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Research Article

Serum Inflammatory Indices and Preeclampsia Risk: A Matched Case-control Study

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Abstract

Background: While numerous studies have linked individual serum inflammatory biomarkers to preeclampsia (PE) risk, few have evaluated how composite inflammatory indices correlate with the condition. Methods: A hospital-based 1:1 matched case-control study including 440 PE cases and 440 controls was conducted. Sociodemographic and lifestyle data were collected through structured questionnaires. Peripheral blood platelet, neutrophil, monocyte, and lymphocyte counts were measured using a fully automated analyzer (Cobas 8000, modules C701/C702/C502), and the corresponding inflammatory indices were subsequently calculated. Results: Multivariable-adjusted regression revealed an inverse risk trend across quartiles for all six evaluated metrics. In the highest-versus-lowest quartile comparison, the most pronounced reduction in odds was observed for PLR (OR = 0.08, 95% CI: 0.05–0.15), followed sequentially by AISI (OR = 0.13, 0.08–0.22), SIRI (OR = 0.23, 0.14–0.37), SII (OR = 0.41, 0.30–0.55), and LMR (OR = 0.53, 0.39–0.71), all presenting a *P*-trend < 0.001. A similar significant trend was noted for NLR (OR = 0.63, 0.48–0.83, *P*-trend < 0.01). Among the individual indicators, PLR showed a relatively higher AUC, while the combined model yielded a slightly higher area under the curve (AUC) overall. Conclusion: Lower levels of SII, LMR, NLR, SIRI, AISI, and PLR were associated with an increased risk of PE, while combining these inflammatory indices provided the best discriminative performance.

Keywords

Inflammatory Indices, Preeclampsia, Chinese, Case-control Study

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1. Introduction

As a complex gestational syndrome emerging after 20 weeks of pregnancy, preeclampsia (PE) manifests predominantly as elevated blood pressure. Although proteinuria remains a hallmark feature, diagnosis can be established in its absence if any signs of systemic organ injury are present, such as localized hepatic or renal dysfunction, low platelet counts (thrombocytopenia), respiratory complications like pulmonary edema, or acute cerebrovascular and visual alterations [1]. Because definitive clinical management for preeclampsia (PE) remains largely restricted to the timely termination of pregnancy—frequently via cesarean delivery—the global burden of this condition is devastating. Annually, PE accounts for approximately 500,000 fetal and 70,000 newborn deaths, positioning it as a primary driver of perinatal and maternal mortality worldwide [2]. At present, the main method of clinical treatment is to terminate pregnancy by cesarean section. Therefore, it is very important to find effective predictors of PE, early diagnosis and early intervention.

Inflammation, a complex host defense response to stimuli, plays a key role in the pathogenesis of PE [3]. Activation of inflammasomes promotes the secretion of the pro-inflammatory cytokines IL-1β and IL-18, promoting apoptosis [1]. In PE, inadequate trophoblast invasion induces placental ischemia, disrupts the Th1/Th2 balance, and increases pro-inflammatory cytokines such as IL-4, IL-6, TNF-α, and CRP [4, 5]. Current research has begun to focus on the association between inflammatory indices and preeclampsia. Z. Seyhanli et al. [6] that among first-trimester inflammatory indices, the systemic inflammation response indices had significant predictive value for preeclampsia risk. Another retrospective study revealed significant positive associations between log2-transformed inflammatory indices (MLR) and the risk of preeclampsia-related kidney injury [7]. A separate retrospective study demonstrated that log2-transformed MLR was positively associated with the risk of kidney injury in patients with preeclampsia [8]. Novel immune-inflammatory indices (SII, AISI, and SIRI) may serve as simple, non-invasive, and cost-effective screening tools for predicting coronary heart disease (CHD) risk among individuals with hypertension [9]. However, most of the studies are carried out in early pregnancy, and limited information in Chinese pregnant women. In addition, these studies did not compare the ability of inflammatory indices to identify PE risk. Therefore, we conducted a 1:1 matched case–control study, matched for age (±3 years), gestational week (±1 week), and gestational diabetes mellitus, to investigate the associations between inflammatory indices (NLR, MLR, SII, AIRI, AISI, and PLR) and the risk of preeclampsia in Chinese pregnant women, and to evaluate their predictive performance.

2. Method

2.1. Study Participants

Participants for this 1:1 matched case-control protocol were enrolled at China's First Affiliated Hospital of Zhengzhou University from March 2016 to June 2019, utilizing an established methodological design [10]. Preeclampsia cases were confirmed based on the 2015 Chinese 'Diagnosis and treatment guideline of hypertensive disorders in pregnancy' [11], which establishes diagnostic thresholds at a systolic blood pressure of 140 mmHg or more, or a diastolic blood pressure of 90 mmHg or more after 20 gestational weeks. Diagnosis further mandated either a 24-hour protein excretion of 0.3 g or more, a protein-to-creatinine ratio of 0.3 or more, or a random urine test showing 1+ or more when quantitative data were omitted. For patients presenting without proteinuria, diagnosis was confirmed via distinct organ or system failure (comprising the cardiac, pulmonary, hepatic, renal, hematological, digestive, and nervous systems, or placental-fetal anomalies). Pregnant controls without any history of high blood pressure or proteinuria were selected from the same facility and matched with cases according to maternal age (± 3 years), weeks of gestation (±1 week), and the presence of gestational diabetes mellitus (GDM). The exclusion criteria for participants were as follows: (1) refusal to participate in the study; (2) heart disease, malignant tumor (s), hyperthyroidism, an immune system disease, chronic renal insufficiency, or other chronic diseases; and (3) mental or cognitive disorders such as schizophrenia or depression. This manuscript follows the specific guideline for observational studies (STROBE Statement rules).

The Ethics Committee of Scientific Research and Clinical Trials at the First Affiliated Hospital of Zhengzhou University granted ethical clearance for this investigation (Approval No. Scientific research 2016-LW-34). All participants provided written informed consent before epidemiological data and biological specimens were collected. All procedures were performed according to the Declaration of Helsinki guidelines and regulations.

2.2. Data Collection

Through a structured questionnaire, we documented participants' baseline characteristics, encompassing age, marital status, educational attainment, household income, and weeks of gestation. Digital instruments were utilized to assess maternal height, weight, and blood pressure, allowing for the determination of body mass index (BMI, kg/m ^{2}), while gestational age was computed from the first day of the last menstrual period.

2.3. Serum Inflammatory Indices

Overnight fasting venous blood samples were collected from participants in the morning. Monocyte count, neutrophil

count, lymphocyte count, and platelet count in serum were measured using a fully automated analyzer (Cobas 8000, modules C701/C702/C502; Roche Molecular Systems, Inc., Basel, Switzerland), with assay kits provided by Roche. Laboratory quality control was maintained according to standard operating procedures, and the coefficient of variation (CV) for repeated measurements of samples from hospitalized patients was controlled at ≤2.5%. In addition, the neutrophil-to-lymphocyte ratio (NLR = neutrophil/lymphocyte), monocyte-to-lymphocyte ratio (LMR = monocyte/lymphocyte), systemic immune-inflammation index(SII = platelet count × neutrophil count / lymphocyte count), systemic inflammation response index (SIRI = neutrophil × monocyte / lymphocyte), aggregate index of systemic inflammation (AISI = neutrophil × monocyte × platelet / lymphocyte), and platelet-to-lymphocyte ratio (PLR = platelet / lymphocyte) were derived from the corresponding peripheral blood cell counts [12, 13].

2.4. Statistical Analysis

Paired t-tests or Wilcoxon signed-rank tests were used to test differences in quantitative variables, and unpaired chi-squared tests were used to identify differences in qualitative variables between cases and controls. For variables with <25% missing data, multiple imputation (five imputations) was performed, and pooled estimates were calculated using Rubin's rules [14]. According to the distribution among the controls, the serum inflammation indices and inflammatory markers were divided into quartiles (Q1–Q4). Conditional logistic regression was used to evaluate the association between serum inflammation indices and inflammatory markers and the risk of PE, and the results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Tests for trends were performed by using the median of each quartile as a continuous variable in the regression models.

Potential confounders were adjusted for in the multivariate models, including age(continuous, years), gestational age(continuous, weeks), pre-pregnancy BMI(continuous, kg/m^2), family history of hypertension (yes or no), education level (junior high school or below, senior high school, college or above), household income (≤ RMB 2,000, RMB 2,001–4,000, RMB 4,001–6,000, RMB > 6,000), physical activity(continuous, MET(hour/day)), parity(0 births, 1 birth, ≥ 2 births) and gestational diabetes mellitus (GDM)(yes or no). Covariates included in the multivariable models were selected based on previous literature [15, 16] and variables that differed significantly between groups at baseline. A sensitivity analysis of the relationship between serum inflammation indices and PE risk was performed by excluding participants with GDM. Potential nonlinear associations of serum inflammatory indices with PE risk were examined using restricted cubic spline (RCS) analysis. The 20th, 50th, and 80th percentiles were retained as knots. Restricted cubic spline plots (RCS), receiver operating characteristic (ROC) curves, areas under the curves (AUCs), and statistical tests were all performed using R4.4.1. All other analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA). A two-tailed P value less than 0.05 was considered statistically significant. The missing values in our study were ignored as they were less than 10%.

3. Results

3.1. Characteristics of Study Participants

Table 1 outlines the baseline characteristics and preeclampsia (PE)-associated variables for the 440 enrolled subjects. No marked disparities were observed between the PE and control cohorts regarding matching and lifestyle factors, including age, gestational duration, GDM status, income, physical activity, passive smoking, polycystic ovarian syndrome, or TNF-α levels. However, the PE group exhibited a higher prevalence of a family history of hypertension, alongside significantly elevated pre-pregnancy BMI and lymphocyte counts. Conversely, diminished values were recorded in PE patients for formal education and parity, as well as for platelet, neutrophil, and monocyte counts, and all evaluated inflammatory metrics (SII, LMR, NLR, SIRI, AISI, and PLR).

Table 1. *Sociodemographic and lifestyle characteristics and selected PE risk factors of the study population (n = 440 pairs).*

	Cases (n = 440)	Controls (n = 440)	*P* [a]
Age (years) [b]	30.9 ±5.03	31.0 ±4.85	0.114
Gestational age (weeks) [b]	34.2 ±2.90	34.2 ±2.67	0.066
Pre-pregnancy BMI (kg/m^2) [b]	23.7 ±3.89	22.4 ±3.35	< 0.001
Gestational diabetes mellitus [c]	59 (13.0)	59 (13.0)	1.000
Polycystic ovarian syndrome [c]	10 (2.3)	6 (1.4)	0.454
Family history of hypertension [c]	167 (38.0)	83 (18.9)	< 0.001
Education level [c]			0.014
Junior high school or below	207 (47.0)	164 (37.4)	

	Cases (n = 440)	Controls (n = 440)	*P* [a]
Senior high school	75 (17.0)	83 (18.9)	
College or above	158 (35.9)	192 (43.7)	
Income (Yuan/month) [c]			0.405
≤ 2,000	61 (13.9)	46 (10.5)	
2,001–4,000	216 (49.1)	211 (48.0)	
4,001–6,000	78 (17.7)	82 (18.6)	
> 6,000	59 (13.4)	81 (18.4)	
Passive smoker [c]	67 (15.2)	58 (13.2)	0.488
Parity [c]			0.001
0 births	185 (42.0)	135 (30.7)	
1 birth	180 (40.9)	211 (48.0)	
≥ 2 births	73 (16.6)	93 (21.1)	
Physical activity (MET-h/day) [b]	27.0 ±3.96	26.6 ±4.48	0.241
PLT(10^9/L) [d]	162.5(165,248)	204.5 (123, 212)	0.001
Neutrophil(10^9/L) [d]	6.87(5.29,8.7)	7.06(5.56,9.51)	0.001
Lymphocyte(10^9/L) [d]	1.63(1.28,2.10)	1.40 (1.10,1.69)	0.001
Monocyte(10^9/L) [d]	0.51 (0.39,0.67)	0.54(0.43, 0.70)	<0.001
CRP(μg/L) [d]	11.25(4.08,37.38)	4.20(2.11,11.14)	0.001
IL-4(pg/ml) [d]	1.87(1.32,2.41)	1.76(0.97,2.15)	0.018
TNF-α(pg/ml) [d]	7.22(5.31,10.13)	5.74(5.06,8.11)	0.152
SII [d]	625.85(407.53,1058.54)	1029.78(694.73, 1629.20)	<0.001
NLR [d]	4.05(2.87,5.87)	5.00(3.66,7.47)	<0.001
MLR [d]	0.3(0.22,0.40)	0.39(0.29,0.50)	<0.001

Abbreviation: BMI, body mass indices; SII, systemic immune inflammation indices; PLT, platelet count; CRP, C-reactive protein;IL-4, interleulkin-4;TNF-α,Tumor necrosis factor-α;SII, systemic immune inflammation indices; LMR,Lymphocyte-to-monocyte ratio; NLR, neutrophil–lymphocyte ratio.

[a] Continuous variables were evaluated using paired *t*-tests or Wilcoxon rank-sum tests. Categorical variables were evaluated using paired chi-squared tests.

[b] Data are presented as the mean ±standard deviation.

[c] Data are presented as the number (%).

[d] Data are presented as the M (P25, P75).

3.2. Association Between Serum Inflammatory Indices and Preeclampsia Risk

The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for preeclampsia risk across different quartiles of serum inflammatory markers are detailed in Table 2. Compared with the lowest quartile, the adjusted OR for the highest quartile was 0.41 (95% CI: 0.30–0.55, *P* trend <0.001) for SII, 0.63 (95% CI: 0.48–0.83, *P* trend <0.001) for NLR, 0.53 (95% CI: 0.39–0.71, *P* trend < 0.001) for MLR, 0.23 (95% CI:0.14-0.37, *P* trend <0.001) for SIRI, 0.13 (95% CI:0.08-0.22, *P* trend <0.001) for AISI, and 0.08 (95% CI:0.05-0.15, *P* trend <0.001) for PLR. Sensitivity analysis suggested that the significant associations of MLR, NLR, PLR, SII, SIRI, and AISI and PE risk remained similar after excluding the participants with GDM (Table S1).

Restricted cubic spline analysis revealed that the correlation between preeclampsia risk and the six inflammatory indices (PLR, AISI, SIRI, MLR, NLR, and SII) followed a pattern that deviated significantly from linearity (with both overall and non-linear *P* < 0.001) (Figure 1). With increasing serum inflammatory indices, the association with the risk of

preeclampsia (PE) showed a sharp decline initially, followed by a gradual stabilization (Figure 1).

Table 2. *Odds ratios (95% CIs) for preeclampsia risk according to the serum inflammatory markers and indices in Chinese pregnant women.*

	Q1	Q2	Q3	Q4	*P*-trend [a]
CRP					
Median (mg/L)	1.50	3.60	9.05	42.30	-
Cases/controls (n)	13/58	12/58	17/53	32/38	-
Basic model	1	0.94(0.43,2.05)	1.33(0.64,2.73)	2.50(1.31,4.76)*	0.004
Model 1[b]	1	0.88(0.40,1.93)	1.31(0.63,2.71)	2.26(1.18,4.33) *	0.011
Model 2[c]	1	0.94(0.42,2.10)	1.46(0.67,3.14)	2.41(1.22,4.76)*	0.015
IL-4					
Median (pg/ml)	0.44	1.47	2.02	2.87	-
Cases/controls (n)	28/42	40/30	33/38	44/25	-
Basic model	1	0.63(0.39,1.01)	0.90(0.58,1.38)	0.73(0.46,1.15)	0.211
Model 1[b]	1	0.60(0.36,1.09)	0.90(0.57,1.40)	0.71(0.45,1.13)	0.199
Model 2[c]	1	0.58(0.34,0.97)*	0.83(0.53,1.30)	0.73(0.46,1.17)	0.204
TNF-α					
Median (pg/ml)	3.99	5.47	7.42	13.58	-
Cases/controls (n)	29/37	22/44	42/24	39/28	-
Basic model	1	0.76(0.47,1.22)	0.61(0.37,1.01)	1.09(0.71,1.69)	0.085
Model 1[b]	1	0.72(0.44,1.19)	0.57(0.33,0.96)*	0.81(0.69,1.66)	0.057
Model 2[c]	1	0.69(0.42,1.15)	0.54(0.31,0.92)*	0.72(0.62,1.55)	0.065
SII					
Median	353.63	651.58	1036.51	2008.31	-
Cases/controls (n)	159/59	120/98	92/127	64/154	-
Basic model	1	0.76(0.60,0.96)*	0.58(0.45,0.75)***	0.40(0.30,0.54)***	<0.001
Model 1[b]	1	0.76(0.60,0.97)*	0.59(0.45,0.76)**	0.40(0.30,0.54)**	<0.001
Model 2[c]	1	0.78(0.61,0.99)*	0.57(0.44,0.73)***	0.41(0.30,0.55)***	<0.001
NLR					
Median	2.44	3.85	5.37	11.78	-
Cases/controls (n)	1410/78	118/101	90/128	87/131	-
Basic model	1	0.84(0.66,1.07)	0.64(0.49,0.84)**	0.62(0.48,0.81)***	0.001
Model 1[b]	1	0.84(0.65,1.08)	0.66(0.50,0.86)**	0.61(0.47,0.80)***	0.001
Model 2[c]	1	0.85(0.66,1.11)	0.69(0.52,0.90)**	0.63(0.48,0.83)***	0.003
MLR					
Median	0.20	0.30	0.40	0.55	-
Cases/controls (n)	70/148	90/128	132/90	142/72	-
Basic model	1	0.91(0.72,1.15)	0.63(0.48,0.82)***	0.49(0.37,0.65)***	<0.001
Model 1[b]	1	0.93(0.73,1.18)	0.63(0.48,0.82)***	0.50(0.38,0.67)***	<0.001

	Q1	Q2	Q3	Q4	*P*-trend [a]
Model 2[c]	1	0.96(0.76,1.23)	0.64(0.49,0.83)***	0.53(0.39,0.71)***	<0.001

Abbreviation: OR, odds ratio; CI, confidence interval; Q, quantiles;CRP, C-reactive protein;IL-4, interleulkin-4; TNF-α,Tumor necrosis factor-α; SII, systemic immune inflammation indices; NLR, Neutrophil -lymphocyte ratio; MLR, Monocyte–lymphocyte ratio.

[a] Performed by entering the median in each quartile as continuous variables in the regression models.

[b] OR adjusted for age, gestational age, household income, educational level.

[c] Additionally adjusted for pre-pregnancy BMI, parental hypertension history, gestational diabetes mellitus, physical activity.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$

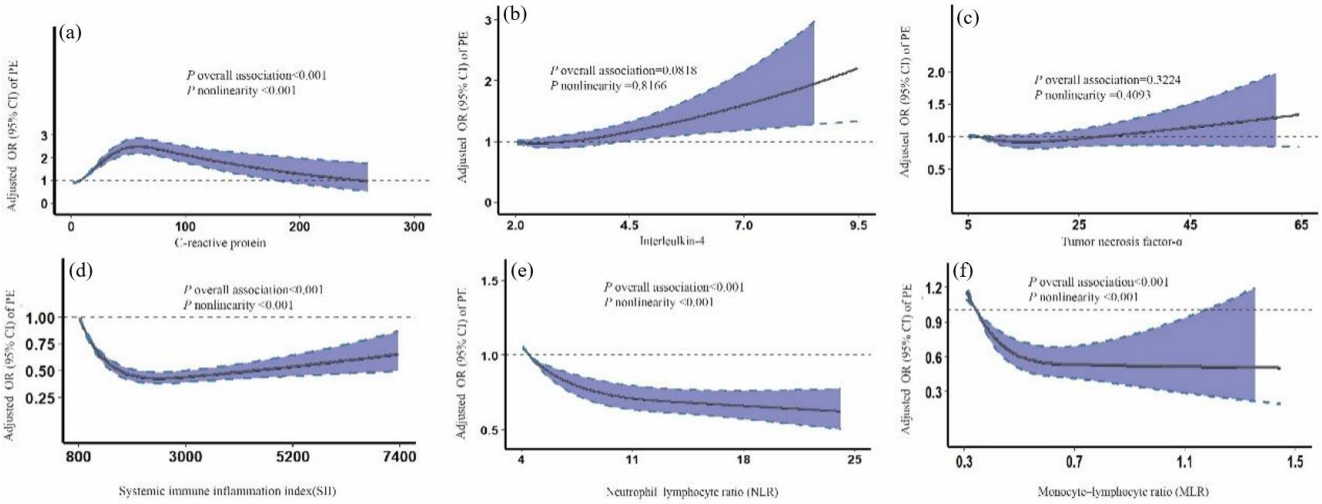

Figure 1. *Multivariable-adjusted ORs (solid lines) and 95% CIs (dashed lines) for PE risk according to serum inflammation markers and indices. The model was adjusted for age, gestational age, pre-pregnancy BMI, family history of hypertension, education level, parity, physical activity, and daily energy intake. OR, odds ratio; CI, confidence interval; PE, pre-eclampsia.*

3.3. Comparison of the Discriminative Efficacy for PE Risk

Figure 2 illustrates the comparative discriminative performance of serum inflammatory indices for predicting preeclampsia. ROC analysis showed that the combined model including all six inflammatory indices yielded the highest AUC (0.747, 95% CI: 0.715–0.779), indicating a moderate discriminative ability. Discrimination analysis revealed that the five-indicator model (NLR + MLR + SII + AISI + PLR) and the four-indicator panel (MLR + SII + AISI + PLR) shared the peak predictive value, each yielding an AUC of 0.746 (95% CI: 0.714–0.779 and 0.713–0.778, respectively). Marginally lower diagnostic capacities were observed when simplifying the combinations to three parameters (SII + AISI + PLR; AUC = 0.744, 95% CI: 0.711–0.776) or two parameters (MLR + PLR; AUC = 0.739, 95% CI: 0.707–0.772). Among the single indicators, PLR showed a relatively higher AUC (0.727, 95% CI: 0.694–0.761) compared with the other individual inflammatory indices. The ROC results, 95% CIs, and cutoff values for the remaining indicators and models are shown in Supplementary Table 2.

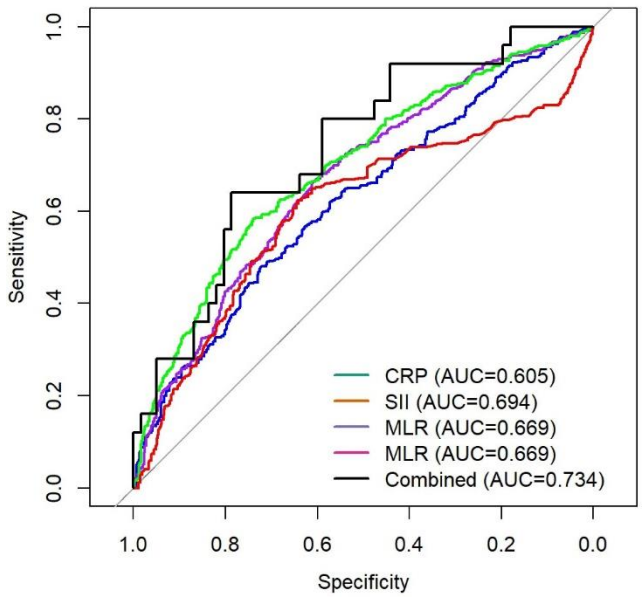

Figure 2. *ROC Curve Comparison for PE Prediction. AUC, Area Under the Curve; SII, systemic immune inflammation indices; LMR, Lymphocyte-to-monocyte ratio; NLR, neutrophil–lymphocyte ratio; CRP, C-reactive protein.*

4. Discussion

This 1:1 matched case–control study found that inflammatory indices were negatively associated with PE risk. Sensitivity analyses excluding participants with GDM yielded similar results, and restricted cubic spline analysis further indicated significant nonlinear associations between these indices and PE risk. Given that these indices are simple and readily obtainable, they may serve as convenient adjunctive indices for PE screening and have important public health implications.

Previous evidence regarding the associations between inflammatory indices (SII, MLR, NLR, SIRI, AISI, and PLR) and the risk of preeclampsia (PE) has been limited. Our findings showed that SII, NLR, MLR, SIRI, AISI, and PLR were negatively correlated with PE risk. However, one study found that among pregnant women aged 18–25 years, PLR and MLR were lower in the PE group, whereas among those aged 26–35 years, PLR and SII were higher in the case group [8]. A retrospective case-control study conducted in the first trimester (6 to 14 weeks) showed that NLR and PLR values were significantly higher in patients compared to controls [17]. A study including women with singleton pregnancies at a gestational age of 11.59 ± 3.98 weeks found that, among women aged ≥35 years, SII was positively associated with the risk of preeclampsia [16]. In addition, a retrospective study found that after $\log_2$ transformation of inflammatory indices (NLR, MLR, PLR, SII, and SIRI), all of these markers were positively associated with the risk of preeclampsia complicated by acute kidney injury (PE-AKI) [7]. The reasons for these discrepancies may include the following aspects: (1) Population heterogeneity, including racial differences, variations in age and gestational age distribution, as well as differences in the spectrum of disease severity; (2) NLR, PLR, and LMR varied significantly according to gestational age at blood testing, pre-pregnancy BMI, parity, and maternal smoking status (never smoker, stopped before pregnancy, stopped because of pregnancy, and continued smoking) ($P < 0.001$) [18]; (3) More importantly, NLR and PLR levels were higher in mothers who had never smoked compared with those who stopped smoking before pregnancy, stopped because of pregnancy, or continued smoking [18]. (4) Preeclampsia is closely associated with Th1/Th2 imbalance, and dynamic immune changes during pregnancy may alter inflammatory status and routine hematologic indices across different trimesters [4, 7, 19]. Therefore, inflammatory indices may have some value in assisting the early identification of preeclampsia risk; however, they are insufficient for direct diagnosis.

Our findings are in agreement with several previous studies. A retrospective study including 320 primiparous women found that, compared with the control group, patients with mild and severe preeclampsia (PE) had higher lymphocyte counts but lower NLR, MLR, and PLR levels, with the differences being more pronounced in the severe PE group [20]. A retrospective study conducted in Turkey also showed that the levels of NLR, SII, SIRI, AISI, and monocyte counts in the preeclampsia (PE) group were significantly lower than those in the control group ($P < 0.05$) [21]. Similarly, contrasting roles for NLR and LMR in relation to premature birth were documented in an extensive Japanese cohort involving 76,853 singleton gestations with deliveries spanning 28 to 41 weeks. Specifically, NLR exhibited an inverse relationship with preterm delivery risk (OR = 0.49, 95% CI: 0.29–0.82), whereas a direct positive correlation was established for LMR (OR = 1.80, 95% CI: 1.02–3.19) [18]. Additionally, an inverse correlation between the systemic immune-inflammation index (SII) and preeclampsia (PE) susceptibility was demonstrated in a single-institution retrospective analysis (OR = 0.998, 95% CI: 0.996–0.999, $P = 0.005$) [3], and another retrospective analysis observed significantly lower SII levels in the PE group compared with controls (813.7 ± 394.1 vs. 1009.8 ± 590.4, $P = 0.031$) [22]. The decreased SII, NLR, and MLR values observed in PE patients may be explained by reductions in platelet, neutrophil, and monocyte counts, accompanied by increased lymphocyte counts [3]. This discrepancy further highlights the need to develop integrative biomarker models to improve the early prediction of preeclampsia. In our study, the restricted cubic spline (RCS) curves demonstrated reverse J-shaped associations between SII, NLR, and MLR and PE risk.

To data, there are few studies comparing the predictive ability of different inflammatory indices for preeclampsia risk. A retrospective study evaluated peripheral blood immune-inflammatory markers during the second trimester and found that the areas under the curve (AUCs) of NLR, SII, and SIRI for predicting preeclampsia (PE) were 0.594, 0.649, and 0.646, respectively ($P < 0.001$) [23]. In a separate retrospective case-

control evaluation, first-trimester values of mean platelet volume (MPV), NLR, and PLR demonstrated significant clinical utility in forecasting preeclampsia. Among these metrics, NLR emerged as the premier predictive marker when applying an optimal cutoff threshold of 4.12 [17]. A retrospective cohort study indicated that low SII and NLR were significantly associated with predicting mortality risk in infants of preeclamptic mothers, and that SII had higher sensitivity than PNI for predicting prematurity in these infants [24]. A case-control study with 1:1 matching for age, parity, and pre-gestational BMI showed that, among individual predictors of PE risk, mean corpuscular hemoglobin concentration (MCHC), platelet-to-mean platelet volume ratio (PC/MPV), and NLR and PLR (AUC = 0.838) exhibited good predictive performance, but the combined model of these indicators demonstrated even better diagnostic performance, with an area under the curve (AUC) of 0.874 [25]. A study evaluating the independent and combined predictive values of platelet count (PC), NLR, and PLR for preeclampsia showed that, compared with individual indicators, the combined index of PC, NLR, and PLR was significantly more predictive of preeclampsia [26]. Among these previous studies, only two studies combined multiple indicators to compare the predictive ability of a single indicator for preeclampsia, but their comprehensive indicators (except for SII) differed from those included in our study. Thus, it may be difficult to compare them directly with our study. Our results showed that among the individual indicators, PLR had a relatively higher AUC (0.727, 95% CI: 0.694–0.761) compared with the other inflammatory indices. Although integrating all six inflammatory markers into a comprehensive configuration marginally elevated the AUC to 0.747 (95% CI: 0.715–0.779), the global predictive performance remained fundamentally limited. These findings suggest that although combining multiple inflammatory markers may slightly improve discriminative performance, the predictive value of these indices alone is limited. Therefore, inflammatory indices may be more appropriately used as simple and readily obtainable adjunctive markers rather than standalone screening tools for preeclampsia.

Widespread endothelial impairment and systemic inflammatory responses fundamentally underpin preeclampsia (PE), a hypertensive disorder unique to pregnancy [27]. During normal pregnancy, immune adaptation maintains immune surveillance while ensuring tolerance to fetal antigens [28]. Inflammation disrupts the dynamic equilibrium of neutrophils, monocytes, lymphocytes, and platelets, rendering their ratios valuable indicators for the indirect assessment of inflammatory status and cell-mediated immune function [29]. An influx of neutrophils triggers a massive release of reactive oxygen species (ROS), neutrophil extracellular traps (NETs), and pro-inflammatory cytokines such as TNF-α and IL-6. This pathological cascade subsequently exacerbates endothelial injury and worsens vascular dysfunction [30]. Concurrently, elevated lymphocyte and monocyte counts intensify inflammatory responses and fetal immune rejection, worsening placental dysfunction [31]. Protection against PE may be successfully conferred by the alleviation of vascular impairment, immunological rejection, and inflammatory pathways. This favorable outcome is typically driven by a lower systemic immune-inflammation index (SII), which reflects diminished platelet and neutrophil counts coupled with an elevated lymphocyte population [32]. Furthermore, endothelial impairment is profoundly driven by the oxidative stress that arises from placental ischemia–reperfusion insult. Elevated concentrations of inflammatory indices are associated with vascular injury, reduced nitric oxide bioavailability, and increased vasoconstriction [33, 34]. Taken together, these aberrations participate in driving both hypertension and proteinuria. Furthermore, circulating markers of inflammation are poised to impact preeclampsia (PE) pathogenesis, operating primarily through the regulation of inflammatory pathways and the exacerbation of endothelial damage.

Several limitations of this study should be considered. First, owing to the inherent nature of a case-control design, a causal relationship between inflammatory indices and the risk of PE cannot be established, and the possibility of reverse causation cannot be completely excluded. Nevertheless, all inflammatory indices were calculated from routinely collected hematological parameters obtained through standard blood tests, which helped reduce the likelihood of information bias. Secondly, although our study did not analyze other inflammatory markers, some literature does not clearly distinguish between inflammatory markers and inflammatory indices [29, 35]. SII, NLR, and MLR can be readily obtained from routine blood tests at a relatively low cost, making them practical biomarkers for the diagnosis and prognostic assessment of preeclampsia (PE). Thirdly, although we matched for age and gestational age and adjusted for potential confounders, residual confounding may still have influenced the associations observed in this study. Moreover, given the inherent limitations of a case–control design, causal relationships cannot be established. Therefore, large-scale prospective cohort studies and experimental studies are needed to further validate these findings.

5. Conclusion

Inflammatory indices were negatively associated with PE risk and may serve as convenient adjunctive indices for PE screening with important public health implications; further prospective and randomized studies are needed for confirmation.

Abbreviations

PE	Preeclampsia
BMI	Body Mass Indices
SII	Systemic Immune Inflammation Indices

PLT	Platelet Count
SIRI	Systemic Inflammation Response Index
AISI	Aggregate Index of Systemic Inflammation
PLR	Platelet-to-lymphocyte Ratio
NLR	Neutrophil–lymphocyte Ratio
LMR	Lymphocyte-to-monocyte Ratio
OR	Odds Ratio
CI	Confidence Interval
Q	Quantiles
IL-1β	interleukin-1β
DBP	Diastolic Blood Pressure
SBP	Systolic Blood Pressure
GDM	Gestational Diabetes Mellitus
RCS	Restricted Cubic Spline
ROS	Reactive Oxygen Species
NETs	Neutrophil Extracellular Traps

Supplementary Material

The supplementary material can be accessed at https://doi.org/10.11648/j.ajcem.20261404.17

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Data Availability Statement

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

Conflicts of Interest

The authors declare no conflicts of interest.

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