represents the fitted curve of SII and PE, and the blue line represents the 95% confidence interval of the curve.
Abbreviations: PE, preeclampsia; SII, systemic immune-inflammation index.

Table 3 Subgroup Analysis of SII and Preeclampsia

Supgroup	No. of PE (%)	OR (95% CI)	*P*-value	*P*-value for Interaction	Adjust OR (95% CI)	*P*-value	*P*-value for Interaction
Age (years)				0.3230			0.0485
<35							
SII Q1	376 (3.80%)	Reference			Reference		
SII Q2	459 (4.66%)	1.24 (1.08–1.42)	0.0027		1.08 (0.93–1.27)	0.3176	
SII Q3	487 (5.02%)	1.34 (1.17–1.53)	<0.0001		1.04 (0.88–1.21)	0.6600	
SII Q4	568 (6.04%)	1.63 (1.42–1.86)	<0.0001		1.13 (0.97–1.33)	0.1136	
≥35							
SII Q1	90 (4.55%)	Reference			Reference		
SII Q2	126 (6.23%)	1.39 (1.05–1.84)	0.0197		1.43 (1.01–2.02)	0.0449	
SII Q3	161 (7.44%)	1.69 (1.29–2.20)	0.0001		1.73 (1.24–2.41)	0.0013	
SII Q4	222 (8.99%)	2.07 (1.61–2.67)	<0.0001		1.59 (1.15–2.20)	0.0055	
BMI (kg/m2)				0.6458			0.7364
<24							
SII Q1	330 (3.29%)	Reference			Reference		
SII Q2	362 (3.79%)	1.16 (1.00–1.35)	0.0554		1.09 (0.93–1.29)	0.2925	
SII Q3	386 (4.21%)	1.29 (1.11–1.50)	0.0008		1.13 (0.96–1.33)	0.1553	
SII Q4	426 (4.88%)	1.51 (1.30–1.75)	<0.0001		1.14 (0.97–1.35)	0.1096	
≥24							
SII Q1	123 (8.09%)	Reference			Reference		
SII Q2	205 (10.50%)	1.33 (1.05–1.68)	0.0163		1.26 (0.96–1.66)	0.0943	
SII Q3	245 (10.79%)	1.37 (1.09–1.72)	0.0062		1.18 (0.90–1.54)	0.2352	
SII Q4	342 (13.37%)	1.75 (1.41–2.18)	<0.0001		1.36 (1.05–1.77)	0.0193	
Parity				0.1263			0.0418
No							
SII Q1	375 (4.47%)	Reference			Reference		
SII Q2	458 (5.53%)	1.25 (1.09–1.44)	0.0017		1.12 (0.96–1.31)	0.1451	
SII Q3	486 (5.87%)	1.33 (1.16–1.53)	<0.0001		1.04 (0.89–1.21)	0.6351	
SII Q4	621 (7.51%)	1.74 (1.52–1.98)	<0.0001		1.16 (0.99–1.35)	0.0605	
Yes							
SII Q1	78 (2.39%)	Reference			Reference		
SII Q2	111 (3.32%)	1.40 (1.05–1.88)	0.0241		1.30 (0.90–1.90)	0.1672	
SII Q3	147 (4.41%)	1.89 (1.43–2.49)	<0.0001		1.79 (1.25–2.56)	0.0014	
SII Q4	152 (4.55%)	1.95 (1.48–2.57)	<0.0001		1.51 (1.05–2.17)	0.0269	

Notes: Adjusted for age, BMI, systolic blood pressure; diastolic blood pressure, aspirin, depressor, hypertension history, tobacco, alcohol, IVF, alanine transaminase, uric acid, creatinine, total serum cholesterol, triglycerides, fast blood glucose, test week, adverse pregnancy history.
Abbreviations: SII, systemic immune-inflammation index; Q, quartile; BMI, body mass index; IVF, In Vitro Fertilization; OR, odds ratio; CI, confidence interval.

a statistically significant difference in the relationship between SII and PE across age subgroups ($P < 0.05$), suggesting that age may affect the association between SII and PE, with a more pronounced positive correlation in women aged 35 years or older.

Discussion

PE is a progressive pregnancy complication that poses a serious threat to maternal and fetal health. Early diagnosis is crucial for clinical monitoring and effective prevention to control the condition, prolong gestational duration, and reduce the occurrence of maternal and fetal complications, thereby improving pregnancy outcomes. Previous studies have focused on identifying maternal blood biomarkers that can predict the onset of PE early, such as placental protein 13,[23] soluble fms-like tyrosine kinase 1,[24] and placental growth factor.[25] However, the effectiveness of these biomarkers remains to be validated. SII, which is calculated as the ratio of inflammatory activators (neutrophils, platelets) to inflammatory regulators (lymphocytes), is

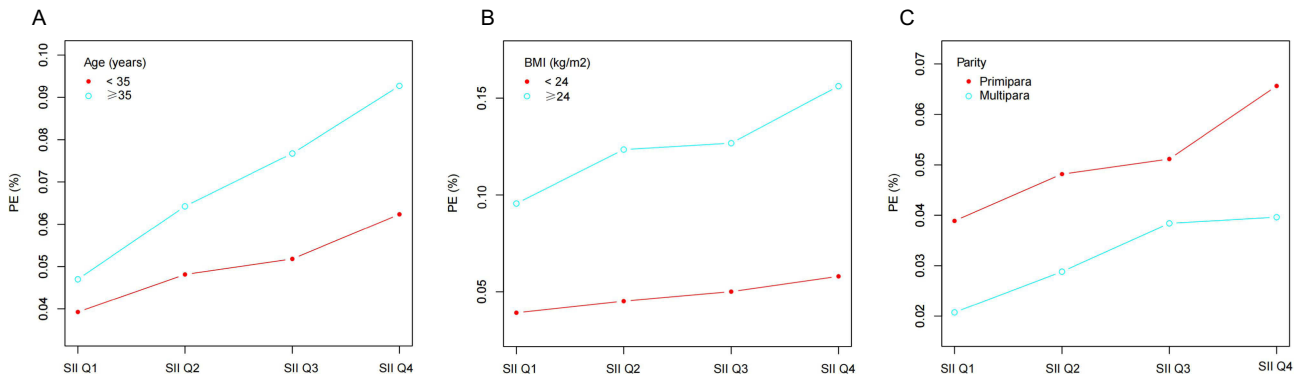

Figure 3 The results of subgroup analysis were adjusted for age (**A**), BMI (**B**), and parity (**C**).
Abbreviations: PE, preeclampsia; SII, systemic immune-inflammation index; BMI, body mass index; Q, quartile; CI, confidence interval.

considered an effective indicator for assessing systemic immune-inflammatory responses. It plays a significant role in the diagnosis, prognosis, and treatment evaluation of various diseases.

In this multicenter cohort study, we found that higher levels of SII are associated with an increased risk of PE. The results of subgroup analysis and interaction tests indicate that BMI and parity do not influence this association, but age does. The association between SII and PE is more pronounced in women aged 35 years or older. These findings suggest that SII may serve as a predictive marker for PE, particularly in women aged 35 years or older, where it holds greater clinical significance.

Previous epidemiological studies have observed associations between blood cell counts or ratios and PE. For example, according to the study by Jing Wang et al,[25] significant differences were found in absolute neutrophil, lymphocyte, and monocyte counts between PE patients and normal pregnant women. The systemic immune-inflammatory indicators, such as the NLR and Plate-Lymphocyte Ratio (PLR), have been proposed as clinical predictors for the severity and prognosis of PE.[17] Ochsner et al' study provided further evidence supporting the predictive value of NLR and PLR for PE.[26] Additionally, moderate levels of monocytes and neutrophils in normal pregnancies can moderately activate systemic immune/inflammatory responses, which are important for maintaining pregnancy.[27] A recent study found that both PE patients and their newborns exhibit changes in systemic inflammation markers, blood cell indices, and platelet indices.[28] However, some studies have reported inconsistent results. For instance, Ali et al found differences in the NLR between PE patients and healthy pregnant women, but no differences in white blood cells, neutrophils, lymphocytes, mean platelet volume (MPV), or platelet-lymphocyte ratio. Another study has reported increased absolute lymphocyte counts in PE patients.[29] Although NLR and PLR are important markers for assessing systemic inflammation and have shown some predictive value for PE, each reflects only partial aspects of the immune-inflammatory response. In contrast, SII integrates neutrophils, lymphocytes, and platelets, providing a more comprehensive assessment of the systemic inflammatory state. This broader representation may enhance its predictive value for PE, particularly when measured in early pregnancy. This study showed that higher SII levels in early pregnancy were associated with an increased risk of PE. Due to its more comprehensive nature, SII may offer distinct advantages over NLR and PLR in identifying pregnant women at risk for PE. While the observed association between elevated SII levels and increased risk of PE (OR = 1.21) may appear modest, it remains statistically significant after multivariable adjustment. Given the complex etiology of PE, SII may serve as a useful adjunct biomarker rather than a stand-alone diagnostic tool. Furthermore, subgroup analysis revealed that the association between SII and PE is of greater clinical significance in women aged 35 years or older. This finding is consistent with the consensus that advanced maternal age is a high-risk factor for PE.

Additionally, the study found that, after adjusting for confounding factors, the risk of preterm birth was 12% higher in SII Q4 patients compared to SII Q1 (OR = 1.12, 95% CI: 1.00–1.26, $P = 0.0480$). This finding suggests a potentially weaker association between SII and preterm birth than previously reported, although the result did not reach statistical significance in our analysis.[30,31] A retrospective study found that white blood cell counts and monocyte levels were significantly elevated in preterm patients, while lymphocyte, platelet, and hemoglobin levels were significantly lower.

However, there was no significant difference in SII between preterm and term groups.[30] Another study also found that SII was not statistically significant in predicting the timing of delivery in patients with preterm premature rupture of membranes.[31] Both of these studies were single-center studies with small sample sizes and did not account for the influence of relevant confounding factors. This study, with a larger and more representative sample size, fully adjusted for potential confounding factors and conducted stratified analyses of SII, revealing a significant difference in the increased risk of preterm birth in the highest quartile (SII Q4) compared to the lowest quartile (SII Q1). Furthermore, numerous studies have confirmed that excessive activation of inflammatory immune responses plays a crucial role in the induction of preterm birth.[32,33] However, the association between the highest quartile of SII and PE in this study reached marginal statistical significance ($P = 0.0488$), highlighting the need for further validation in additional studies.

Systemic inflammatory response plays a crucial role in the development of PE, characterized by the upregulation of various pro-inflammatory factors such as transforming growth factor β1 (TGFβ-1), tumor necrosis factor (TNF-α), interferon γ (IFN-γ), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1).[34–36] These pro-inflammatory factors promote the development of PE by directly or indirectly activating other inflammatory pathways. Maternal immune dysfunction also contributes to the activation of immune responses in the pathogenesis of PE, with changes in the mononuclear phagocyte system being critical for promoting the onset of PE.[37] Additionally, inflammation-induced nitric oxide synthase (iNOS) produces excess NO, leading to endothelial dysfunction, which is also considered a potential cause of PE.[38,39] Although PE is the result of multiple factors acting together, our study suggests that higher levels of the SII are independently associated with the prevalence of PE. SII integrates three hematological indicators, including neutrophil, platelet, and lymphocyte counts, which largely reflect inflammatory responses, adaptive immune responses, and thrombosis. The potential mechanisms by which SII influences PE may involve increased neutrophils promoting platelet aggregation and increased blood viscosity. The interaction between neutrophils and blood cells promotes a prothrombotic state.[40] Increased platelets, in turn, facilitate the recruitment of neutrophils and other white blood cells, leading to vascular endothelial damage and dysfunction, thereby promoting the onset and progression of PE.[41]

Our study has significant clinical implications. Healthcare providers can use SII levels to stratify the risk of PE in early pregnancy. According to our findings, pregnant women with higher SII levels have a 21% increased risk of developing PE compared to those with lower SII levels, and this association is more pronounced in women over the age of 35. Therefore, personalized management, including closer monitoring of blood pressure and proteinuria, early initiation of low-dose aspirin, and lifestyle modification, may help reduce the risk of PE and improve maternal and fetal outcomes among older pregnant women with elevated SII levels. However, due to the modest effect size, SII may serve best as a complementary rather than standalone biomarker, warranting further investigation in combination with other clinical and laboratory parameters.

This study has several strengths. First, the primary strength lies in its design as a multicenter cohort study with a large sample size, which considers relevant confounding factors, making the results more reliable. Second, the exposure factors in this study are based on measurements that are readily available from routine laboratory analyses in most hospitals, making it easier to implement clinically and facilitating broader application. By monitoring these blood indicators, we can better assess the maternal inflammatory immune status, which has significant clinical implications for the prediction and treatment of PE.

However, the study also has some unavoidable limitations. First, as an observational study, we cannot establish a causal relationship between SII and the prevalence of PE, nor can we rule out the possibility of reverse causality. Second, our study did not evaluate the relationship between absolute counts of various blood cells and the risk of PE. However, most previous studies have reported results consistent with ours, suggesting that the relationship between SII and PE may be driven by combined effect of increased neutrophil and platelet counts and decreased lymphocyte counts. Third, our study only obtained blood cell counts at the initial examination and did not dynamically monitor the fluctuations in SII and their impact on the prevalence of PE. Forthly, although we adjusted for many potential confounding factors based on previous research and clinical experience, we acknowledge that some potential confounders may still exist and affect our results. Therefore, the results should be interpreted with caution in clinical practice. Finally, Previous studies have reported that the SII range in non-pregnant populations is 486.46 (345.43, 688.00).[42]

Notably, physiological changes during pregnancy, such as leukocytosis and thrombocytosis, may influence SII levels, suggesting that reference ranges established in non-pregnant individuals may not be applicable to pregnant women. Although the SII range observed in our study was 200–2000, further research is still needed to establish pregnancy-specific cutoff values for SII.

Conclusion

In conclusion, we believe that SII may be a valuable biomarker for PE. It likely reflects systemic inflammation levels accurately by balancing the pathways of inflammation, immunity, and thrombosis, which has significant clinical implications for the prediction and treatment of PE. Future researches should include more large-scale prospective studies to further validate the role of SII in PE.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was approved by the ethics committees of Fudan University Obstetrics and Gynecology Hospital, he ethics committees of Chenzhou First People's Hospital and he ethics committees of Wuxi Maternity and Child Health Care Hospital. All participants provided broad informed consent.

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Disclosure

The authors declare no conflicts of interest in this work.

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