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Original Article

Nomogram for predicting adverse perinatal outcomes in hypertensive disorders of pregnancy complicated by fetal growth restriction

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Abstract: Objectives: Hypertensive disorders of pregnancy (HDP) when combined with fetal growth restriction (FGR) increase the risk of adverse perinatal outcomes (APO). This study aimed to investigate the predictive value of fetal hemodynamic indicators for APO and to construct a nomogram for individualized risk assessment in pregnancies with HDP and FGR. Methods: This retrospective study included 198 pregnant women with HDP and FGR in the training set and 85 patients in the validation set, admitted between January 2022 and December 2024. Demographic, clinical, biochemical (uric acid, free thyroxine [FT4]), and Doppler parameters (umbilical artery pulsatility index [UA-PI], middle cerebral artery PI [MCA-PI], and cerebroplacental ratio [CPR]) were collected. Multivariate logistic regression was used to identify independent predictors, and a nomogram was constructed. Results: Seven independent predictors were identified: family history of hypertension (odds ratio [OR]=2.986), pre-eclampsia or chronic hypertension with superimposed pre-eclampsia (OR=2.811), uric acid (OR=1.036), FT4 (OR=0.813), abnormal UA-PI (OR=7.262), abnormal MCA-PI (OR=6.620), and abnormal CPR (OR=6.702). The nomogram demonstrated good discrimination, with an area under the curve (AUC) of 0.905 in the training set and 0.806 in the validation set. Conclusions: We developed a nomogram integrating maternal clinical history, serum biomarkers (uric acid, FT4), and fetal Doppler indices that showed good predictive accuracy for APO in HDP complicated by FGR. External validation in multi-center cohorts is required before clinical implementation.

Keywords: Hypertensive disorders of pregnancy, fetal growth restriction, adverse perinatal outcomes, fetal hemodynamics, cerebroplacental ratio, nomogram

Introduction

Hypertensive disorders of pregnancy (HDP), encompassing gestational hypertension and preeclampsia, represents a major global health burden and is increasingly prevalent worldwide [1, 2]. Nationally representative data from the United States showed that the rate of HDP per 10,000 delivery hospitalizations increased from 528.9 in 1993 to 912.4 in 2014 [3]. A similar upward trend has been reported in China: HDP incidence increased from 2.88% in 2018 to 7.04% in 2023 in Shenzhen and Hunan Province, while overall prevalence rose from 3.11% to 7.39% between 2012 and 2022 [4, 5]. HDP is strongly associated with severe adverse perinatal outcomes (APO), including preterm birth, placental abruption, and fetal growth restriction (FGR) [4-6].

HDP and FGR frequently co-exist, sharing a common pathophysiological basis of inadequate placental perfusion and villous remodeling [7]. Pregnancies complicated by both HDP

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and FGR carry substantially higher risks than either condition alone. Previous cohort studies have reported that the neonatal mortality in this dual-diagnosis population can reach approximately 15%, the neonatal intensive care unit (NICU) admission rate up to 65%, and nearly half of cases experience at least one adverse perinatal event [8, 9]. These figures are considerably higher than those observed in healthy pregnancies or in those with isolated HDP or FGR. This underscores the need for accurate risk stratification to guide delivery timing, fetal surveillance, and referral to tertiary center.

Current risk-stratification strategies for HDP-complicated FGR have several notable limitations. Conventional Doppler ultrasound parameters, such as umbilical artery (UA) pulsatility index (PI), are widely used in clinical practice but typically rely on a single gestational age-fixed cutoff, which fails to capture dynamic hemodynamic changes and limits diagnostic accuracy [10, 11]. Moreover, evidence specifically addressing predictive modeling in the HDP+FGR high-risk subgroup remains scarce [12]. Advanced fetal hemodynamic assessment, particularly the cerebroplacental ratio (CPR) and middle cerebral artery (MCA) Doppler, has shown promise in predicting APO in growth-restricted fetuses [10, 13]. However, the optimal integration of these Doppler indices with maternal clinical and biochemical markers in HDP-FGR remains unclear.

Accordingly, this study aimed to investigate the predictive value of abnormal fetal hemodynamic indicators for APO in pregnancies with HDP complicated by FGR. Using multivariable logistic regression, we constructed and internally validated a nomogram incorporating maternal clinical history, serum uric acid, free thyroxine (FT4), and fetal Doppler parameters (UA-PI, MCA-PI, CPR), to provide a practical tool for individualized risk assessment in this high-risk population.

Subjects and methods

Research subjects

A retrospective analysis was conducted on clinical data of pregnant women with HDP complicated by FGR admitted to Peking University First Hospital Ningxia Women and Children's Hospital from January 2022 to December 2024. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Peking University First Hospital Ningxia Women and Children's Hospital. Given the retrospective nature of the study and the use of anonymized data, the requirement for obtaining informed consent from individual patients was waived by the Ethics Committee.

Inclusion criteria: (1) Patients with established prenatal care records at Peking University First Hospital Ningxia Women and Children's Hospital, who underwent regular prenatal check-ups and were primiparous; (2) Complete clinical data from prenatal examination; (3) Age between 18 and 50 years; (4) Singleton pregnancy; (5) A clearly documented last menstrual period (LMP), with gestational age confirmed by early pregnancy ultrasound; (6) Gestational age ≥28 weeks; (7) HDP conforms to the diagnostic criteria outlined in the "Guidelines for the Diagnosis and Treatment of Hypertensive Disorders in Pregnancy (2020)" [14], which include gestational hypertension, pre-eclampsia (PE), chronic hypertension complicating pregnancy, and chronic hypertension with superimposed pre-eclampsia (CPE); (8) FGR conforms to the diagnostic criteria outlined in the "Expert Consensus on Fetal Growth Restriction (2019)" [15]: Estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile for the corresponding gestational age [16].

Exclusion criteria: (1) Not naturally conceived; (2) Diagnosed with gestational diabetes mellitus; (3) Presence of autoimmune diseases or hematologic disorders; (4) Diagnosed with malignant tumors; (5) Use of medications during pregnancy that could significantly affect blood pressure or fetal hemodynamics; (6) Fetal structural malformations or chromosomal abnormalities; (7) History of smoking, alcohol abuse, or use of illicit drugs during pregnancy.

Research methodology

Clinical data collection: General maternal information: Including age, gestational age, pre-pregnancy weight, pre-pregnancy body mass index (BMI), weight before delivery, BMI before delivery, weight gain during pregnancy, family history of hypertension, and whether combined with PE or CPE.

Hematological parameters: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr), uric acid, free triiodothyronine (FT3), and FT4 levels were measured using the Beckman AU5800 fully automated biochemical analyzer.

Fetal hemodynamic indicators: The GE Voluson E10 color Doppler ultrasonic diagnostic instrument equipped with C2-9-D, C1-6-D, and RM7C convex array volume probes (frequency range 2-8 MHz) was used to obtain the PI of the UA and MCA. A UA-PI above the 95th percentile for gestational age was considered abnormal. An MCA-PI below the 5th percentile for gestational age was considered abnormal. The CPR is the ratio of MCA-PI to UA-PI. A single cutoff value of 1.08 was used, with values above this threshold considered normal and below considered abnormal.

Definition of adverse perinatal outcomes: We defined a composite adverse perinatal outcome as the occurrence of any of the following events during the perinatal period: (1) Perinatal death (stillbirth or neonatal death); (2) Neonatal hypoxic-ischemic encephalopathy (HIE); (3) Apgar score <7 at 5 minutes after birth; (4) Requirement for endotracheal intubation and mechanical ventilation; (5) Admission to the NICU [12].

Based on the presence or absence of APO, the 198 patients in the training set were divided into a non-APO group (n=103) and an APO group (n=95), and a predictive model was constructed. Additionally, 85 patients who met the same inclusion and exclusion criteria were included to validate the model.

Statistical methods

Statistical analyses were performed using SPSS 29.0 and R 4.2.1. The dataset was randomly divided into a training set (70%, n=198) and a validation set (30%, n=85) using a computer-generated random number sequence. Measurement data were expressed as mean ± standard deviation (SD), and comparisons between groups were conducted using independent samples t-test. Count data were presented as cases (percentage) [n (%)], with intergroup comparisons analyzed by chi-square test. Candidate predictors were initially screened using univariate logistic regression (P<0.05 for entry). Subsequently, multivariate logistic regression with the Enter method was performed to construct the final model. The entry criterion was set at α=0.05, and the removal criterion was set at α=0.10. The predictive value of each risk factor on APO in pregnant women in HDP complicated by FGR was analyzed through receiver operating characteristic (ROC) curves and the area under the curve (AUC). A nomogram prediction model was constructed based on risk predictors. The model was evaluated using a combined ROC curve, calibration curve, and a validation set. A *P*-value <0.05 was considered statistically significant.

As a retrospective derivation and validation study, we referred to the recommended rule of thumb for logistic regression modeling, which suggests a minimum of 10 events per variable (EPV) to avoid model overfitting [17]. In the training set, 7 independent predictors were included in the final model. Given an anticipated incidence of APO of approximately 50% based on previous literature [8, 9], a sample size of 140 patients (70 events) would be sufficient. Our training cohort comprised 198 patients (95 events), yielding an EPV of 13.6, which exceeds the recommended threshold. For internal validation, we allocated approximately 30% of the total sample (n=85) to the validation set, which is consistent with standard practices for split-sample validation in clinical prediction models [18].

Results

Training set

General maternal information in the training set: **Table 1** compares baseline maternal characteristics between the non-APO (n=103) and APO (n=95) groups in the training set. Women who later developed APO were significantly older (30.96 vs. 29.24 years, P=0.005) and had a higher pre-pregnancy BMI (23.92 vs. 22.87 kg/m^2, P=0.046). The APO group had more positive family history of hypertension (28.42% vs. 10.68%, P=0.002). The APO group also had more patients with PE or CPE (64.21% vs. 29.13%, P<0.001). Other parameters, including pre-delivery weight and gestational weight gain, did not differ significantly between the groups. These findings indicate that advanced maternal age, higher pre-pregnancy BMI, familial hypertensive background,

Table 1. Comparison of general maternal information between APO and non-APO groups in the training set

Characteristics	Non-APO group (n=103)	APO group (n=95)	t/χ^2	P
Age, years	29.24 ± 4.18	30.96 ± 4.42	2.815	0.005
Pre-pregnancy weight, kg	62.16 ± 10.82	62.72 ± 11.36	0.359	0.720
Pre-pregnancy BMI, (kg/m^2)	22.87 ± 3.56	23.92 ± 3.78	2.006	0.046
Pre-delivery weight, kg	77.41 ± 11.24	75.65 ± 10.53	1.132	0.259
Pre-delivery BMI, (kg/m^2)	28.45 ± 3.92	28.41 ± 4.12	0.063	0.950
Weight gain during pregnancy, kg	14.83 ± 5.67	14.12 ± 5.35	0.911	0.363
Hypertension family history, n (%)	11 (10.68%)	27 (28.42%)	10.030	0.002
PE or CPE, n (%)	30 (29.13%)	61 (64.21%)	24.492	<0.001

APO, adverse perinatal outcomes; BMI, body mass index; PE, pre-eclampsia; CPE, chronic hypertension with superimposed pre-eclampsia.

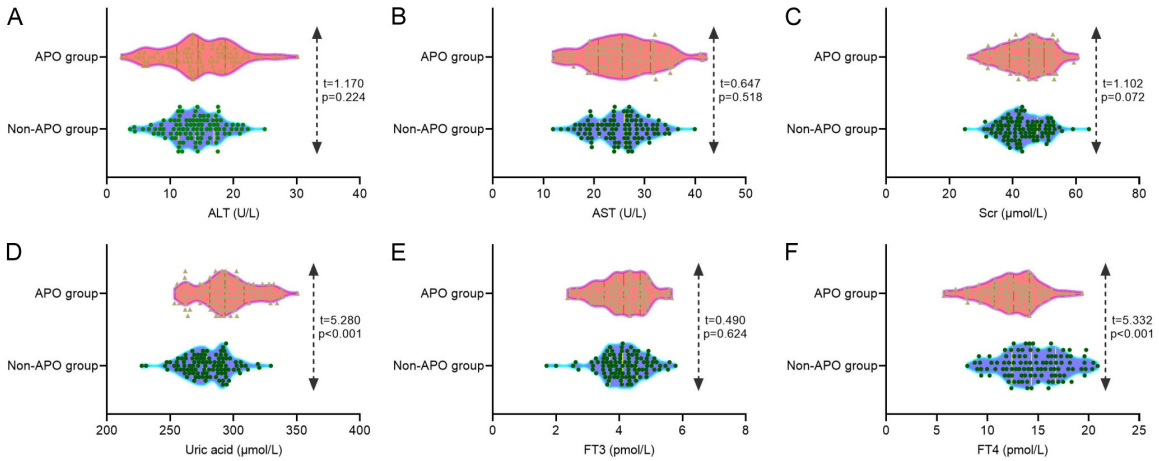

Figure 1. Comparison of hematological parameters between APO and non-APO groups in the training set. A. ALT (U/L); B. AST (U/L); C. Scr (μmol/L); D. Uric acid (μmol/L); E. FT3 (pmol/L); F. FT4 (pmol/L). APO, adverse perinatal outcomes; ALT, alanine aminotransferase; AST, aspartate transaminase; Scr, serum creatinine; FT3, free triiodothyronine; FT4, free thyroxine.

and PE or CPE are important characteristics of the APO group.

Hematological parameters in the training set: Among the laboratory findings (**Figure 1**), only two hematological parameters showed statistically significant differences between the groups. Uric acid levels were substantially elevated in the APO group (294.84 ± 22.41 vs. 279.42 ± 18.26 μmol/L, P<0.001, panel D), whereas FT4 was markedly lower (12.41 ± 2.74 vs. 14.59 ± 2.98 pmol/L, P<0.001, panel F). In contrast, liver enzymes (ALT, AST), serum creatinine, and FT3 showed no significant differences (all P>0.05). Thus, hyperuricemia and reduced FT4 emerged as the predominant biochemical abnormalities associated with APO.

Fetal hemodynamic indicators in the training set: We assessed three fetal Doppler indices (**Figure 2**). The CPR showed the largest difference between the groups. In the APO group, 47.37% had an abnormal CPR. In the non-APO group, only 9.71% had an abnormal CPR. Abnormal UA-PI was found in 37.89% of the APO group and 6.80% of the non-APO group (P<0.001). Abnormal MCA-PI was found in 18.95% of the APO group and 1.94% of the non-APO group (P<0.001). These results suggest that fetal hemodynamic deterioration is associated with APO, with particularly strong associations observed for UA and CPR.

Logistic regression: Univariate logistic regression (**Table 2**) identified a broad set of signifi-

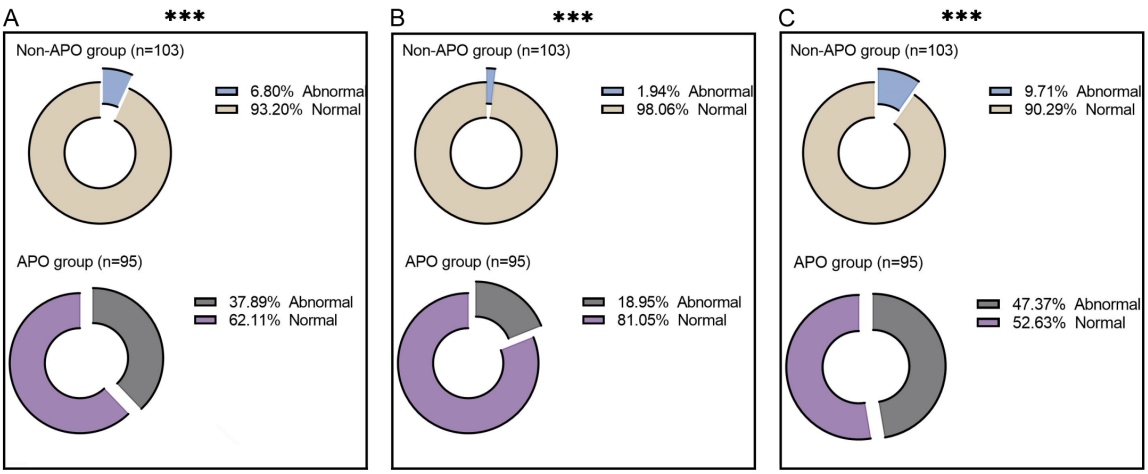

Figure 2. Comparison of fetal hemodynamic indicators between APO and non-APO groups in the training set, n (%). A. UA-PI; B. MCA-PI; C. CPR. APO, adverse perinatal outcomes; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; CPR, cerebroplacental ratio; ***, P<0.001.

Table 2. Univariate logistic regression of risk factors of APO in HDP complicated by FGR in the training set

Characteristics	Coefficient	Std Error	Wald	P	OR	95% CI
Age	0.093	0.034	2.732	0.006	1.098	1.028-1.176
Pre-pregnancy BMI	0.078	0.040	1.976	0.048	1.082	1.002-1.171
Hypertension family history	1.200	0.392	3.063	0.002	3.321	1.577-7.419
PE or CPE	1.474	0.305	4.837	<0.001	4.366	2.425-8.026
Uric acid	0.038	0.008	4.685	<0.001	1.038	1.023-1.056
FT4	-0.266	0.057	4.704	<0.001	0.767	0.682-0.852
Abnormal UA-PI	2.124	0.445	4.774	<0.001	8.368	3.692-21.623
Abnormal MCA-PI	2.469	0.760	3.246	0.001	11.805	3.275-75.689
Abnormal CPR	2.125	0.391	5.432	<0.001	8.370	4.028-18.902

APO, adverse perinatal outcomes; HDP, hypertensive disorders of pregnancy; FGR, fetal growth restriction; OR, odds ratio; CI, confidence interval; BMI, body mass index; PE, pre-eclampsia; CPE, chronic hypertension with superimposed pre-eclampsia; FT4, free thyroxine; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; CPR, cerebroplacental ratio.

cant risk factors. The strongest crude associations were observed for abnormal MCA-PI (odds ratio [OR]=11.805, 95% confidence interval [CI] 3.275-75.689), UA-PI (OR=8.368, 95% CI 3.692-21.623), and CPR (OR=8.370, 95% CI 4.028-18.902). Among maternal factors, PE or CPE carried an OR of 4.366, and a positive family history of hypertension gave an OR of 3.321. Age, pre-pregnancy BMI, uric acid, and FT4 also reached statistical significance (P<0.05 for all). These results suggest that although Doppler abnormalities confer the highest unadjusted risks, several clinical and biochemical variables also contribute significantly.

To account for confounding factors, we employed a multivariate logistic regression approach (**Table 3**). The analysis revealed that independent predictors of APO included a family history of hypertension (OR=2.986, P=0.037), PE or CPE (OR=2.811, P=0.013), uric acid levels (OR=1.036, P<0.001), FT4 (OR=0.813, P=0.004), abnormal UA-PI (OR=7.262, P<0.001), abnormal MCA-PI (OR=6.620, P=0.032), and abnormal CPR (OR=6.702, P<0.001). After multivariate adjustment, age and pre-pregnancy BMI were no longer significant, suggesting that their apparent effects in univariate analysis were largely explained by other correlated factors. Hence, a combination of four domains - clinical history (hypertension family history, PE or CPE), serum markers (uric acid, FT4), and three Doppler parameters - constitutes the set of independent determinants.

Table 3. Multivariate logistic regression of risk factors of APO in HDP complicated by FGR in the training set

Characteristics	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
Age	0.073	0.052	1.398	0.162	1.076	0.971	1.191
Pre-pregnancy BMI	0.039	0.061	0.633	0.527	1.040	0.922	1.173
Hypertension family history	1.094	0.525	2.085	0.037	2.986	1.068	8.353
PE or CPE	1.033	0.418	2.475	0.013	2.811	1.240	6.372
Uric acid	0.036	0.011	3.357	<0.001	1.036	1.015	1.058
FT4	-0.207	0.072	-2.868	0.004	0.813	0.706	0.937
Abnormal UA-PI	1.983	0.596	3.324	<0.001	7.262	2.256	23.377
Abnormal MCA-PI	1.890	0.880	2.147	0.032	6.620	1.179	37.164
Abnormal CPR	1.902	0.483	3.937	<0.001	6.702	2.600	17.278

APO, adverse perinatal outcomes; HDP, hypertensive disorders of pregnancy; FGR, fetal growth restriction; OR, odds ratio; CI, confidence interval; BMI, body mass index; PE, pre-eclampsia; CPE, chronic hypertension with superimposed pre-eclampsia; FT4, free thyroxine; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; CPR, cerebroplacental ratio.

Table 4. Prediction value of each risk factor on APO in HDP complicated by FGR in the training set

Characteristics	Best threshold	Sensitivities	Specificities	AUC	Youden index	F1 score
Age	30.530	0.589	0.621	0.617	0.210	0.589
Pre-pregnancy BMI	25.170	0.400	0.777	0.580	0.177	0.487
Hypertension family history	0.500	0.284	0.893	0.589	0.177	0.406
PE or CPE	0.500	0.642	0.709	0.675	0.351	0.656
Uric acid	294.500	0.474	0.845	0.695	0.319	0.577
FT4	14.505	0.832	0.485	0.698	0.317	0.199
Abnormal UA-PI	0.500	0.379	0.932	0.655	0.311	0.522
Abnormal MCA-PI	0.500	0.189	0.981	0.585	0.170	0.313
Abnormal CPR	0.500	0.474	0.903	0.688	0.377	0.600

APO, adverse perinatal outcomes; HDP, hypertensive disorders of pregnancy; FGR, fetal growth restriction; AUC, area under the curve; BMI, body mass index; PE, pre-eclampsia; CPE, chronic hypertension with superimposed pre-eclampsia; FT4, free thyroxine; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; CPR, cerebroplacental ratio.

Prediction value: We evaluated the predictive performance of each risk factor (**Table 4**). The AUC ranged from 0.580 to 0.698. FT4 had the highest AUC (0.698). Its sensitivity was high (0.832). Its specificity was low (0.485). Abnormal CPR had the best Youden index (0.377). Its specificity was high (0.903). Its sensitivity was moderate (0.474). Uric acid had an AUC of 0.695. Its specificity was 0.845. Abnormal MCA-PI alone had low sensitivity (0.189). Its AUC was 0.585. No single indicator demonstrated sufficient predictive accuracy for clinical use, supporting the need for a multivariable model.

Model construction: A nomogram was developed based on independent predictors. **Figure 3A** presents the nomogram, which assigns points to each predictor. The predictive factors included family history of hypertension, PE or CPE, uric acid levels, FT4, UA PI, MCA PI, and CPR. These metrics aid in assessing the individualized risk for each patient. **Figure 3B** illustrates the ROC curve, demonstrating the model's excellent discriminative ability. In the training set, the AUC reached 0.905, with a sensitivity of 0.832 and a specificity of 0.883. **Figure 3C** displayed that the Hosmer-Lemeshow goodness-of-fit test yielded a χ^2 value of 8.364 (P=0.398) for the training set, indicating good model calibration. This combined model outperforms any single factor by integrating hemodynamic and clinical variables, enabling robust prediction of APO in HDP complicated by FGR.

Validation set

General maternal information in the validation set: We then validated these risk patterns in an independent validation cohort (**Table 5**). The

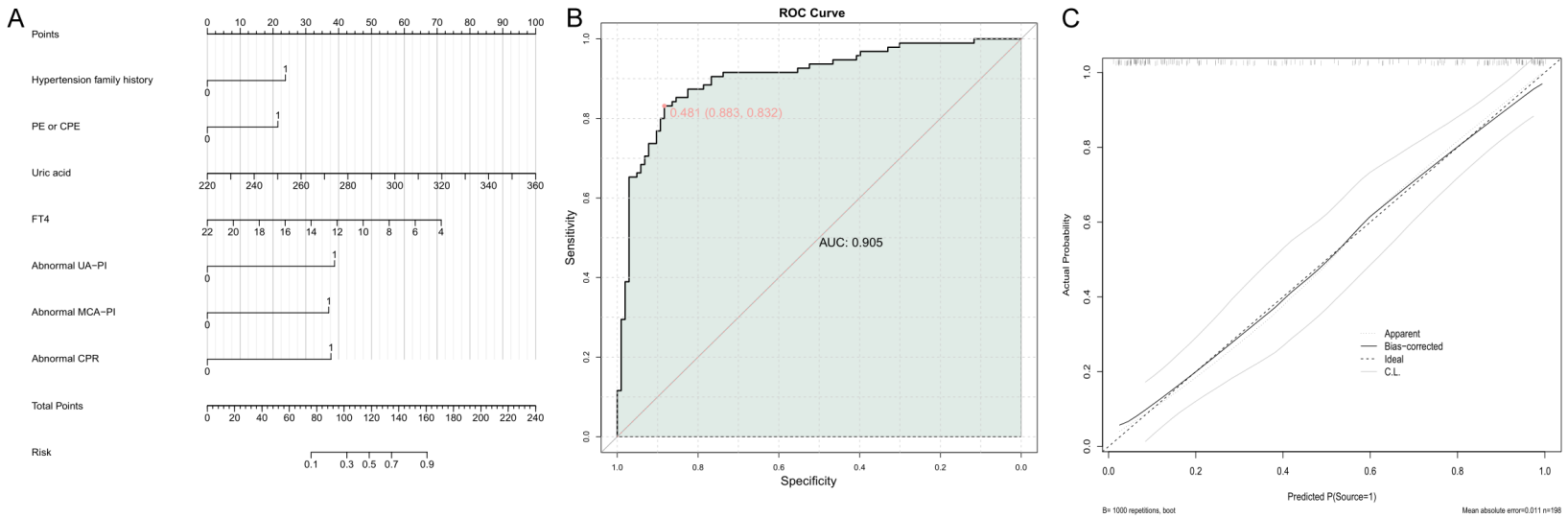

Figure 3. Construction of a predictive model of risk of APO in HDP complicated by FGR in the training set. A. Nomogram; B. ROC curve; C. Calibration curve. APO, adverse perinatal outcomes; HDP, hypertensive disorders of pregnancy; FGR, fetal growth restriction; PE, pre-eclampsia; CPE, chronic hypertension with superimposed pre-eclampsia; FT4, free thyroxine; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; CPR, cerebroplacental ratio; ROC, receiver operating characteristic; AUC, area under the curve.

Table 5. Comparison of general maternal information between APO and non-APO groups in the validation set

Characteristics	Non-APO group (n=46)	APO group (n=39)	t/χ^2	P
Age, years	29.14 ± 4.22	31.07 ± 4.38	2.059	0.043
Pre-pregnancy weight, kg	62.36 ± 10.95	62.88 ± 11.24	0.215	0.830
Pre-pregnancy BMI, (kg/m^2)	22.81 ± 3.47	24.06 ± 3.82	1.579	0.118
Pre-delivery weight, kg	77.53 ± 11.16	75.71 ± 10.44	0.773	0.442
Pre-delivery BMI, (kg/m^2)	28.38 ± 3.89	28.43 ± 4.06	0.061	0.952
Weight gain during pregnancy, kg	14.79 ± 5.62	14.06 ± 5.29	0.614	0.541
Hypertension family history, n (%)	5 (10.87%)	11 (28.21%)	4.151	0.042
PE or CPE, n (%)	14 (30.43%)	25 (64.10%)	9.635	0.002

APO, adverse perinatal outcomes; BMI, body mass index; PE, pre-eclampsia; CPE, chronic hypertension with superimposed pre-eclampsia.

Table 6. Comparison of hematological parameters between APO and non-APO groups in the validation set

Characteristics	Non-APO group (n=46)	APO group (n=39)	t	P
ALT (U/L)	13.96 ± 4.08	14.72 ± 5.52	0.737	0.463
AST (U/L)	25.24 ± 5.32	25.91 ± 6.85	0.509	0.612
Scr (μmol/L)	43.22 ± 6.65	44.36 ± 7.63	0.738	0.463
Uric acid (μmol/L)	280.08 ± 18.36	295.24 ± 22.57	3.414	<0.001
FT3 (pmol/L)	4.13 ± 0.69	4.07 ± 0.74	0.373	0.710
FT4 (pmol/L)	14.61 ± 2.94	12.54 ± 2.92	3.248	0.002

APO, adverse perinatal outcomes; ALT, alanine aminotransferase; AST, aspartate transaminase; Scr, serum creatinine; FT3, free triiodothyronine; FT4, free thyroxine.

APO group had a higher age distribution (31.07 vs. 29.14 years, P=0.043). Additionally, the APO group had a higher proportion of individuals with a family history of hypertension (28.21% vs. 10.87%, P=0.042). Furthermore, the APO group had a significantly higher prevalence of PE or CPE (64.10% vs. 30.43%, P=0.002). Although pre-pregnancy BMI was higher in the APO group, this difference was not statistically significant (P=0.118), possibly due to the smaller sample size of the validation cohort. These findings show that older maternal age, familial hypertension, and PE or CPE were linked to adverse outcomes in both datasets.

Hematological parameters in the validation set: Biochemical markers in the validation set are shown in **Table 6**. The results were similar to the training set. Uric acid was higher in the APO group. The values were 295.24 vs. 280.08 μmol/L (P<0.001). FT4 was lower in the APO group. The values were 12.54 vs. 14.61 pmol/L (P=0.002). ALT, AST, Scr, and FT3 showed no differences (all P>0.05). These results confirm that uric acid and FT4 are reliable biomarkers. They can predict APO in this setting.

Fetal hemodynamic indicators in the validation set: Fetal Doppler findings in the validation cohort (**Table 7**) were similar to those in the training set. In the APO group, abnormal UA-PI was 38.46%. In the non-APO group, it was 6.52% (P<0.001). Abnormal MCA-PI was 23.08% in the APO group and 2.17% in the non-APO group (P=0.008). Abnormal CPR was 48.72% in the APO group and 8.70% in the non-APO group (P<0.001). These results confirmed the strong association between abnormal fetal hemodynamics and APO. CPR again showed the largest difference between the two groups.

Model validation: We tested the predictive model on the validation set (**Figure 4**). The ROC curve gave an AUC of 0.806, with a sensitivity of 0.664 and a specificity of 0.824. Although these values were slightly lower than those in the training set, they still indicated good discriminative ability. The modest drop in sensitivity may be due to differences in case mix or

Table 7. Comparison of fetal hemodynamic indicators between APO and non-APO groups in the validation set, n (%)

Characteristics	Non-APO group (n=46)	APO group (n=39)	χ^2	P
UA-PI			12.899	<0.001
Abnormal	3 (6.52%)	15 (38.46%)		
Normal	43 (93.48%)	24 (61.54%)		
MCA-PI			6.984	0.008
Abnormal	1 (2.17%)	9 (23.08%)		
Normal	45 (97.83%)	30 (76.92%)		
CPR			17.129	<0.001
Abnormal	4 (8.70%)	19 (48.72%)		
Normal	42 (91.30%)	20 (51.28%)		

APO, adverse perinatal outcomes; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; CPR, cerebroplacental ratio.

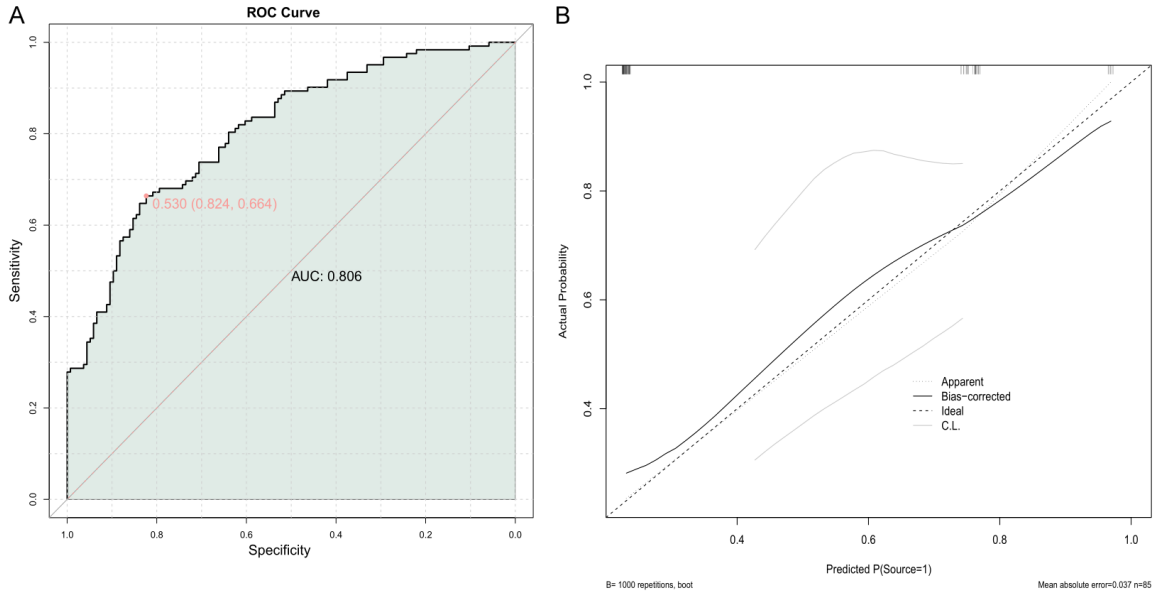

Figure 4. Validation of the predictive model of risk of APO in HDP complicated by FGR in the validation set. A. ROC curve; B. Calibration curve. APO, adverse perinatal outcomes; HDP, hypertensive disorders of pregnancy; FGR, fetal growth restriction; ROC, receiver operating characteristic; AUC, area under the curve.

sample size between the two cohorts. The model retains clinically useful predictive ability for APO in pregnancies with HDP and FGR. The Hosmer-Lemeshow test yielded a χ^2 value of 9.127 (P=0.332), confirming acceptable calibration of the model in the independent cohort.

Sensitivity analysis

To address potential confounding by obstetric management, we conducted a sensitivity analysis by re-defining the outcome using only objective endpoints (perinatal death and HIE). The multivariable logistic regression was re-run with this restricted outcome. The results showed that the seven predictors remained statistically significant, and the nomogram maintained excellent discrimination (Training set AUC: 0.892; Validation set AUC: 0.798), confirming the robustness of our model regardless of the inclusion of intervention-dependent indicators.

Discussion

In this study, we identified several independent predictors of APO, including maternal clinical characteristics, serum biomarkers, and fetal

Doppler indices, and constructed a nomogram incorporating these seven factors. The nomogram showed good discriminative ability in both the training and validation cohorts. These findings support the utility of a multidimensional approach for risk stratification in this high-risk population.

In univariate analysis, women with APO were older and had a higher pre-pregnancy BMI; however, these associations did not remain significant in multivariate analysis, suggesting that they were confounded by other factors such as PE or a family history of hypertension. A positive family history of hypertension, as well as PE or CPE, remained independent predictors. This is consistent with the concept that PE or CPE reflects a more severe placental vasculopathy that directly exacerbates fetal compromise [19-21]. Other studies have reported similar results. Di Martino et al. [8], found that pregnancies with HDP and FGR and PE had more placental ischemic lesions. Wang et al. [9] found that PE with chronic hypertension led to worse perinatal outcomes than gestational hypertension alone. A family history of hypertension also independently contributed to risk. This factor is less often emphasized. It may reflect genetic susceptibility to endothelial dysfunction or abnormal angiogenic regulation. Kwak et al. [1] recently discussed this genetic predisposition in the context of long-term cardiovascular risk after HDP.

Among the hematological parameters examined, only elevated uric acid and reduced FT4 distinguished the APO group from the non-APO group in both the training and validation sets, while liver enzymes, creatinine, and FT3 showed no material differences. Hyperuricemia in HDP-FGR is thought to arise from reduced renal excretion due to impaired glomerular filtration and increased production from placental ischemia-induced tissue breakdown [8, 22, 23]. Our findings corroborate those of Zhou et al. [5, 6], who reported that rising uric acid levels are associated with a higher likelihood of severe maternal and perinatal complications in HDP cohorts. Mechanistically, uric acid may cause oxidative stress and endothelial inflammation. This can reduce uteroplacental blood flow. It may also worsen FGR [24-26]. Low FT4 was also associated with adverse outcomes - a relatively novel finding. Thyroid hormones are important for fetal brain development. They are also important for metabolism. A small drop in maternal FT4 can occur within the normal range. This decline is linked to poorer outcomes for newborns [27]. In pregnant women with HDP and FGR, the placenta may alter deiodinase activity or reduce thyroid hormone transport. Ohtani et al. [7] similarly reported that Doppler anomalies may increase susceptibility to postpartum intestinal disorders in FGR infants, potentially linking this effect to lower thyroid hormone levels. Our research findings further support this view: after controlling for other factors, lower FT4 levels remained an independent predictor of the occurrence of APO.

We analyzed three Doppler parameters: UA-PI, MCA-PI, and CPR. All three were associated with APO. This was true in both univariate and multivariate analyses. Abnormal UA-PI was the strongest predictor among the Doppler indices. Its adjusted odds ratio was about seven. UA-PI reflects increased placental resistance. This finding agrees with the known pathophysiology of HDP-FGR. In this condition, failed spiral artery remodeling leads to higher UA impedance and reduces oxygen and nutrient delivery to the fetus [28-30]. Ohtani et al. [7] also reported that abnormal UA Doppler predicted postnatal complications in FGR infants. Abnormal MCA-PI, reflecting cerebral vasodilation (brain-sparing), was also an independent predictor, although its prevalence was lower. CPR combines placental and cerebral circulations. In our training set, CPR had the highest specificity and Youden index among all single indicators. Some studies suggest that CPR is better than UA-PI or MCA-PI alone [10]. Dall'Asta et al. [12] found that a low CPR at diagnosis of late-onset FGR improved prediction of adverse outcomes compared with UA-PI alone. Our study confirmed this in HDP pregnancies with FGR. In these pregnancies, both conditions often impair the fetoplacental unit. CPR is especially useful. The predictive power of each individual Doppler index was only moderate, with AUC values all below 0.70, indicating that no single indicator is sufficient for clinical diagnosis. Yang et al. [11] also noted this, which is why they employed the uteroplacental cerebral ratio.

The nomogram integrates seven factors, including a family history of hypertension, PE or CPE, uric acid levels, FT4 levels, abnormal UA-PI,

abnormal MCA-PI, and abnormal CPR. In the training set, its AUC reached 0.905; in the validation set, the AUC was 0.806. This nomogram performs better than any single factor and provides individual risk estimates. It uses points from routine clinical, biochemical, and ultrasound data. These calculations can be done at the bedside. Second, it enables identification of a subset of HDP-FGR pregnancies at very high risk of APO, such as those with multiple Doppler abnormalities, hyperuricemia, and low FT4, who may benefit from intensified fetal surveillance, timely delivery, or referral to a tertiary center. Conversely, pregnancies with few or no risk factors could be managed with less intensive monitoring, optimizing resource allocation. Third, the model's internal validity is supported by consistent performance in the validation cohort, albeit with a modest decline in sensitivity, which is expected when moving from a derivation to a validation sample. Compared with existing prognostic tools, such as those developed by Thangaratinam et al. [31] for early-onset PE, our model specifically targets the dual diagnosis of HDP and FGR and includes novel hemodynamic and thyroid parameters that are not traditionally incorporated.

Several limitations should be acknowledged. First, this was a single-center retrospective study, with internal validation performed using data from the same institutional database. Although the 70:30 split allowed for initial assessment of model performance, the similarity between the training and validation sets limits our ability to claim true generalizability. External validation using prospective data from different regions or medical centers is essential before this nomogram can be widely adopted in clinical practice. Second, we used a fixed CPR cutoff of 1.08. Gestational age-specific thresholds may give better accuracy. Future studies should explore centile-based CPR values. Third, we did not collect longitudinal Doppler measurements. Repeated assessments might capture dynamic changes and improve predictive accuracy. Fourth, we did not evaluate other emerging parameters, such as the modified myocardial performance index and the placenta-fetal brain ratio. Future research could explore the use of machine learning, which can handle nonlinear interactions between variables and may enhance predictive accuracy. Additionally, external validation in different populations and the integration of placental biomarkers such as soluble fms-like tyrosine kinase-1 and placental growth factor are promising avenues for future research. Our nomogram provides a clinically accessible tool for reasonably accurate prediction of APO in HDP complicated by FGR, but further prospective validation is required.

Conclusion

In pregnant women with HDP and FGR, APO is associated with multiple factors, including a family history of hypertension, PE or CPE, elevated uric acid, low FT4, and abnormal Doppler ultrasound indices. These abnormalities primarily involve the UA-PI, MCA-PI, and CPR. Based on these findings, we developed a nomogram integrating these seven predictors, which demonstrated excellent discriminative ability and outperformed any single predictive indicator. The tool may assist clinicians in risk stratification and guide subsequent fetal monitoring. However, prospective, multi-center validation is warranted before this tool can be adopted in routine clinical practice.

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Disclosure of conflict of interest

None.

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