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ORIGINAL RESEARCH

Predicting the Risk of Adverse Events in Pregnant Women With Congenital Heart Disease

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BACKGROUND: Women with congenital heart disease are considered at high risk for adverse events. Therefore, we aim to establish 2 prediction models for mothers and their offspring, which can predict the risk of adverse events occurred in pregnant women with congenital heart disease.

METHODS AND RESULTS: A total of 318 pregnant women with congenital heart disease were included; 213 women were divided into the development cohort, and 105 women were divided into the validation cohort. Least absolute shrinkage and selection operator was used for predictor selection. After validation, multivariate logistic regression analysis was used to develop the model. Machine learning algorithms (support vector machine, random forest, AdaBoost, decision tree, k-nearest neighbor, naïve Bayes, and multilayer perceptron) were used to further verify the predictive ability of the model. Forty-one (12.9%) women experienced adverse maternal events, and 93 (29.2%) neonates experienced adverse neonatal events. Seven high-risk factors were discovered in the maternal model, including New York Heart Association class, Eisenmenger syndrome, pulmonary hypertension, left ventricular ejection fraction, sinus tachycardia, arterial blood oxygen saturation, and pregnancy duration. The machine learning–based algorithms showed that the maternal model had an accuracy of 0.76 to 0.86 (area under the receiver operating characteristic curve=0.74–0.87) in the development cohort, and 0.72 to 0.86 (area under the receiver operating characteristic curve=0.68–0.80) in the validation cohort. Three high-risk factors were discovered in the neonatal model, including Eisenmenger syndrome, preeclampsia, and arterial blood oxygen saturation. The machine learning–based algorithms showed that the neonatal model had an accuracy of 0.75 to 0.80 (area under the receiver operating characteristic curve=0.71–0.77) in the development cohort, and 0.72 to 0.79 (area under the receiver operating characteristic curve=0.69–0.76) in the validation cohort.

CONCLUSIONS: Two prenatal risk assessment models for both adverse maternal and neonatal events were established, which might assist clinicians in tailoring precise management and therapy in pregnant women with congenital heart disease.

Key Words: congenital heart disease ■ machine learning ■ prediction model ■ pregnancy

With the progress of medical care for patients with congenital heart disease (CHD), their life expectancy has increased significantly over the past decades, and more women with CHD survive into their childbearing years.[1] Between 1998 and 2007, the number of deliveries of pregnant women

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CLINICAL PERSPECTIVE

What Is New?

- This cohort study of 318 pregnant women with congenital heart disease who gave birth after 28 gestational weeks found that 12.9% women experienced adverse maternal events, and 29.2% neonates experienced adverse neonatal events.
- The models constructed by our study for both adverse maternal and neonatal events had obtained a good prediction accuracy in the development and validation cohorts.

What Are the Clinical Implications?

- We established the first prenatal risk assessment model for pregnant women with congenital heart disease during the last trimester of pregnancy.
- More importantly, the models in our study are particularly suitable for clinical use in developing countries where prepregnancy counseling and pregnancy monitoring systems are deficient.
- These models may also be used in the design of optimal treatment strategies for pregnant women with congenital heart disease.

Nonstandard Abbreviations and Acronyms

AUC	area under the receiver operating characteristic curve
CHD	congenital heart disease
ES	Eisenmenger syndrome
LASSO	least absolute shrinkage and selection operator
ML	machine learning
NYHA	New York Heart Association
PAH	pulmonary arterial hypertension
SaO_2	arterial blood oxygen saturation

with CHD increased by 34.9% compared with 21.3% in the general population in the United States.[2] For patients with a significant residua or those who are surgically uncorrected, pregnancy is often considered to be contraindicated.[3] In these cases, pregnancy is accompanied by an increase in maternal morbidity and mortality. According to the different kinds of underlying defect and previous treatment strategies, pregnancy is a physiological stress, and complications during pregnancy such as gestational diabetes mellitus or pregnancy-induced hypertension place those women at a higher risk for adverse events in the third trimester.[4,5]

Despite earlier interventional or operative therapy, pulmonary arterial hypertension (PAH) is common and predisposes women with CHD to more symptoms and further clinical deterioration.[6] Women with CHD have an increased risk of poor pregnancy outcomes, so clinical counseling and multidisciplinary specialist care should be provided before conception.[7] Meanwhile, preexisting heart disease should be highlighted before conception counseling, and necessarily, information on the potential risk of adverse obstetric and fetal outcomes should be provided to pregnant women with CHD.[8]

In developing countries, the long-term health follow-up monitoring system for patients with CHD is not perfect. For pregnant women with CHD who lack prepregnancy assessment and health monitoring during pregnancy, medical management in the perinatal period is a huge challenge for healthcare professionals. For attending cardiologists and obstetricians, adequate risk assessment is critical in optimizing pregnancy management, especially for pregnant women who are about to give birth shortly after diagnosis.

Therefore, the aim of the present study is to develop prognostic models to optimize the prenatal management of pregnant women with CHD and to obtain better prognostic outcomes for mothers and infants.

METHODS

Researchers may contact the corresponding authors for the data within the article for future analysis.

Study Population

Patients with CHD who gave birth after 28 gestational weeks in Qilu Hospital of Shandong University from January 2004 to June 2019 were recruited. The model development cohort included 213 pregnant women with CHD, and data were collected from January 2004 to May 2016; an independent validation cohort included 105 patients with CHD, and data were collected from June 2016 to June 2019. A summary of the research procedure is shown in Figure 1. All patients had echocardiography results and were diagnosed with CHD by cardiologists. This study was guided by the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement (Table S1).[9]

Data Collection

Therapeutic records were used to collect patients' information. From the original list of risk factors, the following candidate predictors were selected: maternal age, parity, New York Heart Association (NYHA) functional status, type of maternal congenital heart lesion,

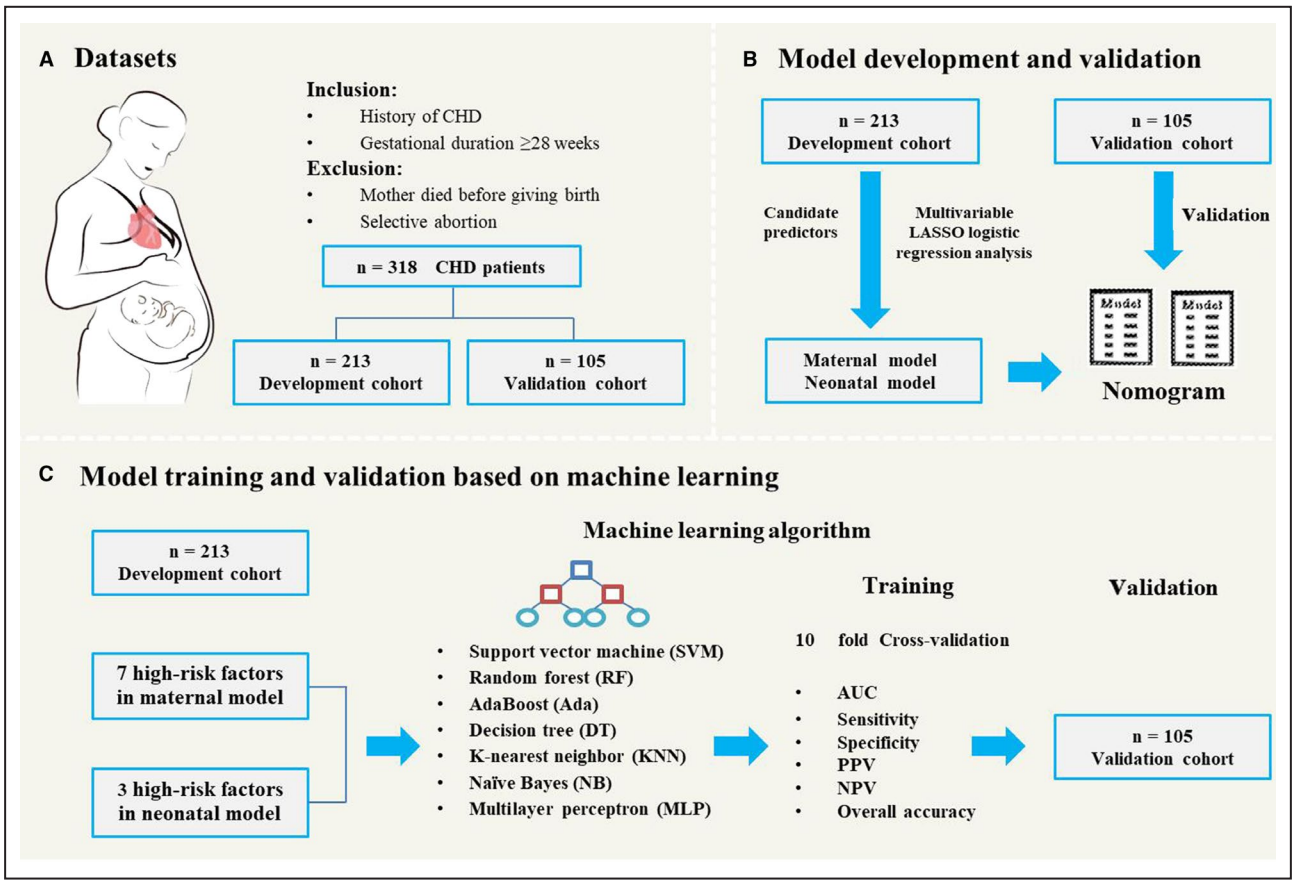

Figure 1. Flowchart of the study.
(**A**) datasets; (**B**) model development and validation; (**C**) model training and validation based on machine learning. AUC indicates area under the receiver operating characteristic curve; CHD, congenital heart disease; LASSO, least absolute shrinkage and selection operator; NPV, negative predictive value; and PPV, positive predictive value.

Eisenmenger syndrome (ES), history of cardiac surgery before pregnancy, preeclampsia, gestational diabetes mellitus, mode of delivery, pulmonary infection, hemoptysis, left ventricular ejection fraction, ascending aorta diameter, mitral regurgitation, PAH, sinus tachycardia, ectopic cardiac rhythm, arterial blood oxygen saturation (SaO_2), hemoglobin, platelet, total serum protein, and pregnancy duration.

Definitions and Outcomes

Adverse maternal and neonatal events for each case were defined as the outcomes. Maternal and neonatal outcomes were composites of major adverse events. Maternal outcomes included cardiac death, heart failure, arrhythmia requiring treatment, and peripartum cardiomyopathy. Neonatal outcomes included preterm labor (<37 gestational weeks), small-for-gestational-age birth weight (<10th percentile), low birth weight (<2500 g), intrauterine fetal death, and neonatal death. The cause of death of each patient was also collected in detail. Patients and children were following up for 6 weeks after delivery.

Ethics Statement

This retrospective study was approved by the Ethical Committee of Qilu Hospital of Shandong University (protocol number 2018 064) and obtained a waiver for informed consent.The names of the patients and their hospital admission numbers were anonymized before the analysis.

Statistical Analysis

Univariable logistic regression analysis was used for preliminary screening of clinical features, variables with a $P<0.10$ were selected. In addition, to find the optimal predictor selection algorithm, we compared the performances of several predictor selection methods, including least absolute shrinkage and selection operator (LASSO), maximum relevance minimum redundancy, and random forest. A comparison of these methods was also performed, and LASSO performs best in predictor selection. Afterward, multivariate logistic regression analysis was used to develop the risk prediction models for both mothers and offspring. The results are described as odds ratio, 95% CI,

and *P* values. Then we developed 2 nomogram lists to predict the individual incidence of adverse events for each patient. The receiver operating characteristic curves and the area under the receiver operating characteristic curve (AUC) values were used to evaluate the classification of the model in both the development and validation cohorts. If the AUC was closer to 1, the model was seen as having a good efficacy ability of classification. The calibration slope with pointwise 95% confidence limits was used to estimate the calibration ability of the model.[10]

Machine learning (ML) algorithms can perform better than traditional regression methods when the research aims to generate a model that can predict an outcome more accurately.[11] ML offers an alternative approach to standard prognostic modeling, and its potential has been demonstrated in some recent studies.[12–14] Therefore, we further used ML algorithms to model the selected high-risk factors. We selected 7 widely used ML algorithms (support vector machine, RF, AdaBoost, decision tree, k-nearest neighbor, naïve Bayes, and multilayer perceptron) to comprehensively evaluate our hypothesis. Tenfold cross validation was applied as a criterion for each classifier in the development cohort. The patients in the development cohort were randomly partitioned into 10 equal-sized subsamples, where 9 subsamples were used as the training data, and 1 single subsample was retained as the validation data for testing. The average and standard deviation of the AUCs over the 10 tests performed in the multiple rounds of cross validation, as well as the corresponding sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy, were used to assess the performance of the 2 models. Then we retrained the models in the development cohort using the same hyperparameters as those in cross-validation and evaluated their predictive ability in the independent validation cohort.

Statistical analysis was conducted with IBM SPSS statistics (version 24.0), R software (version 3.6.1), and Python (version 3.6.4) ML library scikit-learn (version 0.19.1).

RESULTS

The clinical characteristics of all patients in the development and validation cohorts are summarized in Table 1. The median age at the time of pregnancy was 27 years (range, 16–45 years). Vaginal delivery was observed in 32 (10.1%) patients, and cesarean section was observed in 286 (89.9%) patients. Two hundred sixty-five (83.3%) patients delivered after 36 gestational weeks. Forty-one (12.9%) women experienced adverse maternal events, and 93 (29.2%) neonates experienced adverse neonatal events. The details of the adverse maternal cardiac and neonatal events encountered during the perinatal period are presented in Table S2. Maternal mortality occurred in 13 patients, 2 of whom terminated the pregnancy attributable to intrauterine death and death caused by irreversible heart failure after cesarean section. One patient abandoned treatment because of family financial burden and cardiac arrest on the way home (Table S3).

Model Development and Validation

Risk factors related to adverse events are shown in Table S4. The results of predictor selection were summarized in Table S5. In the development cohort of both mother and offspring, the *P* values of LASSO, maximum relevance minimum redundancy, and random forest were all <0.0001. Using the AUC value as an evaluation, the LASSO method showed the best performances. In the validation cohort of both mother and offspring, the *P* value for LASSO method was the lowest, while its AUC was the highest. Therefore, the LASSO method was chosen as the optimal method in our study.

After predictor selection by LASSO analysis (Figure S1), the following 7 predictors were included in the maternal events model, including NYHA class, ES, PAH, left ventricular ejection fraction, sinus tachycardia, SaO_2, and pregnancy duration. In addition, 3 high-risk factors showed a correlation with adverse neonatal events, including ES, preeclampsia, and SaO_2. Two nomogram lists were built according to the regression coefficients of the models (Figure 2A and 2B). The maternal events model yielded an AUC of 0.92 (95% CI, 0.86–0.97) in the development cohort and 0.80 (95% CI, 0.64–0.97) in the validation cohort. The AUC of the neonatal events model was 0.77 (95% CI, 0.70–0.84) in the development cohort and 0.76 (95% CI, 0.66–0.87) in the validation cohort (Figure 2C and 2D). The risk score for each patient and risk calculation equations of the prediction models are shown in Figure S2, and the calibration curves are illustrated in Figure S3.

Model Training and Validation Based on ML

The results of 10-fold cross validation in the development and validation cohort are shown in Table 2. Seven ML algorithms showed that the adverse maternal model had an accuracy of 0.76 to 0.86 (AUC=0.74–0.87) in the development cohort, and 0.72 to 0.86 (AUC=0.68–0.80) in the validation cohort. In addition, 7 ML-based algorithms showed that the adverse neonatal model had an accuracy of 0.75 to 0.80 (AUC=0.71–0.77) in the development cohort and 0.72 to 0.79 (AUC=0.69–0.76) in the validation

Table 1. Patient's Characteristics (Before Delivery)

Characteristic	Total (n=318)	Development Cohort (n=213)	Validation Cohort (n=105)
Age at delivery, y	27 (16–45)	26 (16–45)	29 (19–41)
Parity			
0	220 (69.2)	160 (75.1)	60 (57.1)
≥1	98 (30.8)	53 (24.9)	45 (42.9)
Cardiac functional status			
NYHA class I–II	248 (78.0)	159 (74.6)	89 (84.8)
NYHA class III–IV	70 (22.0)	54 (25.4)	16 (15.2)
Maternal congenital lesion			
Atrial septal defect	123 (38.7)	76 (35.7)	47 (44.8)
Ventricular septal defect	101 (31.8)	75 (35.2)	26 (24.8)
Persistent ductus arteriosus	28 (8.8)	20 (9.4)	8 (7.6)
Tetralogy of Fallot	23 (7.2)	13 (6.1)	10 (9.5)
Ventricular outflow tract obstruction*	19 (6.0)	9 (4.2)	10 (9.5)
Other†	24 (7.5)	20 (9.4)	4 (3.8)
PAH, mm Hg			
PAH <30	153 (48.1)	97 (45.5)	56 (53.3)
30 ≤PAH <60	87 (27.4)	58 (27.2)	29 (27.6)
60 ≤PAH <90	39 (12.3)	31 (14.6)	8 (7.6)
90 ≤PAH	39 (12.3)	27 (12.7)	12 (11.4)
Eisenmenger syndrome	26 (8.2)	18 (8.5)	8 (7.6)
Cardiac surgery before pregnancy			
Corrected	111 (34.9)	72 (33.8)	39 (37.1)
Uncorrected	207 (65.1)	141 (66.2)	66 (62.9)
Preeclampsia	31 (9.7)	22 (10.3)	9 (8.6)
Gestational diabetes mellitus	13 (4.1)	8 (3.8)	5 (4.8)
Mode of delivery			
Vaginal	32 (10.1)	21 (9.9)	11 (10.5)
Cesarean	286 (89.9)	192 (90.1)	94 (89.5)
Pregnancy duration, wk			
28 ≤GW <32	47 (14.8)	30 (14.1)	17 (16.2)
32 ≤GW <36	6 (1.9)	5 (2.3)	1 (1.0)
36 ≤GW	265 (83.3)	178 (83.6)	87 (82.9)
Adverse maternal cardiac event	41 (12.9)	29 (13.6)	12 (11.4)
Adverse neonatal event	93 (29.2)	63 (29.6)	30 (28.6)

Values are median (range) or n (%). GW indicates gestational weeks; NYHA, New York Heart Association; and PAH, pulmonary hypertension.
*Ventricular outflow tract obstruction including aortic valve stenosis and pulmonary valve stenosis.
†Other including Marfan syndrome, mitral regurgitation, single ventricle, atrioventricular septal defect, congenitally corrected transposition of the great arteries, transposition of the great arteries, and so on.

cohort. The diagnostic performance of the logistic regression analysis and the ML algorithms (AUCs) are shown in Figure 3.

Clinical Use

The decision curve analysis for the maternal and neonatal events models are presented in Figure S4. The maternal model showed a positive net benefit when predicted probability thresholds were between 0.05 and 0.92, and the neonatal model showed a positive net benefit when the predicted probability thresholds were between 0.16 and 0.90.

DISCUSSION

This study established 2 prenatal assessment models to predict adverse events in both mothers and offspring, which are particularly suitable for clinical use in developing countries where prepregnancy counseling and pregnancy monitoring systems are

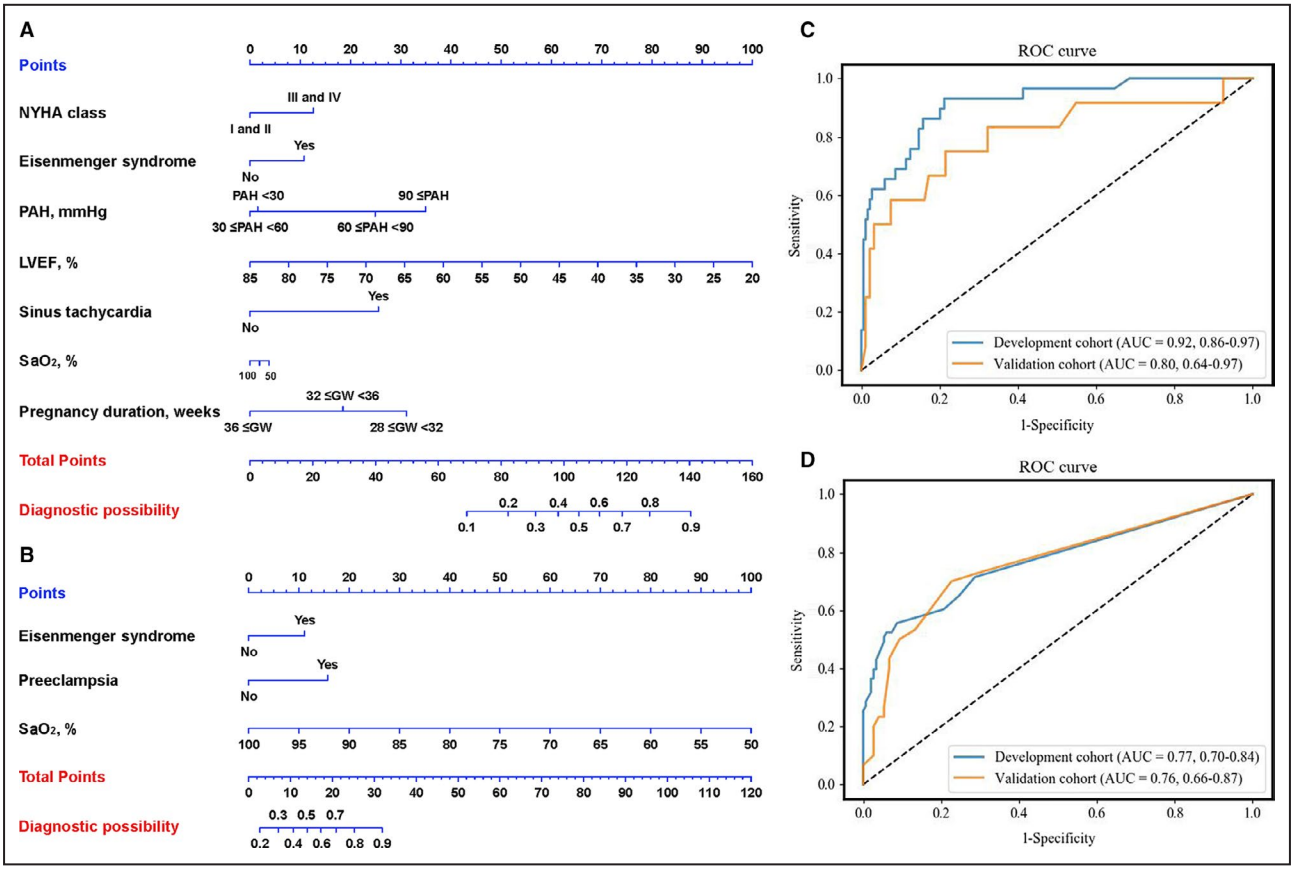

Figure 2. Nomogram lists of the maternal model (A) and neonatal model (B); ROC curves of the maternal model (C) and neonatal model (D).

Example of the maternal model in (**A**): A 37-week pregnant woman with CHD (0 points) who had NYHA class III (12.5 points) without ES (0 points), and had a PAH of 35 mm Hg (2.5 points) and a left ventricular ejection fraction of 40% (70 points) with symptoms of sinus tachycardia (25 points) and an SaO_2 of 98% (1 point) has a total score of 111 points; the corresponding probability of experiencing adverse events in this pregnancy was more than 50%. Example of the neonatal model (**B**): the pregnant woman described above who did not have ES (0 points) but had preeclampsia (15.5 points) with an SaO_2 of 98% (2.5 points) has a total score of 18 points, and the corresponding probability of experiencing adverse neonatal events was more than 60%. AUC indicates area under the receiver operating characteristic curve; CHD, congenital heart disease; ES, Eisenmenger syndrome; GW, gestational week; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAH, pulmonary hypertension; ROC, receiver operating characteristic; and SaO_2, arterial blood oxygen saturation.

deficient. The developed nomogram lists allow the model to be used conveniently in clinical practice. The ML-based algorithms achieved high prediction accuracy, which suggests the effectiveness of these ML algorithms as well as the strong association between high-risk predictors and adverse maternal and neonatal events.

Ideally, women with CHD should seek counseling about pregnancy during the pubertal years. The advice given usually includes the importance of pregnancy planning, effective contraception options, and the impact of pregnancy on maternal heart diseases.[15] However, in developing countries, because of the lack of complete health monitoring systems, many patients do not obtain a prepregnancy evaluation. For example, in our study, 216 (68%) patients visited our hospital for the first time and gave birth there, and 114 (36%) patients were unaware of their clinical history of CHD until the time of delivery. For patients with poor cardiac function and a first visit to a hospital, emergency assessment before delivery is critical for both doctors and patients.

Three popular risk assessment criteria are commonly used, including the Zwangerschap bij Aangeboren HARtAfwijkingen I,[16] Cardiac Disease in Pregnancy,[17] and World Health Organization classification systems.[18] In a prospective study by Balci et al,[19] for assessing the cardiovascular events of 203 women with CHD, the AUC was 0.57 (95% CI, 0.43–0.70) for the Cardiac Disease in Pregnancy risk score and 0.71 (95% CI, 0.59–0.83) for the Zwangerschap bij Aangeboren HARtAfwijkingen I risk score; the World Health Organization classification was the best risk assessment model for maternal cardiovascular events (AUC=0.77; 95% CI, 0.67–0.87); for the prediction of adverse events in offspring, there was no functional

Table 2. Prediction of the 2 Models by LR and ML Analysis

	Threshold	AUC	Sensitivity	Specificity	PPV	NPV	Overall Accuracy
Maternal model in development cohort (n=213)							
LR	0.13±0.09	0.85±0.14	0.80±0.11	0.73±0.29	0.95±0.05	0.42±0.21	0.79±0.08
SVM	0.17±0.05	0.85±0.12	0.84±0.08	0.65±0.27	0.94±0.05	0.40±0.16	0.81±0.08
RF	0.41±0.05	0.81±0.17	0.80±0.11	0.69±0.24	0.95±0.04	0.39±0.15	0.78±0.09
DT	0.58±0.05	0.74±0.10	0.83±0.08	0.58±0.20	0.93±0.03	0.37±0.12	0.79±0.07
KNN	0.33	0.77±0.16	0.86±0.09	0.63±0.31	0.94±0.05	0.41±0.19	0.83±0.08
NB	0.10±0.30	0.87±0.18	0.82±0.09	0.78±0.32	0.96±0.05	0.41±0.18	0.82±0.08
Ada	0.49±0.005	0.79±0.21	0.78±0.09	0.68±0.28	0.94±0.05	0.34±0.12	0.76±0.07
MLP	0.47±0.35	0.76±0.17	0.91±0.09	0.53±0.27	0.92±0.04	0.59±0.34	0.86±0.09
Neonatal model in development cohort (n=213)							
LR	0.35±0.05	0.77±0.12	0.92±0.06	0.51±0.21	0.82±0.07	0.74±0.22	0.79±0.08
SVM	0.31±0.04	0.77±0.12	0.92±0.06	0.51±0.19	0.82±0.07	0.75±0.19	0.80±0.07
RF	0.50±0.05	0.76±0.11	0.92±0.06	0.51±0.19	0.82±0.07	0.75±0.19	0.80±0.07
DT	0.75±0.03	0.71±0.10	0.92±0.06	0.48±0.19	0.81±0.07	0.73±0.22	0.79±0.07
KNN	0.34±0.08	0.75±0.12	0.85±0.11	0.56±0.23	0.83±0.09	0.66±0.23	0.76±0.10
NB	0.08±0.22	0.74±0.08	0.92±0.06	0.51±0.19	0.82±0.07	0.75±0.19	0.80±0.07
Ada	0.50±0.004	0.77±0.12	0.84±0.10	0.59±0.19	0.83±0.08	0.65±0.20	0.77±0.10
MLP	0.33±0.04	0.72±0.17	0.85±0.11	0.51±0.20	0.81±0.08	0.63±0.25	0.75±0.11
Maternal model in validation cohort (n=105)							
LR		0.80 (0.64–0.97)	0.78	0.67	0.95	0.29	0.77
SVM		0.80 (0.64–0.97)	0.87	0.58	0.94	0.37	0.84
RF		0.79 (0.64–0.94)	0.86	0.58	0.94	0.35	0.83
DT		0.68 (0.53–0.84)	0.85	0.50	0.93	0.30	0.81
KNN		0.79 (0.64–0.94)	0.88	0.67	0.95	0.42	0.86
NB		0.78 (0.61–0.95)	0.82	0.67	0.95	0.32	0.80
Ada		0.78 (0.61–0.95)	0.73	0.67	0.94	0.24	0.72
MLP		0.74 (0.59–0.89)	0.92	0.50	0.93	0.46	0.88
Neonatal model in validation cohort (n=105)							
LR		0.76 (0.66–0.87)	0.91	0.50	0.82	0.68	0.79
SVM		0.76 (0.66–0.87)	0.91	0.50	0.82	0.68	0.79
RF		0.76 (0.66–0.87)	0.81	0.67	0.86	0.59	0.77
DT		0.69 (0.59–0.79)	0.91	0.47	0.81	0.67	0.78
KNN		0.75 (0.65–0.86)	0.75	0.67	0.85	0.51	0.72
NB		0.76 (0.65–0.86)	0.91	0.50	0.82	0.68	0.79
Ada		0.76 (0.65–0.86)	0.73	0.70	0.86	0.51	0.72
MLP		0.74 (0.63–0.85)	0.75	0.67	0.85	0.51	0.72

Ada indicates AdaBoost; AUC, area under the receiver operating characteristic curve; DT, decision tree; KNN, k-nearest neighbor; LR, logistic regression; ML, machine learning; MLP, multilayer perceptron; NB, naïve Bayes; NPV, negative predictive value; PPV, positive predictive value; RF, random forest; and SVM, support vector machine.

differentiation among the models. The adequate and accurate prenatal prediction of maternal and descendant risk is crucial for the counseling and management of pregnant women with CHD. The proposed models in our study have high prediction accuracies. Therefore, the 2 models can help cardiologists and obstetricians identify high-risk pregnant patients with CHD.

The risk assessment studies for pregnancy with CHD are shown in Table S6. In our study, adverse maternal events were observed in 12.9% of pregnancies. International research on the event rate ranges from 4.0% to 23.5%.[2,3,16,17,19–25] Heart failure and arrhythmias requiring treatment were the 2 most common adverse cardiac complications, which is consistent with results from previous research.[22] In this study, women with CHD had a markedly higher risk of death during childbirth (n=13; 4.1%), and this proportion was higher than that reported from other authors,[2,3,17,19–25] mainly because of the lack of prenatal assessment and close monitoring during the

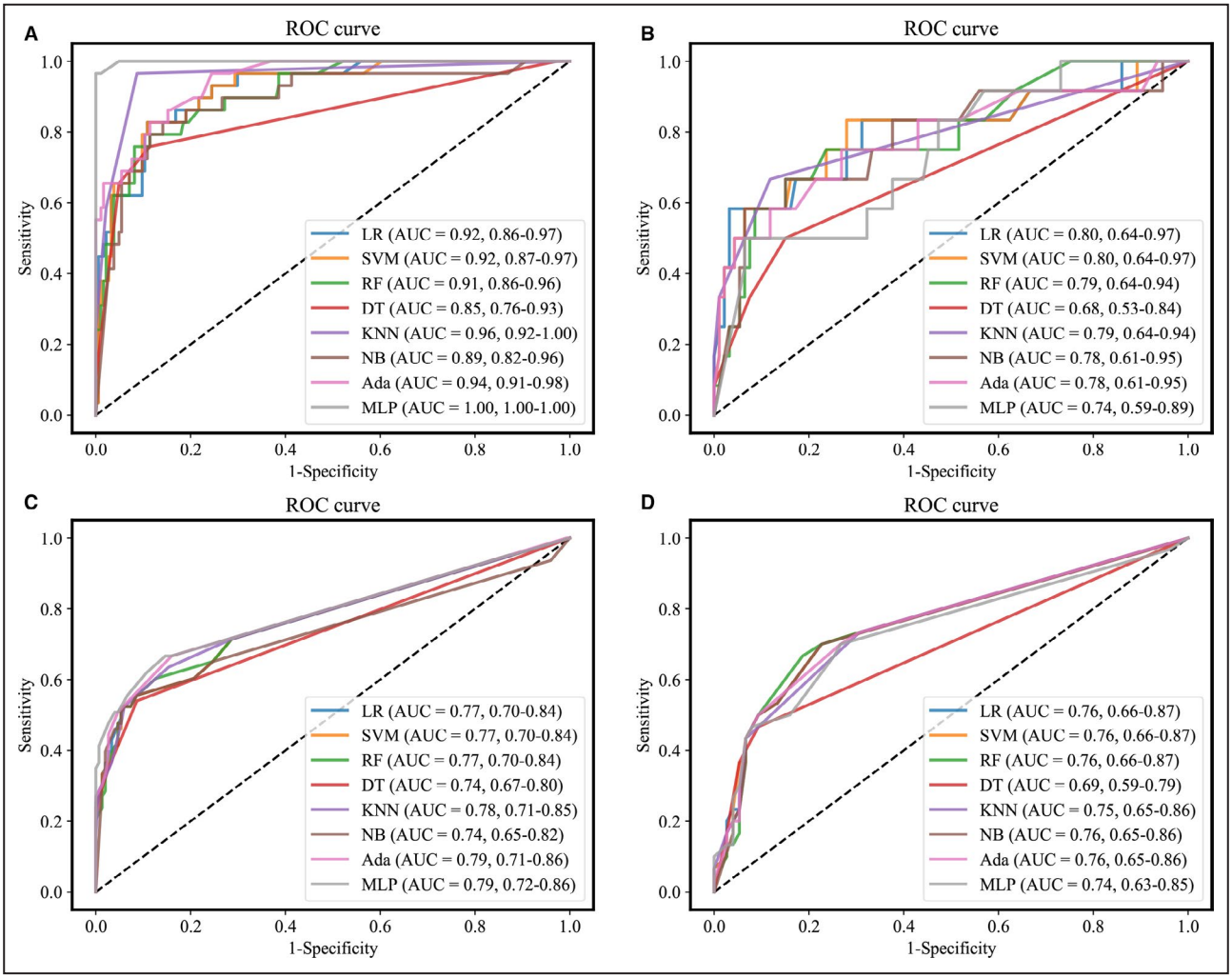

Figure 3. ROC curves of the LR and ML analysis.
(**A**), Training cohort of the maternal model; (**B**) validation cohort of the maternal model; (**C**) training cohort of the neonatal model; (**D**) validation cohort of the neonatal model. Ada indicates AdaBoost; AUC, area under the receiver operating characteristic curve; DT, decision tree; KNN, k-nearest neighbor; LR, logistic regression; MLP, multilayer perceptron; NB, naïve Bayes; RF, random forest; ROC, receiver operating characteristic; and SVM, support vector machine.

pregnancy period, especially for patients with ES. Engelfriet et al[6] found that 20% of patients with CHD died over a 5-year follow-up period, and patients with ES had a higher frequency of major bleeding events and associated right ventricular dysfunction. The European Society of Cardiology and the European Respiratory Society acknowledge that pregnancy is associated with higher mortality in patients with PAH, that the patient should be kept informed of the high risk associated with pregnancy, and that the termination of pregnancy should be discussed.[26]

The adverse neonatal event rate was 29.2% in our study, which is consistent with previous studies that reported an incidence of 7.4% to 37.3%.[3,8,16,17,19–22,25,27] Because of the limitations of medical progress in China, the survival rate of fetuses who do not reach 28 weeks is much worse than that of fetuses in developed countries. Moreover, because of the financial burden, many families could not afford the cost of treatment in the neonatal intensive care unit, further increasing neonatal mortality.

NYHA functional class III/IV served as an independent predictor of adverse maternal events in patients with CHD in our study. In a retrospective study of 1302 completed pregnancies (>20 weeks of gestation) in patients with CHD, Drenthen et al[16] proposed NYHA functional class as an independent high-risk predictor of maternal cardiac complications. In addition, Cardiac Disease in Pregnancy and Zwangerschap bij Aangeboren HARtAfwijkingen I maternal cardiovascular and offspring risk scores also selected NYHA class III/IV as a predictor in pregnant women with CHD.[19] The presence of PAH increases morbidity in patients with CHD, and the end of the spectrum of

PAH in the setting of CHD is ES.[5] In our study, a total of 13 patients died, 12 of whom were complicated with ES. At the same time, ES is also a high-risk factor for adverse neonatal events. Left ventricular ejection fraction and SaO_2 were independent predictors in patients with CHD, which was consistent with the finding of previous studies.[19,20] Therefore, cardiac function and oxygen saturation in patients with CHD are essential predictors of adverse events in pregnant women and their offspring. Preeclampsia was significantly correlated with neonatal adverse events in our study, and patients with CHD need to pay attention to the detection and treatment of pregnancy complications to reduce the occurrence of neonatal adverse events during pregnancy.

A logistic regression model is commonly used in the field of medical research, so we chose this method to construct predictive models and establish nomogram lists that are convenient for clinician use. ML has emerged as efficient computer algorithms for identifying patterns in large data sets with many variables and facilitating data-driven prediction or categorical modeling.[11,28] In this study, ML algorithms were used to further train the models and verify the high-risk factors in the 2 models. The 7 ML algorithms obtained similar predictive results in both the development cohort and validation cohort. Analysis of clinical data by ML methods offers considerable advantages for the evaluation of complex healthcare data.

Strengths and Limitations

The strengths of the study are as follows: First, we established the first prenatal risk assessment model for pregnant women with CHD during late pregnancy; second, the 2 prenatal assessment models have good accuracy and can be effectively applied to the assessment of adverse events in the last trimester of pregnancy in patients with CHD, especially in developing countries that lack well-developed preconception counseling and pregnancy monitoring systems; third, in clinical practice, the application of prediction models can significantly improve the poor maternal and infant prognosis of pregnant women with CHD. This study has some limitations, one of which might be a potential bias caused by the small sample size in the development cohort. The rule of thumb is that the number of events per variable should to reach at least 10 for logistic regression modeling to ensure a small expected relative bias. However, Vittinghoff and McCulloch found that the requirement of events per variable could be relaxed to 5 to 9 in the context of confounder adjustment.[29] In our study, the number of events per variable is 5.9 in maternal model development cohort and 31 in neonatal model development cohort. The sample size in our study meets the requirements. In addition, the nature of retrospective study is inevitably leading to the absence of previous medical history data such as cardiac surgery history details and medications during pregnancy. Increasing the sample size of patients in the development cohort, as well as to conduct prospective validation, will compensate for the above research limitations.

CONCLUSIONS

Two prenatal assessment models for mothers and offspring with reliable predictive accuracy were successfully established, which will benefit pregnant women with CHD worldwide, especially in developing countries where preconception counseling is inadequate. The proposed prediction models have benefits in helping clinicians to determine the patients at high risk of adverse events and provide a reference for clinicians' management decisions. Assessing the accuracy of our prediction model in a prospective validation study is necessary before clinical use.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S6
Figures S1–S4

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Supplemental Material

Table S1. Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis Checklist.

Section/Topic			Checklist Item	Section/Paragraph
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Title page
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	Abstract
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	Introduction 1-2
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	Introduction 3
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	Methods 1
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	Methods 1
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	Methods 1
	5b	D;V	Describe eligibility criteria for participants.	Methods 1 & Figure 1
	5c	D;V	Give details of treatments received, if relevant.	n/a
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Methods 3
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	n/a
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Methods 2
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	n/a
Sample size	8	D;V	Explain how the study size was arrived at.	Methods 1
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	n/a
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	Methods 2 & 5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	Methods 5 & 6
	10c	V	For validation, describe how the predictions were calculated.	Figure S2
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Figure 2
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	Figure S2
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Methods 1 & Table 1
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Results 1 & Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1 & Table S2
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Table S2
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Table S4
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Figure 2 A & B
	15b	D	Explain how to the use the prediction model.	Figure 2 A & B
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Figure 2 A & B
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	Discussion 8
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	Discussion 3
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	Discussion 1-7
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	Conclusion 1
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Supplemental
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Funding

Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Table S2. Adverse maternal and neonatal events.

	Cardiac adverse events (n=41)					Neonatal adverse events (n=93)				
	Total	Development cohort (n=29)		Validation cohort (n=12)		Total	Development cohort (n=63)		Validation cohort (n=30)	
	n (%)	n (%)	Types of events	n (%)	Types of events	n (%)	n (%)	Types of events	n (%)	Types of events
Atrial septal defects	7(17.1)	4(13.8)	1Arr, 2HF, 1HF+Arr	3(25.0)	3Arr	29(31.2)	18(28.6)	7PTL, 1PTL+ND, 8PTL+LBW, 2LBW+SGW	11(36.7)	2LBW, 3PTL, 1SGW, 3PTL+LBW, 1LBW+SGW, 1PTL+LBW+SGW
Ventricular septal defects	16(39.0)	12(41.2)	3HF, 2HF+Arr, 5HF+CD, 2HF+CD+Arr	4(33.3)	1Arr, 1HF, 1HF+ PPCM, 1HF+CD	34(36.6)	27(42.9)	1LBW, 7PTL, 15PTL+LBW, 2LBW+SGW, 1PTL+LBW+SGW , 1PTL+LBW+SGW + IFD	7(23.3)	1LBW, 4PTL+LBW, 1PTL+LBW+SGW, 1PTL+LBW+ ND
Tetralogy of Fallot	2(4.9)	2(6.9)	1Arr, 1HF+CD	0(0)	-	7(7.5)	3(4.8)	1PTL+LBW+SGW , 2PTL+LBW+ IFD	4(13.3)	2PTL, 2PTL+LBW
Persistent ductus artriosus	10(24.4)	7(24.1)	1Arr, 1HF, 2HF+CD, 1HF+Arr, 1HF+CD+Arr, 1HF+Arr+PPCM	3(25.0)	2Arr, 1HF	11(11.8)	8(12.7)	2PTL, 1LBW, 2PTL+LBW+SGW +ND, 3PTL+LBW	3(10.0)	2PTL+LBW, 1PTL+LBW+SGW
Ventricular Outflow tract obstruction	3(7.3)	1(3.4)	1Arr	2(16.7)	2Arr	6(6.5)	2(3.2)	1 PTL, 1LBW+SGW	4(13.3)	1LBW, 2 PTL, 1PTL+LBW
Other	3(7.3)	3(10.3)	1Arr, 1HF+Arr, 1HF+Arr+PPCM	0(0)	-	6(6.5)	5(7.9)	3PTL+LBW, 1PTL+LBW+SGW , 1LBW+SGW	1(3.3)	1LBW

CD, cardiac death; HF, heart failure; Arr, arrhythmia requiring treatment; PPCM, peripartum cardiomyopathy; PTL, preterm labor; SGW, small for gestational age birth weight; LBW, low birth weight; IFD, intrauterine fetal death; ND, neonatal death.

Table S3. Maternal death.

CHD	Age (years)	NYHA class	LVEF (%)	Pulmonary pressures (mm Hg)	Pregnancy duration (GW)	Delivery mode	When	Reason	Neonatal Wight (g)	Neonatal outcome	Year
TOF	20	IV	63	90	29^{+3}	CS	20 hours after postpartum	Respiratory and cardiac arrest	1200	Death	2007
PDA+ES	25	IV	45	121	33^{+1}	CS†	6 hours after postpartum	Hemorrhagic shock and DIC	-	-	2007
VSD+ES	24	IV	35	110	39^{+4}	CS	5 days after postpartum	Respiratory and cardiac arrest	2400	Survival	2008
VSD+ES	27	IV	61	110	34^{+3}	VD	1 days after postpartum	Heart failure	1650	Survival	2009
ASD+ES	24	IV	65	136	34^{+4}	CS	20 mins after postpartum	Ventricular fibrillation, respiratory and cardiac arrest	2400	Survival	2009
VSD+ES	24	III	53	131	30^{+3}	CS	1 hour after postpartum	Heart failure	1300	Survival	2012
VSD+ES	24	III	50	133	39	CS	17 days after postpartum	Hyoxemia	2800	Survival	2013
VSD+ES	24	III	58	110	33^{+3}	CS†	7 hours after postpartum	Respiratory and cardiac arrest	-	-	2013
PDA+ES	24	III	60	174	35^{+4}	CS	18 hours after postpartum	Respiratory and cardiac arrest	1750	Survival	2014
PDA+ES	25	II	60	110	36^{+4}	CS	4 days after postpartum	Cardiogenic shock	2200	Survival	2015
VSD+ES	22	III	60	108	35	VD	2 days after postpartum	Non-available	1950	Survival	2016
PDA+ES	32	IV	62	157	34^{+5}	CS	20 hours after postpartum	Respiratory and cardiac arrest	1900	Survival	2016
VSD+ES	27	IV	55	71*	35^{+3}	CS	16 hours after postpartum	Respiratory arrest and shock	2000	Survival	2017

*Pulmonary pressure here is pulmonary artery mean pressure, others are pulmonary arterial systolic pressure. †The pregnancy was terminated by cesarean section due to intrauterine fetal death.

CHD, congenital heart disease; TOF, tetralogy of Fallot; VSD, ventricular septal defect; ES, Eisenmenger syndrome; ASD, atrial septal defect; PDA, persistent ductus arteriosus; CS, cesarean section; VD, vaginal delivery; GW, gestational weeks; DIC, disseminated intravascular coagulation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

Table S4. Univariable LR analysis: predictors of adverse maternal and neonatal events.

	Maternal cardiac adverse event		Neonatal adverse event	
	Odds ratio (95%CI)	***P* Value**	**Odds ratio (95%CI)**	***P* Value**
Baseline characteristic				
NYHA class III-IV (VS. I-II)	6.73 (2.90-15.50)	<0.001	2.46 (1.29-4.70)	0.006
Eisenmenger syndrome	20.94 (6.98-62.85)	<0.001	25.19 (5.59-113.60)	<0.001
Cardiac uncorrected before pregnancy	2.14 (0.83-5.53)	0.115	2.49 (1.25-4.98)	0.010
Pulmonary infection	3.33 (0.58-19.09)	0.176	1.20 (0.21-6.71)	0.838
Hemoptysis	2.65 (0.49-14.36)	0.258	6.38 (1.20-33.81)	0.029
Cesarean section	1.56 (0.34- 7.06)	0.568	1.39 (0.49-3.96)	0.543
Congenital heart disease		0.055		0.489
Atrial septal defect	Reference		Reference	
Ventricular septal defect	3.43 (1.05-11.17)	0.041	1.81 (0.89-3.68)	0.100
Persistent ductus artriosus	9.69 (2.48-37.88)	0.001	2.15 (0.76-6.07)	0.149
Tetralogy of Fallot	3.27 (0.53-20.04)	0.200	0.97 (0.24-3.90)	0.962
Ventricular Outflow tract	2.25 (0.22-22.66)	0.491	0.92 (0.18-4.83)	0.922
Other	3.18 (0.65-15.54)	0.154	1.07 (0.34-3.37)	0.902
Pregnancy complication				
Preeclampsia	4.63 (1.74-12.32)	0.002	10.72 (3.75-30.65)	<0.001
Gestational diabetes mellitus	0.90 (0.11-7.62)	0.925	4.22 (0.98-18.25)	0.054
Echocardiographic				
LVEF, %	0.89 (0.84-0.94)	<0.001	0.96 (0.92-0.99)	0.023
AO, mm	1.12 (1.02-1.22)	0.017	1.03 (0.96-1.10)	0.436
Mitral regurgitation (moderate or severe)	3.74 (1.44-9.73)	0.007	2.06 (0.88-4.82)	0.098
PAH, mmHg		<0.001		<0.001
PAH <30	Reference		Reference	
30 ≤PAH <60	0.54 (0.11-2.78)	0.462	2.46 (1.08-5.59)	0.031
60 ≤PAH <90	3.64 (1.08-12.27)	0.037	5.32 (2.13-13.32)	<0.001
90 ≤PAH	18.96 (6.17-58.22)	<0.001	18.46 (6.52-52.24)	<0.001
Electrocardiograph				
Sinus tachycardia	4.79 (2.10-10.95)	<0.001	1.91 (0.96-3.81)	0.067
Ectopic cardiac rhythm	2.74 (0.90-8.37)	0.077	0.91 (0.31-2.67)	0.861
Laboratory examination				
SaO_2, %	0.87 (0.82-0.93)	<0.001	0.74 (0.65-0.84)	<0.001
HB, g/L	1.02 (1.00-1.05)	0.065	1.03 (1.01-1.05)	0.004
PLT, 10^9/L	0.99 (0.98-1.00)	0.002	1.00 (0.99-1.00)	0.028
TSP, g/L	0.90 (0.84-0.96)	0.001	0.92 (0.87-0.96)	<0.001
Pregnancy duration, weeks		<0.001		
28 ≤GW <32	17.57 (2.71-114.07)	0.003	-	-
32 ≤GW <36	7.81 (3.14-19.44)	<0.001	-	-
36 ≤GW	Reference		-	-

LR, logistic regression; CI, confidence interval; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; AO, aortic diameter; PAH, pulmonary hypertension; SaO_2, arterial blood oxygen saturation; HB, hemoglobin; PLT, platelet; TSP, total serum protein; GW, gestational week.

Table S5. Predictive performances of different predictor selection methods.

Methods	Development cohort				Validation cohort			
	Sensitivity	Specificity	AUC (95% CI)	*P* Value	Sensitivity	Specificity	AUC (95% CI)	*P* Value
Maternal model								
LASSO	78.8%	93.1%	0.92(0.86-0.97)	<0.0001	78.5%	75.0%	0.81(0.64-0.97)	0.0003
mRMR	79.3%	89.7%	0.91(0.85-0.97)	<0.0001	79.6%	75.0%	0.80(0.64-0.96)	0.0004
RF	91.3%	75.9%	0.89(0.82-0.96)	<0.0001	93.5%	58.3%	0.80(0.64-0.95)	0.0005
Neonatal model								
LASSO	91.3%	55.6%	0.77(0.70-0.84)	<0.0001	78.5%	75.0%	0.76(0.66-0.87)	<0.0001
mRMR	88.7%	58.7%	0.77(0.73-0.87)	<0.0001	84.0%	60.0%	0.74(0.63-0.86)	<0.0001
RF	77.3%	73.0%	0.82(0.76-0.88)	<0.0001	53.3%	80.0%	0.71(0.60-0.82)	0.0003

AUC, area under the receiver operating characteristic curve; CI, confidence interval; LASSO, least absolute shrinkage and selection operator; mRMR, maximum relevance minimum redundancy; RF, random forest.

Table S6. The risk of adverse events of pregnant women with CHD in previous studies.

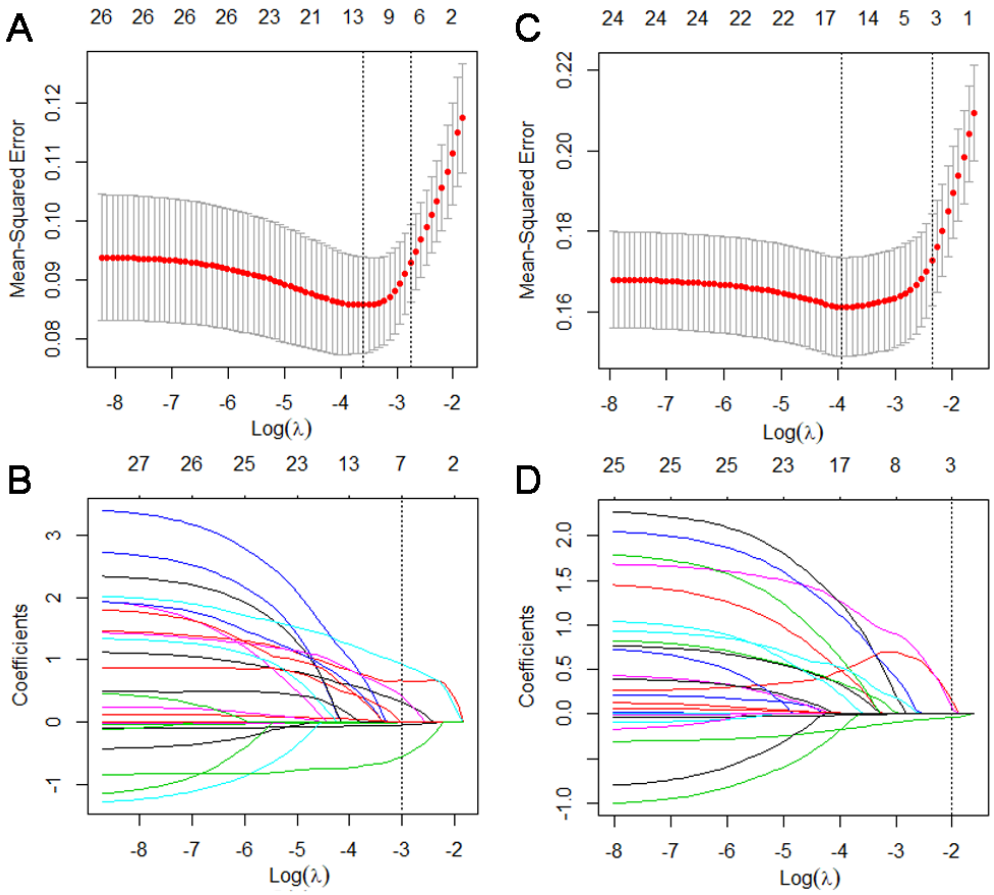
Reference		Author	Year	Type of CHD	Maternal events	Morbidity	Mortality	Neonatal events	Morbidity	Mortality
1.	[2]	Opotowsky AR, et al.	1998-2007	All types of CHD	Arrhythmia, heart failure, cerebrovascular accident, embolism, death and combined outcome.	4.0%	0.15%	-	-	-
2.	[3]	Greutmann M, et al.	2001-2010	Right ventricular outflow tract	Arrhythmias Heart failure Hospitalisation for cardiac indication	9.0% 9.0% 1.3%	0%	Preterm labor(< 37 weeks of gestation) Stillbirths Neonatal death	17.0% 1.3% 1.3%	2.6%
3.	[8]	van Hagen IM, et al.	2008-2014	Structural heart disease (mainly congenital and valvular disease)	-	-	-	Premature birth <37 weeks, small for gestational age (<10th centile), poor Apgar score (<7 at 1 min), fetal death ≥14 weeks of gestation or neonatal death up to 1 week after delivery (combined end point).	23.7%	1.7%
4.	[16]	Drenthen W, et al.	1980-2007	All types of CHD	Episodes of arrhythmia Heart failure Cardiovascular complications Endocarditis	4.8% 1.6% 1.3% 0.2%	-	Premature delivery (delivery <37 weeks) Small for gestational age Offspring mortality Combined	12.3% 13.8% 4.0% 25.0%	4.0%
5.	[17]	Siu SC, et al.	1994-1999	Congenital and acquired cardiac lesions	Pulmonary edema，sustained symptomatic tachyarrhythmia or bradyarrhythmia requiring treatment, stroke, cardiac arrest, and cardiac death (combined end point).	13.0%	1.0%	Premature birth (<37 weeks gestation), small for gestational age, respiratory distress syndrome, intraventricular hemorrhage, fetal death (≥20 weeks gestation), and neonatal death (within 28 days after birth) (combined end point).	20.0%	2.0%
6.	[19]	Balci A, et al.	2008-2011	All types of CHD	Cardiovascular mortality, clinically significant (needing treatment) arrhythmia, clinically significant (needing treatment) heart failure, thromboembolic events (eg, pulmonary embolism, valve thrombosis or deep venous thrombosis), vascular events (eg, stroke, myocardial infarction or	10.3%	0%	Fetal death, neonatal death, premature birth (delivery <37 weeks gestation), small for gestational age birth weight (<10th percentile), respiratory distress syndrome, infections leading to hospital admission, neonatal intensive care unit admission, cerebral intraventricular haemorrhage, occurrence of CHD and occurrence	37.3%	2.8%

Reference	Author	Year	Type of CHD	Maternal events	Morbidity	Mortality	Neonatal events	Morbidity	Mortality
				dissection), need for urgent or invasive cardiovascular intervention up to 6 months postpartum, and endocarditis (combined end point).			of other congenital disease (combined end point).		
7. [20]	Liu H, et al.	1993-2010	All types of CHD	Cardiac death, heart failure, severe arrhythmia, and cardiac syncope (combined end point).	6.2%	0.8%	Premature delivery (< 37 weeks of gestation), small birth weight for gestational age (< 10th percentile), neonatal asphyxia (Apgar score ≤ 7 at 1 minute after delivery; scores of 0–3 and 4–7 were defined as severe asphyxia and mild asphyxia, respectively), neonatal malformation; and neonatal death within 28 days of delivery (combined end point).	27.4%	4.8%
8. [21]	Avila WS, et al.	1989-1999	Rheumatic heart disease, congenital heart disease, Chagas' disease, cardiac arrhythmias, cardiomyopathies, and others.	Congestive heart failure Cardiac arrhythmias thromboembolism Thromboembolism Angina Hypoxemia Infective endocarditis Other complications Combined end point	12.3% 6.0% 1.9% 1.4% 0.7% 0.5% 0.7% 23.5%	2.7%	Premature delivery (< 37 weeks of gestation)	13%	2.9%
9. [22]	Fesslova VM, et al.	1995-2005	All types of CHD	Severe arrhythmias, initial heart failure, increased gradient, desaturation, hypertensive crisis, rupture of isthmic aneurysm cardiac tamponade and maternal death (combined end point).	4.5%	0.5%	Premature delivery(< 37 weeks of gestation) Intrauterine death Neonatal death	7.4% 1.0% 0.5%	1.5%
10. [23]	Balint OH, et al.	1995-2007	All types of CHD	Cardiac death/arrest, pulmonary oedema, arrhythmia and stroke (combined end point).	12.3%	0.74%	-	-	-

Reference	Author	Year	Type of CHD	Maternal events	Morbidity	Mortality	Neonatal events	Morbidity	Mortality
11. [24]	Silversides CK, et al.	1994-2014	CHD and other type of heart disease	Maternal cardiac death; cardiac arrest; sustained arrhythmia requiring treatment; left-sided heart failure defined as pulmonary edema; right-sided heart failure; stroke or transient ischemic attack; cardiac thromboembolism; myocardial infarction; and vascular dissection	15.8%	0.6%	-	-	-
12. [25]	Khairy P, et al.	1998-2004	All types of CHD	Pulmonary edema Sustained arrhythmias Combined end point	16.7% 2.8% 19.4%	0%	Premature delivery(< 37 weeks of gestation) Small for gestational age Respiratory distress syndrome Intraventricular hemorrhage Intrauterine fetal demise Neonatal death Combined end point	20.8% 8.3% 8.3% 1.4% 2.8% 1.4% 27.8%	4.2%
13. [27]	Ouyang DW, et al.	1998-2005	All types of CHD	-	-	-	Pre-eclampsia, preterm delivery, placental abruption, preterm premature rupture of membranes, intrauterine fetal demise, and post-partum hemorrhage (combined end point).	32.6%	3.3%

CHD, congenital heart disease.

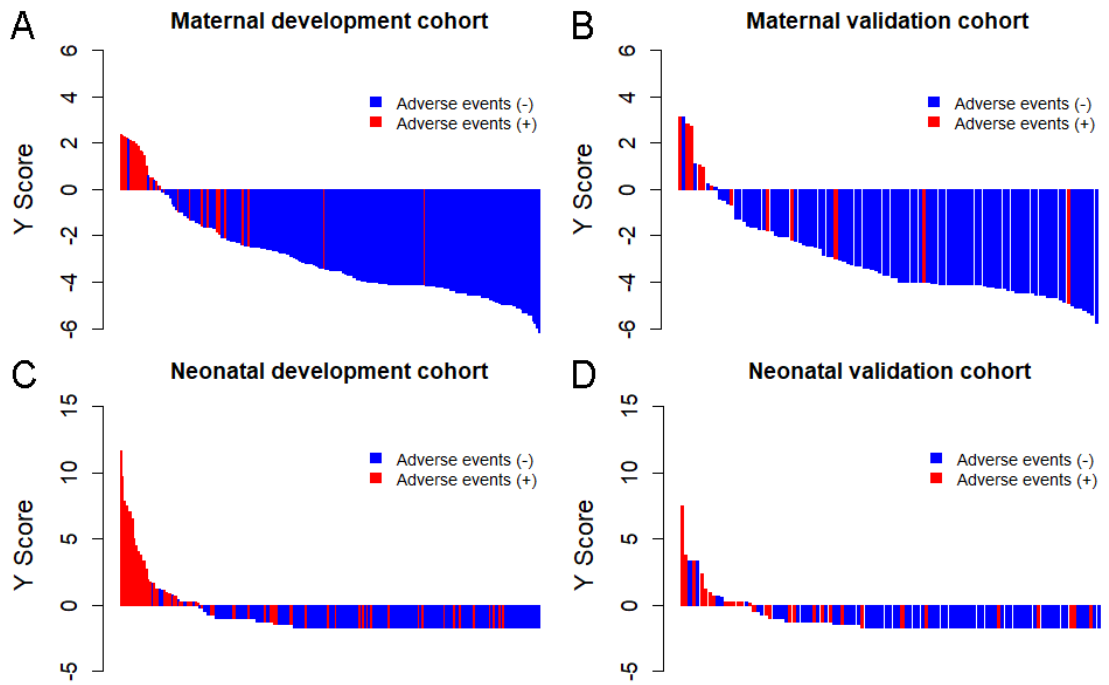
Figure S1. Predictor selection by LASSO analysis.



(A) and (B) are clinical predictors for maternal cardiac adverse events; (C) and (D) are clinical predictors for neonatal adverse events. (A) and (C) show the tuning penalization parameter lambda (λ) using 5-fold cross-validation and minimum mean square error in the LASSO model. Log (λ) = -2.659 with λ = 0.070 and Log (λ) = -2.263 with λ = 0.104 were chosen for the adverse maternal and neonatal events, respectively; (B) and (D) show the LASSO coefficient profiles of all the clinical predictors. The vertical gray line was drawn at the values selected in (A) and (C), where the optimal λ yields seven predictors with nonzero coefficients in (A) and three predictors with nonzero coefficients in (C).

LASSO, least absolute shrinkage and selection operator.

Figure S2. Y score in the equation of the prediction model for the risk of adverse events in women with CHD.



Y score of the maternal development (A) and validation (B) cohorts, and neonatal development (C) and validation (D) cohorts. The equation of the prediction models for risk of adverse events in women with CHD was as follow:

probability (adverse events) = exp (Y)/(1 + exp (Y))

Y in the maternal cardiac model= 2.17 + 0.78 [1(NYHA class III - IV)/0(NYHA class I-II)] + 0.67[1(with Eisenmenger syndrome)/0(without Eisenmenger syndrome)] − 0.10(30 ≤PAH <60) + 1.44(60 ≤PAH <90) + 2.06(90 ≤PAH) − 0.10(LVEF, %) + 1.58[1(with sinus tachycardia)/0(without sinus tachycardia)] − 0.01(SaO_2, %) + 1.14(32 ≤GW <36) + 1.92(28 ≤GW <32).

Y in the neonatal model= 22.84 + 0.1.37[1(with Eisenmenger syndrome)/0(without Eisenmenger syndrome)] + 1.93[1(with preeclampsia)/0(without preeclampsia)] − 0.25 (SaO_2, %).

CHD, congenital heart disease; NYHA, New York Heart Association; PAH, pulmonary hypertension; LVEF, left ventricular ejection fraction; SaO_2, arterial blood oxygen saturation; GW, gestational week.

Figure S3. Calibration curves of the prediction model in the maternal development (A) and validation (B) cohorts, and neonatal development (C) and validation (D) cohorts.

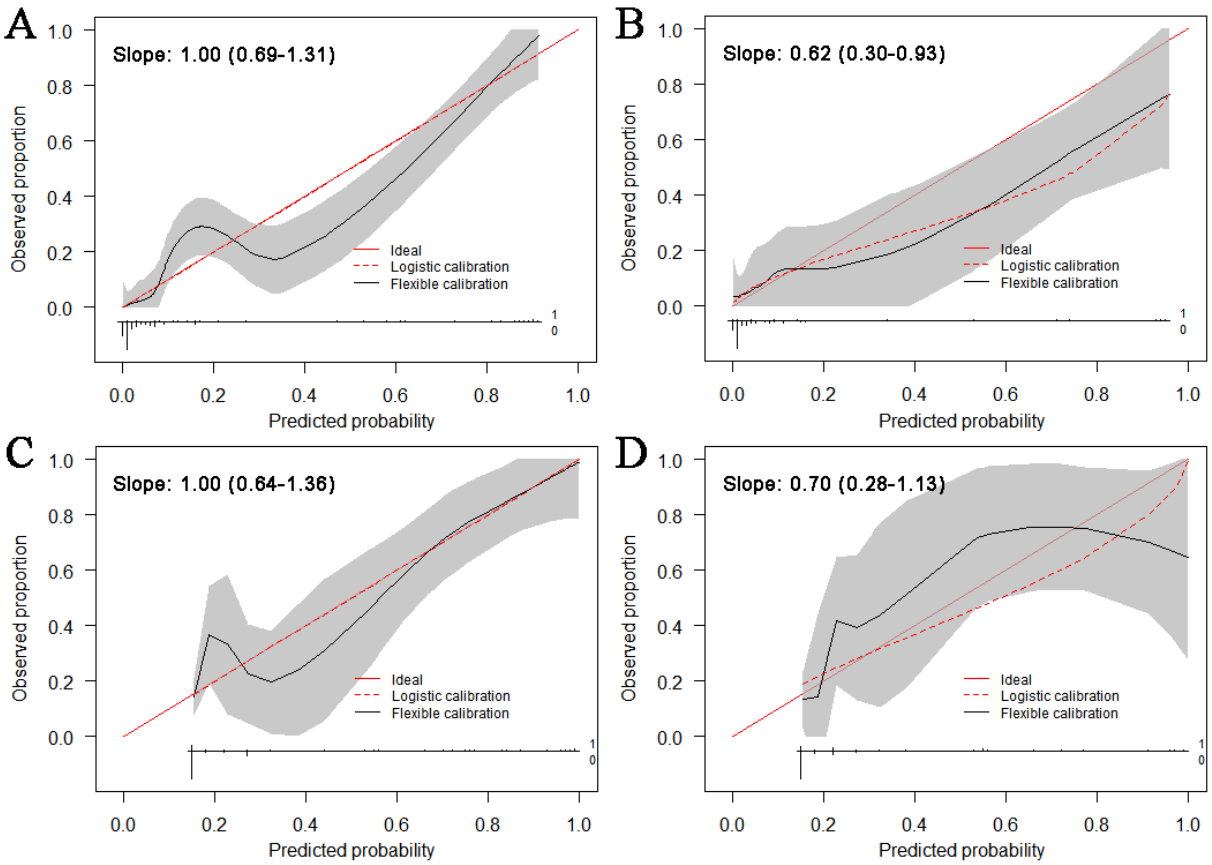
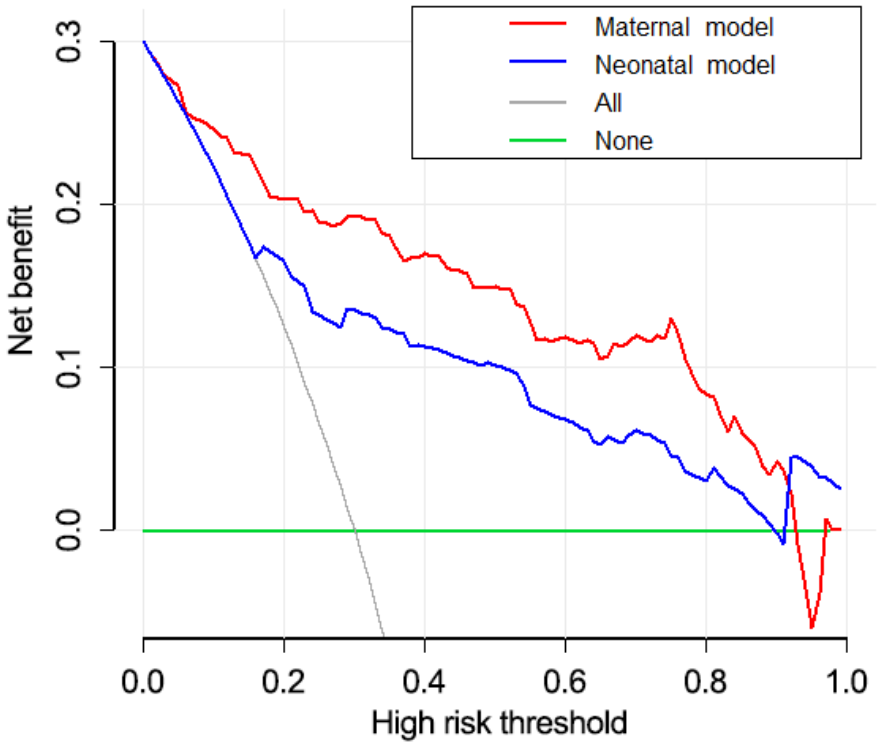


Figure S4. Decision curve analysis for the prediction models.



The grey line and green line represents the assumption of all patients with or without adverse events respectively; the red line and blue line represents the net benefit of the maternal and neonatal cardiac model, respectively. When the predicted probability thresholds were between 0.05 and 0.92, the maternal model showed a positive net benefit, and when the predicted probability thresholds were between 0.16 and 0.90, the neonatal model showed a positive net benefit.