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Development and validation of a preeclampsia prediction model for the first and second trimester pregnancy based on medical history

Qi Xu[1†], Lili Xing[1†], Ting Zhang[2] and Guoli Liu[1*]

Abstract

Objective The study aimed to identify the risk factors of preeclampsia (PE) and establish a novel prediction model.

Study design A retrospective, single-center analysis was conducted using clinical data from 5099 pregnant women who gave birth at Peking University People's Hospital between June 2015 and December 2020 who had placental growth factor (PlGF) levels records at 13–20 + 6 gestation weeks. The participants were randomly divided into a training set (70%, $n = 3569$) and a validation set (30%, $n = 1030$), between which the consistency was checked, and the analysis was performed according to whether PE occurred during pregnancy. Factors with univariate logistic analysis outcome of $p < 0.2$ were incorporated into the multivariate logistic regression analysis model, then variable selection by stepwise regression with AIC as the criterion was executed to finally identify the variables used for modeling. The model's discriminative ability was assessed using the receiver operating characteristic (ROC) curve, and its calibration was evaluated through calibration curves and Hosmer-Lemesow test. In addition, decision curve analysis (DCA) was used for clinical net benefit appraisal.

Results Logistic regression analysis identified nine risk factors for PE, including: maternal age (OR = 1.072, 95%CI = 1.025–1.120), parity(OR = 0.718,95%CI = 0.470–1.060), pre-pregnancy BMI (OR = 2.842,95%CI = 1.957–4.106), family hypertension history (OR = 3.604,95%CI = 2.433–5.264), pregestational diabetes mellitus(PGDM) (OR = 8.399, 95%CI = 4.138–15.883), pregnancy complicating nephropathy (OR = 7.931, 95% CI = 2.584–20.258),pregnancy complicating immune system disorders (OR = 3.134, 95% CI = 1.624–5.525), mean arterial pressure(MAP) at 11–13 + 6 gestational weeks (OR = 1.098, 95% CI = 1.078–1.119) and PlGF (OR = 0.647, 95% CI = 0.448–0.927) at 13–20 + 6 gestational weeks ($P < 0.05$). The restricted spline regression analysis (RCS) analysis results showed that PlGF and the risk of PE presented an approximately "L-shaped" relationship, with the risk of PE rising sharply with the decrease of PlGF when PlGF < 90 pg/ml, and little change with the increase of PlGF when PlGF > 90 pg/ml. A risk prediction model for PE during the first and second trimester was constructed based on the above selected 11 factors. The area under

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the ROC curve (AUC) for the model was 0.781(95%CI = 0.709–0.853), and the sensitivity and specificity at the optimal cut-off value (threshold probability) were 0.571 and 0.879 respectively. Chi-square of 9.616 and *P* value of 0.293 from Hosmer-Lemeshow test indicated that the model was well calibrated. Finally, the model showed good clinical net benefits in the threshold range of 0.03–0.3.

Conclusion The incidence of PE was associated with maternal age, pre-pregnancy weight and BMI, family hypertension history, PGDM, pregnancy complicating nephropathy, gestational complicating immune system disorders, blood pressure (systolic, diastolic, mean arterial pressure) at 11–13 + 6 gestational weeks, and PIGF at 13–20 + 6 gestational weeks. When PIGF < 90 pg/ml at 13–20 + 6 gestational week, the risk of PE increased significantly with the reduction of PIGF. The nomogram based on the above results was simpler and more practical in clinical application for PE predicting during the first and second trimester, and may provide an important reference for doctors and patients.

Keywords Preeclampsia prediction model, The first and second trimester, Multivariate logistic regression, Nomogram, Medical history

Introduction

Preeclampsia (PE) is a most frequently encountered gestational hypertension related diseases [1]. As a complex multisystem disease, PE can be diagnosed [2, 3] by occurrence of SBP ≥ 140 mmHg and(or) DBP ≥ 90 mmHg at > 20 weeks of gestation and at least one other associated complication, including proteinuria(≥ 0.3 g/24 h, or Urine Albumin/Creatinine Ratio ≥ 0.3 mg/dl or Urine Dipstick reading positive), or without proteinuria but suffered with at least one of the following diseases: maternal organ dysfunction (heart, lung, liver, or kidney), system disorders (circle system, digestive system, or nerves system) or uteroplacental dysfunction. PE had morbidity of 2–8% worldwide and is a leading cause of maternal and neonatal mortality [4–6]. The high occurrence of Hypertensive disorders of pregnancy increased the urgency of PE research [7], of which the underlying etiology remains uncertain and pathogenesis is complex. More than 50,000 maternal deaths, and over 70,000 fetal deaths worldwide was attributed to PE [8]. PE, which posing a serious threat to the safety of the mother and fetus, can deteriorate rapidly without warning [9] and can also occur after delivery, termed postpartum preeclampsia [10]. There has already reports confirmed that aspirin had potential beneficial effects for PE prophylaxis, especially for early-onset PE [11–13]. So, early diagnosis and prevention are of great significance in clinical work. From a health economics perspective, it is clinical imperative task to use the risk factor stratification method to rapidly identify pregnant women with high risk of PE, and use Low-Dose aspirin according to updated recommendations the USPSTF published in September 2021 based on previous recommendation from ACOG and SMFM as early as possible to reduce the incidence of PE and perinatal mortality [14].

The Federation International of Gynecology and Obstetrics (FIGO) had proposed a two-stage screening strategy with accuracy of 90% (< 37 weeks) and 89% (≥ 37 weeks) [15]. The proposal recommended that in medical resources underdeveloped areas, high risk maternity screened by high-risk factors plus mean arterial pressure should be further subjected to individual risk prediction; while in areas with developed medical resources, the Fetal Medicine Foundation (FMF) proposed first-trimester PE screening model [16] could be used to predict the individual risk and corresponding preventive measures should be taken for the screened high-risk groups. Subsequently, the American College of Obstetricians and Gynecologists (ACOG) also applied the model in its issued practice bulletin on gestation hypertension and PE [17]. The predication accuracy of the FMF model, 90% and 75% for early PE and preterm PE respectively, had already been proved in Italian, Australian, Basilia, European and Dutch [18]. Liona C Poon et al. [19] reported their prospective evaluation of screening performance in an Asian population, and this study verified the efficacy, tolerance and safety of the model. However, the model had only approximately 700 women from Jiangsu and Yunnan province in mainland China have been recruited. The first randomized controlled trial [ChiCTR2100043520||http://www.chictr.org.cn/Registration Date:2021-02-21] to assess its adoption in China was initiated in 2021 without published conclusions. What's more, the application was restrained in developing areas due to its need for substantial medical resources including detailed patient data such as medical history, MAP, maternal serology and ultrasound indicators for which ultrasound equipment is required, and the trained and qualified staffs. Even in hospitals of many developed arears, the measurement of uterine artery blood flow is not a required inspection item. That lead to another limit for the popular of FMF model. Accordingly, developing a model suitable for the Chinese conditions and population is necessary.

On account of the limitations of existing models and the need for simple and practical PE prediction tools in

clinical practice, this study aimed to screen out the risk factors closely related to PE by retrospectively analyzing the clinical data of hospitalized pregnant women in Peking University People's Hospital, and to construct a PE risk prediction model based on multivariate Logistic regression analysis. The objectives included: (1) identifying key risk factors associated with PE; (2) develop and validate a PE risk prediction model based on medical history and clinical characteristics; (3) evaluate the predictive performance of the model and its clinical application value. The PE prediction model constructed in this study is expected to provide clinicians with a simple and effective tool for early identifying of high-risk pregnant women, timely intervention and monitoring, thereby reducing the incidence of PE and related complications, in order to improve maternal and infant outcomes, and promote the prevention and management of PE.

Materials and methods

Study design

This retrospective cohort study aimed to screen out the risk factors closely related to PE by analyzing the clinical data of pregnant women who delivered in Peking University People's Hospital, and to construct a risk prediction model for PE based on multivariate Logistic regression analysis.

Study object

Study participants were recruited from pregnant women who delivered in Peking University People's Hospital from January 2016 to December 2020. Inclusion criteria included:1) at >20 gestational weeks; 2) available complete records of clinical and laboratory data. Exclusion criteria included:1) multiple pregnancy;2) diagnosed with chronic hypertension.

Data collection

Clinical data of the participants including basic information, pregnancy management records and delivery outcome data were extracted from the electronic medical record system. The variables collected included:

Demographic characteristics: age, height, pre-pregnancy body weight and BMI;

Medical history: diabetes mellitus, kidney disease, rheumatism or immune system disorders, hematological disease or Family history of hypertension;

Gestational characteristics: gravidity, parity, pre-pregnancy body weight and gestational weight gain;

Clinical index: SBP, DBP and MAP at 11–13 + 6 gestational weeks, PIGF level at 13–20 + 6 gestational weeks;

Outcome variable: PE incidence or not.

Definition of PE: According to the ACOG [20], PE is diagnosed by: Hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) and proteinuria (urinary protein ≥ 0.3 g/24 h) or absence of proteinuria but with other organ dysfunction (e.g., thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or new-onset encephalopathy) after 20 weeks of gestation [20–21].

Statistical analysis

Descriptive statistics: Normality test was performed for continuous variables. If the variable was normally distributed, it could be described with mean ± standard deviation(SD) and the Between Group Variation was analyzed with T-test if the equal variance assumption was met; Otherwise, the variable would be described with the median (upper quartile and lower quartile) with Wilcoxon rank sum test for comparison between groups. Categorical variables were described as frequencies (percentages) and the Between Group Variation was analyzed by chi-square test or Fisher's exact test.

Model development: The data were randomly divided into training set and validation set in a 7:3 ratio. The Logistic regression models were trained on the training set, then the trained model was evaluated on the validation set.

Predictor selection: Firstly, the univariate analysis was carried out, and the variables with statistically differences ($P < 0.2$) were incorporated into multivariate analysis for variable selection by stepwise regression with AIC as criteria to identify the variables for model construction.

Model evaluation: The ROC curve was used to evaluate the discriminative ability of the model, the calibration curve was used to evaluate the calibration of the model, and the DCA curve was used to evaluate its clinical benefit.

Results

Participant characteristics comparison

To assess the comparability of the training and validation sets, we compared the clinical characteristics of the two sets (Table 1). The results showed that there were no significant differences in most clinical features between the two sets ($P > 0.05$), which indicated that the data segmentation was reasonable and the two sets were well comparable. This meant that the application of the model on different datasets would have high reliability.

RCS analysis of PIGF

According to the RCS of PIGF (Fig.1), we found that there was a significant association between the PIGF level at 13–20 + 6 gestational weeks and the risk of PE. RCS analysis result showed an approximately L-shaped relationship between PIGF and the risk of PE. When PIGF was less than 90 pg/ml, the risk of PE increased sharply with the decrease of PIGF; When PIGF was more than 90 pg/ml, the risk of PE changed little with the increase of PIGF.

Table 1 Comparison of clinical characteristics between the training set and the test set

Clinical characteristics	Training set (*n* = 2498)	Validation set (*n* = 1071)	*P* value
Maternal age (years)	31.00 (29.00–34.00)	31.00 (29.00–34.00)	0.642
Gravidity	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.864
Parity	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.869
Height (m)	1.63 (1.60–1.66)	1.63 (1.60–1.66)	0.884
Pre-pregnancy body weight (kg)	56.00 (51.20–62.00)	56.00 (51.00-62.50)	0.863
BMI			0.947
Healthy Weight	2438 (68.3%)	1038 (67.8%)	
Underweight	428 (12.0%)	186 (12.2%)	
Overweight	703 (19.7%)	306 (20.0%)	
Family history of hypertension			0.666
No	3103 (86.9%)	1337 (87.4%)	
Yes	466 (13.1%)	193 (12.6%)	
GDM			0.525
No	3514 (98.5%)	1510 (98.7%)	
Yes	55 (1.5%)	20 (1.3%)	
Pregnancy complicating nephropathy			0.424
No	3546 (99.4%)	1523 (99.5%)	
Yes	23 (0.6%)	7 (0.5%)	
Pregnancy complicating immune disorders			0.462
No	3433 (96.2%)	1465 (95.8%)	
Yes	136 (3.8%)	65 (4.2%)	
Pregnancy complicating hematological diseases			0.356
No	3342 (93.6%)	1422 (92.9%)	
Yes	227 (6.4%)	108 (7.1%)	
SBP at 11–13 + 6 gestational weeks (mmHg)	113.00 (104.00-123.00)	113.00 (105.00-122.00)	0.409
DBP at 11–13 + 6 gestational weeks (mmHg)	72.00 (66.00–78.00)	72.00 (65.00–78.00)	0.43
MAP (mmHg)	86.00 (79.33–92.33)	86.00 (80.00–92.00)	0.68
PIGF at 13–20 + 6 gestational weeks (pg/ml)	94.00 (56.40–152.00)	91.15 (55.30–152.00)	0.656
Incidence of preeclampsia	125 (3.5%)	49 (3.2%)	0.589

Abbreviations: BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: mean arterial pressure; PIGF: placental growth factor

BMI criterion: Healthy Weight: BMI 18.5–24.9; underweight: BMI < 18.5; overweight: BMI ≥ 25.0

This suggested that pregnant women with PIGF below 90 pg/ml are at higher risk of developing PE, and validated the importance of PIGF as an early predictive biomarker for PE. This finding was confirmed by further analysis, indicating that the measurement of PIGF may contribute to early identification of high-risk pregnant women and early intervention.

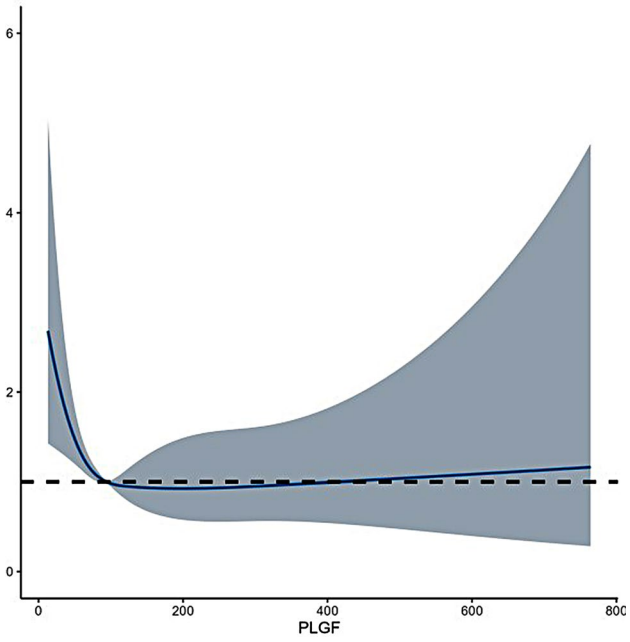

Fig. 1 RCS analysis of PIGF

Univariate and multivariate logistic regression analysis

As listed in Table 2, the results of univariate analysis showed that, clinical characteristics such as maternal age, pre-pregnancy body weight and BMI, family history of hypertension, PGDM, pregnancy complications of nephropathy or immune system disorders, SBP, DBP and MAP at 11–13 + 6 gestational weeks and PIGF level at 13–20 + 6 gestational weeks were significantly correlated with PE incidence risk ($P < 0.05$).

The multivariate regression analysis results (Table 2) further validated that the variables identified by univariate analysis could be independent predictors of PE. In detail, 1 unit increase in maternal age increased the risk of pre-eclampsia by 1.054 times (OR = 1.054, 95%CI = 1.000-1.111, $P = 0.047$). The risk of PE in overweight pregnant women (BMI > 25) was 1.659 times higher than that in healthy weight (OR = 1.659, 95%CI = 1.097–2.486, $P = 0.015$). The risk of PE in pregnant women with family hypertension history was 2.834 times higher than those without family history (OR = 2.834, 95%CI = 1.857–4.264, $P < 0.001$). Pregnant women with diabetes mellitus were 3.668 times more likely to develop PE than those without diabetes mellitus (OR = 3.668, 95%CI = 1.635–7.727, $P < 0.001$). The risk of PE in pregnant women with nephropathy was significantly increased by 9.082 times (OR = 9.082, 95%CI = 2.525–27.168, $P < 0.001$). The risk of PE in pregnant women with immune system disorders increased by 3.240 times (OR = 3.240, 95%CI = 1.632–5.993, $P < 0.001$). For every 1 mmHg increase in MAP at 11–13 + 6 weeks of gestation, the risk of PE increased by 7.6% (OR = 1.076, 95%CI = 1.055–1.098, $P < 0.001$).

Table 2 Univariate and multivariate logistic regression analysis of risk factors for preeclampsia

Characteristic	univariate analysis					multivariate analysis				
	OR[1]	SE[1]	Z	95% CI[1]	*p*-value	OR[1]	SE[1]	Z	95% CI[1]	*p*-value
Maternal age	1.072	0.023	3.091	1.025, 1.120	0.002	1.054	0.027	1.983	1.000, 1.111	0.047
Gravidity	1.006	0.091	0.068	0.835, 1.195	0.946					
Parity	0.718	0.207	-1.604	0.470, 1.060	0.109	0.618	0.234	-2.060	0.385, 0.963	0.039
Height	2.665	1.824	0.537	0.073, 93.661	0.591					
pre-pregnancy weight	1.059	0.008	7.010	1.042, 1.076	< 0.001					
BMI					< 0.001					0.008
healthy	—	—	—	—		—	—	—	—	
underweight	0.329	0.517	-2.151	0.100, 0.799	0.032	0.429	0.523	-1.620	0.129, 1.058	0.105
overweight	2.842	0.189	5.541	1.957, 4.106	< 0.001	1.659	0.208	2.432	1.097, 2.486	0.015
Family history of hypertension					< 0.001					< 0.001
No	—	—	—	—		—	—	—	—	
Yes	3.604	0.196	6.530	2.433, 5.264	< 0.001	2.834	0.212	4.925	1.857, 4.264	< 0.001
GDM					< 0.001					< 0.001
No	—	—	—	—		—	—	—	—	
Yes	8.399	0.34	6.256	4.138, 15.883	< 0.001	3.668	0.394	3.298	1.635, 7.727	< 0.001
Pregnancy complicating nephropathy					< 0.001					< 0.001
No	—	—	—	—		—	—	—	—	
Yes	7.931	0.514	4.029	2.584, 20.258	< 0.001	9.082	0.597	3.696	2.525, 27.168	< 0.001
Pregnancy complicating immune disorders					< 0.001					< 0.001
No	—	—	—	—		—	—	—	—	
Yes	3.134	0.307	3.72	1.642, 5.525	< 0.001	3.240	0.330	3.567	1.632, 5.993	< 0.001
Pregnancy complicating hematological diseases					0.985					
No	—	—	—	—						
Yes	1.007	0.372	0.019	0.447, 1.960	0.985					
SBP at 11–13 + 6 gestational weeks (mmHg)	1.045	0.005	8.599	1.034, 1.055	< 0.001					
DBP at 11–13 + 6 gestational weeks (mmHg)	1.085	0.010	8.297	1.064, 1.106	< 0.001					
MAP (mmHg)	1.098	0.009	9.916	1.078, 1.119	< 0.001	1.076	0.010	7.249	1.055, 1.098	< 0.001
PlGF at 13–20 + 6 gestational weeks (pg/ml)					0.018					0.045
< 90	—	—	—	—		—	—	—	—	
≥ 90	0.647	0.185	-2.36	0.448, 0.927	0.018	0.676	0.196	-2.005	0.459, 0.989	0.045

Abbreviations: BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: mean arterial pressure; PlGF: placental growth factor

BMI criterion: Healthy Weight: BMI 18.5–24.9; underweight: BMI < 18.5; overweight: BMI ≥ 25.0

PlGF level less than 90 pg/ml at 13–20 + 6 weeks of gestation increased the risk of PE by 32.4% (OR = 0.676, 95%CI = 0.459–0.989, $P = 0.045$). On the contrary, parity was a protective factor, and the risk of PE was 0.618 times that of the last time. These results indicated that maternal age, pre-pregnancy overweight (BMI > 25), family history of hypertension, PGDM, pregnancy complicating nephropathy, pregnancy complicating immune system disorders, MAP at 11–13 + 6 weeks of gestation and PlGF levels at 13–20 + 6 weeks of gestation are important independent predictors of PE with significant clinical significance.

Considering of its indispensable clinical significance, all the 9 identified factors were included regardless of possible collinearity if evaluated by multicollinearity diagnostics.

Even conditional importance maternal age (OR = 1.054) showed borderline significant when assessed without segmentation, reports [21, 22] indicated that advanced maternal age was an independent risk factor for PE. Regarding the possible synergistic effect with BMI or MAP in advanced age pregnancy, maternal age was included in the model with a low weight to avoid ignoring possible individual risk.

Model evaluation

ROC analysis

To evaluate the performance of the multivariate Logistic regression model in predicting the risk of PE, ROC curve analysis was performed. The AUC of the training set (Fig. 2) was 0.793 (95%CI:0.750–0.836, $P < 0.001$), indicating that the model had conspicuous discrimination capacity. According to the Youden index, the best cutoff value of the model was set to 0.032, and the accuracy of the model then was 0.732 (95%CI: 0.732–0.733), the sensitivity was 0.736 (95%CI: 0.659–0.813), and the

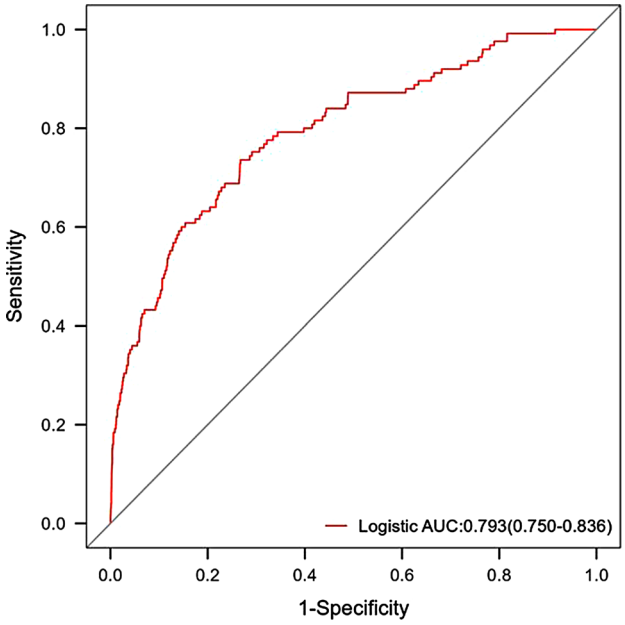

Fig. 2 ROC curve of training set

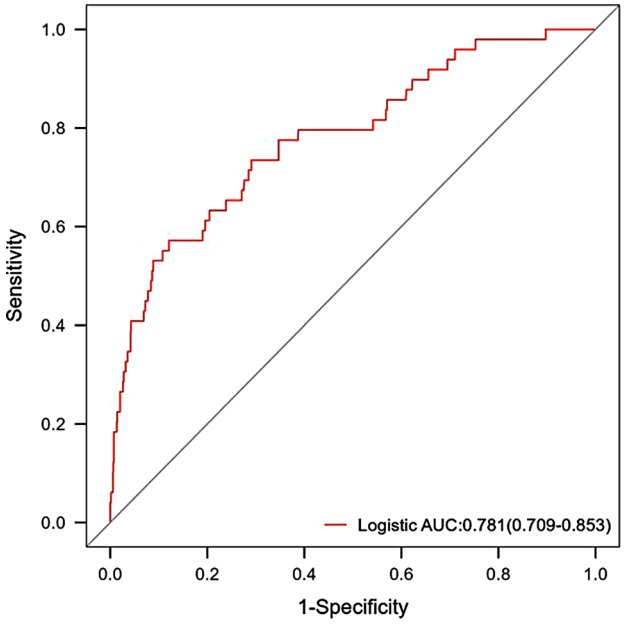

Fig. 3 ROC curve of validation set

specificity was 0.732 (95%CI: 0.659–0.813). The positive predictive value was 0.091 (95%CI:0.073–0.108), and the negative predictive value was 0.987 (95%CI: 0.983–0.991). In the validation cohort (Fig. 3), the AUC of the model was 0.781 (95%CI:0.709–0.853, $P<0.001$), and the standard error (SE) was 0.037, which further verified the discriminative capacity of the model. The accuracy of the model was 0.869 (95%CI:0.869–0.869), the sensitivity was 0.571 (95%CI:0.433–0.710), and the specificity was 0.879 (95%CI:0.863–0.896). The positive predictive value was

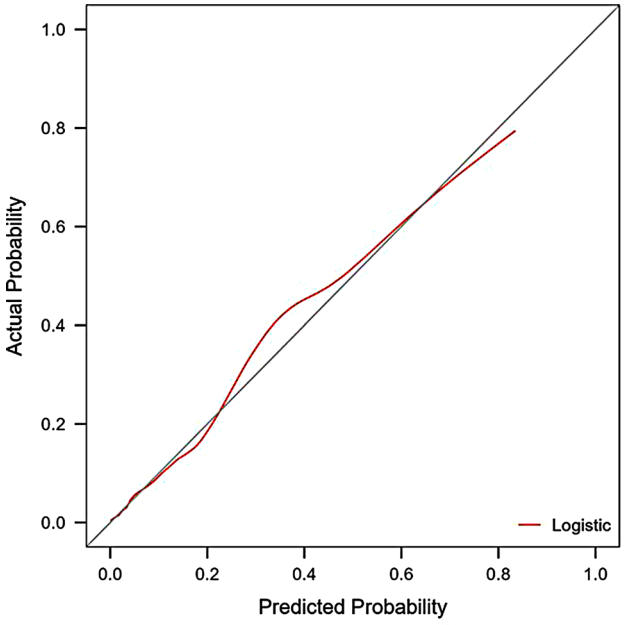

Fig. 4 Validation curve of training set

0.135 (95%CI:0.089–0.182), and the negative predictive value was 0.984 (95%CI:0.977–0.991).

In general, the results of ROC curve analysis showed that the PE prediction model constructed in this study had high discrimination ability in the training set and test set, and could effectively identify high-risk pregnant women.

Validation curve analysis

The agreement between the predicted probability and the observed incidence of PE was assessed by calibration curve analysis. As shown in Fig. 4, the predicted probabilities were highly consistent with the actual incidence in the training set, particularly in the range of low to moderate predicted probabilities (0.0 to 0.6). The P value of Hosmer-Lemeshow test was 0.428, indicating that the model was well calibrated. As indicated in Fig. 5, which is similar to Fig. 4, further verified the good calibration and reliability of the model on new data set. The P value of Hosmer-Lemeshow test of the validation set was 0.293, which supported the aforesaid conclusion. Overall, the results of calibration curve analysis showed that the PE risk prediction model constructed in this study was highly calibrated and could accurately predict the risk of PE on different datasets.

Decision curve analysis

The net clinical benefit of the constructed multivariate logistic regression model at different threshold probabilities was evaluated by decision curve analysis (DCA). Figures 6 and 7 illustrated the results of the DCA for the training and validation sets, respectively. In the training

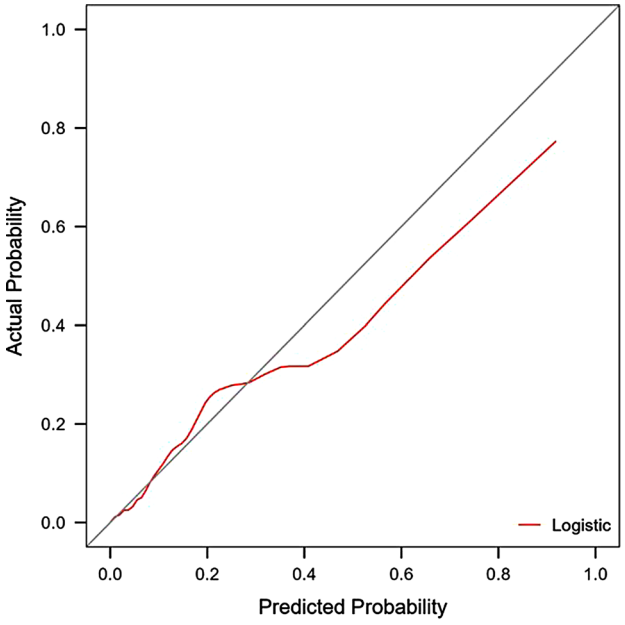

Fig. 5 Validation curve of validation set

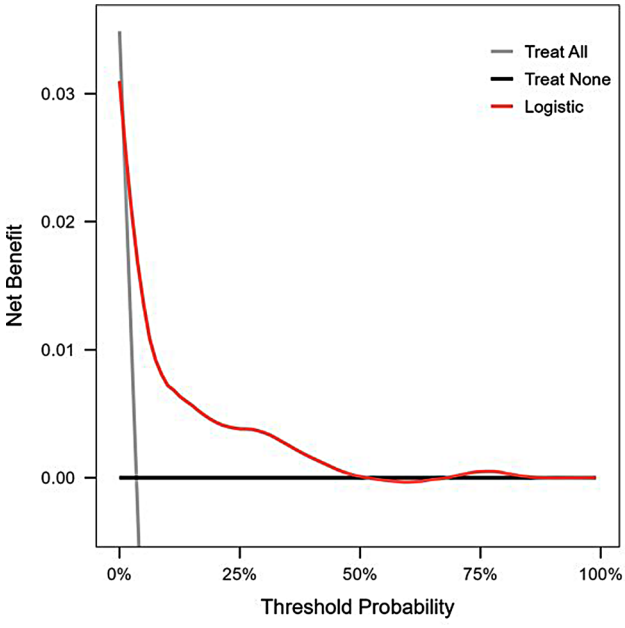

Fig. 6 DCA of training set

set, the net benefit of the model was significantly higher than the none-treat decision without using the model in the threshold probability range from 10 to 50%. Especially, when the threshold probability was 10–20%, the net benefit was the highest, reaching about 0.03. The results of the validation set showed a similar trend, with the net benefit being significantly higher than the none-treat decision not to use the model in the threshold probability range between 10% and 30%, further validating the clinical utility of the model.

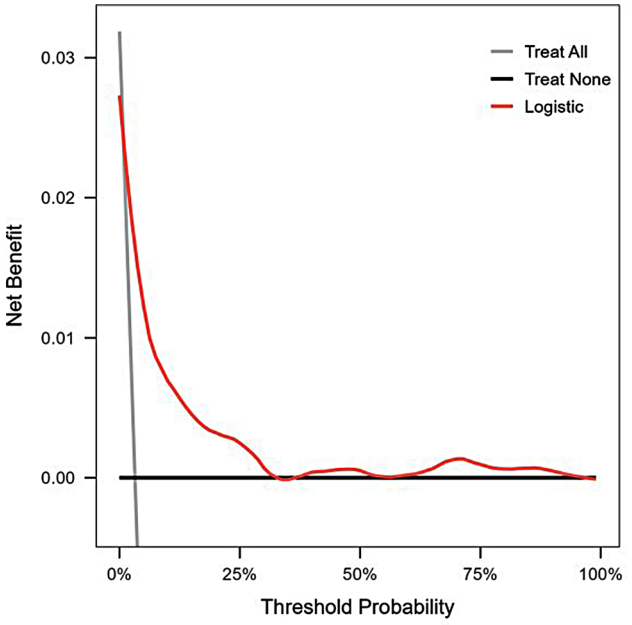

Fig. 7 DCA of validation set

Nomogram construction and application

Based on the multivariate Logistic regression model, a Nomogram (Fig. 8) for predicting the risk of PE was constructed. The Nomogram converts the complex regression model results into an intuitive chart, which is convenient for clinicians to quickly assess the PE risk of patients. The main predictive variables included maternal age, parity (P), BMI, family history of hypertension, pregnancy complicating nephropathy or immune system diseases, MAP at 11–13 + 6 weeks of gestation, PLGF levels at 13–20 + 6 weeks of gestation, and PGDM. The total score obtained by adding the scores of the variables was used to predict the risk of PE. In conclusion, Nomogram provided an intuitive and practical tool for clinicians, improved the accuracy of risk assessment, and had high clinical application value.

Discussion

In this study, a medical history-based PE risk prediction model for the first and second trimester pregnancy was constructed by multivariate Logistic regression analysis, and its performance was systematically validated in the training and validation sets. The results showed that the model had high performance in the risk prediction of PE. Compared with the current FMF model proposed by FIGO, with similar false positive rate and detection rate, of which the parameters were mostly the patient's medical history obtained directly by inquiry, is simple and convenient. The PE prediction by uterine artery flow indicators measured by Doppler ultrasonography is based on the fact that insufficient trophoblast invasion leads to dysfunction of spiral artery remodeling [23]. The

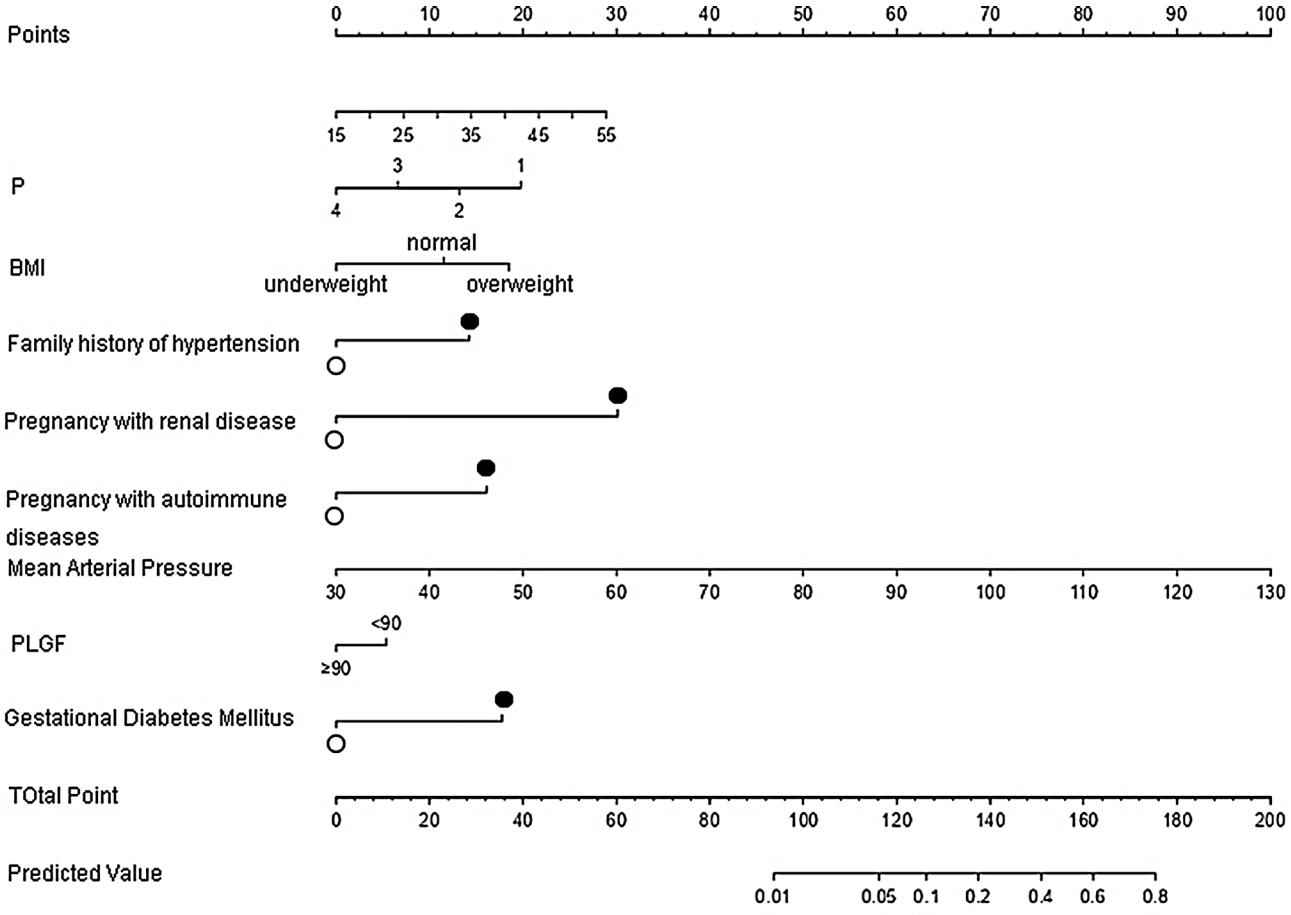

Fig. 8 Nomogram to predict risk of PE

uterine artery pulsatility index (UTPI), which includes the average of all maximal velocities during the cardiac cycle, is more stable than the resistance index (RI). When diastolic blood flow is absent or reversed, UTPI is more stable than the RI, for that it does not approach infinity [24]. In 2019, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) released a practice guideline on the role of ultrasound in PE screening and follow-up and recommended UTPI for uterine artery resistance examination for PE screening [25]. However, our model was simpler, and did not require ultrasonographic parameters. At the same time, the only mandatory serological biomarker was PlGF, the conditionally recommended measurement for high-risk pregnancies or those with clinical abnormalities, which did not increase additional medical costs and could be implemented in most resource-constrained primary hospitals in China. So, the model had good cost-effectiveness and feasibility. In total, in the case of similar false positive rate and detection rate, our medical history-based model for PE predication in the first and second trimesters pregnancy was simpler and more practical than the FIGO model, and more suitable for China's national conditions.

In addition, the key role of PlGF level in the PE prediction was validated by RCS analysis. The results showed an approximately L-shaped relationship between PlGF level and the risk of PE. When PIGF < 90 pg/ml, the risk of PE increased sharply with the decrease of PlGF; but when PIGF > 90, the risk of PE changed little with the increase of PlGF. Our study also presented for the first time a cutoff value of PlGF for patients at 13–20 + 6 weeks of gestation. PlGF, an angiogenic protein secreted by syncytiotrophoblasts, promotes placental angiogenesis. During a healthy pregnancy, PlGF levels rise steadily as the pregnancy progresses, usually peaking at 26 to 30 weeks of gestation and then decreasing before labor. Patients with PE usually have low PlGF levels before clinical manifestations appear. The existing FIGO and ACOG models are all for first trimester, which require PlGF detection before 12 + 6 weeks of gestation, while some studies believed that PlGF detection after 14 weeks of gestation was more accurate [26]. In clinical practice, we found that there might be two situations in PlGF detection in the first or second trimester of pregnancy: (1) PlGF level was lower in the first trimester, and reached normal level after the second trimester. Under this situation, there

may be excessive intervention and treatment according to the low PlGF value in early pregnancy. In our prediction model, through relaxing the restrictions of the gestational weeks, it could effectively reduce the occurrence of this problem. Meanwhile, for patients whose PlGF value was still low in the early second trimester, aspirin could still be used as an effective prevention. (2) The PlGF values in the first or early second trimester were higher in the normal range, but neared the normal lower limit. For these patients, the risk of PE was prone to be ignored according to the FIGO model. To cope with the situation, the cut-off value in our model was set to help distinguish these patients and strengthen the follow-up and monitoring of pregnancy by reexamining of PIGF, so as to diagnose patients with PE as early as possible and improve their outcomes. Therefore, our model was superior to the FIGO model in predicting gestational age and PlGF cut-off value.

Although the model achieved acceptable training sensitivity (73%), it showed a 16-percentage-point decline in validation sensitivity (57%), precluding its standalone use. However, given its satisfactory performance in decision curve analysis (DCA), it could still serve as a first-stage screening tool alongside PlGF monitoring in clinical practice.

Study limitations

However, the constructed model still had some limitations in spite of its strong predication ability. First, this study was a single-center study, and potential selection bias might limit its application in other populations. So, the external validity needed to be performed in different regions and multi-center populations in the future. Second, due to the retrospective design of this study, certain inadequately controlled confounders could potentially have influenced the results. Future studies should incorporate a prospective design to further optimize the model and verify its stability in a broader population. Finally, supplementation with angiogenic factors such as uterine artery pulsatility index (UtA-PI) or soluble fms-like tyrosine kinase-1 to placental growth factor ratio (sFlt-1/PlGF ratio) should be incorporated to significantly improved the PPV from 13.5% to reduce false-positive diagnoses. In addition, with the development of bioinformatics technology, multi-omics data, aiming to integrate genomics, metabolomics and proteomics is expected to further improve the accuracy and personalized application value of the PE prediction model. Future studies should broaden the inclusion of more biomarkers and metabolic indicators in the prediction models, such as placental vimentin expression [27] and pregnancy-associated plasma protein-a [28], especially predicators involved in the identification of different subtypes of PE, which would provide more accurate evidence for clinical intervention and significantly improve the efficiency of clinical management.

Conclusion

In conclusion, this study constructed a medical history-based risk prediction model for PE by multivariate Logistic regression analysis and provided a simple and intuitive risk assessment tool based on nomograms. In the case of similar false positive rate and detection rate, the model which was more suitable for Chinese population, simpler and more practical, provided an effective tool for PE screening of the first and second trimester pregnancy and precise intervention in clinical practice. By identifying high-risk pregnant women in the first and second trimester, clinicians could develop more personalized monitoring and management plans, reduce the incidence of PE and its related complications, and improve the health of mother and child.

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Author contributions

The experiment was designed and supervised by Guoli Liu; Qi Xu performed data collection and analysis and drafted the manuscript; Lili Xing helped with the ethical application works and statistical analysis; Ting Zhang helped with the thesis revision. All authors read and approved the manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available in consideration of patient privacy but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of the Peking University People's Hospital (Approval NO.: 2024PHB298-001) and was conducted in accordance with the regulation of Measures for the Ethical Review of Life Science and Medical Research Involving Humans issued in 2023 in China and the Helsinki Declaration. Informed Consent to participate was waived by the Ethics Committee due to the study characteristics.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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