British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(8): 50744
https://doi.org/10.31083/BJHM50744

Article

Predictive Value of Inflammatory and Placental-Related Markers for Adverse Neonatal Outcomes in Pregnant Women With Gestational Diabetes Mellitus and Preeclampsia

Ting Chen[1], Lichun Wang[1], Li Chen[2], Weihui Yang[1], Xiaolei Long[3,*]

[1]Department of Obstetrics, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, 410007 Changsha, Hunan, China
[2]Reproductive Medicine Center, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, 410007 Changsha, Hunan, China
[3]Chronic Noncommunicable Diseases Institute, Hunan Provincial Center for Disease Control and Prevention, 410153 Changsha, Hunan, China
*Correspondence: 19974941793@163.com (Xiaolei Long)
Academic Editor: John Alcolado
Submitted: 5 February 2026 Revised: 21 April 2026 Accepted: 30 April 2026 Published: 6 August 2026

Abstract

Aims/Background: The coexistence of gestational diabetes mellitus (GDM) and preeclampsia (PE) significantly increases the risk of adverse neonatal outcomes. However, effective predictive tools for this high-risk population remain limited. This study aimed to evaluate the predictive value of inflammatory and placental-related biomarkers for adverse neonatal outcomes in pregnant women with GDM and PE. **Methods:** This retrospective observational study enrolled 230 pregnant women with GDM and PE between February 2022 and February 2025. Participants were divided into an event group (n = 53) and a non-event group (n = 177) based on the occurrence of adverse neonatal outcomes. Baseline characteristics, inflammatory markers, and placental growth factor (PlGF) levels were collected. Independent predictive factors were identified using univariate and multivariate logistic regression analyses, with collinearity diagnostics performed. Receiver operating characteristic (ROC) curves were plotted to evaluate the discriminative performance of individual markers and combined predictive models. **Results:** Univariate analysis indicated that fasting blood glucose, PlGF, glycated hemoglobin (HbA1c), neutrophil-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII), and systemic inflammatory response index (SIRI) were significantly associated with adverse neonatal outcomes (all $p < 0.05$). Multivariate logistic regression, after adjustment for collinearity, identified elevated fasting blood glucose, reduced PlGF, increased HbA1c, and elevated SII as independent risk factors for adverse neonatal outcomes (all $p < 0.001$). ROC curve analysis demonstrated that the combined model incorporating these four variables achieved the highest predictive accuracy, with an area under the curve (AUC) of 0.944 (95% confidence interval [CI]: 0.902–0.986), sensitivity of 94.3%, and specificity of 84.7%, significantly outperforming individual markers. **Conclusion:** In pregnant women with GDM and PE, fasting blood glucose, PlGF, HbA1c, and SII represent independent predictors of adverse neonatal outcomes. A composite panel integrating metabolic, placental, and inflammatory biomarkers exhibits strong discriminative value and may provide objective evidence for neonatal risk stratification in this high-risk population, thereby informing targeted clinical management.

Keywords: gestational diabetes mellitus; adverse neonatal outcomes; preeclampsia; placental growth factor

1. Introduction

Gestational diabetes mellitus (GDM) is a leading metabolic complication during pregnancy, with a steadily increasing global incidence in recent years [1]. Epidemiological studies indicate that, with recent changes in the social environment, the age of pregnant women has increased, obesity rates have risen, and assisted reproductive technologies have been widely adopted; consequently, the population affected by GDM has expanded [2]. GDM substantially elevates the risk of pregnancy and perinatal complications. Additionally, it is strongly associated with a range of adverse neonatal outcomes, including macrosomia, preterm birth, neonatal hypoglycemia, respiratory distress syndrome, and neonatal intensive care unit (NICU) admission [3]. Although glycemic control is considered the cornerstone measure for improving GDM outcomes, even among pregnant women receiving standardized management, adverse neonatal outcomes cannot be completely prevented, suggesting that the underlying mechanisms may not be solely driven by hyperglycemia [4].

Preeclampsia (PE) is a significant and multifaceted obstetric disorder characterized by the onset of hypertension after 20 weeks of gestation, accompanied by proteinuria or evidence of end-organ dysfunction [5]. PE remains one of the major causes of maternal and perinatal morbidity and mortality worldwide. In many cases, pregnancy is terminated prematurely due to medical indications, which leads to preterm birth, fetal growth restriction (FGR), placental abruption, and other adverse neonatal outcomes [6].

Notably, GDM and PE frequently coexist in clinical practice, with overlapping pathophysiological characteristics [7]. Insulin resistance, chronic low-grade inflamma-

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

tion, endothelial dysfunction, and oxidative stress are recognized as key shared mechanisms underlying both conditions [8,9,10]. Evidence indicates that pregnant women with GDM have a markedly increased risk of developing PE compared with those without GDM [11]. Moreover, the coexistence of these two conditions is associated with a further increase in the incidence of adverse neonatal outcomes [12,13]. Specifically, a study by Li et al. [12] demonstrated that, compared with pregnant women with PE alone, those with both GDM and PE had a significantly higher risk of adverse neonatal outcomes, including an approximately 2.5-fold increase in preterm birth and a 1.8-fold increase in NICU admissions. This marked difference suggests that the coexistence of these conditions exerts a synergistic effect, resulting in a risk profile that is not merely additive but potentially multiplicative. Therefore, predictive models developed for a single condition may be inadequate for this high-risk subgroup, underscoring the need for a dedicated risk assessment approach.

However, most current studies continue to analyze GDM and PE as relatively independent diseases. There is a lack of systematic investigation focusing on the high-risk population with coexisting GDM and PE, especially in terms of neonatal outcome prediction, and a stable, clinically applicable indicator system remains lacking. From a pathophysiological perspective, placental dysfunction is considered a central mechanism in the onset and progression of PE. This process is characterized not only by structural abnormalities but also by dysregulated angiogenesis at the maternal-fetal interface, impaired perfusion, and consequent hypoxia and inflammatory cascades [14]. During this process, placental angiogenic factors and inflammatory mediators may enter the maternal circulation, forming detectable biological signals [15,16].

In recent years, inflammatory responses and placental-related biomarkers have emerged as key areas of interest in perinatal medicine research. Inflammatory markers, such as C-reactive protein, white blood cell count, and derived indices, have been closely associated with the onset and progression of both GDM and PE. Moreover, placental-derived factors and alterations in placental structure and function play a critical role in regulating the maternal-fetal interface and shaping fetal outcomes [17,18,19,20]. However, most existing studies focus on single disease states or individual marker categories, with limited integration of inflammatory and placental-related markers, and few address neonatal outcome prediction in patients with coexisting GDM and PE.

Therefore, systematically evaluating the predictive value of inflammatory responses and placental-related indicators for adverse neonatal outcomes in high-risk pregnancies, such as those complicated by both GDM and PE, is of significant clinical importance. On the one hand, this approach may deepen our understanding of the pathological mechanisms at the maternal-fetal interface under coexisting conditions; on the other hand, it may offer objective evidence to support early risk stratification and individualized perinatal management. Accordingly, this study aimed to evaluate the predictive value of inflammatory and placental-related markers for adverse neonatal outcomes in pregnant women with GDM and PE, to inform improvements in clinical risk assessment and targeted intervention strategies.

2. Methods

2.1 Study Design and Patients

This retrospective observational study included 230 pregnant women who delivered at Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University between February 2022 and February 2025 and were diagnosed with GDM complicated by PE. All participants were identified through the hospital's electronic medical record system, and the corresponding clinical data and laboratory test results were complete, standardized, and traceable.

This study adhered to the ethical principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University (Approval No.[2026]-050). Given the retrospective design and the use of de-identified electronic medical record data, the requirement for informed consent was waived by the Ethics Committee of Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University.

The diagnosis of GDM was based on a 75 g oral glucose tolerance test (OGTT) performed at 24–28 weeks of gestation, following the criteria established by the International Association of Diabetes and Pregnancy Study Groups. A diagnosis was confirmed if any of the following thresholds were met: fasting blood glucose ≥5.1 mmol/L, 1-hour post-load blood glucose ≥10.0 mmol/L, or 2-hour post-load blood glucose ≥8.5 mmol/L [21].

The diagnosis of PE was established based on the criteria outlined in the Guidelines for the Diagnosis and Treatment of Hypertensive Disorders in Pregnancy (2020), consistent with the current consensus of the American College of Obstetricians and Gynecologists (ACOG). Diagnostic criteria included new-onset hypertension after 20 weeks of gestation, defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, measured on at least two occasions at least 4 hours apart. This was accompanied either by proteinuria (≥300 mg/24 h) or, in the absence of proteinuria, by evidence of end-organ dysfunction, including renal impairment, abnormal liver function, thrombocytopenia, pulmonary edema, or new-onset cerebral or visual symptoms [22].

The inclusion criteria were as follows: (1) meeting the diagnostic criteria for both GDM and PE; (2) gestational age at delivery ≥28 weeks; and (3) availability of complete clinical data and perinatal outcome records during preg-

nancy. The exclusion criteria were: (1) pre-existing chronic hypertension, gestational diabetes mellitus, chronic kidney disease, cardiovascular disease, or severe hepatic dysfunction; (2) autoimmune disorders, active infections, malignant tumors, or other systemic inflammatory conditions; (3) missing or incomplete key laboratory indicators. Based on neonatal outcomes, participants were divided into an adverse neonatal outcome group and a non-adverse neonatal outcome group.

Adverse neonatal outcomes were defined as the occurrence of any of the following events after birth [23]: preterm birth (<37 weeks of gestation); stillbirth; neonatal death (within 28 days postpartum); a 5-minute Apgar score <7; neonatal metabolic acidosis (umbilical arterial pH <7.0 and base excess ≤−16 mmol/L); hypoxic-ischemic encephalopathy; necrotizing enterocolitis (Bell stage II or higher); intraventricular hemorrhage (grade III or IV); bronchopulmonary dysplasia (grade III or IV); or admission to the neonatal intensive care unit (NICU) due to severe complications. Because preterm birth was incorporated as a component of adverse neonatal outcomes, gestational age at delivery differed inherently between the event and non-event groups by definition. Therefore, it was not included in subsequent statistical analyses to avoid collinearity and overadjustment.

2.2 Collection of Baseline Data and Laboratory Indicators

All laboratory indicators were obtained from the electronic medical records of the study subjects during routine prenatal examinations and hospitalizations. Blood samples were collected during routine follow-up visits or hospital admissions after the diagnosis of GDM and PE and prior to delivery. In this study, all blood samples were obtained between 24 and 36 weeks of gestation, consistent with routine prenatal care and disease monitoring schedules. All samples were analyzed by the hospital's laboratory department following standardized operating procedures and quality control measures.

Peripheral venous blood samples were collected in the morning under fasting conditions to evaluate complete blood count parameters and inflammation-related markers. A fully automated hematology analyzer (Sysmex Corporation, Kobe, Japan) was used to determine neutrophil, lymphocyte, monocyte, and platelet counts. C-reactive protein (CRP) levels were measured using immunoturbidimetric methods, while glycated hemoglobin (HbA1c) was quantified by high-performance liquid chromatography (HPLC) and expressed as a percentage (%). Placental growth factor (PlGF) levels were determined using enzyme-linked immunosorbent assay (ELISA) (Shanghai Zhen Ke Biological Technology Co., Shanghai, China).

Based on peripheral blood cell count results, several derived inflammatory markers reflecting systemic inflammatory status were further calculated, including:

The neutrophil-lymphocyte ratio (NLR), defined as neutrophil count divided by lymphocyte count.

The platelet-to-lymphocyte ratio (PLR), defined as platelet count divided by lymphocyte count.

The monocyte-to-lymphocyte ratio (MLR), defined as monocyte count divided by lymphocyte count.

The systemic immune-inflammation index (SII), calculated as neutrophil count × platelet count ÷ lymphocyte count.

The systemic inflammatory response index (SIRI), calculated as neutrophil count × monocyte count ÷ lymphocyte count.

All inflammation-related indices were derived from blood test results obtained at the same time point to minimize potential bias arising from temporal variability.

Baseline clinical data were also collected as covariates, including maternal age, pre-pregnancy or early pregnancy body mass index (BMI), history of miscarriage, family history of hypertension, family history of diabetes, parity (primiparous or multiparous), and plurality (singleton or multiple gestation). All data were extracted from the electronic medical record system and independently verified by two investigators to ensure data integrity and accuracy.

2.3 Statistical Analysis

Statistical analyses were conducted using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Data distribution was initially evaluated using the Kolmogorov-Smirnov test, and homogeneity of variance was assessed using Levene's test. Continuous variables with a normal distribution and homoscedasticity are presented as mean ± standard deviation ($\bar{x} \pm SD$), and intergroup comparisons were performed using the independent-samples *t*-test. Non-normally distributed continuous variables are reported as median with interquartile range [M (Q_1, Q_3)], with comparisons performed using the Mann-Whitney *U* test. Categorical variables are presented as frequencies and percentages, and intergroup differences were evaluated using the chi-square (χ^2) test, with Yates' continuity correction applied where appropriate.

Participants were categorized into two groups based on the presence or absence of adverse neonatal outcomes. To evaluate associations between inflammatory markers, placental-related indicators, clinical characteristics, and adverse neonatal outcomes, univariate logistic regression analysis was initially performed. Variables with $p < 0.05$ in univariate analyses were then entered into a multivariate logistic regression model using a backward stepwise elimination approach to identify independent predictors. Multicollinearity among the candidate variables was assessed prior to model construction using variance inflation factors (VIFs), with VIF < 5 indicating no significant collinearity.

To evaluate the discriminative performance of individual markers identified in the multivariate model, receiver

Table 1. Comparison of baseline data between the two groups of patients.

Variables	Non-event group (n = 177)	Event group (n = 53)	Statistic	*p*-value
BMI (kg/m^2)	25.12 ± 3.46	25.81 ± 3.01	t = 1.328	0.186
Age (years)	31.94 (28.60–34.79)	31.76 (28.32–34.69)	Z = 0.139	0.890
CRP (mg/L)	2.68 ± 1.31	3.07 ± 1.13	t = 1.978	0.049
Neutrophils (/mm^3)	4479.27 ± 931.76	6813.81 ± 2284.68	t = 7.260	<0.001
Lymphocytes (/mm^3)	1877.09 ± 508.16	2004.79 ± 545.16	t = –1.578	0.116
Monocytes (/mm^3)	548.75 ± 137.23	615.12 ± 192.83	t = –2.335	0.022
Platelets (/mm^3)	236,123.40 ± 37,068.53	244,880.84 ± 59,974.92	t = –1.007	0.318
PlGF (pg/mL)	128.67 ± 31.54	95.89 ± 26.69	t = 6.864	<0.001
HbA1c (%)	5.90 ± 0.77	6.76 ± 0.97	t = –6.713	<0.001
Fasting blood glucose (mg/dL)	100.23 (88.66–111.66)	118.13 (106.16–135.24)	Z = 6.276	<0.001
NLR	2.46 (1.84–3.10)	3.64 (2.62–4.30)	Z = 4.991	<0.001
PLR	128.39 (100.91–156.13)	123.50 (95.75–159.83)	Z = 0.645	0.519
MLR	0.29 (0.23–0.37)	0.28 (0.21–0.41)	Z = 0.139	0.890
SII	562,991.28 (443,179.49–735,631.39)	844,786.73 (614,613.79–1,074,434.56)	Z = 4.793	<0.001
SIRI	1291.01 (998.62–1713.94)	1999.45 (1361.24–2944.23)	Z = 4.718	<0.001
History of miscarriage, n (%)			χ^2 = 2.214	0.137
No	160 (90.40)	44 (83.02)		
Yes	17 (9.60)	9 (16.98)		
Parity, n (%)			χ^2 = 0.095	0.758
Primiparous	123 (69.49)	38 (71.70)		
Multiparous	54 (30.51)	15 (28.30)		
Family history of hypertension, n (%)			χ^2 = 0.414	0.520
No	144 (81.36)	41 (77.36)		
Yes	33 (18.64)	12 (22.64)		
Family history of diabetes, n (%)			χ^2 = 0.250	0.617
No	161 (90.96)	50 (94.34)		
Yes	16 (9.04)	3 (5.66)		
Number of fetuses, n (%)			χ^2 = 1.105	0.293
Single	164 (92.66)	46 (86.79)		
Multiple births	13 (7.34)	7 (13.21)		

Abbreviations: BMI, body mass index; CRP, C-reactive protein; PlGF, placental growth factor; HbA1c, glycated hemoglobin; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index.

operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated. A combined predictive model based on multivariate logistic regression analysis was further established, and its overall predictive performance was evaluated using a composite ROC curve. All statistical tests were two-sided, and *p*-values < 0.05 were considered statistically significant.

3. Results

3.1 Baseline Data Analysis

This study included 230 pregnant women with gestational diabetes mellitus and preeclampsia. According to the occurrence of adverse neonatal outcomes, participants were divided into a non-event group (177 cases) and an event group (53 cases). A comparative analysis of sociodemographic characteristics and relevant clinical indicators between the two groups is presented in Table 1.

As shown in Table 1, the two groups were comparable in age, BMI, lymphocyte and platelet counts, PLR, MLR, history of miscarriage, parity, family history of hypertension or diabetes, and plurality (all $p > 0.05$). In contrast, significant differences were observed in several metabolic and inflammatory parameters. Notably, levels of CRP, fasting blood glucose, neutrophil count, monocyte count, HbA1c, NLR, SII, and SIRI were significantly higher in the event group compared with the non-event group (all $p < 0.05$), whereas PlGF levels were markedly lower in the event group ($p < 0.001$).

3.2 Univariate Regression Analysis

To preliminarily identify potential predictive factors, univariate logistic regression analysis was performed for each variable. In the analysis of inflammatory markers, given that individual blood cell counts (e.g., neutrophils and lymphocytes) are components of composite inflammatory

Table 2. Univariate logistic regression analysis.

Variables	β	SE	Z	*p*-value	OR (95% CI)
History of miscarriage					
No					1.000 (Reference)
Yes	0.655	0.446	1.469	0.142	1.925 (0.803–4.614)
Parity					
Primiparous					1.000 (Reference)
Multiparous	–0.106	0.346	0.307	0.759	0.899 (0.456–1.771)
Family history of hypertension					
No					1.000 (Reference)
Yes	0.245	0.381	0.643	0.521	1.277 (0.606–2.694)
Family history of diabetes					
No					1.000 (Reference)
Yes	–0.505	0.650	0.777	0.437	0.604 (0.169–2.157)
Number of fetuses					
Single					1.000 (Reference)
Multiple births	0.652	0.498	1.311	0.190	1.920 (0.724–5.091)
Age	0.013	0.035	0.360	0.719	1.013 (0.945–1.086)
BMI	0.062	0.047	1.323	0.186	1.064 (0.971–1.166)
Fasting blood glucose	0.062	0.011	5.910	<0.001	1.064 (1.043–1.087)
CRP	0.239	0.122	1.952	0.051	1.270 (0.999–1.614)
PlGF	–0.036	0.006	5.706	<0.001	0.964 (0.953–0.977)
HbA1c	1.171	0.211	5.539	<0.001	3.225 (2.131–4.882)
NLR	0.688	0.143	4.814	<0.001	1.989 (1.503–2.631)
PLR	–0.002	0.003	0.703	0.482	0.998 (0.991–1.004)
MLR	1.211	1.149	1.054	0.292	3.357 (0.353–31.885)
SII	0.001	0.000	4.763	<0.001	1.001 (1.001–1.001)
SIRI	0.001	0.000	5.096	<0.001	1.001 (1.001–1.001)

Abbreviations: OR, odds ratio; CI, confidence interval; SE, standard error.

indices (such as NLR and PLR), these composite indicators were preferentially included to minimize multicollinearity and improve model stability. The final results are presented in Table 2. Fasting blood glucose, PlGF, HbA1c, NLR, SII, and SIRI were significantly associated with adverse neonatal outcomes (all $p < 0.05$).

3.3 Multivariate Logistic Regression Analysis

All variables with statistical significance in the univariate analysis (fasting blood glucose, PlGF, HbA1c, NLR, SII, and SIRI) were included in the initial multivariate logistic regression model. Variance inflation factor analysis indicated that NLR exhibited collinearity with other inflammatory markers (VIF >5) and that its regression coefficients were unstable. To optimize model performance and ensure robustness, NLR was excluded, and the model was reconstructed using the remaining variables. Following stepwise regression screening, SIRI was also excluded due to collinearity. The final model results are presented in Table 3.

After adjustment for potential confounders, elevated fasting blood glucose, increased HbA1c, elevated systemic immune-inflammatory index (SII), and reduced placental growth factor were identified as independent risk factors for adverse neonatal outcomes in pregnant women with GDM and PE (all $p < 0.05$). Multicollinearity diagnostics for all variables retained in the final model yielded variance inflation factor values <5, indicating the absence of significant collinearity and supporting the stability and reliability of the model.

3.4 ROC Curve Analysis of Predictive Performance

To evaluate and compare the discriminative performance of each predictor, ROC curves were constructed. Based on the independent predictors identified in the multivariate regression analysis, a combined predictive probability was calculated using the regression coefficients of four variables: fasting blood glucose, PlGF, HbA1c, and SII. For comparative analysis, ROC curves for each of the four individual indicators were also plotted. The area under the curve (AUC) values and comparative results are presented in Table 4 and Fig. 1. The combined model comprising the four indicators demonstrated the highest predictive performance. At the optimal cutoff value, the combined model achieved a sensitivity of 94.3% and a specificity of 84.7%, outperforming each predictor.

Table 3. Multivariate logistic regression analysis.

Variables	β	SE	Z	*p*-value	VIF	OR (95% CI)
Fasting blood glucose	0.085	0.017	4.957	<0.001	1.099	1.089 (1.053–1.126)
PlGF	–0.042	0.009	4.461	<0.001	1.058	0.959 (0.942–0.977)
HbA1c	1.566	0.313	5.001	<0.001	1.074	4.787 (2.591–8.842)
SII	0.001	0.000	3.610	<0.001	1.887	1.001 (1.001–1.001)

Abbreviation: VIF, variance inflation factor. For SII, the odds ratio (OR) and 95% confidence interval (CI) are presented per one-unit increase.

Table 4. ROC curve analysis of individual indicators and the combined predictive model for adverse neonatal outcomes.

Variables	AUC	95% CI	Sensitivity (%)	Specificity (%)
Combined indicator panel	0.944	0.902–0.986	94.3	84.7
Fasting blood glucose	0.784	0.714–0.854	67.8	75.5
PlGF	0.783	0.717–0.850	65.5	79.2
HbA1c	0.759	0.679–0.839	78.5	67.9
SII	0.717	0.633–0.801	84.2	52.8

Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve.

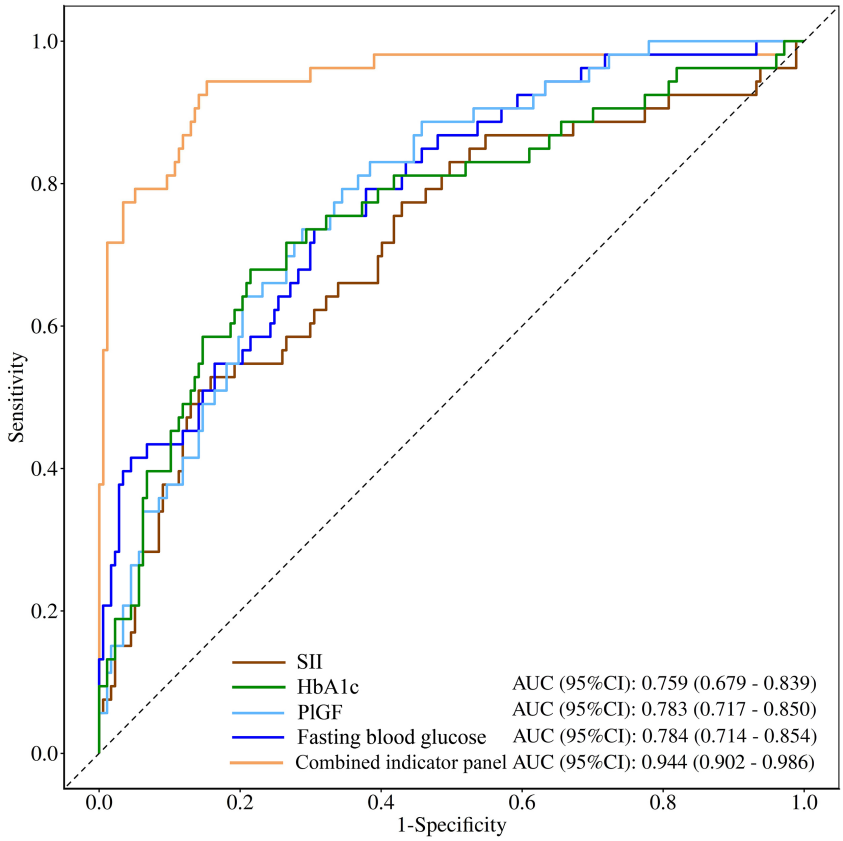


Fig. 1. ROC curve analysis for predicting adverse neonatal outcomes.

4. Discussion

GDM and PE are both common complications of pregnancy. Previous studies have demonstrated that GDM can significantly increase the risk of PE by exacerbating insulin resistance, promoting chronic low-grade inflammation, and inducing endothelial dysfunction; when both conditions coexist, their adverse effects on maternal and fetal outcomes often exhibit additive or even synergistic effects [24,25]. Adverse neonatal outcomes, as one of the most direct and clinically relevant indicators of pregnancy complications, are closely linked to perinatal management decisions and long-term health outcomes. Therefore, identifying a stable, reproducible, and clinically applicable predictive indicator system for the high-risk population with GDM combined with PE is of considerable significance.

In the present study, we systematically evaluated the potential value of inflammation-related indicators and placental-related biomarkers in predicting adverse neonatal outcomes in a cohort of pregnant women with GDM and PE without severe characteristics, admitted to a single center between February 2022 and February 2025. The results showed that, compared with the non-event group, pregnant women in the adverse outcome group had significantly higher levels of fasting blood glucose, HbA1c, NLR, SII, and SIRI, while PlGF levels were significantly lower.

Further univariate logistic regression analysis indicated that fasting blood glucose, PlGF, HbA1c, NLR, SII, and SIRI were all significantly associated with adverse neonatal outcomes. In the multivariate regression model, fasting blood glucose, PlGF, HbA1c, and SII remained independent predictors. The VIF for each variable in the model was within an acceptable range, indicating no significant multicollinearity. The combined panel constructed based on these independent predictors demonstrated excellent discriminative performance in ROC analysis, with an AUC higher than that of any single indicator, suggesting strong potential for clinical application.

The core metabolic features of GDM are insulin resistance and impaired glucose metabolism. A persistent hyperglycemic state not only directly affects fetal energy supply and metabolic homeostasis but also impairs placental function by promoting oxidative stress and inflammatory responses [10,26]. In this study, fasting blood glucose and HbA1c were both important indicators of glycemic control during pregnancy. In multivariate analysis, they emerged as independent risk factors for adverse neonatal outcomes, suggesting that even in the absence of severe PE, inadequate glycemic control may still increase the risk of neonatal complications through placental dysfunction or imbalance at the maternal-fetal interface. The study by Yang et al. [27] indicates that glycemic control during pregnancy in patients with gestational diabetes mellitus adversely affects the maternal and neonatal outcomes, consistent with the findings of the present study.

PlGF, as a placental-derived pro-angiogenic factor, plays a key role in maintaining normal placental vascular development and adequate perfusion at the maternal-fetal interface. The study by Tousty et al. [28] suggests that the onset and progression of PE are accompanied by reduced PlGF levels and angiogenic imbalance, and that the degree of PlGF reduction is closely associated with adverse pregnancy outcomes. The present study further demonstrates that, in the specific population with coexisting GDM and PE, PlGF remains an independent protective factor against adverse neonatal outcomes, and its decreased level is significantly associated with increased risk. Although this study did not directly evaluate placental histopathological alterations, PlGF, as a quantifiable biomarker of placental function, is practically applicable for reflecting the functional status of the maternal-fetal interface and predicting neonatal outcomes, and provides a basis for its broader application in high-risk pregnancy populations.

Inflammation plays a central role in the shared pathophysiology of GDM and PE. Chronic low-grade inflammation may adversely affect the intrauterine growth environment by disrupting insulin signaling, vascular endothelial function, and placental perfusion through multiple mechanisms. In this study, several composite inflammatory markers (NLR, SII, SIRI) derived from peripheral blood cell counts were significantly elevated in the adverse outcome group, and SII retained independent predictive value in multivariate regression analysis. SII integrates information from neutrophils, platelets, and lymphocytes, thereby reflecting the dynamic balance between inflammatory activation and immune regulation. Its consistent performance in this study suggests that it may be more suitable for risk stratification in complex pregnancy conditions than individual inflammatory markers. This finding is generally consistent with previous studies on the clinical application value of inflammatory markers in PE and GDM, and further extends their applicability to populations with coexisting conditions.

Notably, the combined model constructed in this study integrates metabolic indicators (fasting blood glucose, HbA1c), PlGF, and SII, demonstrating significantly superior predictive performance compared with individual indicators in ROC analysis. These findings suggest that adverse neonatal outcomes in GDM complicated by PE are not driven by a single pathological pathway, but rather reflect the combined effects of multiple functional abnormalities. Integrating information across different biological dimensions allows a more comprehensive assessment of the true disease risk and is more consistent with the multifactorial nature of clinical conditions.

From a clinical practice perspective, the above indicators are all derived from laboratory data obtainable during routine prenatal examinations or hospitalization. The testing methods are standardized, widely available, and relatively low-cost, supporting their potential for broad clinical application. In clinical management, for pregnant women with GDM and PE, poor glycemic control, markedly reduced PlGF levels, and persistently elevated SII may indicate an increased risk of adverse neonatal outcomes. This may assist obstetricians in implementing more proactive risk assessment and management strategies, including optimization of delivery timing, enhanced neonatal monitoring, and multidisciplinary collaboration.

However, this study has limitations. First, it is a single-center retrospective study with a relatively limited sample size, which may introduce selection bias and restrict the generalizability of the findings. Additionally, because preterm birth is included as a component of the composite adverse neonatal outcome, gestational age at delivery was not adjusted for in the regression model; consequently, the extent to which the predictive value of the iden-

tified markers is independent of gestational age cannot be fully determined. Future studies with larger sample sizes should consider subgroup analyses restricted to term deliveries or the application of competing risk models to further validate whether these markers retain predictive value beyond the influence of prematurity. The absence of an external validation cohort represents an important limitation, as it precludes evaluation of the stability and reproducibility of the predictive performance across different populations. Accordingly, further validation through multicenter, large-sample studies is warranted. Second, although adverse neonatal outcomes were defined as a composite endpoint based on shared pathophysiological mechanisms and to ensure adequate statistical power, stratified analyses according to outcome type or severity were not performed due to the limited sample size. Future studies with larger cohorts are required to determine whether the predictive value of these markers differs across specific outcomes. Third, although this study included several inflammatory and placental-related indicators, it did not dynamically assess their longitudinal changes at different stages of pregnancy, thus failing to reflect the time-series characteristics of these indicators as the disease progresses. Furthermore, other angiogenesis-related factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), were not included, and placental histopathological validation was not performed; therefore, the assessment of placental functional status relied primarily on serological indicators. Finally, although the combined indicator panel demonstrated strong discriminative performance, its clinical utility in prospective decision-making requires further validation.

5. Conclusion

In summary, this study demonstrates that metabolic dysregulation, enhanced systemic inflammatory response, and imbalance in placental function-related factors are closely associated with adverse neonatal outcomes in pregnant women with GDM and PE. Fasting blood glucose, HbA1c, PlGF, and SII may serve as independent predictors, and the combined panel of these parameters exhibits high predictive performance in assessing the risk of adverse neonatal outcomes. These findings provide novel insights into neonatal risk stratification in GDM patients with PE and establish a basis for future development of individualized perinatal management strategies based on multi-indicator integration. These predictive indicators may help reduce the incidence of perinatal mortality in clinical practice.

Key Points

• The coexistence of gestational diabetes mellitus and preeclampsia creates a synergistic pathological state characterized by metabolic dysregulation, systemic inflammation, and placental dysfunction, which collectively contribute to an elevated risk of adverse neonatal outcomes beyond that associated with either condition alone.

• Fasting blood glucose, glycated hemoglobin, placental growth factor, and the systemic immune-inflammatory index were identified as independent predictors of adverse neonatal outcomes in this high-risk population, reflecting the multifactorial nature of the underlying pathophysiological mechanisms.

• The combined predictive model integrating metabolic, inflammatory, and placental biomarkers demonstrated superior discriminatory ability compared to any single indicator, highlighting the value of a multidimensional approach for risk stratification in pregnancies complicated by both gestational diabetes mellitus and preeclampsia.

• These readily available laboratory markers offer a practical and cost-effective strategy for early identification of high-risk pregnancies, facilitating timely clinical decision-making and individualized perinatal management to improve neonatal outcomes.

Availability of Data and Materials

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

TC and XLL designed the research study. TC, LCW and LC performed the research. TC, WHY and LC analyzed the data. TC and XLL drafted this article. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study strictly followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Hunan Provincial People's Hospital (Approval No.[2026]-050). Given the retrospective design and the use of de-identified electronic medical record data, the requirement for informed consent was waived by the Ethics Committee of Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Modzelewski R, Stefanowicz-Rutkowska MM, Matuszewski W, Bandurska-Stankiewicz EM. Gestational Diabetes Mellitus-Recent Literature Review. Journal of Clinical Medicine. 2022; 11: 5736. https://doi.org/10.3390/jcm11195736

[2] Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. Endocrine Reviews. 2022; 43: 763–793. https://doi.org/10.1210/endrev/bnac003

[3] Greco E, Calanducci M, Nicolaides KH, Barry EVH, Huda MSB, Iliodromiti S. Gestational diabetes mellitus and adverse maternal and perinatal outcomes in twin and singleton pregnancies: a systematic review and meta-analysis. American Journal of Obstetrics and Gynecology. 2024; 230: 213–225. https://doi.org/10.1016/j.ajog.2023.08.011

[4] Ye W, Luo C, Huang J, Li C, Liu Z, Liu F. Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis. BMJ (Clinical Research Ed.). 2022; 377: e067946. https://doi.org/10.1136/bmj-2021-067946

[5] Magee LA, Nicolaides KH, von Dadelszen P. Preeclampsia. The New England Journal of Medicine. 2022; 386: 1817–1832. https://doi.org/10.1056/NEJMra2109523

[6] Roberts JM. Preeclampsia epidemiology(ies) and pathophysiology(ies). Best Practice & Research. Clinical Obstetrics & Gynaecology. 2024; 94: 102480. https://doi.org/10.1016/j.bpobgyn.2024.102480

[7] Yang Y, Wu N. Gestational Diabetes Mellitus and Preeclampsia: Correlation and Influencing Factors. Frontiers in Cardiovascular Medicine. 2022; 9: 831297. https://doi.org/10.3389/fcvm.2022.831297

[8] Veiga ECDA, Korkes HA, Salomão KB, Cavalli RC. Association of LEPTIN and other inflammatory markers with preeclampsia: A systematic review. Frontiers in Pharmacology. 2022; 13: 966400. https://doi.org/10.3389/fphar.2022.966400

[9] Tezikov YV, Lipatov IS, Azamatov AR, Tyutyunnik VL, Kan NE, Zumorina EM, et al. Preeclampsia as a separate gestational clinical and pathogenetic form of insulin resistance syndrome. Obstetrics and Gynecology. 2022; 15: 64–74. https://doi.org/10.18565/aig.2022.4.64-74

[10] Saucedo R, Ortega-Camarillo C, Ferreira-Hermosillo A, Díaz-Velázquez MF, Meixueiro-Calderón C, Valencia-Ortega J. Role of Oxidative Stress and Inflammation in Gestational Diabetes Mellitus. Antioxidants (Basel, Switzerland). 2023; 12: 1812. https://doi.org/10.3390/antiox12101812

[11] Ye Y, Zhang L, Han Y, Yu X. Prevalence and Risk Factors of Preeclampsia in Pregnant Women With Gestational Diabetes Mellitus. British Journal of Hospital Medicine. 2025; 86: 1–13. https://doi.org/10.12968/hmed.2024.0990

[12] Li H, Yin B, Jiang N, Zhu B. Effect of combined gestational diabetes mellitus and preeclampsia on pregnancy outcomes. Clinical and Experimental Obstetrics & Gynecology. 2025; 52: 27065.

[13] Aziz F, Khan MF, Moiz A. Gestational diabetes mellitus, hypertension, and dyslipidemia as the risk factors of preeclampsia. Scientific Reports. 2024; 14: 6182. https://doi.org/10.1038/s41598-024-56790-z

[14] Zhang Y, Zhong Y, Zou L, Liu X. Significance of Placental Mesenchymal Stem Cell in Placenta Development and Implications for Preeclampsia. Frontiers in Pharmacology. 2022; 13: 896531. https://doi.org/10.3389/fphar.2022.896531

[15] Ortega MA, Fraile-Martínez O, García-Montero C, Sáez MA, Álvarez-Mon MA, Torres-Carranza D, et al. The Pivotal Role of the Placenta in Normal and Pathological Pregnancies: A Focus on Preeclampsia, Fetal Growth Restriction, and Maternal Chronic Venous Disease. Cells. 2022; 11: 568. https://doi.org/10.3390/cells11030568

[16] Hu M, Li J, Baker PN, Tong C. Revisiting preeclampsia: a metabolic disorder of the placenta. The FEBS Journal. 2022; 289: 336–354. https://doi.org/10.1111/febs.15745

[17] Wang Y, Li B, Zhao Y. Inflammation in Preeclampsia: Genetic Biomarkers, Mechanisms, and Therapeutic Strategies. Frontiers in Immunology. 2022; 13: 883404. https://doi.org/10.3389/fimmu.2022.883404

[18] Zhang T, He X. Systemic immune-inflammation index and risk of gestational diabetes and preeclampsia: a systematic review and meta-analysis. Journal of Obstetrics and Gynaecology: the Journal of the Institute of Obstetrics and Gynaecology. 2025; 45: 2548814. https://doi.org/10.1080/01443615.2025.2548814

[19] Yanachkova V, Staynova R, Stankova T, Kamenov Z. Placental Growth Factor and Pregnancy-Associated Plasma Protein-A as Potential Early Predictors of Gestational Diabetes Mellitus. Medicina (Kaunas, Lithuania). 2023; 59: 398. https://doi.org/10.3390/medicina59020398

[20] Nishi K, Modi D. Placental exosomes in pregnancy and preeclampsia. American Journal of Reproductive Immunology (New York, N.Y.: 1989). 2024; 91: e13857. https://doi.org/10.1111/aji.13857

[21] International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Gabbe B, Buchanan TA, Catalano PA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010; 33: 676–682. https://doi.org/10.2337/dc09-1848

[22] Hypertensive Disorders in Pregnancy Subgroup, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association. Diagnosis and treatment of hypertension and pre-eclampsia in pregnancy: a clinical practice guideline in China. Chinese Journal of Obstetrics and Gynecology. 2020; 55: 227–238. https://doi.org/10.3760/cma.j.cn112141-20200114-00039 (In Chinese)

[23] Todd S, Bowen J, Ibiebele I, Patterson J, Torvaldsen S, Ford F, et al. A composite neonatal adverse outcome indicator using population-based data: an update. International Journal of Population Data Science. 2020; 5: 1337. https://doi.org/10.23889/ijpds.v5i1.1337

[24] He Y, Wu N. Research Progress on Gestational Diabetes Mellitus and Endothelial Dysfunction Markers. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2021; 14: 983–990. https://doi.org/10.2147/DMSO.S295737

[25] Mittal R, Prasad K, Lemos JRN, Arevalo G, Hirani K. Unveiling Gestational Diabetes: An Overview of Pathophysiology and Management. International Journal of Molecular Sciences. 2025; 26: 2320. https://doi.org/10.3390/ijms26052320

[26] Ellerbrock J, Spaanderman B, Drongelen JV, Mulder E, Lopes van Balen V, Schiffer V, et al. Role of Beta Cell Function and Insulin Resistance in the Development of Gestational Diabetes Mellitus. Nutrients. 2022; 14: 2444. https://doi.org/10.3390/nu14122444

[27] Yang F, Liu H, Ding C. Gestational diabetes mellitus and risk of neonatal respiratory distress syndrome: a systematic review and meta-analysis. Diabetology & Metabolic Syndrome. 2024; 16: 294. https://doi.org/10.1186/s13098-024-01539-x

[28] Tousty P, Fraszczyk-Tousty M, Ksel-Hryciów J, Łoniewska B, Tousty J, Dzidek S, et al. Adverse Neonatal Outcome of Pregnancies Complicated by Preeclampsia. Biomedicines. 2022; 10: 2048. https://doi.org/10.3390/biomedicines10082048