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ORIGINAL RESEARCH

Predictive Factors for Fetal Growth Restriction in Patients with Preeclampsia: A Clinical Prediction Study

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Background: Preeclampsia (PE) is a significant pregnancy complication associated with adverse maternal and fetal outcomes, particularly fetal growth restriction (FGR). Identifying risk factors for FGR in PE patients can facilitate timely management and improve neonatal outcomes.

Methods: This retrospective case-control study analyzed 714 singleton pregnancies complicated by preeclampsia at Fujian Maternity and Child Health Hospital from January 2016 to October 2023. Participants were categorized based on the presence of FGR. Clinical data, including demographic characteristics, laboratory parameters, intrapartum complications and neonatal outcomes, were collected and analyzed. We employed least absolute shrinkage and selection operator (LASSO) logistic regression to identify independent risk factors for FGR. An individualized predictive nomogram was then developed and validated using a training (499 participants) and a validation cohort (215 participants). The model's discrimination, clinical usefulness, and calibration were assessed using the area under the receiver operating characteristic (ROC) curve, decision curve, and calibration analysis.

Results: The study identified 256 women with FGR and 458 without FGR.The research identified nine significant predictors for FGR in PE patients, including family history of hypertension, aspartate aminotransferase (AST), uric acid (URIC), mode of delivery, mean platelet volume (MPV), prothrombin time (PT), severity of preeclampsia, post-pregnancy weight, and gestational age. The nomogram demonstrated excellent predictive performance, with an area under the ROC curve (AUC) of 0.93 (95% CI 0.91–0.96) in the training cohort and 0.90 (95% CI 0.85–0.95) in the validation cohort. Calibration plots indicated that predicted probabilities closely matched observed outcomes in both cohorts, while decision curve analysis (DCA) indicated that the nomogram provided a satisfactory net benefit for patients at risk of FGR.

Conclusion: The nomogram developed in this study serves as a reliable tool for predicting FGR in pregnant individuals with preeclampsia. Its application could enhance clinical decision-making and improve fetal outcomes in at-risk populations. Further validation in diverse populations is recommended to strengthen its clinical utility.

Keywords: preeclampsia fetal growth restriction predictive model nomogram risk factors

Introduction

Preeclampsia (PE) is a common complication during pregnancy characterized by the onset of high blood pressure and proteinuria, usually occurring after 20 weeks of gestation.[1] PE significantly contributes to maternal and perinatal morbidity and mortality, manifesting as seizures, acute renal impairment, pulmonary edema, severe hypertension, cerebrovascular events, and hepatic injury, with a global incidence of 3–8% of pregnancies.[2] It is also associated with adverse neonatal outcomes, usually secondary to iatrogenic preterm delivery and an elevated risk of fetal growth restriction and placental abruption.[3]

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PE is characterized by abnormal placentation, which begins with inadequate remodeling of spiral arteries. In normal pregnancies, trophoblastic cells invade these arteries, facilitating their dilation and enhancing uteroplacental blood flow. However, in PE, this physiological process is impaired, resulting in poorly remodeled, high-resistance vessels. Consequently, this leads to compromised uteroplacental blood flow, which restricts the delivery of essential oxygen and nutrients to the developing fetus.

As a result of impaired placental perfusion, the fetus is subjected to hypoxic conditions and a deficiency in essential nutrients, leading to fetal growth restriction (FGR). FGR occurs when the fetus does not receive adequate resources to support growth and development, ultimately increasing the risk for adverse neonatal outcomes. Moreover, the placental dysfunction associated with PE may activate inflammatory pathways and induce oxidative stress, further exacerbating the limitations of fetal growth.

FGR occurs when a fetus does not achieve its growth potential due to placental insufficiency.[4] It is a significant risk factor for adverse perinatal outcomes, including neonatal mortality, neonatal morbidity, and long-term developmental disabilities.[5] Early identification of preeclamptic patients at risk of developing FGR is crucial for appropriate antenatal monitoring and management to optimize pregnancy outcomes.

Several maternal factors have been identified as potential predictors of FGR in preeclamptic patients. Advanced maternal age is linked to a higher risk of FGR due to decreased uteroplacental blood flow and function.[6] Furthermore, pre-pregnancy weight, parity, and platelet count are potential risk factors for FGR in preeclamptic pregnancies.[7] Prothrombin time and other coagulation parameters have been suggested as indicators of placental dysfunction that could lead to FGR in preeclamptic patients.[8] Predicting adverse pregnancy outcomes, like FGR, in women with gestational hypertension and PE continues to be challenging in clinical practice. Traditional approaches based on individual risk factors may lack accuracy and fail to capture the complexity of interactions among multiple predictors. Therefore, the development of predictive models incorporating multiple risk factors for the accurate assessment of pregnancy outcomes is paramount.

Logistic regression is a statistical method used to model binary outcomes and is widely applied in clinical prediction studies to identify key predictors of adverse events in pregnant women with hypertensive disorders.[9,10] By considering multiple risk factors concurrently, these models offer personalized risk assessments and enhance clinical decision-making in managing high-risk pregnancies.

Nomograms, graphical tools that provide a visual representation of predictive models, have also gained popularity in clinical research for their intuitive presentation of complex statistical analyses.[11] These user-friendly tools enable healthcare providers to calculate individualized risk scores for specific outcomes based on the values of predictive factors, facilitating risk assessment and treatment planning in obstetric practice.

This study aims to identify the factors that predict FGR in patients with PE. We will employ logistic regression to determine key predictors of FGR and create a nomogram to estimate the risk of this adverse outcome. We aim to improve the accuracy of risk assessment and clinical decision-making for high-risk pregnancies by incorporating multiple risk factors into a comprehensive predictive model.

Materials and Methods

Study Populations

This study was a retrospective case-control investigation of pregnant individuals diagnosed with PE who were admitted to and delivered at Fujian Maternity and Child Health Hospital, affiliated with Fujian Medical University, a tertiary obstetric facility in southeast China, between January 2016 and October 2023. We collected data on singleton pregnancies diagnosed with PE from the hospital's electronic medical records, which included baseline information, laboratory results, intrapartum complications, and fetal outcomes.

Participants were selected based on the following inclusion criteria: (1) natural conception, singleton live birth, (2) aged between 18 and 40 years; (3) no prior history of hypertension before pregnancy; (4) complete clinical data availability; and (5) adherence to scheduled prenatal inspections. Exclusion criteria included pregnant women with (1) a history of long-term alcohol consumption, smoking, or illicit drug use during gestation; (2) the presence of other

serious complications during pregnancy; and (3) substantial gaps in clinical data. In total, 714 pregnant women diagnosed with PE were analyzed. They were divided into two groups based on the adverse outcome of FGR: 256 women with FGR and 458 without FGR. The study received approval from the Ethics Committee of Fujian Maternity and Child Health Hospital (2024KY274). Informed consent was unnecessary because the study was retrospective and used anonymized data.

Diagnostic Criteria

The "Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy: A Clinical Practice Guideline in China (2020)"[12] outlines the criteria for diagnosing mild PE as follows: a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg, along with urine protein levels of ≥0.3 g/24 h or a random urine protein result of ≥(+) after 20 weeks of gestation. The diagnosis of severe preeclampsia is based on several criteria: 1) persistent high blood pressure (systolic ≥160 mmHg or diastolic ≥110 mmHg); 2) urinary protein levels of 2.0 g or more over 24 hours or a random urinary protein result of at least two pluses; 3) serum creatinine levels of 1.2 mg/dL or higher (unless previously elevated); 4) a platelet count below 100,000/mL (<100×10^9/L); 5) evidence of microangiopathic hemolysis, shown by increased lactate dehydrogenase (LDH) levels; 6) elevated serum transaminases; 7) persistent headaches or other neurological or visual disturbances; and 8) ongoing epigastric pain.

FGR is diagnosed: 1)[4] prenatal ultrasound estimates fetal weight below the 10th percentile for the corresponding gestational age; and 2) a more severe condition in which the birth weight is below the third percentile for the same gestational age. Ultrasound was used to monitor fetal weight every 2–3 weeks starting at 24 weeks of gestation until birth.

Clinical Data Collection

The data collected from maternal medical records included several aspects: (1) demographic details and medical history such as age, height, prepregnancy weight, postpregnancy weight, prepregnancy body mass index (BMI), postpregnancy BMI, parity, gravidity, gestational age, abortion history, and family history of hypertension; (2) blood pressure recordings, consisting of systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements; (3) laboratory test parameters, including routine blood tests, liver and kidney function indicators, blood glucose levels, lipid profiles, and coagulation indices; (4) neonatal outcomes, such as birth weight, length, and the 1-minute Apgar score; and (5) intrapartum conditions, characterized by delivery mode, postpartum hemorrhage (PPH), amniotic fluid contamination, and the severity of preeclampsia.

Statistical Analysis

Missing data were addressed using multiple imputation. Normally distributed measurement data were summarized as ($\bar{x}\pm$ s), whereas non-normally distributed data were presented as median (interquartile ranges). An independent sample *t*-test was used for normally distributed data with heterogeneous variance, while a Mann–Whitney *U*-test was used for non-normally distributed data. Categorical variables were expressed as percentages, and group comparisons were performed using either the Chi-square (χ^2) test or Fisher's exact test.

The collected dataset was randomly divided into training and validation cohorts at a 7:3 ratio, enabling a comparison of the variables. Within the training cohort, the least absolute shrinkage and selection operator (LASSO) logistic regression analysis was employed for the multivariate analysis to identify independent risk factors for preeclampsia complicated by FGR. Nomograms were plotted using the "rms" package in R. The nomogram's efficacy was assessed using the receiver operating characteristic (ROC) curve and calibration curve. The area under the ROC curve (AUC) indicated the discriminative ability, ranging from 0.5 (no discrimination) to 1 (perfect discrimination). A decision curve analysis (DCA) was also conducted to assess the net benefit threshold for prediction. Statistical analyses were conducted using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.2.2). All tests were two-sided, with P values < 0.05 deemed statistically significant.

Results

Patient Characteristics

The study involved 714 pregnant women diagnosed with PE. The cohort was divided into training and validation datasets in a 7:3 ratio, with 499 participants in the training set and 215 in the validation set. The incidence rates of FGR were observed to be 34.67% (173/499) and 38.60% (83/215) in the training and validation datasets, respectively. Notably, both cohorts exhibited comparable characteristics concerning maternal features, fetal outcomes, and laboratory examinations (Table 1). The average maternal age of all patients was 29.77 ± 4.88 years, with 17.51% over 35 years of age. Approximately half of the participants were classified as severe (52.24%) and mild preeclampsia (47.76%).

Table 1 Comparison of Demographic and Clinical Characteristics Between the Training and Validation Dataset

Variables	Total (n = 714)	Test (n = 215)	Train (n = 499)	*P*
Maternal Age (y)	29.77 ± 4.88	29.73 ± 4.60	29.79 ± 5.00	0.887
Maternal Age (y)				0.725
<35	589 (82.49)	179 (83.26)	410 (82.16)	
≥35	125 (17.51)	36 (16.74)	89 (17.84)	
Prepregnancy weight (kg)	55.06 ± 9.23	54.97 ± 9.75	55.09 ± 9.01	0.872
Postpregnancy weight (kg)	68.41 ± 11.09	67.96 ± 11.64	68.61 ± 10.85	0.477
Height (cm)	159.16 ± 5.15	159.20 ± 5.30	159.14 ± 5.08	0.884
Prepregnancy BMI (kg/m^2)	21.70 ± 3.31	21.64 ± 3.42	21.73 ± 3.26	0.742
Postpregnancy BMI (kg/m^2)	26.98 ± 4.07	26.76 ± 4.09	27.08 ± 4.06	0.342
Gravidity	2.13 ± 1.31	2.03 ± 1.22	2.17 ± 1.34	0.182
Early abortion	0.72 ± 0.98	0.64 ± 0.93	0.76 ± 1.00	0.139
Gestational Age (wk)	37.67 ± 2.83	37.77 ± 2.77	37.63 ± 2.86	0.548
Family history of hypertension, n(%)				0.249
No	663 (92.86)	196 (91.16)	467 (93.59)	
Yes	51 (7.14)	19 (8.84)	32 (6.41)	
ALT (U/L)	19.87 ± 24.64	21.85 ± 23.81	19.01 ± 24.97	0.158
AST (U/L)	23.74 ± 19.02	24.16 ± 12.50	23.56 ± 21.23	0.702
GGT (U/L)	22.77 ± 32.94	25.01 ± 37.24	21.81 ± 30.90	0.234
LDH (U/L)	308.24 ± 173.75	313.46 ± 169.89	305.99 ± 175.51	0.598
URIC (umol/L)	390.00 ± 221.90	384.56 ± 114.69	392.34 ± 254.61	0.668
ALB (g/L)	32.79 ± 16.52	32.97 ± 12.92	32.71 ± 17.87	0.851
FPG (mmol/L)	4.95 ± 1.32	5.08 ± 1.43	4.90 ± 1.27	0.084
TG (mmol/L)	3.74 ± 1.78	3.49 ± 1.33	3.84 ± 1.94	**0.005**
TC (mmol/L)	6.64 ± 5.38	6.26 ± 1.47	6.80 ± 6.36	0.225
BUN (mmol/L)	5.56 (5.22, 7.67)	5.34 (5.01, 7.35)	5.78 (5.40, 7.89)	0.324
Cr (umol/L)	56.24 (48.12, 67.38)	56.87 (47.92, 66.38)	55.61 (51.9, 76.3)	0.234
WBC, $\times 10^9$/L	8.37 (7.23, 10.11)	8.45 (7.12, 10.05)	8.28 (7.16, 9.96)	0.656
RBC, $\times 10^9$/L	4.10 (3.91, 4.77)	4.06 (3.8, 4.37)	4.15 (3.75, 4.58)	0.061
HGB, g/L	122.25 (110, 137)	120 (110, 130)	124.5 (115, 137)	0.068
NE, $\times 10^9$/L	7.21 (5.77, 9.38)	7.24 (5.92, 9.57)	7.21 (5.72, 9.38)	0.411
LYM, $\times 10^9$/L	1.74 (1.38, 2.16)	1.71 (1.39, 2.12)	1.77 (1.37, 2.17)	0.631
MO, $\times 10^9$/L	0.66 (0.50, 0.81)	0.68 (0.51, 0.81)	0.65 (0.50, 0.79)	0.303
PLT, $\times 10^9$/L	203.50 (164.00, 243.00)	202.00 (163.00, 243.50)	205.00 (164.00, 242.50)	0.867
MPV (fL)	11.10 (10.20, 11.90)	11.00 (10.00, 12.00)	11.10 (10.30, 11.88)	0.495
PCT (%)	0.22 (0.18, 0.26)	0.21 (0.18, 0.26)	0.22 (0.19, 0.26)	0.285
HCT(%)	36.10 (33.40, 38.27)	36.00 (33.60, 38.40)	36.10 (33.30, 38.20)	0.682
MCV (fL)	88.00 (84.20, 91.00)	87.80 (84.05, 91.00)	88.10 (84.30, 90.95)	0.665
TT (s)	17.63 ± 9.90	17.58 ± 11.27	17.65 ± 9.26	0.926
APTT (s)	30.43 ± 18.83	30.76 ± 20.85	30.29 ± 17.91	0.76

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 714)	Test (n = 215)	Train (n = 499)	*P*
PT (s)	10.90 ± 0.75	10.89 ± 0.74	10.91 ± 0.76	0.835
Fib (g/L)	4.09 ± 1.01	4.08 ± 1.14	4.09 ± 0.95	0.935
D-D (ug/l)	2.50 ± 2.43	2.32 ± 1.74	2.57 ± 2.67	0.195
SBP (mmHg)	148.09 ± 17.28	147.82 ± 17.84	148.20 ± 17.05	0.79
DBP (mmHg)	93.83 ± 12.25	93.63 ± 11.84	93.92 ± 12.43	0.773
Preeclampsia (%)				0.21
Mild	341 (47.76)	95 (44.19)	246 (49.30)	
Severe	373 (52.24)	120 (55.81)	253 (50.70)	
Group (%)				0.314
Control	458 (64.15)	132 (61.40)	326 (65.33)	
FGR	256 (35.85)	83 (38.60)	173 (34.67)	
Delivery Mode (%)				0.487
Vaginal delivery	262 (36.69)	83 (38.60)	179 (35.87)	
Cesarean section	452 (63.31)	132 (61.40)	320 (64.13)	
Neonate Birth Weight (kg)	2675.14 ± 798.33	2669.42 ± 770.42	2677.61 ± 810.80	0.9
Neonatal length (cm)	46.77 ± 4.40	46.84 ± 3.79	46.75 ± 4.64	0.789
Apgar score, M (Q_1, Q_3)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	0.704
Amniotic fluid, n(%)				0.843
Clear	625 (87.54)	189 (87.91)	436 (87.37)	
Pollution	89 (12.46)	26 (12.09)	63 (12.63)	
Postpartum hemorrhage (mL)	347.20 ± 169.18	350.23 ± 196.57	345.90 ± 156.11	0.754
Classification of newborn, n(%)				0.669
Premature infant	185 (25.91)	58 (26.98)	127 (25.45)	
Term infant	529 (74.09)	157 (73.02)	372 (74.55)	
Intensive care unit, n(%)				0.11
No	376 (52.66)	123 (57.21)	253 (50.70)	
Yes	338 (47.34)	92 (42.79)	246 (49.30)	

Notes: -: Fisher exact; $P < 0.05$ (two-sided) was considered statistically significant.

Abbreviations: t, *t*-test; Z, Mann–Whitney test; χ^2, Chi-square test; Q_1, 1st Quartile; Q_3, 3st Quartile; SD, standard deviation; M, Median; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; LDH, lactic dehydrogenase; URIC, uric acid, ALB, albumin, FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; BUN, Blood urea nitrogen; Cr, creatinine; WBC, white blood cell, RBC, red blood cell, HGB, hemoglobin; NE, neutrophil granulocyte; LYM, lymphocyte; MO, monocyte; PLT, platelet count; MPV, mean platelet volume; PCT, thrombocytocrit; HCT, hematocrit; MCV, mean corpuscular volume; TT, thrombin time; APTT, activated partial thromboplastin time; PT, prothrombin time; Fib, fibrinogen; D-D, d-dimer; SBP, Systolic Blood Pressure; DBP, diastolic blood pressure.

A significant portion of the patients opted for cesarean delivery (63.31%), while 36.69% chose vaginal delivery. The mean gestational age among the patients was (37.67±2.83) wk. All variables were well balanced between the two datasets, ensuring comparability. A univariate analysis was performed to compare maternal, neonatal, obstetric characteristics, and laboratory indexes between women with PE who experienced FGR and those who did not in the training cohort (Table 2). The univariate analysis identified the following variables as statistically significant ($P < 0.05$):

Table 2 Comparison of Characteristic Variables Between FGR Group and Non-FGR Group in Training Cohort

Variables	Control (n = 326)	FGR (n = 173)	Statistic	*P*
Maternal Age (y)	29.95 ± 4.54	29.49 ± 5.76	t=0.93	0.355
Maternal Age (y)			χ^2=2.28	0.131
<35	274 (84.05)	136 (78.61)		
≥35	52 (15.95)	37 (21.39)		

(*Continued*)

Table 2 (Continued).

Variables	Control (n = 326)	FGR (n = 173)	Statistic	*P*
Prepregnancy weight (kg)	56.26 ± 9.47	52.90 ± 7.61	t=4.31	<0.001
Postpregnancy weigh (kg)	69.81 ± 11.42	66.35 ± 9.30	t=3.64	<0.001
Height (cm)	159.76 ± 4.89	157.98 ± 5.25	t=3.77	<0.001
Prepregnancy BMI (kg/m^2)	22.01 ± 3.40	21.20 ± 2.92	t=2.66	0.008
Postpregnancy BMI (kg/m^2)	27.32 ± 4.18	26.61 ± 3.77	t=1.88	0.061
Gravidity	2.11 ± 1.22	2.28 ± 1.55	t=−1.30	0.195
Early abortion	0.65 ± 0.91	0.95 ± 1.12	t=−2.97	0.003
Gestational Age (wk)	38.87 ± 1.82	35.30 ± 3.02	t=14.26	<0.001
SBP (mmHg)	146.37 ± 17.93	151.64 ± 14.71	t=−3.31	<0.001
DBP (mmHg)	92.84 ± 11.72	95.94 ± 13.46	t=−2.66	0.008
Preeclampsia, n(%)			χ^2=46.61	<0.001
Mild	197 (60.43)	49 (28.32)		
Severe	129 (39.57)	124 (71.68)		
ALT (U/L)	17.29 ± 18.29	22.25 ± 34.00	t=−2.12	0.035
AST (U/L)	21.64 ± 12.10	27.19 ± 31.74	t=−2.80	0.005
GGT (U/L)	19.69 ± 31.99	25.80 ± 28.39	t=−2.11	0.036
LDH (U/L)	288.42 ± 145.05	339.10 ± 218.50	t=−3.10	0.002
URIC (umol/L)	364.45 ± 100.57	444.89 ± 405.39	t=−3.39	<0.001
ALB (g/L)	33.65 ± 21.86	30.94 ± 4.07	t=1.61	0.107
Glu (mmol/L)	4.89 ± 1.23	4.92 ± 1.35	t=−0.27	0.787
TG (mmol/L)	3.85 ± 1.98	3.82 ± 1.86	t=0.19	0.853
CHOL (mmol/L)	6.94 ± 7.76	6.53 ± 1.76	t=0.69	0.492
BUN (mmol/L)	3.18 (2.98, 3.54)	3.32 (3.08, 4.12)	Z=−0.67	0.456
Cr (umol/L)	39.7 (35.4, 43.2)	42.8 (40.7, 45.3)	Z=−1.66	0.089
TT (s)	17.82 ± 10.37	17.34 ± 6.71	t=0.55	0.585
APTT (s)	29.17 ± 17.19	32.41 ± 19.07	t=−1.93	0.054
PT (s)	10.81 ± 0.65	11.10 ± 0.90	t=−3.73	<0.001
Fib (g/L)	4.10 ± 0.98	4.06 ± 0.89	t=0.48	0.633
D-D (ug/l)	2.67 ± 2.61	2.39 ± 2.77	t=1.10	0.273
WBC, × 10^9/L	12.5 (10.1, 13.4)	13.1 (11.8, 15.4)	Z=−0.56	0.678
RBC, ×10^9/L	3.89 (3.50, 4.12)	3.37 (3.19, 3.53)	Z=0.78	0.457
HGB, g/L	123 (108.00, 136.00)	120 (103.00, 132.00)	Z=1.25	0.768
NE, × 10^9/L	7.15 (5.70, 9.45)	7.38 (5.88, 9.20)	Z=−0.35	0.725
LYM, × 10^9/L	1.68 (1.34, 1.98)	2.00 (1.54, 2.38)	Z=−5.27	<0.001
MO, × 10^9/L	0.65 (0.51, 0.76)	0.67 (0.46, 0.86)	Z=−0.61	0.542
PLT, × 10^9/L	206.00 (170.00, 243.75)	198.00 (155.00, 238.00)	Z=−1.66	0.098
MPV (fL)	11.20 (10.50, 12.10)	10.60 (9.60, 11.60)	Z=−5.14	<0.001
PCT (%)	0.23 (0.20, 0.27)	0.21 (0.17, 0.25)	Z=−5.43	<0.001
HCT (%)	36.30 (33.30, 38.20)	35.70 (33.50, 38.40)	Z=−0.66	0.512
MCV (fL)	87.70 (83.90, 90.57)	88.80 (85.00, 92.00)	Z=−2.31	0.021
Family history of hypertension, n(%)			χ^2=9.21	0.002
No	313 (96.01)	154 (89.02)		
Yes	13 (3.99)	19 (10.98)		
Delivery Mode, n(%)			χ^2=32.48	<0.001
Vaginal delivery	146 (44.79)	33 (19.08)		
Cesarean section	180 (55.21)	140 (80.92)		
Classification of newborn, n(%)			χ^2=151.35	<0.001
Premature infant	26 (7.98)	101 (58.38)		
Term infant	300 (92.02)	72 (41.62)		

(*Continued*)

Table 2 (Continued).

Variables	Control (n = 326)	FGR (n = 173)	Statistic	*P*
Postpartum hemorrhage (mL)	343.44 ± 147.83	350.53 ± 170.97	t=−0.48	0.63
Neonate Birth Weight (kg)	3133.29 ± 522.87	1818.92 ± 501.61	t=27.10	<0.001
Neonatal length (cm)	49.10 ± 2.15	42.30 ± 4.83	t=17.64	<0.001
Amniotic fluid, n(%)			χ^2=0.80	0.371
Clear	288 (88.34)	148 (85.55)		
Pollution	38 (11.66)	25 (14.45)		
ICU, n(%)			χ^2=0.19	0.667
No	163 (50.00)	90 (52.02)		
Yes	163 (50.00)	83 (47.98)		

Notes: -: Fisher exact; $P < 0.05$ (two-sided) was considered statistically significant.
Abbreviations: t, *t*-test, Z, Mann–Whitney test; χ^2, Chi-square test; SD, standard deviation; M, Median; Q_1, 1st Quartile; Q_3, 3st Quartile.

prepregnancy weight, postpregnancy weight, height, prepregnancy BMI, history of early abortion, gestational age, systolic blood pressure, diastolic blood pressure, severity of PE, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GCT), lactic dehydrogenase (LDH), uric acid (URIC), prothrombin time (PT), lymphocyte count (LYM), mean platelet volume (MPV), plateletcrit (PCT), family history of hypertension, delivery mode, classification of newborns, neonatal birth weight, and neonatal length.

Feature Selection

In our study, we assessed variables such as demographic characteristics, intrapartum complications, neonatal outcomes, and laboratory test results. Using the LASSO regression model on the training cohort, we identified nine variables with non-zero coefficients out of a total of 47. These variables included family history of hypertension, AST, URIC, MO, MPV, PT, severity of PE, post-pregnancy weight, and gestational age (Figure 1).

Development of Individualized Prediction Nomogram

We used the feature variables identified by the LASSO regression model to develop the prediction model. The predictive model was constructed using the multiple logistic regression (LR) approach (Table 3). The model is illustrated as a nomogram in Figure 2.

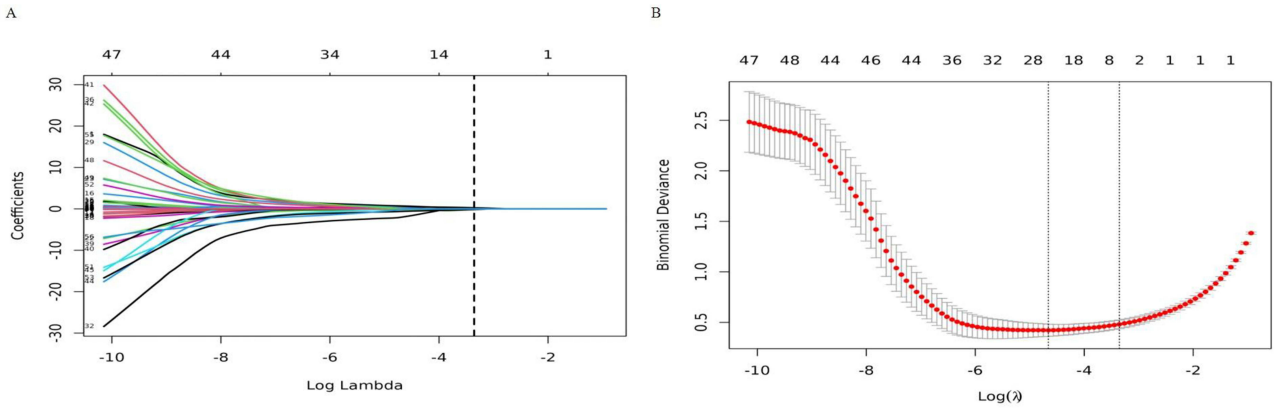

Figure 1 Characteristic variables selection using the least absolute shrinkage and selection operator (LASSO) logistic regression model. (**A**) The partial likelihood deviance (binomial deviance) curve was plotted vs log (lambda). Optimal parameter (lambda) selection in the LASSO logistic regression model used cross-validation, and dotted vertical lines were drawn via minimum criteria and the 1 s.e. of the minimum criteria. (**B**) LASSO coefficient profiles of the 44 features. A coefficient profile plot was produced against the log (lambda) sequence, where optimal lambda resulted in ten features with nonzero coefficients.

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Table 3 Results of Multivariate Logistic Regression for Training Cohort

Characteristic	OR	95% CI	p-value
Family history of hypertension			
No	—	—	
Yes	3.16	0.83, 12.05	0.093
AST	1.02	1.00, 1.04	0.09
URIC	1	1.00, 1.01	0.039
MO	1.39	1.11, 1.74	0.004
MPV	0.59	0.46, 0.76	<0.001
PT	2.75	1.75, 4.32	<0.001
Preeclampsia			
Mild	—	—	
Severe	1.59	0.79, 3.23	0.197
Postpregnancy weight	0.94	0.91, 0.98	0.002
Gestational age	0.5	0.42, 0.59	<0.001

Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Model Validation and Clinical Use

In the training cohort, the AUC for the predicted nomogram was 0.93 (95% CI 0.91–0.96) (Figure 3A) (i), showing that the model has robust predictive performance. In the validation cohort, the AUC for the prediction model was 0.90 (95% CI 0.85–0.95) (Figure 3A) (ii), indicating the model's strong discriminative ability. The calibration plot illustrated that the predicted probabilities closely matched with the actual observed outcomes in both the development (Figure 3B) (i) and validation cohorts (Figure 3B) (ii). Additionally, Figure 3C illustrates the clinical DCA for the prediction nomogram. The DCA shows that using this nomogram to predict FGR in women with PE is beneficial when the threshold probability is between 5% and 100%.

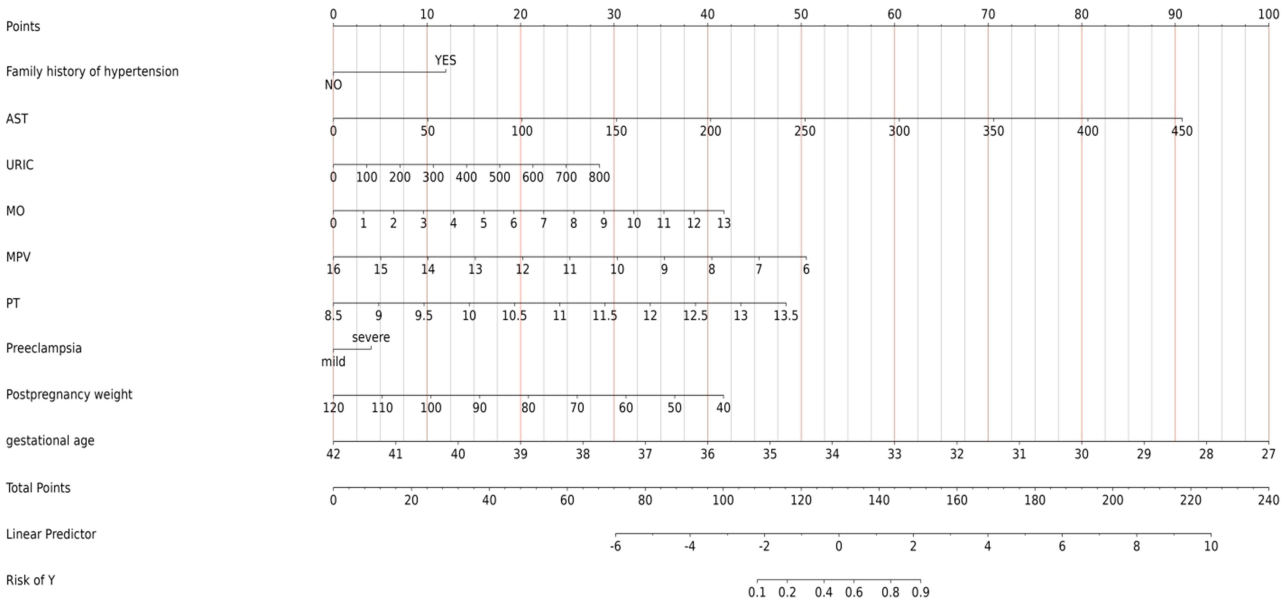

Figure 2 A nomogram to predict the development of FGR in patients with preeclampsia. A The nomogram incorporates nine variables, with points allocated according to the scale for each variable. A total score was awarded from the sum of the individual scores, and used to calculate the predicted probability of FGR in patients with preeclampsia.

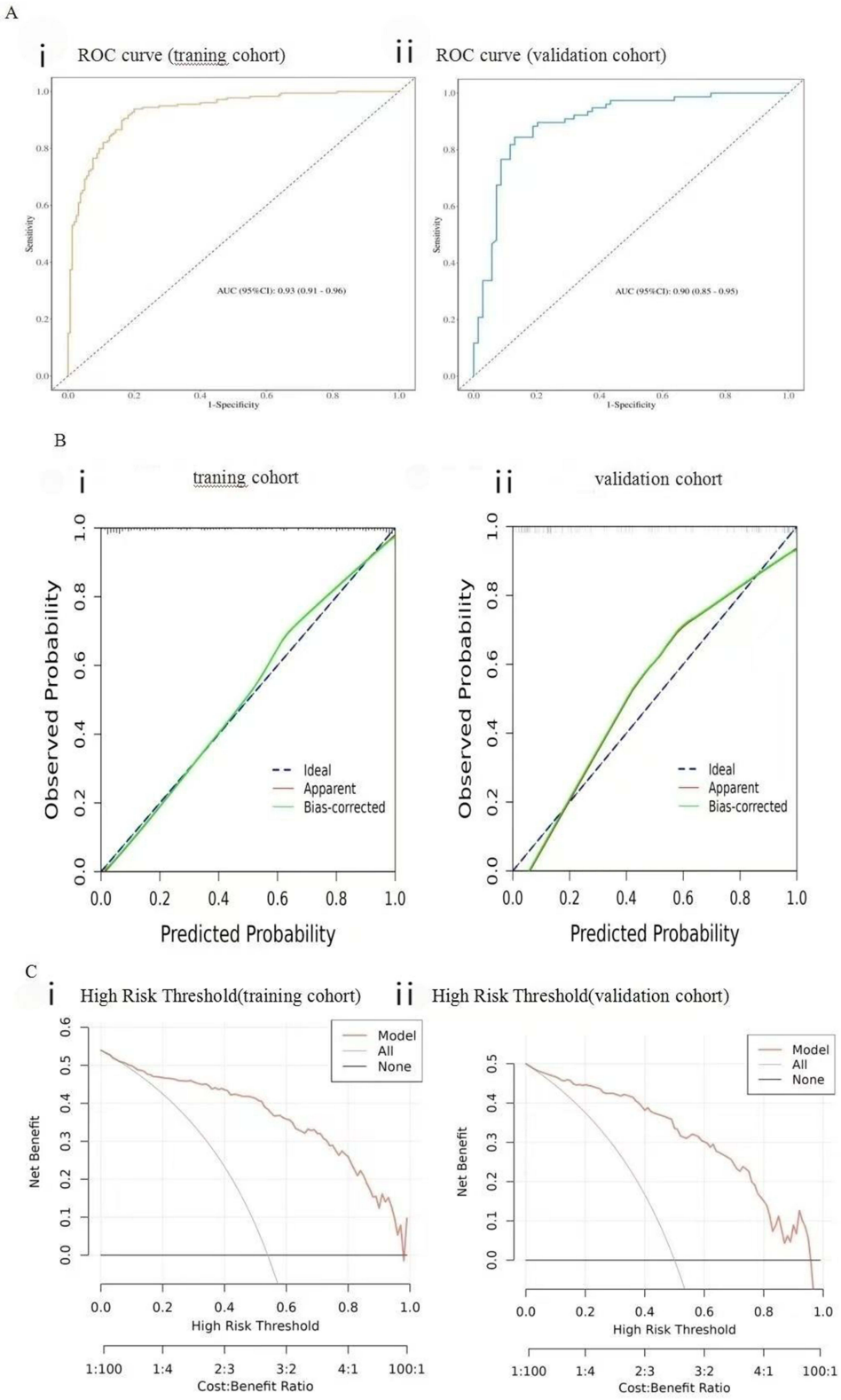

Figure 3 (**A**) (i and ii) ROC curves for the nomogram in the training (i) and validation cohorts (ii). (**B**) (i and ii) Calibration curves for the nomogram in the Development (i) and Validation (**ii**) cohorts. The diagonal blue dotted line represents a perfect prediction by an ideal model, the solid line represents the predictive power of the actual model. The calibration plot illustrates the accuracy of the original prediction ("Apparent": red solid line) and bootstrap models ("Bias-corrected": green solid line) in predicting the probability of FGR. (**C**) (i and ii) DCA for the nomogram in the Development (i) and Validation (ii) cohorts. The y-axis indicates the net benefit, which is the sum of the benefits (true positives) minus harm (false positives). The x-axis indicates the threshold probability. The red line represents the nomogram net benefit. The thick and thin solid lines represent the hypotheses that all or no patients experienced FGR.

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Discussion

Main Findings

This study successfully established a nomogram to predict the risk of FGR in patients with PE. The model exhibited excellent predictive accuracy in both the training and validation groups, with AUC values of 0.93 and 0.90, respectively. The nomogram incorporates various clinical and laboratory parameters such as a family history of hypertension, AST levels, URIC concentrations, MO, MPV, PT, severity of PE, maternal post-pregnancy weight, and gestational age. Our findings emphasize the importance of these factors in assessing the risk of FGR in women with PE, potentially guiding clinical management and intervention strategies.

Comparison with Previous Studies

Previous research[13] has demonstrated a strong association between maternal hypertensive disorders and adverse maternal/fetal outcomes, highlighting the importance of identifying risk factors for FGR in women with PE. Jiangyuan Zheng[14] identified key risk factors for adverse outcomes in PE, such as gestational age, 24-hour urine protein assessment, and thromboplastin time. Furthermore, Bohan Lv[15] developed a nomogram model aimed at predicting adverse outcomes in preterm PE, incorporating factors such as PLT, UA levels, blood urea nitrogen (BUN), PT, and LDH, achieving an AUC of 0.788. Another study[16] conducted in China identified 13 predictors of severe maternal outcomes, including gestational age, placenta previa, HBsAg positivity, heart disease, iron deficiency anemia, dyspnea, systolic blood pressure at admission, and various log-transformed laboratory results, contributing to an AUC of 82.2% for predicting adverse maternal outcomes in preeclampsia.

However, the specific risk factors associated with FGR in preeclamptic women remain poorly defined. A previous study[17] identified 15 factors associated with PE complicated by FGR, including maternal age, pre-pregnancy BMI, inflammatory markers, coagulation and lipid parameters, platelet metrics, uric acid, lactate dehydrogenase, and total bile acids. The neural network model using these factors had an 84.3% predictive accuracy for PE with FGR. In our research, we utilized LASSO regression to select 9 predictors and developed a nomogram model to predict the occurrence of FGR in preeclamptic patients. The internal validation of the predictive model indicated an AUC of 0.93 (95% CI 0.91–0.96) in the training cohort and 0.90 (95% CI 0.85–0.95) in the validation cohort. The AUC value of 0.93 confirmed the superior discriminative capacity of the nomogram. The model exhibited excellent calibration, reflecting its reliability through the consistency of predicted versus observed values. The DCA revealed that the proposed model for early risk stratification of FGR offers greater clinical advantages compared to treating none or all PE patients across various threshold probabilities.

The application of LASSO logistic regression methodology is crucial in our study as it allows for the identification of independent risk factors associated with FGR in patients with PE. This powerful analytical tool not only facilitates the selection of relevant predictors from a large set of variables but also helps to prevent overfitting, thereby enhancing the reliability of our predictive models.

Included Predictors

Drawing upon existing literature and the availability of clinical indicators, this study identified 47 potential predictors categorized into four domains: demographic characteristics, basic pregnancy situations, pregnancy and childbirth histories, and laboratory test results. Ultimately, nine variables were included in the optimal logistic regression model. Our findings show that these nine variables serve as predictors in the logistic regression model. Our findings reveal that gestational age at admission is a significant predictor of FGR in preeclampsia cases. The early onset of pregnancy may adversely influence the development of maternal organs and placenta, potentially leading to abnormal placental perfusion, which can result in fetal ischemia and hypoxia,[18,19] subsequently culminating in adverse pregnancy outcomes such as FGR. Notably, a family history of hypertension and severe PE are recognized risk factors that can worsen placental dysfunction, leading to FGR.[20,21]

This research highlights that elevated uric acid levels significantly increase the risk of FGR in women with PE. Previous studies[22–24] have demonstrated a correlation between increased uric acid levels during pregnancy and adverse outcomes for both pregnancy and childbirth. This establishes high uric acid levels as an independent risk factor for delivering low-birth-weight infants. According to studies,[25,26] when uric acid levels exceed 400 μmol/L, the incidence of

FGR rises to 46.92%, and perinatal mortality rates significantly increase. Uric acid hinders the remodeling of placental beds by obstructing trophoblast invasion and decreasing placental perfusion, leading to ischemic reperfusion injury and oxidative stress within the placenta.[27] Elevated AST levels, commonly associated with impaired placental perfusion and insufficiency, further verified our findings regarding their significance in the risk stratification of affected mothers. Maternal and fetal mortality associated with PE was independently correlated with illness severity at admission, gestational age, and increased AST levels (OR 1.004 [1.001–1.006]).[28]

Notably, Factors like MPV and MO were chosen to highlight how inflammatory and blood-related profiles contribute to the pathophysiology of PE and its effects on fetal development.[29] Recent research [30–32] suggests that these markers may predict adverse pregnancy outcomes, thereby strengthening the reliability of our predictive model. Furthermore, PT is an important marker for coagulopathy, illustrating the complexity of PE. This condition can occur alongside coagulopathies that negatively impact placental health and fetal nutrition.[33,34]

Recent studies have highlighted the role of inflammatory markers such as fractalkine and MIP-1β in relation to intrauterine growth restriction (IUGR). For instance, a prospective cohort study[35] published in the Turkish Journal of Medical Sciences demonstrated that high levels of amniotic fluid fractalkine and MIP-1β are associated with intrauterine growth restriction. While another study[36] indicated that elevated serum angiopoietin-like protein-4 levels have been similarly linked to gestational hypertension and preeclampsia. These studies underscored the importance of monitoring inflammatory markers in understanding the complexities of preeclampsia and its effects on fetal development.

Implication of Our Model

This study examines the lesser-known relationship between PE and FGR, a subject that has not been extensively studied before. Our research not only highlights essential maternal and laboratory factors related to FGR but also introduces a predictive nomogram for clinical risk assessment. This nomogram provides a visual and personalized prediction, helping obstetricians assess the risk of FGR for each woman with PE based on her individual score, which can inform customized treatment strategies. Additionally, using this nomogram for early detection of high-risk patients may enhance management and intervention strategies for pregnant women with PE, potentially reducing morbidity and mortality rates.

Study Strengths and Limitations

This research presents several notable strengths. Firstly, to our knowledge, it is the predictive model aimed at estimating the likelihood of FGR in women diagnosed with PE in Asian. Secondly, we developed a nomogram that effectively visualizes the model, making it user-friendly and comprehensible. Concurrently, this study incorporates maternal characteristics and commonly used prenatal laboratory data, ensuring that the indicators are easily identifiable and applicable. Thirdly, we implemented internal validation, calibration curves, and clinical DCA to assess the model's effectiveness and clinical relevance. The results of these evaluations were promising and reduced the bias linked to relying on a single evaluation method.

However, our study is not without limitations. First, it is a retrospective cohort study. Due to the low incidence of FGR in women with PE, obtaining a sufficient sample size for prospective studies is challenging. Consequently, we opted for a retrospective design. Second, there may be unaccounted confounding variables, such as certain imaging indicators, that were not included in our model. Third, the current research was restricted to model development and internal validation conducted at a single center, which may limit its representativeness of broader populations. Future investigations should focus on the external validation of our nomogram across diverse populations and environments. Furthermore, the incorporation of innovative predictors or biomarkers could potentially improve the predictive accuracy of the nomogram, thereby necessitating additional exploration.

Conclusion

In summary, our research introduces an innovative nomogram to estimate the risk of FGR in patients with PE, based on essential clinical and laboratory parameters. This predictive model shows strong discrimination and calibration, making it a valuable tool for clinical risk evaluation. By integrating it into routine obstetric care, we could significantly enhance risk management strategies and reduce adverse pregnancy outcomes related to FGR. It is imperative to validate these results through multicenter studies. Such research endeavors will not only confirm the robustness of our findings but also

allow for a broader application of the LASSO logistic regression methodology across varied clinical populations. This step is essential for strengthening the generalizability of our conclusions and ultimately enhancing clinical practices regarding the management of patients with PE.

Ethical Approval

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved by ethics approval from Ethics Committee of Fujian Maternity and Child Health Hospital (2024KY274). This article is a retrospective study. Therefore the Institutional waived the requirement to obtain distinct written informed consent from the patients.

Research Involving Human Participants

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards.

Author Contributions

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

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Disclosure

All authors declare that there was no conflict of interest.

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