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A nomogram for predicting adverse perinatal outcome with fetal growth restriction: a prospective observational study

Ying Zhao[1†], Lei Xu[2†], Ping An[1], Jizi Zhou[1], Jie Zhu[1], Shuangping Liu[1], Qiongjie Zhou[1], Xiaotian Li[3*†] and Yu Xiong[1*†]

Abstract

Background Fetal growth restriction (FGR) is a major determinant of perinatal morbidity and mortality. Our study aimed to develop a prediction model for the risk of FGR developing adverse perinatal outcome (APO) and evaluate its performance.

Methods This was a prospective observational cohort study of consecutive singleton gestations meeting the ACOG-endorsed criteria for FGR from January 2022 to June 2023 at Obstetrics and Gynecology Hospital of Fudan University. Clinical information, ultrasound indicators and serum biomarkers were collected. The primary composite APO comprised one or more of: perinatal death, intrauterine demise, intraventricular hemorrhage, periventricular leukomalacia, seizures, necrotizing enterocolitis, neonatal respiratory distress syndrome, sepsis and the length of stay in the neonatal intensive care unit > 7 days. Least absolute shrinkage and selection operator regression was used to screen variables for nomogram model construction. The discrimination, calibration and clinical effectiveness of the nomogram were evaluated using receiver operating characteristic curve, calibration plots and decision curve analysis in training and validation cohorts.

Results A total of 122 pregnancies were enrolled in the final statistical analysis. Five variables were identified to establish a nomogram, including gestational weeks at diagnosis, abnormal umbilical artery Doppler, abnormal uterine artery Doppler, and multiples of the median values of placental growth factor and soluble fms-like tyrosine kinase-1. The area under the receiver-operating-characteristics curve of 0.87 (95% CI, 0.75–0.99) and 0.86 (95% CI, 0.74–0.98) in the training and validation cohort respectively, indicated satisfactory discriminative ability of the nomogram. The calibration plots showed favorable consistency between the nomogram's predictions and actual observations. Decision curve analysis supported its practical value in a clinical setting.

†Ying Zhao and Lei Xu contributed equally to this work and should be considered co-first authors.

†Xiaotian Li and Yu Xiong contributed equally to this work and should be considered co-corresponding authors.

*Correspondence:
Xiaotian Li
xiaotianli555@163.com
Yu Xiong
xiongyu1535@163.com

Full list of author information is available at the end of the article

Conclusions A nomogram was developed and validated to possess the promising capacity of predicting APO in FGR-afflicted neonates, and may prove useful in counseling and management of pregnancies complicated by FGR.

Keywords Fetal growth restriction, Prognostic model, Umbilical artery Doppler, Uterine artery Doppler, Placental growth factor, Soluble fms-like tyrosine kinase-1

Background

Fetal growth restriction (FGR), defined as the fetus failing to reach its genetically predetermined growth potential [1], affects 10% of pregnancies worldwide [2]. FGR carries significant risks of stillbirth, neonatal morbidity and mortality, neurodevelopmental impairment, and long-term health problems [3–5]. A fetus is considered to be FGR when its sonographic estimated fetal weight (EFW) falls below the 10th percentile for its gestational age [6]. However, it is important to note that the use of EFW does not perform well in isolation for the risk prediction of adverse perinatal outcomes (APO) in newborns [7, 8], as the approach is merely a snapshot of fetal size, incapable of differentiating between the fetus that is constitutionally small and fulfilling its growth potential and the small fetus that is not fulfilling its growth potential because of an underlying pathologic condition. Therefore, the current challenge is how to accurately predict the APO risk in FGR-afflicted newborns, as the risk can be significantly reduced via close monitoring and appropriate timing of delivery if the condition is identified prenatally [9].

Uteroplacental insufficiency represents one of the most frequent causes of abnormal growth in an otherwise normal fetus [10], and is associated with impaired placental growth factor (PlGF) secretion and excessive soluble fms-like tyrosine kinase-1 (sFlt-1) release [11–13], as well as increased impedance in the umbilical and uterine arteries [14–16]. Numerous studies have investigated predictive models for the development of FGR based on maternal biomarkers and ultrasound indicators [17–19], but fewer have studied the prediction of APO when FGR is diagnosed. The inability to predict APO leads to repeated hospitalizations for antenatal monitoring, increased maternal anxiety and health resource waste. It also limits clinicians' abilities to personalize management and counseling.

Nomograms, which are widely used for cancer prognosis, have the capacity to generate an individual probability by integrating diverse determinant variables. Therefore, nomograms can meet our desire for a clinically integrated model which facilitates our construction of personalized medicine. In this prospective observational cohort study, we aimed to develop and validate a nomogram model to predict the APO in FGR-afflicted neonates by incorporating clinical characteristics, maternal serum biomarkers and ultrasound indicators.

Methods

Study design and participants

We conducted a prospective observational cohort study from January 2022 to June 2023 at Obstetrics and Gynecology Hospital of Fudan University, the protocol of which was granted approval by the Ethics Committee. Each subject was required to sign informed consent prior to participating in the study.

Pregnancies were recruited following their routine ultrasound scans for performing biometry which were scheduled at approximately 22, 28, 32 and 37 weeks of gestational age. The inclusion criteria were set as follows: singleton pregnancies with FGR, aged 18 or older. The exclusion criteria were referred to as fetal chromosomal abnormalities, congenital defects, and incomplete delivery information. FGR was defined as fetuses with an EFW or abdominal circumference (AC) below the 10th percentile of its gestational age according to the American College of Obstetricians and Gynaecologists (ACOG) guidelines in 2021 [6]. EFW was calculated based on the Hadlock formula I with biparietal diameter, head circumference, abdominal circumference, and femur length and adjusted according to gestational age against NICHD-Asian growth standards. Gestational age was determined by fetal crown-rump length measurement at 11^{+0}-14^{+0} weeks of gestation [20].

The individual information was obtained through Hospital Electronic Case System including maternal age, gravidity and parity history, BMI at the first visit, aspirin intake, smoking, chronic disease conditions and delivery outcomes.

Ultrasound indicators

All pregnancies underwent routine ultrasound examinations transabdominally using a Voluson E10 machine (GE Healthcare, Zipf, Austria). The measurements of fetal biometry and Doppler velocimetry were performed by two specially trained and experienced sonographers, strictly complied with the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Practice Guidelines [21, 22], with each ultrasound examination lasting no more than 20 min.

Fetoplacental circulation was assessed by Doppler ultrasound consisting of the measurement of uterine artery (UtA) pulsatility index (PI), umbilical artery (UA) PI, middle cerebral artery (MCA) PI and ductus venosus (DV) PI and diastolic flow (a-wave present, absent, or reversed). The proximal uterine arteries were located in

a standard manner using color flow imaging at the crossover point with the external iliac artery; a pulsed Doppler gate was placed just above this crossover point to obtain the PI. The left and right UtA-PI were measured to calculate the mean UtA-PI. MCA Doppler measurements were performed by the sphenoid wings, close to the internal carotid artery origin. UA waveforms were obtained in free loops of cord by pulsed Doppler to derive PI values and record absent end-diastolic velocity (AEDV) or reversed end-diastolic velocity (REDV).

Abnormal UA Doppler was defined as UA PI greater than the 95th percentile for gestational age or AEDV or REDV; abnormal MCA Doppler as MCA PI below the fifth centile and/or cerebroplacental ratio (CPR) below the fifth centile; and abnormal UtA Doppler as UtA PI>95th percentile. Abnormal DV Doppler meant an absent or reversed a-wave of ductus venosus.

Serum biomarkers

Eligible subjects had their blood taken on the day of recruitment. Blood samples of 5 mL were collected by skilled nurses into vacuum polypropylene tubes from the cubital vein. The serum samples were immediately separated by centrifugation at 1400 rpm for 10 min at room temperature, coded and stored at -80℃ for further analysis. Maternal serum concentrations of PlGF and sFlt-1 in pg/mL were analyzed at the time of diagnosis by electrochemiluminescence with sFlt-1 and PlGF kits of iMAGIN 1800 (Aucheer, Ningbo, China). Serum biomarker data were standardized using multiples of the median (MoM).

Clinical management

All enrolled patients were followed up through standard antenatal management based on current clinical guidelines. Management decisions relating to the frequency of antenatal surveillance, timing of admission, and timing and mode of delivery were at the discretion of the supervising clinicians. Our institutional practice includes inpatient management for pregnancies complicated by preeclampsia, UA absent or reversed end-diastolic flow, and/or non-reassuring cardiotocography (CTG). Furthermore, our recommended delivery timing for FGR pregnancies is as follows: no later than 37 weeks in pregnancies with UA-PI > 95th percentile, MCA-PI < 5th percentile, or preeclampsia without severe features, or with severe FGR with EFW less than the 3rd percentile; no later than 34 weeks for those with AEDV or preeclampsia with severe features; and no later than 32 weeks for those complicated by REDV. Antenatal corticosteroid treatment and administration of magnesium sulfate are routinely practiced in accordance with the ACOG guidelines.

Study outcomes

The primary outcome was a composite of APO in neonates, defined as one or more of the following:

1. Perinatal death occurring from 28 weeks of gestation until one week after birth;
2. Intrauterine demise before 28 gestational weeks;
3. Intraventricular hemorrhage (IVH) of any grade diagnosed by ultrasound;
4. Periventricular leukomalacia (PVL) ascertained by ultrasonography;
5. Seizures on two or more occasions within 72 h after birth;
6. Necrotizing enterocolitis (NEC) diagnosed by radiography, surgery, or autopsy;
7. Neonatal respiratory distress syndrome (RDS);
8. Sepsis ascertained by blood culture;
9. Length of stay in the neonatal intensive care unit (NICU) > 7 days.

Statistical analysis

Statistical analyses were performed with RStudio (version 4.2.0) and SPSS Statistics for Windows, Version 20.0 (IBM Corp, NY, USA). The continuous data were expressed as the means ± standard deviation (SD); the categorical data as n (%); and the non-normal variables as the medians (25th and 75th). *P* value for the differences was calculated using unpaired Student's t-test for the continuous variables with normal distribution and Mann-Whitney U test for the continuous variables with non-normal distribution between the two groups. The Chi-square test was used for the categorical variables. $P < 0.05$ was considered statistically significant.

The steps for the construction and validation of the nomogram were described below. (1) The participants were divided into the training and validation cohorts with a ratio of 1:1. (2) Least absolute shrinkage and selection operator (lasso) regression was used to screen variables for model construction in the training cohort. (3) The performance of each predictor was evaluated by the area under the receiver operating characteristic (ROC) curve (AUC). (4) The prediction model was evaluated in both the training and validation cohorts. The AUC calculated by bootstrapping were used to evaluate discriminative ability. Calibration plots were used to evaluate calibrating ability, using the Hosmer-Lemeshow test with $p > 0.05$ indicating good model calibration [23]. Decision curve analysis (DCA), a method for evaluating the clinical benefit of alternative model [24], was applied to nomograms by quantifying net benefits at different threshold probabilities. The curves of the treat-all-patients scheme (representing the highest clinical costs) and the treat-none scheme (representing no clinical benefit) were plotted as two references. The cut-off point for the prediction

model was selected to maximize sensitivity and specificity according to the Youden index.

Results

General characteristics

A total of 125 pregnancies with FGR were enrolled. After exclusion, the analysis included 122 eligible participants who could be evaluate. In the total cohort, 27 (22.1%) pregnancies were complicated by the composite APO, including one perinatal death and three intrauterine demises, and one case had IVH, two had NEC, 11 had RDS, 4 had sepsis, and 22 had a length of stay in the neonatal intensive care unit (NICU) > 7 days. The incidence of the composite APO was 21.3% (13/61) in the training cohort and 23.0% (14/61) in the validation cohort (Fig. 1).

The baseline characteristics of the study population are summarized in Table 1. In the APO group, the gestational weeks at diagnosis of FGR was earlier, sFlt-1 MoM were higher and PlGF MoM were lower. The APO group had a higher rate of abnormal UA and UtA Doppler. Pregnant outcome of the study subjects is displayed in Table S1. Pregnancies in the APO group had a higher incidence of preeclampsia and preterm premature rupture of membrane (PPROM). The fetuses in the APO group were delivered earlier, with a higher rate of preterm birth and a lower birth weight, compared with control fetuses. Additionally, caesarean section showed a higher incidence of APO group.

Predictor selection

To prevent overfitting and ensure the stability of the model, lasso logistic regression was used to screen parameters. The variation characteristics of the coefficient of these variables were shown in Figure S1**A**, and the 10-fold cross-validation method was applied to the model with excellent performance but minimum number of variables was obtained when $\log(\lambda) = -3.38$ (Figure S1**B**). Five predictors were selected to construct the nomogram, including gestational weeks at diagnosis, abnormal UA Doppler, abnormal UtA Doppler, maternal serum PlGF MoM and sFlt-1 MoM.

Predictors were grouped into three types: P1, the clinical feature (gestational weeks at diagnosis of FGR); P2, ultrasound indicators (abnormal UA Doppler + abnormal UtA Doppler); P3, serum biomarkers (PlGF MoM + sFlt-1 MoM). Table 2 showed the predictive performance of each individual predictor and predictor combination, which indicated that combining all predictors (P1 + P2 + P3) had optimal predictive performance.

Nomogram construction and evaluation

The nomogram prediction model was constructed using five variables selected by the lasso algorithm (Fig. 2). Figure S2 shows an example of using the nomogram to predict APO risk of a given patient. The patient was diagnosed as FGR at 32 gestational weeks, with abnormal UA and UtA Doppler and MoM values of PlGF and sFlt-1 of 0.6 and 1.17, respectively. Her final score would be 15 (gestational weeks at diagnosis) + 37 (PlGF MoM) + 10 (sFlt-1 MoM) + 21 (abnormal UA Doppler) + 20 (abnormal UtA Doppler) = 103, which corresponds to a risk of FGR of 0.51.

In the training cohort, the AUC was 0.87 (95% CI, 0.75–0.99), using a cut-off value of 0.22 with 85.7% specificity

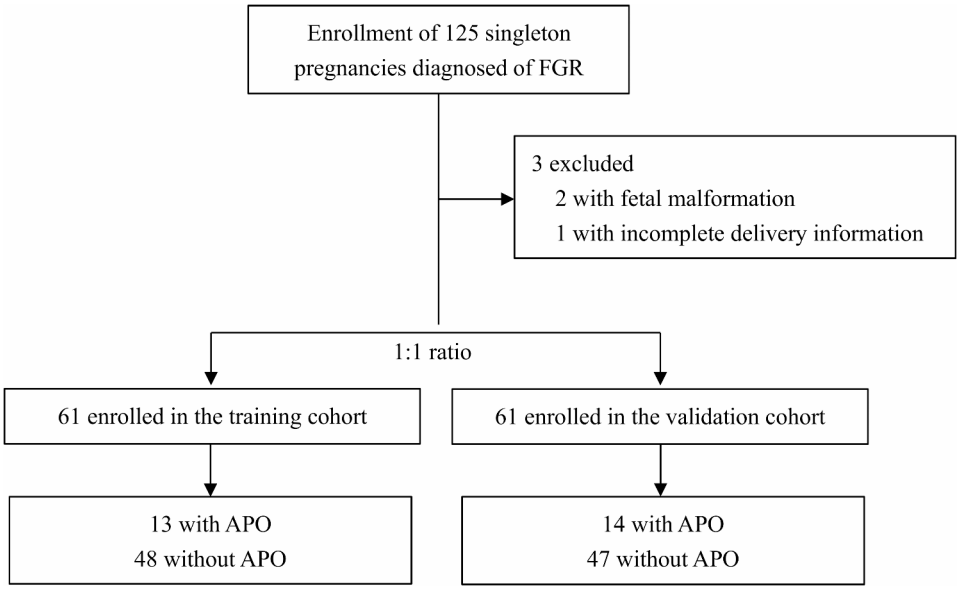

Fig. 1 Numbers of participants enrolled and outcomes in the training and validation cohorts. APO: adverse perinatal outcome; FGR: fetal restricted growth

Table 1 Baseline characteristics of the study population

Characteristic	Training Cohort			Validation Cohort		
	With APO (*n* = 13)	No APO (*n* = 48)	P	With APO (*n* = 14)	No APO (*n* = 47)	P
Demographic characteristics						
Age (yrs), mean ± SD	30.15 ± 2.94	30.88 ± 4.13	0.558	31.14 ± 5.08	30.21 ± 3.71	0.454
BMI at the first visit (kg/m^2), mean ± SD	23.44 ± 4.99	21.55 ± 3.30	0.108	23.02 ± 3.33	21.07 ± 2.49	0.021
Overweight or obesity, n (%)	2(15.4%)	7(14.6%)	0.942	3(21.4%)	5(10.6%)	0.294
Primiparous, n (%)	12(92.3%)	41(85.4%)	0.514	10(71.4%)	42(89.4%)	0.097
Miscarriage			0.04			0.091
0	7	35		7	34	
1	4	12		2	9	
2	2	0		3	2	
≥ 3	0	1		2	2	
Aspirin intake, n (%)	5(38.5%)	13(27.1%)	0.425	5(35.7%)	10(21.3%)	0.271
Smoking, n (%)	0	0		0	0	
Gestational age at diagnosis (weeks), mean ± SD	29.94 ± 4.58	33.11 ± 5.11	0.047	29.29 ± 4.27	32.05 ± 4.52	0.047
Clinical characteristics						
Chronic hypertension, n (%)	1(7.7%)	3(6.3%)	0.852	1(7.1%)	0	0.065
Pregestational diabetes mellitus, n (%)	0	2(4.2%)	0.453	0	0	
Chronic kidney disease, n (%)	0	0		0	1(2.1%)	0.582
Immunological disease, n (%)	0	0		0	1(2.1%)	0.582
Prior FGR, n (%)	0	1(2.1%)	0.600	0	1(2.1%)	0.582
Prior preeclampsia, n (%)	1(7.7%)	0	0.053	0	1(2.1%)	0.582
Maternal serum biomarkers						
sFlt-1 MoM, median (IQR)	2.08 (1.09–4.29)	0.78 (0.61–1.34)	0.000	1.42 (0.49–4.70)	0.86 (0.57–1.41)	0.160
PlGF MoM, median (IQR)	0.11 (0.04–0.18)	0.17 (0.08–0.36)	0.063	0.11 (0.05–0.23)	0.29 (0.14–0.44)	0.007
Ultrasonic characteristics						
Abnormal UA Doppler, n (%)	6(46.2%)	4(8.3%)	0.001	5(35.7%)	4(8.5%)	0.012
Abnormal MCA Doppler, n (%)	3(23.1%)	3(6.3%)	0.071	2(14.3%)	2(4.3%)	0.183
Abnormal UtA Doppler, n (%)	5(38.5%)	6(12.5%)	0.031	6(42.9%)	6(12.8%)	0.013
Abnormal DV Doppler, n (%)	0	0		0	0	

APO, adverse perinatal outcome; BMI, body mass index; DV, ductus venosus; MCA: middle cerebral artery; MoM, multiples of the median; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UA, umbilical artery; UtA, uterine artery

Table 2 Area under receiver-operating-characteristics curve (AUC) for individual predictors and combinations of predictors for prediction of adverse perinatal outcome (APO)

Predictors	AUC (95%CI)
Gestational weeks at diagnosis (P1)	0.70 (0.60–0.79)
Abnormal UA Doppler	0.66 (0.56–0.76)
Abnormal UtA Doppler	0.64 (0.54–0.74)
sFlt-1 MoM	0.73 (0.61–0.85)
PlGF MoM	0.70 (0.59–0.82)
Abnormal UA Doppler + Abnormal UtA Doppler (P2)	0.75 (0.65–0.85)
sFlt-1 MoM + PlGF MoM (P3)	0.75 (0.64–0.87)
P1 + P2	0.80 (0.70–0.89)
P1 + P3	0.79 (0.69–0.90)
P2 + P3	0.80 (0.71–0.90)
P1 + P2 + P3	0.85 (0.76–0.94)

MoM, multiples of the median; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UA, umbilical artery; UtA, uterine artery

and 75.0% sensitivity according to the Youden index. In the validation cohort, the AUC was 0.86 (95% CI, 0.74–0.98), using a cut-off value of 0.35 with 91.3% specificity and 73.3% sensitivity (Fig. 3A-B). This indicates that the model has a favorable performance in distinguishing the APO group.

The calibration curves showed high consistencies between the predicted values and observed values in the training and validation cohorts, and the results of the Hosmer–Lemeshow test were $P = 0.55$ and $P = 0.68$ respectively, indicating good model calibration (Fig. 3C-D).

DCA curves showed that the nomogram yields great Net Benefit over a large threshold probability range in the training and validation cohorts, with both the treat-all-patients scheme and the treat-none scheme (Fig. 3E-F).

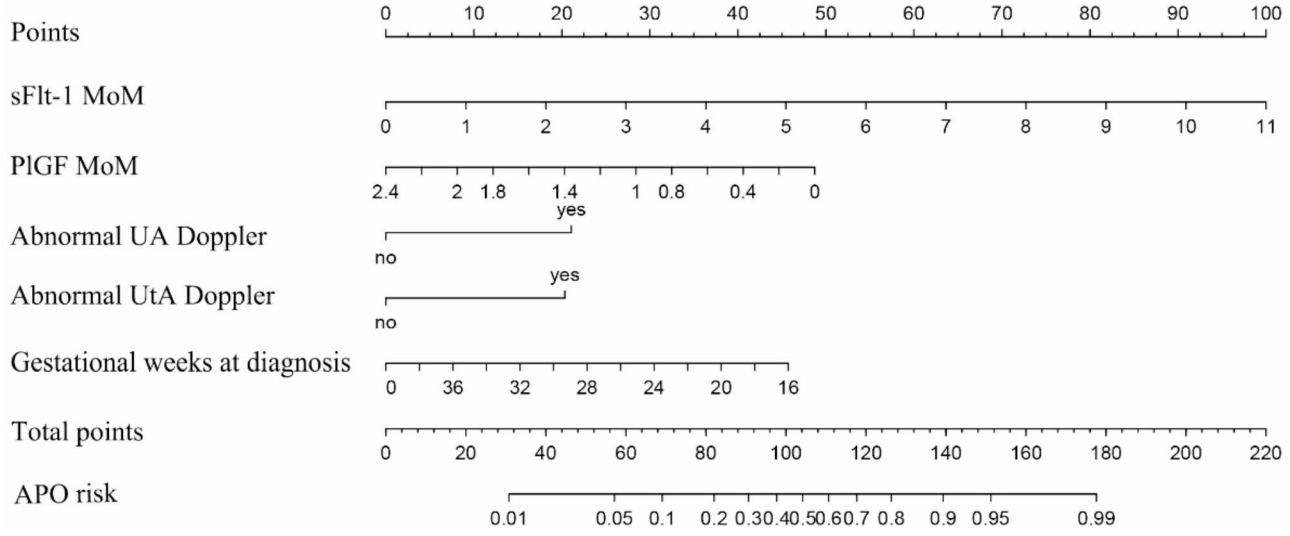

Fig. 2 Nomogram prediction model for adverse perinatal outcome (APO) in FGR patients. APO, adverse prenatal outcome; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; UA, umbilical artery; UtA, uterine artery

Discussion

In this study, we pioneered the construction and validation of a nomogram to predict the APO risks in FGR-afflicted neonates. The nomogram combines gestational weeks at diagnosis, abnormal UA Doppler, abnormal UtA Doppler, maternal serum PlGF MoM and sFlt-1 MoM. These findings show that combining multiple indicators could effectively predict the APO risks under routine conditions, and can be used to inform personalized and precise counseling, efficient allocation of resources and optimization of clinical management.

Earlier studies of FGR have also attempted to look for predictive indexes of APO [25, 26]. By comparison, our study was characterized by the prospective design and dataset of perinatal registry data and hospital records. Thanks to this, the information of predictors was acquired at the time of FGR diagnosis, which in our cohort was on average three weeks prior to delivery.

In general, a single factor such as biometric measurement or growth trajectory alone, is not adequately identify the risk of adverse perinatal outcomes. Previous studies suggested that cerebroplacental (CPR) and umbilicocerebral (UCR) ratios on their own are poor prognostic predictors of APO (AUC 0.44 and 0.56, respectively) [27, 28]. Using a slow growth trajectory as stand-alone criterion for FGR was reported not to be associated with a higher risk of APO in a low-risk population [29]. The large Pregnancy Outcome Prediction (POP) study found that EFW < 10th percentile was associated with the risk of neonatal morbidity only when the AC growth velocity was in the lowest decile [30]. In this context, the sFlt-1/PlGF ratio could be used to complement ultrasound examinations. As reported by a small size study, a sFlt-1/PlGF ratio ≥ 86.2 resulted in maximum detection of pregnancies at risk of APO in a cohort of 34 pregnancies with FGR diagnosed at < 34 weeks [31]. In the present study, the analysis of only FGR cases provided an opportunity to reconsider the factors that could be integrated into the predictive model. The nomogram integrates multiple factors into a quantitative model and has been shown to perform better (AUC 0.87 and 0.86 in the training and validation cohorts respectively) than some conventional single indexes.

Previous studies have applied screening models of multiple factors to the general population and demonstrated the ability to identify small-for-gestational-age (SGA) neonates, without much success at delineating those at risk of APO [17, 18, 32]. For example, a competing-risks model, based on maternal factors and biophysical (UtA-PI) and biochemical (PlGF) markers at 11–13 weeks' gestation, was reported to be effective for prediction of FGR (defined as birth weight < 3rd percentile) in pregnant patients with preeclampsia [32]. For obstetricians, it is more important to identify the constitutionally small fetus from one who is pathologically growth restricted and at risk for postnatal complications. However, use of these models was not associated with a reduced risk of perinatal death or perinatal morbidity.

Our study has important clinical implications. The nomogram has shown good performance for detecting FGR pregnancies at a higher risk of APO, which require more frequent scans and should be closely monitored for the early detection of fetal or maternal complications. On the contrary, the cases at a lower risk might be possible to extend the interval between scans, which would significantly reduce the number of fetal ultrasounds, thereby lowering parental anxiety and the burden on the healthcare system.

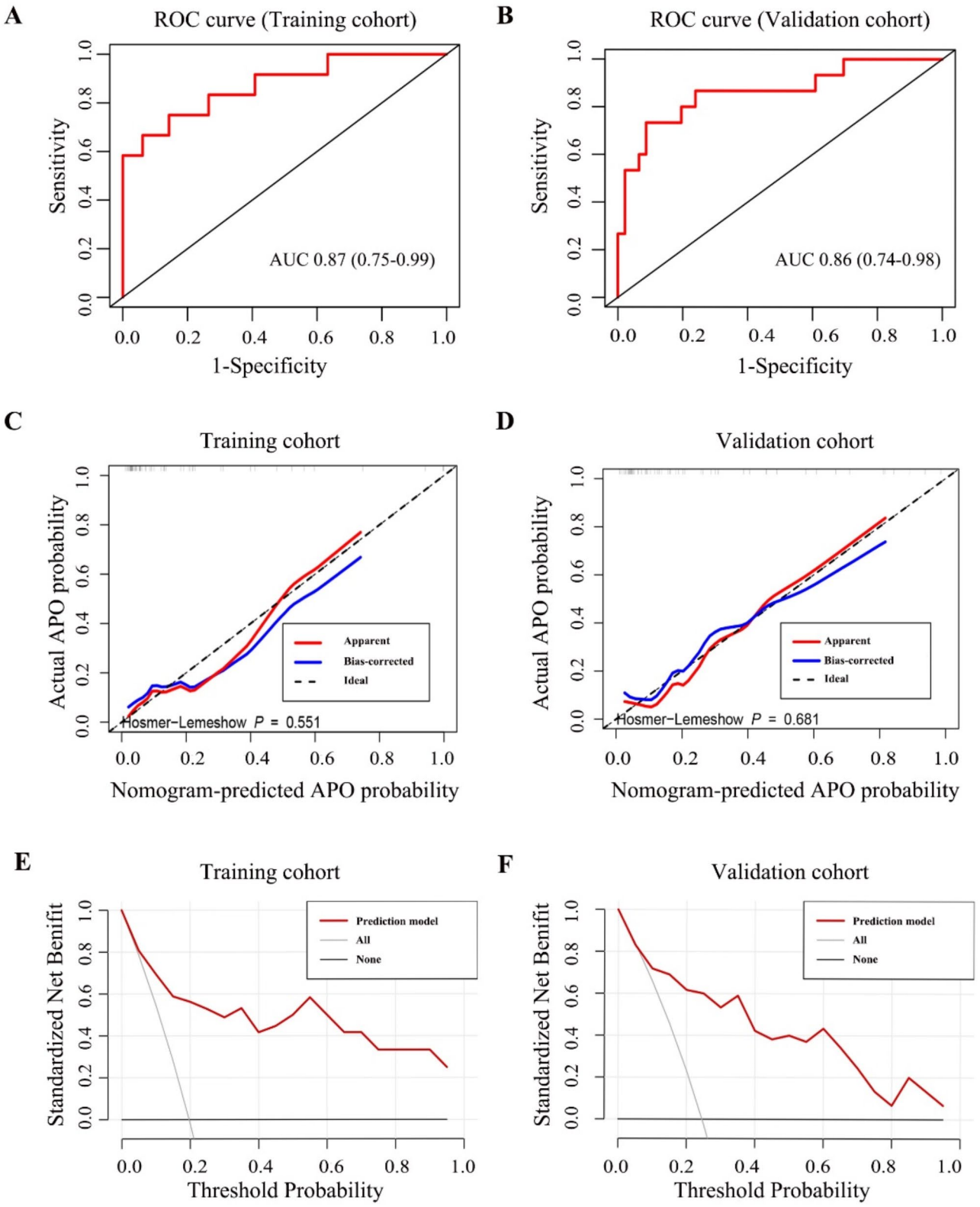

Fig. 3 (See legend on next page.)

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Fig. 3 Nomogram performance. **A-B**: Receiver operating characteristic (ROC) curves of prediction model for adverse perinatal outcome (APO) in FGR patients. **C-D**: The calibration plots used to illustrate the association between actual APO rates and predicted APO rates in the training and validation cohort; calibration plots showing the apparent (actual), bias-corrected (adjusted), and ideal (100% agreement) curves with bootstrapping samples. Bootstrapping involved 500 repetitions. Nomogram-predicted probability of APO rates is plotted on the x-axis, and the observed probability of APO rates is plotted on the y-axis. **E-F**: Decision curve analysis of the nomogram for the prognosis prediction of patients with FGR in the training and validation cohort. The abscissa is the threshold probability, and the ordinate is the net benefit rate. The horizontal image indicates net benefit when all patients with FGR are considered have not developing APO and not treated. The oblique image indicates net benefit when all patients with FGR are considered having develop APO and treated

We acknowledge some limitations of this study. First, due to our focus on a specific population of FGR, the relatively narrow inclusion criteria limited our sample size and generalizability of our findings. The sample size means our study was underpowered to demonstrate small or medium effects, which was illustrated by 95% CI, thus larger cohorts or randomized controlled trials are expected in the future. The exclusion of pregnancies with known chromosomal and structural abnormalities means our findings cannot be applied to the whole spectrum of FGR. Another issue that limits the external validity of the data for our study populations is that the pregnancies were Asian and their fetal-weight percentile was calculated using the NICHD-Asian growth standards, and the majority of participants did not have clinical risk factors for FGR. Secondly, some perinatal outcomes had a low incidence, such as seizures and PVL, and only 27 cases were severe FGR (ultrasonographic EFW or AC below the 3rd percentile), so the results should be interpreted with caution. Finally, Doppler measurements were not blinded to clinicians, and indeed, many management decisions will have been influenced by the ultrasound findings, which could increase the potential for bias.

In the future, our findings should be independently and externally validated. Given the incidence of FGR, this would require another multicenter study. The integration of nomogram into mobile apps may be useful for further research that is needed to determine whether the use of these models would have benefit in practice, both on the parental mental health and on the use of health resources. Finally, our primary outcome only provides short-term information, and the long-term neurodevelopmental outcomes of FGR fetuses remain to be studied.

In conclusion, the newly developed nomogram, composed of five factors readily available in daily clinical practice at the time of FGR diagnosis, is feasible and capable of predicting APO in FGR-afflicted neonates. Before incorporation into clinical practice, the performance of the prediction model should be evaluated in lager cohorts and different populations. We expect that other indicators could also improve the predictive value of the model. If findings are reassuring, the nomogram may then be used for personalized counseling, allocation of resources, risk stratification and optimization of management of pregnancies complicated by FGR.

Abbreviations

AC	Abdominal circumference
AEDV	Absent end-diastolic velocity
APO	Adverse perinatal outcome
AUC	Receiver operating characteristic curve
CPR	Cerebroplacental ratio
DCA	Decision curve analysis
DV	Ductus venosus
EFW	Estimated fetal weight
FGR	Fetal growth restriction
IVH	Intraventricular hemorrhage
MCA	Middle cerebral artery
MoM	Multiples of the median
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PI	Pulsatility index
PlGF	Placental growth factor
RDS	Respiratory distress syndrome
REDV	Reversed end-diastolic velocity
PVL	Periventricular leukomalacia
sFlt-1	Soluble fms-like tyrosine kinase-1
UA	Umbilical artery
UCR	Umbilicocerebral ratio
UtA	Uterine artery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07252-5.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

YZ designed the study, performed all the data analysis, and drafted the original manuscript; LX collected the clinical data and samples, and carried out the experiments; PA and JZZ collected the clinical data and samples; JZ provided statistical methodology support; SPL and QJZ supervised the study, and interpreted the results; XTL and YX conceived the study, directed the experiments, interpreted the results, and revised the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the Gynecology and Obstetrics Hospital of Fudan University reviewed and approved all the study procedures (approval number 2022-18). All participants were fully informed of the content and purpose of the study and provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China
[2]Chang Ning Maternity & Infant Health Hospital, Shanghai, China
[3]Shenzhen Maternity & Child Healthcare Hospital, Southern Medical University, Shenzhen, China

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References

1. Lees CC, Stampalija T, Baschat A, da Silva Costa F, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, et al. ISUOG Practice guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56(2):298–312.
2. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, Borghi E, Hayashi C, Estevez D, Cegolon L, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. Lancet Glob Health. 2019;7(7):e849–60.
3. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, Khong TY, Silver RM, Smith GCS, Boyle FM, et al. Stillbirths: recall to action in high-income countries. Lancet. 2016;387(10019):691–702.
4. Miller SL, Huppi PS, Mallard C. The consequences of fetal growth restriction on brain structure and neurodevelopmental outcome. J Physiol. 2016;594:807–23.
5. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med. 2005;353:1802–9.
6. Fetal Growth Restriction. ACOG Practice Bulletin, Number 227. Obstet Gynecol. 2021;137(2):e16–28.
7. Roeckner JT, Pressman K, Odibo L, Duncan JR, Odibo AO. Outcome-based comparison of SMFM and ISUOG definitions of fetal growth restriction. Ultrasound Obstet Gynecol. 2021;57:925–30.
8. Molina LCG, Odibo L, Zientara S, Običan SG, Rodriguez A, Stout M, Odibo AO. Validation of Delphi procedure consensus criteria for defining fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56:61–6.
9. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, Berghella V, Nazareth A, Tahlak M, McIntyre HD, et al. FIGO (international federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet. 2021;152(1Suppl 1):3–57.
10. Abbas Y, Turco MY, Burton GJ, Moffett A. Investigation of human trophoblast invasion in vitro. Hum Reprod Update. 2020;26:501–13.
11. Stepan H, Galindo A, Hund M, Schlembach D, Sillman J, Surbek D, Vatish M. Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction. Ultrasound Obstet Gynecol. 2023;61(2):168–80.
12. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected Preeclampsia. N Engl J Med. 2016;374(1):13–22.
13. Garcia-Manau P, Bonacina E, Martin-Alonso R, Martin L, Palacios A, Sanchez-Camps ML, Lesmes C, Hurtado I, Perez E, Tubau A et al. Angiogenic factors versus fetomaternal doppler for fetal growth restriction at term: an open-label, randomized controlled trial. Nat Med Published Online January 7, 2025.
14. Ruiz-Martinez S, Papageorghiou AT, Staines-Urias E, Villar J, Gonzalez De Agüero R, Oros D. Clinical impact of Doppler reference charts on management of small-for-gestational-age fetuses: need for standardization. Ultrasound Obstet Gynecol. 2020;56:166–72.
15. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52:430–41.
16. Parra-Saavedra M, Crovetto F, Triunfo S, Savchev S, Peguero A, Nadal A, Gratacós E, Figueras F. Association of Doppler parameters with placental signs of underperfusion in late-onset small-for-gestational-age pregnancies. Ultrasound Obstet Gynecol. 2014;44:330–7.
17. Gaccioli F, Sovio U, Cook E, Hund M, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using ultrasound and the sFLT1/PlGF ratio in nulliparous women: a prospective cohort study. Lancet Child Adolesc Health. 2018;2:569–81.
18. Ciobanu A, Rouvali A, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates: screening by maternal factors, fetal biometry, and biomarkers at 35–37 weeks' gestation. Am J Obstet Gynecol. 2019;220:486. e1-486 e11.
19. Zheng C, Ji C, Wang B, Zhang J, He Q, Ma J, Yang Z, Pan Q, Sun L, Sun N, et al. Construction of prediction model for fetal growth restriction during first trimester in an Asian population. Ultrasound Obstet Gynecol. 2024;63(3):321–30.
20. Bilardo CM, Chaoui R, Hyett JA, Kagan KO, Karim JN, Papageorghiou AT, Poon LC, Salomon LJ, Syngelaki A, Nicolaides KH. ISUOG Practice guidelines (updated): performance of 11-14-week ultrasound scan. Ultrasound Obstet Gynecol. 2023;61:127–43.
21. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T, Glanc P, Khalil A, Lee W, Napolitano R, et al. ISUOG Practice guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol. 2019;53(6):715–23.
22. Bhide A, Acharya G, Baschat A, Bilardo CM, Brezinka C, Cafici D, Ebbing C, Hernandez-Andrade E, Kalache K, Kingdom J, et al. ISUOG Practice guidelines (updated): use of Doppler velocimetry in obstetrics. Ultrasound Obstet Gynecol. 2021;58(2):331–9.
23. Davies DR, Redfield MM, Scott CG, Minamisawa M, Grogan M, Dispenzieri A, Chareonthaitawee P, Shah AM, Shah SJ, Wehbe RM, et al. A simple score to identify increased risk of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. JAMA Cardiol. 2022;7(10):1036–44.
24. Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. JAMA. 2015;313:409–10.
25. Powel JE, Zantow EW, Bialko MF, Farley LG, Lawlor ML, Mullan SJ, Vricella LK, Tomlinson TM. Predictive index for adverse perinatal outcome in pregnancies complicated by fetal growth restriction. Ultrasound Obstet Gynecol. 2023;61:367–76.
26. Spencer R, Maksym K, Hecher K, Maršál K, Figueras F, Ambler G, Whitwell H, Nené NR, Sebire NJ, Hansson SR et al. Maternal PlGF and umbilical Dopplers predict pregnancy outcomes at diagnosis of early-onset fetal growth restriction. J Clin Invest. 2023, 133(18).
27. Kahramanoglu O, Demirci O, Eric Ozdemir M, Rapisarda AMC, Akalin M, Sahap Odacilar A, Ismailov H, Dizdarogullari GE, Ocal A. Cerebroplacental doppler ratio and perinatal outcome in late-onset foetal growth restriction. J Obstet Gynaecol. 2022;42:894–9.
28. Villalain C, Galindo A, Di Mascio D, Buca D, Morales-Rosello J, Loscalzo G, Giulia Sileo F, Finarelli A, Bertucci E, Facchinetti F, et al. Diagnostic performance of cerebroplacental and umbilicocerebral ratio in appropriate for gestational age and late growth restricted fetuses attempting vaginal delivery: a multicenter, retrospective study. J Matern Fetal Neonatal Med. 2022;35:6853–9.
29. Kamphof HD, van Roekel M, Henrichs J, de Vreede H, Verhoeven CJ, Franx A, de Jonge A, Ganzevoort W, Gordijn SJ. Predictive value of fetal growth trajectory from 20 weeks of gestation onwards for severe adverse perinatal outcomes in low-risk population: secondary analysis of IRIS study. Ultrasound Obstet Gynecol. 2023;62:796–804.
30. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the pregnancy outcome prediction (POP) study: a prospective cohort study. Lancet. 2015;386:2089–97.
31. Shinohara S, Uchida Y, Kasai M, Sunami R. Association between the high soluble fms-like tyrosine kinase-1 to placental growth factor ratio and adverse outcomes in asymptomatic women with early-onset fetal growth restriction. Hypertens Pregnancy. 2017;36:269–75.

32. Papastefanou I, Wright D, Syngelaki A, Souretis K, Chrysanthopoulou E, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from biophysical and biochemical markers at 11–13 weeks' gestation. Ultrasound Obstet Gynecol. 2021;57:52–61.

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