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Externally validated nomogram for predicting short-term pregnancy outcome of singleton pregnancies with fetal growth restriction (FGR)

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ABSTRACT

Objective This study aimed at developing an available predictive model of singleton pregnancies with fetal growth restriction (FGR) for accurate and individualised prognosis assessment.

Methods The prediction nomogram was developed by using multivariable Cox regression with data for 301 singleton FGR pregnancies at Peking University People's Hospital. External validation was performed in 321 eligible singleton FGR pregnancies at the Affiliated Hospital of Qingdao University.

Results Absent umbilical arterial flow, fetal anomaly, history of abnormal pregnancy, non-cephalic presentation and history of caesarean section were independent prognostic factors for adverse perinatal outcomes in singleton FGR pregnancies in the training set. In the training cohort of the internal validation set, the nomogram estimated pregnancy prognosis of FGR singleton pregnancies based on these five variables, with a concordance index (C-index) of 0.859 (95% CI: 0.81 to 0.90) for predicting termination of pregnancy (TOP), which included intrauterine fetal death and therapeutic lethal induction, with a C-index of 0.92 (95% CI: 0.86 to 0.98) for predicting stillbirth, and a C-index of 0.87 (95% CI: 0.83 to 0.92) for predicting therapeutic lethal induction with indications. Encouragingly, consistent results were observed in the external validation set, with a C-index of 0.776 (95% CI: 0.71 to 0.84) for predicting TOP, which included intrauterine fetal death and therapeutic lethal induction, with a C-index of 0.773 (95% CI: 0.70 to 0.84) for predicting stillbirth, and a C-index of 0.776 (95% CI: 0.70 to 0.85) for predicting therapeutic lethal induction with indications. Furthermore, the calibrations of the nomograms predicting the 28th and 34th TOP-free gestation week strongly corresponded to the actual survival outcome.

Conclusion This prediction model may help clinicians in decision-making for singleton pregnancies with FGR, especially for patients with a single abnormal umbilical arterial flow or fetal anomaly, without induced labour indications for these abnormalities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In clinical context, attempts to prolong early-onset fetal growth restriction (FGR) pregnancies have to be balanced against the risk of intrauterine demise, and one of the main challenges of antenatal care is to identify the at-risk fetuses. So, to develop an available predictive model to predict the prognosis of singleton FGR pregnancies was very important.

WHAT THIS STUDY ADDS

⇒ In this paper, we developed a nomogram to predict short-term adverse perinatal outcomes in singleton FGR pregnancies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This prediction model may help clinicians in decision-making for singleton pregnancies with FGR and provide accurate and individualised prenatal counselling.

INTRODUCTION

Fetal growth restriction (FGR) will be used to describe fetuses with an estimated fetal weight (EFW) that is less than the 10th percentile for gestational age, whereas the term small for gestational age (SGA) will be used exclusively to describe newborns whose birth weight is less than the 10th percentile for gestational age.[1 2] FGR included early FGR (<32 weeks) and late FGR (≥32 weeks) with different parameters.[2] FGR is characterised by the failure of the fetus to achieve its normal growth potential and is associated with perinatal morbidity and mortality.[3–5] FGR infants have been reported to be associated with an increased risk of adverse perinatal outcomes (APOs) and half of stillbirths are due to FGR in utero.[6 7] Gestational age (GA) is considered as the strongest predictor of postnatal development.[8 9] However, in a clinical context, attempts to prolong early-onset FGR pregnancies have to be balanced against the risk of intrauterine demise. One of the main challenges of antenatal care is to identify at-risk fetuses to enable optimum

surveillance, timely delivery and even timely termination of pregnancy. For those with adverse pregnancy outcomes, such as stillbirth or iatrogenic labour induction, termination of pregnancy (TOP) before the third trimester would reduce physical and psychological damage to the pregnant woman. Predictive algorithms for the selection of FGR pregnancies have preliminarily been well developed.[10 11] Nevertheless, the prediction models can only identify FGR patients, without predicting the pregnancy outcomes. So, to develop an available predictive model to predict the prognosis of singleton FGR pregnancies for accurate and individualised prognosis assessment was very important.

The nomogram has been widely used as a predictive method in disease in recent years.[12 13] It meets the requirements for an integrated model, plays a part in the drive towards personalised medicine[13] and is convenient for clinicians to use in prognosis prediction.[14 15]

In the current study, the primary outcome of FGR was TOP, which included intrauterine fetal death and therapeutic lethal induction. We selected the FGR singleton pregnancies as the research objects and developed a nomogram to predict TOP, in singleton pregnancies of FGR in China. An available nomogram for predicting the prognosis of singleton FGR pregnancies in Chinese women was preliminarily developed and externally validated.

MATERIALS AND METHODS

Patients and study design

A retrospective study was conducted on 301 singleton FGR pregnancies at the Peking University People's Hospital (Beijing, China) from January 2010 to September 2021 as the training set. Inclusion criteria included the following: singleton FGR pregnancies; newborns whose EFW and birth weight were both less than the 10th percentile for gestational age; with definite pregnancy outcome. Exclusion criteria were as follows: twin pregnancy, no pregnancy outcome, pregnancies with chromosome abnormalities, intrauterine infection and the missing data of the clinical factors such as age, history of induced abortion, history of caesarean section, history of abnormal pregnancy, amniotic fluid, umbilical artery flow, fetal anomaly, labour presentation, maternal complication, history of allergy, in vitro fertilisation and embryo transfer (IVF-ET), pre-pregnancy body mass index (BMI), umbilical cord abnormal, placenta abnormality, anaemia and albumin level. From January 2010 to September 2021, an external cohort of 321 singleton FGR pregnancies at the Affiliated Hospital of Qingdao University (validation dataset) were collected, using the same inclusion and exclusion criteria. The excluded patients in each group and the data flow chart were detailed in figure 1. The study was censored on 10 September 2021. The primary outcome in this paper was defined as TOP, which included intrauterine fetal death and therapeutic lethal induction with indications.

Statistical analysis

We estimated the sample size based on the principle of 10 outcome events per variable.[16] In this study, 5 predictors were included to establish the nomogram, and at least 50 FGR patients of APO should be enrolled, and 56 FGR patients of APO were included in the training cohort.

Statistical analyses to identify risk factors were performed using R V.4.1.1 (http://www.r-project.org/). Categorical variables were grouped based on clinical findings, and decisions on the groups were made before modelling. Survival curves were depicted using the Kaplan-Meier method and compared using the log-rank test. Cox regression analysis was used for multivariate analyses. Associations are represented by the HR.

A nomogram was formulated based on the results of multivariate analysis and by using the package of rms in R V.4.1.1 (http://www.r-project.org/). A final model selection was performed by a backward step-down selection process with the Akaike information criterion.[17] The discrimination ability of the prediction models was estimated using the concordance index (C-index). C-index was calculated by Cox regression models of 1000 random bootstrap resamples with the same sample size for assessing the discrimination ability of prediction model.[17] The calibration curve was used to evaluate the validity of the nomogram. During the validation of the nomogram, the total points of each patient in the validation cohort were calculated according to the established nomogram, then Cox regression in this cohort was performed using the total points as a factor, and finally, the C-index and calibration curve were derived based on the regression analysis. Calibration plots were examined by graphic charts for monitoring the average and maximal errors between the predicted 28-week and 34-week probability of termination of pregnancy and the actual outcome frequencies by the Kaplan-Meier method. Groups were compared using the χ^2 test or Fisher's exact test. P<0.05 was considered statistically significant.

RESULTS

Clinicopathological characteristics of patients

We selected 16 clinical factors including age, history of induced abortion, history of caesarean section, history of abnormal pregnancy, amniotic fluid, umbilical artery flow, fetal anomaly, labour presentation, maternal complication, history of allergy, IVF-ET, pre-pregnancy BMI, umbilical cord abnormal, placenta abnormality, anaemia and albumin level. Clinical characteristics of patients in the training cohort and the validation cohort were listed in table 1. Patients younger than 35 years old were 80.73% and 78.82% in the training cohort and validation cohort, respectively (p>0.05). The proportions of patients with a history of induced abortion were 23.59% and 47.66% in training and validation cohorts, respectively (p<0.05). The number of patients with a history of caesarean section was 38 (12.62%) and 52 (16.20%) in the two groups (p>0.05). The proportions of patients

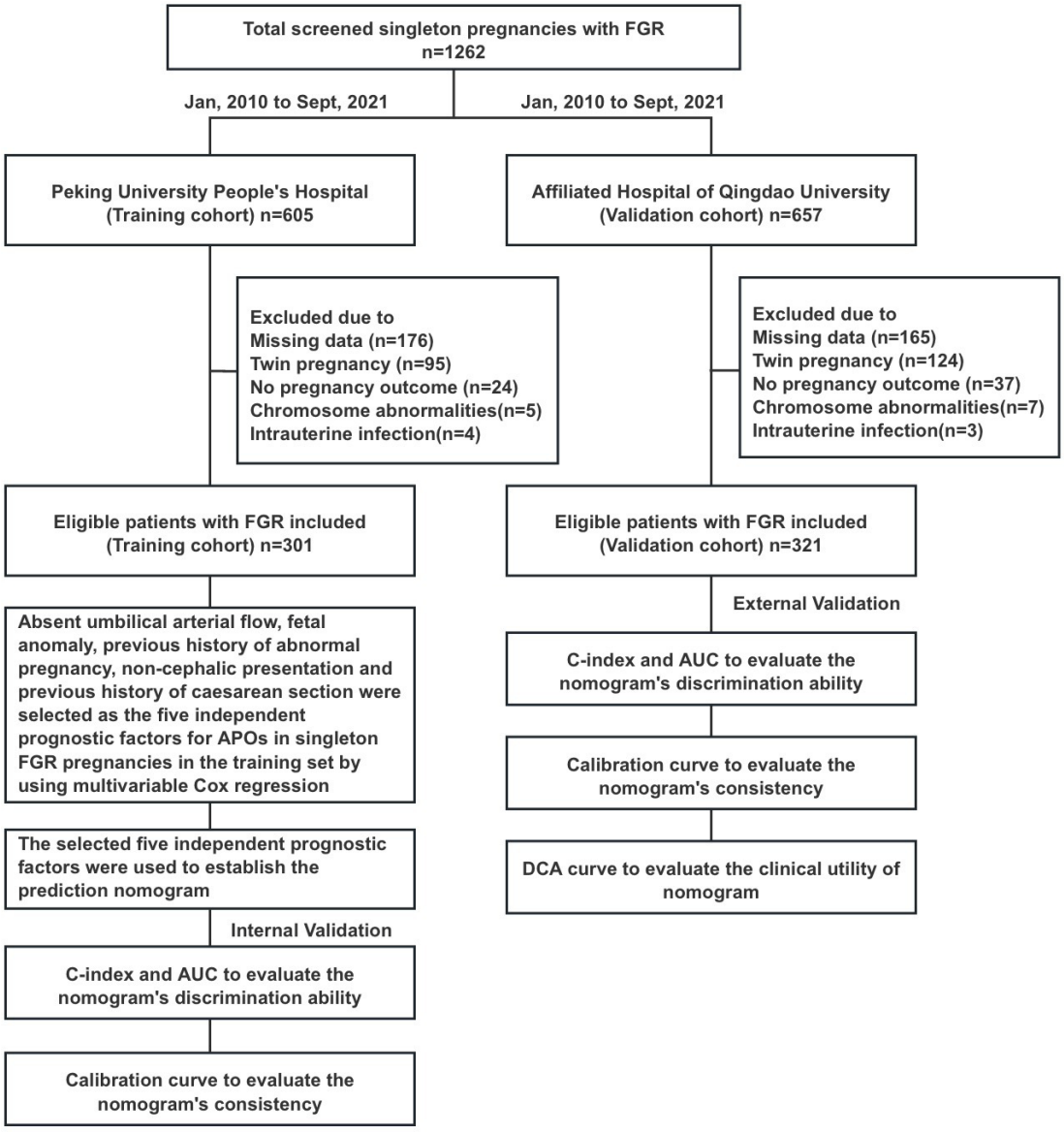

Figure 1 Flow chart of study participants in training and external validation groups. APOs, adverse perinatal outcomes; AUC, area under the receiver operating characteristic curve; DCA, decision-making curve; FGR, fetal growth restriction.

with a history of abnormal pregnancy were 14.95% and 18.38% in the two cohorts (p>0.05). The proportions of patients with abnormal amniotic fluid were 35.88% and 39.25% in the two groups (p>0.05). The proportions of patients with abnormal umbilical artery flow were 45.18% and 24.61% in the training and validation cohorts, respectively (p<0.05). The clinical characteristics of blood type, fetal anomaly and labour presentation showed no significant difference between the training cohort and validation cohort (p<0.05).

Independent prognostic factors in the primary cohort

First, we selected risk factors by using univariate analysis from the previous 16 factors. The univariate analysis of the 16 factors showed that history of abnormal pregnancy, umbilical artery flow, fetal anomaly, labour presentation and history of caesarean section were significantly correlated with pregnancy outcome of singleton FGR pregnancies (table 2, p<0.05, partial results were shown). Multivariate analyses demonstrated that absent umbilical artery blood, fetal anomaly, history of abnormal pregnancy and non-cephalic presentation were independent risk factors for pregnancy outcome of singleton FGR pregnancies (table 2, p<0.05).

Nomogram of prediction model

The prognostic nomogram integrated all significant factors including history of abnormal pregnancy, umbilical artery flow, fetal anomaly, labour presentation and history of caesarean section for pregnancy outcome of singleton FGR pregnancies in the training cohort as shown in figure 2. For a given patient, points were assigned to each of the predictor variables in the nomogram and a total score was derived from the sum of present variables. The total score corresponds to a predicted probability of APOs of singleton FGR pregnancies.

Table 1 Characteristics of patients in the training cohort and validation cohort

Variables	Training cohort N (%)	Validation cohort N (%)	P value
Age (years)			0.553
<35	243 (80.73)	253 (78.82)	
≥35	58 (19.27)	68 (21.18)	
Blood type			0.049
A	79 (26.25)	85 (26.47)	
B	110 (36.54)	104 (32.40)	
AB	32 (10.63)	20 (6.23)	
O	80 (26.58)	112 (34.9)	
History of induced abortion			<0.01
No	230 (76.41)	168 (52.34)	
Yes	71 (23.59)	153 (47.66)	
History of caesarean section			0.205
No	263 (87.38)	269 (83.80)	
Yes	38 (12.62)	52 (16.20)	
History of abnormal pregnancy			0.252
No	256 (85.05)	262 (81.62)	
Yes	45 (14.95)	59 (18.38)	
Amniotic fluid			0.386
Normal	193 (64.12)	195 (60.75)	
Abnormal	108 (35.88)	126 (39.25)	
Umbilical artery flow			<0.001
Normal	165 (54.82)	242 (75.39)	
High	95 (31.56)	60 (18.69)	
AEDF	31 (10.30)	11 (3.43)	
REDF	10 (3.32)	8 (2.49)	
Fetal anomaly			0.084
No	278 (92.36)	307 (95.64)	
Yes	23 (7.64)	14 (4.36)	
Labour presentation			
Cephalic	251 (83.39)	264 (82.24)	
Non-cephalic	50 (16.61)	57 (17.76)	
Complication			0.054
No	42 (13.95)	32 (9.97)	
PE/SPE/HELLP	152 (50.50)	192 (59.81)	
Others	107 (35.55)	97 (30.22)	

AEDF, absent end-diastolic flow of umbilical artery flow; HELLP, HELLP syndrome; PE, pre-eclampsia; REDF, reverse end-diastolic flow of umbilical artery flow; SPE, severe pre-eclampsia.

Internal validation of the prediction models

The performance of the final model was assessed through discrimination and calibration. In the internal validation of training cohort, there was a C-index of 0.859 (95% CI: 0.81 to 0.90) for predicting TOP, which included intrauterine fetal death and therapeutic lethal induction, a C-index of 0.92 (95% CI: 0.86 to 0.98) for predicting stillbirth and a C-index of 0.87 (95% CI: 0.83 to 0.92) for predicting therapeutic lethal induction with indications. The sensitivity was 71.43%, specificity was 87.35%, positive likelihood ratio was 1. 29 and negative likelihood ratio was 0.07. P value of likelihood ratio test was <0.05. The AUCs (area under the receiver operating characteristic curves) for the 28th and 34th TOP-free gestation week (GW) were 0.90 and 0.89 (figure 3A,B), respectively. The calibrations of the nomogram predicting the 28th

and 34th TOP-free GW showed an optimal agreement between the prediction by nomogram and actual observation (figure 4A,B).

External validation of the prediction models

Encouragingly, consistent results were observed in the external validation set, with a C-index of 0.776 (95% CI: 0.71 to 0.84) for predicting TOP, which included intrauterine fetal death and therapeutic lethal induction, with a C-index of 0.773 (95% CI: 0.70 to 0.84) for predicting stillbirth and a C-index of 0.776 (95% CI: 0.70 to 0.85) for predicting therapeutic lethal induction with indications. The cut-off points for the nomogram was 88 points which was defined as the median points. The sensitivity was 72.10% (95% CI: 0.65% to 0.81%), specificity was 70.00% (95% CI: 0.64% to 0.79%), positive likelihood ratio was 0.63 and negative likelihood ratio was 0.06. P value of likelihood ratio test was <0.05. The AUCs for predicting the 28th and 34th TOP-free GW were 0.76 and 0.77 (figure 3C,D), respectively. Encouragingly, the calibration plot for the prediction of the 28th and 34th

Table 2 Univariate and multivariate analyses of predictors of pregnancy outcome in the training cohort

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age (years)				
<35	1			
≥35	1.044 (0.54 to 2.02)	0.899		
ABO				
A	1			
B	0.75 (0.38 to 1.49)	0.411		
AB	1.34 (0.57 to 3.12)	0.504		
O	0.90 (0.45 to 1.84)	0.791		
History of induced abortion				
No	1			
Yes	1.62 (0.92 to 2.83)	0.093		
History of caesarean section				
No	1		1	
Yes	1.94 (1.75 to 5.49)	**0.049**	1.70 (0.85 to 3.40)	0.137
History of abnormal pregnancy				
No	1		1	
Yes	3.10 (1.81 to 6.78)	**<0.001**	2.76 (1.51 to 5.05)	**0.001**
Amniotic fluid				
Normal	1			
Abnormal	1.06 (0.62 to 1.83)	0.742		
Umbilical artery flow				
Normal	1		1	
High	1.78 (0.83 to 3.80)	0.138	1.79 (0.83 to 3.86)	0.135
AEDF	17.64 (8.82 to 35.27)	**<0.001**	15.80 (7.80 to 32.00)	**<0.001**
REDF	19.36 (7.64 to 49.03)	**<0.001**	16.05 (6.09 to 42.32)	**<0.001**
Fetal anomaly				
No	1		1	
Yes	4.38 (2.35 to 8.15)	**<0.001**	3.93 (2.03 to 7.60)	**<0.001**
Labour presentation				
Cephalic	1		1	
Non-cephalic	2.60 (1.47 to 4.60)	**<0.001**	2.25 (1.25 to 4.05)	**0.007**
Complication				
No	1			
PE/SPE/HELLP	2.15 (0.89 to 5.21)	0.091		
Others	1.03 (0.42 to 2.54)	0.948		

To highlight statistically significant indicators more prominently, we have bolded those with P values less than 0.05.
AEDF, absent end-diastolic flow of umbilical artery flow; HELLP, HELLP syndrome; PE, pre-eclampsia; REDF, reverse end-diastolic flow of umbilical artery flow; SPE, severe pre-eclampsia.

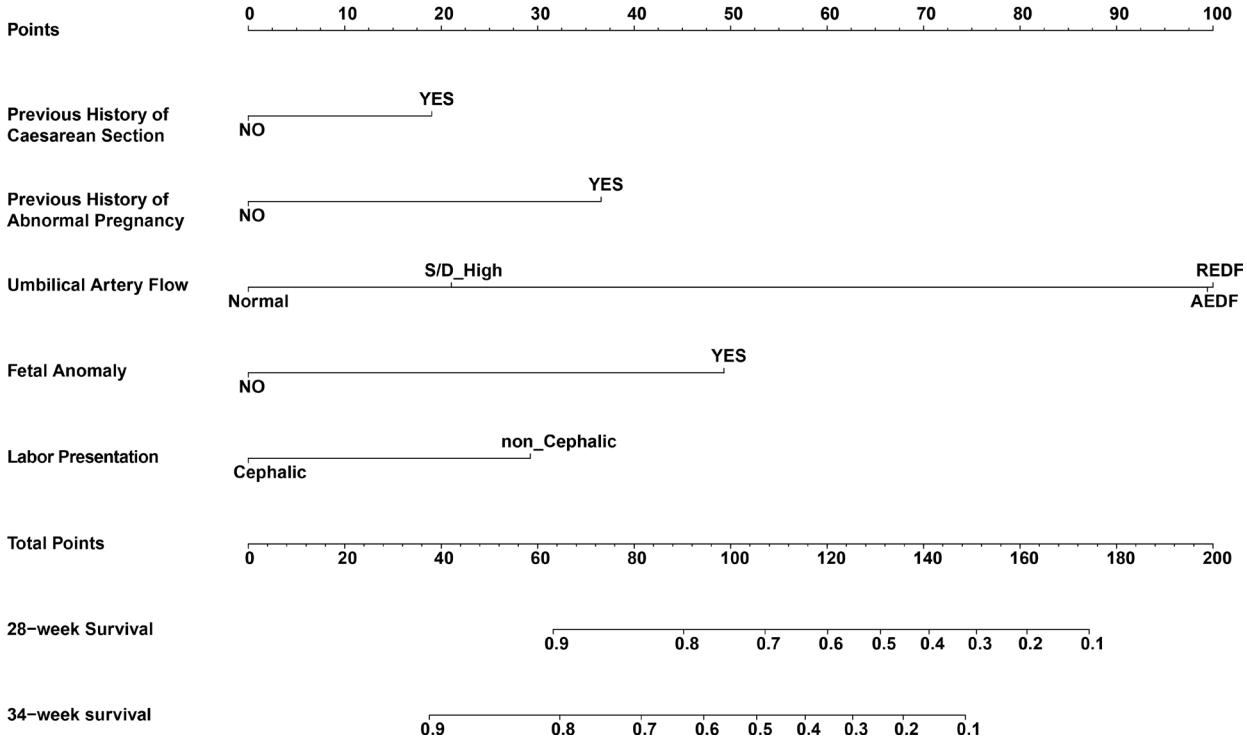

Figure 2 Nomograms for predicting 28th week and 34th TOP-free gestation week (GW) in singleton pregnancies with FGR. In order to evaluate the TOP-free gestation rate of each singleton FGR patient, the score of each variable was calculated by the value of the 'points' axis, and the sum of the values of all variables was corresponding to the number of the 'total points' axis. The vertical line of the total score was corresponding to 28th TOP-free GW and 34th TOP-free GW. AEDF, absent end-diastolic flow of umbilical artery flow; FGR, fetal growth restriction; REDF, reverse end-diastolic flow of umbilical artery flow; TOP, termination of pregnancy.

TOP-free GW also showed an optimal agreement between the prediction by nomogram and actual observation (figure 4C,D). P values of DeLong test of 28th and 34th TOP-free GW between curves for the training and validation sets were 0.043 and 0.035, respectively.

Risk score model indicated strong association with clinical characteristics in singleton FGR pregnancies

We further analysed the distribution of patients in the low-risk and high-risk groups estimated by the nomogram scores. A median cut-off value (88 points) was applied to stratify singleton FGR pregnancies into a high-risk group (n=43, score ≤87 points) and a low-risk group (n=258, score ≥89 points). The clinical factors of training and validation cohorts between high-risk and low-risk groups were presented in the heatmap (figure 5A and D). The results showed that there were significant differences between the high-risk and low-risk groups in terms of history of abnormal pregnancy, umbilical artery flow and fetal anomaly ($p<0.05$). The prognostic status of training and validation cohorts was shown in figure 5B and E. Obviously, it was observed that most APOs of singleton FGR pregnancies were distributed in the high-risk part. Both in training and validation cohorts, prognostic analysis in the form of Kaplan-Meier curve showed that the high-risk group had a significant shorter GA than the low-risk group (figure 5C and F, $p<0.05$).

The clinical decision-making curve (figure 6) shows that within a threshold probability from 3% to 49%, patients could benefit from the application of this predictive model.

DISCUSSION

FGR infants, those with an EFW that is less than the 10th percentile for GA,[18] have been reported to be associated with increased risk of short-term and long-term APOs.[19] Predictive algorithms for the selection of FGR pregnancies have preliminarily been well developed.[10 11] Nevertheless, these prediction models can only identify FGR pregnancies, without predicting the pregnancy outcomes of these FGR patients. Prediction of FGR patients' outcome is an important step of a multidimensional approach, which includes adequate management, termination in time or long-term follow-up of these newborns. Apart from only monitoring FGR patients regularly during pregnancy, early prediction of FGR prognosis was a key to clinic decisions. In the present study, we developed a nomogram to predict APOs in singleton FGR pregnancies.

The independent risk factors of singleton FGR pregnancies' APOs selected by univariate analysis in the present study were somewhat different from those in the previous studies. Umbilical arterial flow, fetal anomaly, history of abnormal pregnancy, labour presentation and

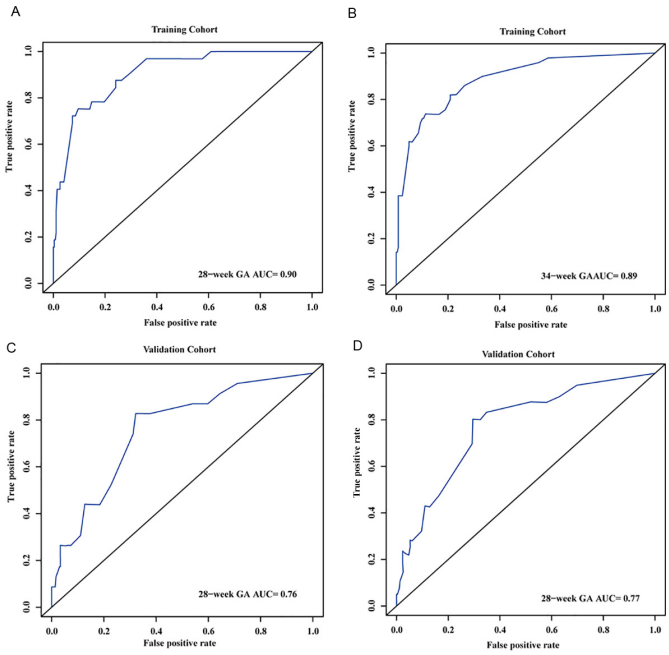

Figure 3 Area under the receiver operating characteristic curve (AUC) values of the nomogram. (A) AUC of nomogram in the training group for predicting 28th TOP-free gestation week (GW) in singleton FGR pregnancies. (B) AUC of nomogram in the training group for predicting 34th TOP-free GW in singleton FGR pregnancies. (C) AUC of nomogram in the validation group for predicting 28th TOP-free GW in singleton FGR pregnancies. (D) AUC of nomogram in the validation group for predicting 34th TOP-free GW in singleton FGR pregnancies. FGR, fetal growth restriction; GA, gestational age; TOP, termination of pregnancy.

history of caesarean section were significantly related to the short-term pregnancy outcome of singleton FGR pregnancies in the training group in this study. One or more of these indicators have been included in previous

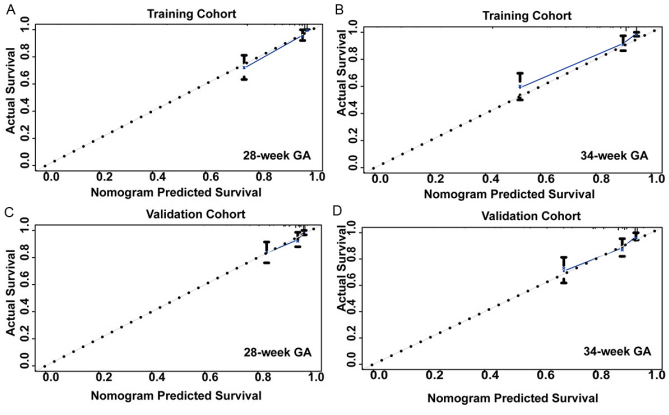

Figure 4 The calibration curve for predicting pregnancy outcome of singleton FGR pregnancies. (A) 28th TOP-free gestation week (GW) in the training cohort. (B) 34th TOP-free GW in the training cohort. (C) 28th TOP-free GW in the validation cohort. (D) 34th TOP-free GW in the validation cohort. Nomogram-predicted probability of overall survival is plotted on the x-axis; actual overall survival is plotted on the y-axis. FGR, fetal growth restriction; GA, gestational age; TOP, termination of pregnancy.

studies[20]; however, the combination of these five indicators included in a predictive model was the first time in this study. Absent end-diastolic flow of umbilical artery flow or reverse end-diastolic flow of umbilical artery flow (REDF) was recognised as a sign of severely impaired placental perfusion and was an indicator of adverse outcome.[21 22] Nevertheless, a previous study showed that in early-onset FGR, up to 30–32 weeks' gestation, umbilical artery Doppler was usually not part of management protocols.[23] In this paper, the results showed that REDF was an important independent factor associated with the prognosis of singleton FGR pregnancies (table 2). The clinical decision-making curve (figure 6) shows that within a threshold probability from 3% to 49%, patients could benefit from the application of this predictive model.

The Growth Restriction Intervention Study showed better neurological outcome when timely decisions are made in early FGR in a randomised trial based on a combination of computerised cardiotocography and ductus venosus (DV) Doppler assessment.[24] DV was an important factor in predicting the outcome of fetuses. We could not include DV in establishing the model owing to the missing data. In future studies, adding DV in the model may further improve the prediction accuracy of the model.

Doppler abnormalities can predict the occurrence of complications in the short term, but normal fetal Doppler values at the time of diagnosis do not exclude their occurrence in the long term.[25 26] Especially in the case of late-onset SGA (>32 weeks' gestation), umbilical artery Doppler is commonly normal.[27] For these reasons, counselling of parents with an affected fetus at that time might not be very accurate and this uncertainty may arouse anxiety and distress in parents.[28] Other parameters that aid the detection of cases at higher risk of APOs were of great importance.

FGR fetuses have been reported to be complicated with structural abnormalities or in the middle trimester, abnormal soft indicators of ultrasound, such as intestinal echo enhancement, may occur at a high rate of 37%, but the study did not rule out genetic abnormalities.[29] In the absence of chromosomal karyotype abnormalities, the incidence of ultrasound abnormalities in FGR was about 25%; femur shortening, omphalocele and abdominal wall fissure were the most common.[30 31] Fetal chromosomal abnormalities account for 15~20% of the causes of FGR, and triploid and aneuploid are the most common.[31] Therefore, when FGR fetuses are associated with structural abnormalities or abnormal ultrasonic genetic markers, interventional prenatal diagnosis, chromosomal microarray and karyotype analysis are recommended. In this paper, we included only singleton FGR pregnancies with non-chromosomal abnormalities and found fetal structural abnormalities were related to the APOs of singleton FGR patients, most of those did not have an indication of induced labour in terms of the structural abnormalities themselves. Therefore, for those

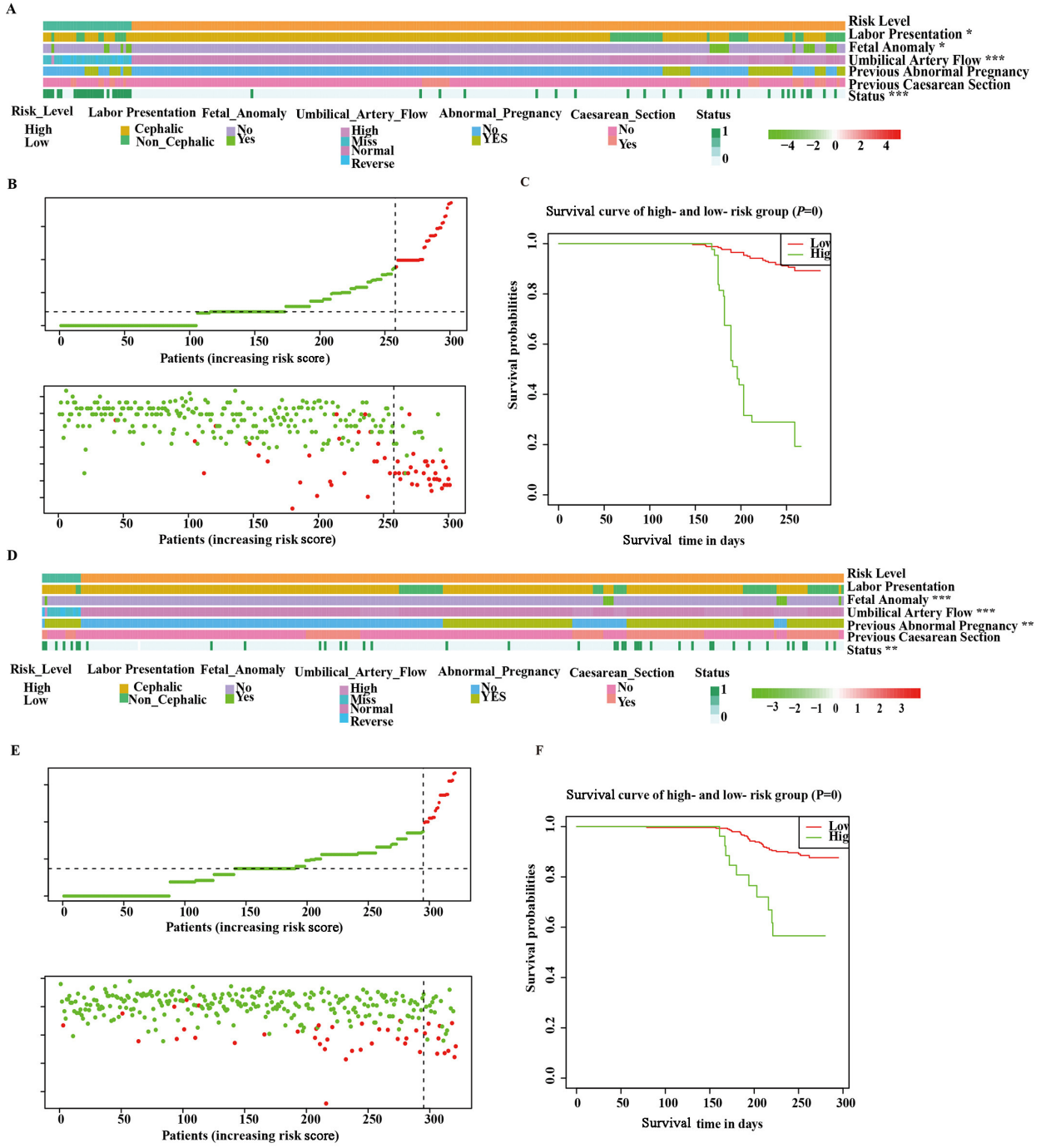

Figure 5 Differential clinical factors and predictive accuracy of singleton FGR pregnancies in high-risk and low-risk groups. (A) Heatmap and clinical features of high-risk and low-risk groups in the training group. The samples are ordered by risk score, and the score decreases from left to right. *P<0.05, **p<0.01 and ***p<0.001. (B) Risk score distribution in low-risk and high-risk groups in the training group. (C) Kaplan-Meier survival analysis of the low-risk and high-risk group in the training group. (D) Heatmap and clinical features of high-risk and low-risk groups in the validation group. The samples are ordered by risk score, and the score decreases from left to right. *P<0.05, **p<0.01 and ***p<0.001. (E) Risk score distribution in low-risk and high-risk groups in the validation group. (F) Kaplan-Meier survival analysis of the low-risk and high-risk group in the validation group. FGR, fetal growth restriction.

non-chromosomal abnormal singleton FGR pregnancies that had structural abnormalities without indications for induced labour, other indicators need to be considered to determine the final indication of induced labour.

History of abnormal pregnancy like stillbirth increased the risk of other abnormal pregnancy outcomes in the subsequent pregnancy such as FGR placental abruption, caesarean delivery and preterm delivery.[32] In the present study, we found that history of abnormal pregnancy was related to APOs of singleton FGR pregnancies. Abnormal labour presentation was related to the causes of stillbirth during labour.[33] In this paper, we first found that breech/

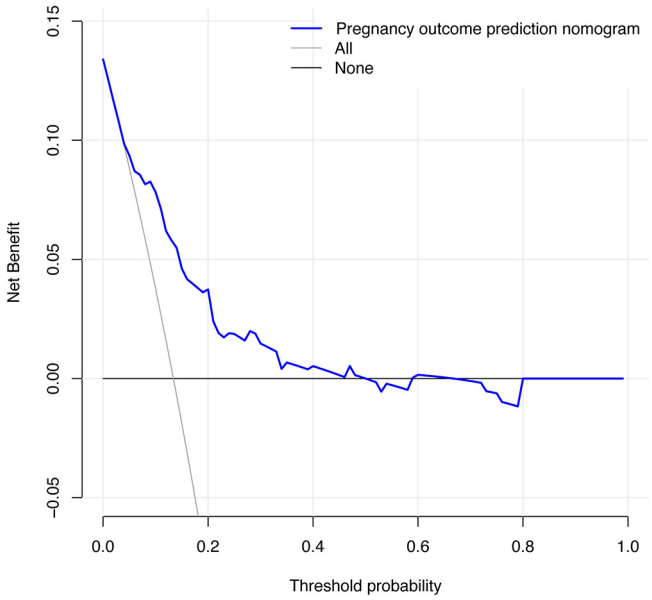

Figure 6 The clinical decision-making curve of the predictive model for singleton fetal growth restriction pregnancy outcome.

transverse position was an independent pregnancy prognostic factor of singleton FGR pregnancies, revealing that abnormal labour presentation may be a sign of APOs of singleton FGR pregnancies, though it may not be a cause of the APOs. The result of our paper showed that the history of caesarean section may be related to APOs of FGR patients. So, for those singleton FGR pregnancies with a history of abnormal pregnancy, abnormal labour presentation or history of caesarean section, pregnancy monitoring and strict management should be further strengthened.

A median cut-off value (88 points) was applied to stratify single pregnant women into a high-risk group and a low-risk group. Though the results showed that there were significant differences between the high-risk and low-risk groups in terms of clinical factors such as umbilical artery flow, fetal anomaly and history of abnormal pregnancy, individual differences in singleton FGR pregnancies after redistribution were found in the high-risk group and low-risk group. So, the results further demonstrated that individual clinical factor was difficult to accurately determine FGR patient outcome; an algorithm based on several related clinical factors may be more useful to predict the prognosis of singleton FGR pregnancies. It was found in this study that within a threshold probability from 3% to 49%, singleton FGR patients could benefit from the application of this predictive model.

For the clinical implications of this work, first, as for the fetus at high risk of TOP predicted by the prediction model, pregnancy should be closely monitored and treated more aggressively. Second, the prediction model for death in this paper mainly could predict the short outcome of fetuses and clinical trials should be further taken to demonstrate whether this predictive model could improve the outcome of fetuses with FGR. We hypothesised that after verification of the present findings in prospective studies, proactive perinatal clinical protocols, taking into account this predictive model when deciding on the time of termination of FGR patients, might reduce physical and psychological harm to FGR pregnant women.

There were some limitations in the current research. First, FGR patients were not divided into early-onset FGR and late-onset FGR in the cohorts due to the limited number of cases. Second, twin pregnant women were not included in this study. Third, there were short-term and long-term APOs of FGR patients, but we only predicted the short-term pregnancy outcome of the FGR patients, so long-term APOs could be further predicted in future research and clinical trials should be taken to demonstrate whether this predictive model could improve the outcome of fetuses with FGR. Fourth, owing to the limited sample size, APO in this paper was defined as TOP, which included intrauterine fetal death and therapeutic lethal induction with definite indications given by prenatal diagnostician. It may lead to bias and it makes more sense to predict intrauterine fetal death in the future study. Fifth, samples of the training and validation sets came from completely two different hospitals, which may lead to some bias. In the future study, further enlarging the sample size may help reduce the bias. In addition, the research was a retrospective study, and prospective validation was needed to verify the promotion and application of the model. Finally, there is a risk of heterogeneity of the study variables and population; further optimisation of this model in a national multicentre study is needed.

Conclusion

Our data indicated that the predictive model can accurately assess the short-term pregnancy outcome of singleton FGR patients, as determined by internal and external validation. The identification of singleton FGR patients who have a high risk of TOP might allow timely treatment and improve the fetus live birth rate.

Contributors FY designed and wrote the manuscript. MJ, YuL and YaL collected the clinical data. XY and JX edited the manuscript. XZ developed the study and checked the manuscript. XZ act as the guarantor.

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Competing interests XZ has served as an editorial member of *GOCM*. All other authors declare no competing interest.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of Peking University People's Hospital (ethics number: 2023PHB291-001). As this was a clinical retrospective study, we have applied for approval regarding this study's exemption from informed consent.

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