Hindawi
Journal of Cardiac Surgery
Volume 2023, Article ID 8831107, 12 pages
https://doi.org/10.1155/2023/8831107

Research Article

A Prediction Model for Neonatal Coarctation Repair Involving Fetal and Neonatal Echocardiographic Parameters

Qi Shi,[1] **Jiazhong Tang**,[1] **Minjie Zhang**,[2] **Sun Chen**,[2] **Yurong Wu**,[2] **and Yanan Lu**[1]

[1]*Department of Pediatric Cardiothoracic Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China*
[2]*Department of Pediatric Cardiology, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China*

Correspondence should be addressed to Yanan Lu; luyanan@xinhuamed.com.cn

Received 12 June 2023; Revised 7 October 2023; Accepted 25 October 2023; Published 8 November 2023

Academic Editor: Oktay Korun

Objective. The aim of this study is to investigate the predictive value of fetal and neonatal echocardiographic parameters for neonatal coarctation repair in fetuses suspected of coarctation of the aorta (CoA), establish a prediction model for neonatal coarctation repair, and verify its predictive effectiveness and clinical applicability. *Methods*. From September 2017 to September 2022, fetuses suspected with CoA were enrolled. They were divided into two groups based on the need for neonatal coarctation repair. Fetal and neonatal echocardiographic parameters and clinical characteristics were collected retrospectively. Univariate and multivariate logistic regressions were applied to select significant predictors, which were further used to establish the nomogram prediction model. The area under the curve (AUC) of the receiver operating characteristic (ROC) was employed to quantify its discrimination ability. The calibration curve was drawn for internal verification, and the decision curve analysis (DCA) and clinical impact curve (CIC) were used to evaluate the clinical applicability of the prediction model. *Results*. This study included 50 infants suspected of CoA prenatally, of which 16 (32%) received aortic coarctation repair in the neonatal period and 34 (68%) did not. Multivariable logistic regression analysis revealed that the fetal echocardiographic parameter aortic isthmus/ductus arteriosus (AoI/DA) diameter ratio and the neonatal echocardiographic parameters such as the distance from left common carotid to left subclavian artery (LCSA) and the diameter of distal transverse aortic arch (DTAA) were independent predictors for neonatal coarctation repair. The ROC curve of the model showed excellent predictive value (AUC = 0.943). The calibration curve of the prediction model exhibited good fitness. The DCA and CIC demonstrated that the model had good clinical utility. *Conclusion*. The prediction model, which combines the fetal echocardiographic parameter AoI/DA diameter ratio and the neonatal echocardiographic parameters distance of LCSA and DTAA diameter, has an exceptional level of clinical value and prediction accuracy.

1. Introduction

Coarctation of the aorta (CoA), a localized narrowing of the aortic arch, accounts for approximately 5% to 8% of congenital heart diseases (CHDs) [1, 2]. It is a potentially life-threatening diagnosis [3]. In neonates with severe coarctation of the aorta, in which perfusion of the lower body is almost exclusively dependent on the opening of the ductus arteriosus. When the ductus arteriosus is closed, a significant reduction in blood flow to the systemic circulation may lead to shock, and cardiac failure may occur due to an increase in the left ventricular afterload caused by stenosis [4, 5]. Without timely and appropriate intervention, the conditions of these infants may rapidly deteriorate and even result in mortality. Therefore, early diagnosis and accurate prediction of treatment timings are very important for critical CoA newborns to optimize cardiopulmonary management and undergo surgical intervention.

Although there are a large number of studies [6] concerning the early diagnosis of aortic coarctation using fetal echocardiography, CoA remains one of the most challenging congenital heart diseases to diagnose in utero [7]. Evaluating the structure of the aortic arch is extremely challenging at any stage of pregnancy, and even experienced fetal

echocardiologists are prone to misjudge. It has been reported that the true positive rate of fetal CoA diagnosed by echocardiography alone is only 20%–35% [8]. Despite the increasing popularity of neonatal echocardiography and pulse oxygen saturation screening [9], many newborns with severe coarctation of the aorta are still unable to get a timely diagnosis. In recent years, there has been more research on cardiovascular imaging and functional evaluation using novel ultrasound techniques and fetal cardiac magnetic resonance to establish predictive models and scoring systems for CoA patients [6, 10], but their technical dependence hinders the applicability in primary care units, so this study integrated relatively easily accessible echocardiographic parameters to establish the predictive model and explore their predictive value for neonatal surgery in CoA patients. Most prediction models focus only on either the fetal or neonatal echocardiographic parameters. The prognostic value of prenatal and neonatal echocardiographic data had never been concurrently assessed and combined in a prediction model before. Therefore, this study aimed to investigate the discriminative power, as well as its clinical usefulness, of the prediction model containing both fetal and neonatal echocardiographic parameters for neonatal coarctation repair.

2. Methods and Materials

2.1. Study Population. The research was conducted retrospectively on patients who underwent fetal echocardiographic examination at the Shanghai Jiao Tong University School of Medicine affiliated to Xinhua Hospital from July 2017 to September 2022. During the research period, fetuses with suspicion of CoA were enrolled. All patients were followed up to infancy. Depending on whether the patients had coarctation surgery during the neonatal era, the patients were divided into two groups as follows: the neonatal CoA repair group (NCoAR group) and the non-neonatal CoA repair group (non-NCoAR group).

Inclusion criteria were as follows: (1) fetuses suspected of CoA with prenatal and neonatal (within 24 hours after birth) echocardiography and (2) fetuses with complete clinical data and postnatal follow-up.

Exclusion criteria were as follows: (1) complicated with other critical congenital heart diseases, (2) complicated with extracardiac congenital malformations, and (3) missing or poor-quality of echocardiographic images.

2.2. Perinatal Treatment and Surgical Indication. Fetuses suspected with CoA were recommended by cardiologists for a series of fetal echocardiograms at a 4-week interval in the following pregnancy. Postnatal clinical and echocardiographic examination was given within 24 hours after delivery. For every newborn who was suspected of CoA prenatally, the prostaglandin E1 infusion was initiated after birth and maintained until the suspicion of CoA was ruled out or confirmed according to clinical and echocardiographic evaluation. Indications for surgical intervention were based on clinical assessment, echocardiographic, and radiologic findings. The decision to surgery was made by the cardiac surgeons and cardiologists together.

2.3. Data Collection. The clinical and echocardiographic data were reviewed. Clinical data, including the age of mothers, gestational age at the last prenatal echocardiographic examination in the third trimester, gender, birth weight, birth length, diagnosis, and surgical time, were retrospectively collected from electronic medical records. Fetal and neonatal echocardiographic studies were reviewed from the DICOM system.

2.4. Fetal Echocardiographic Measurement. Fetal echocardiograms were performed using a Voluson E8 machine (GE Healthcare Ultrasound, WI, USA). Fetal echocardiography examinations were accomplished by an experienced sonographer according to the recommended guideline [11], reviewed by an expert, and the images were submitted to the DICOM system. The fetal echocardiogram taken in the early-third trimester was reviewed. The nonstandard quantitative and morphological measurements obtained by one observer were blinded to the final results based on the imaging from the DICOM system. A second observer remeasured 10 studies, selected randomly, to calculate interobserver correlation. The Z-scores were calculated based on the gestational age, employing Cardio Z software [12, 13].

The standard measurements included aortic valve (AoV) diameter, main pulmonary artery (MPA) diameter, ascending aorta (AAo) diameter, aortic isthmus (AoI) diameter, mitral valve (MV) annulus diameter, tricuspid valve (TV) annulus diameter, right ventricle (RV) width, and left ventricle (LV) width. MV diameter, TV diameter, RV width, and LV width were measured in the apical four-chamber view at end diastolic phase. The AoV diameter and AAo diameter were measured in the LV outflow tract view. MPA diameter was assessed in the RV outflow tract view. AoI diameters were measured from both the three vessels and tracheal view (3VT) (Figure 1(a)) and the sagittal view (SAG). The ratios of MV/TV diameter, RV/LV width, AoI/DA diameter, and MPA/AAo diameter were further computed.

In addition to standard measurements, we evaluated three morphometric parameters with demonstrated predictive value from prior studies [14, 15]. The transverse aortic arch-descending aorta angle (TAo-DAo angle) and ascending aorta-descending aorta angle (AAo-DAo angle) were obtained from the sagittal view of the aortic arch at systolic phase (Figure 1(c)). The TAo-DAo angle was measured between two lines, the first drawn from proximal (from the start of the innominate artery) to distal (from the end of the left subclavian artery) along the internal boundary to the transverse aortic arch, and the second drawn along the descending aorta. The AAo-DAo angle was formed by the second line mentioned above and the third line identified as one drawn from the point just above the aortic valve to the point at the start of the innominate artery along the internal boundary of the ascending aorta. The distance between the left common carotid artery and left subclavian artery (LCSA)

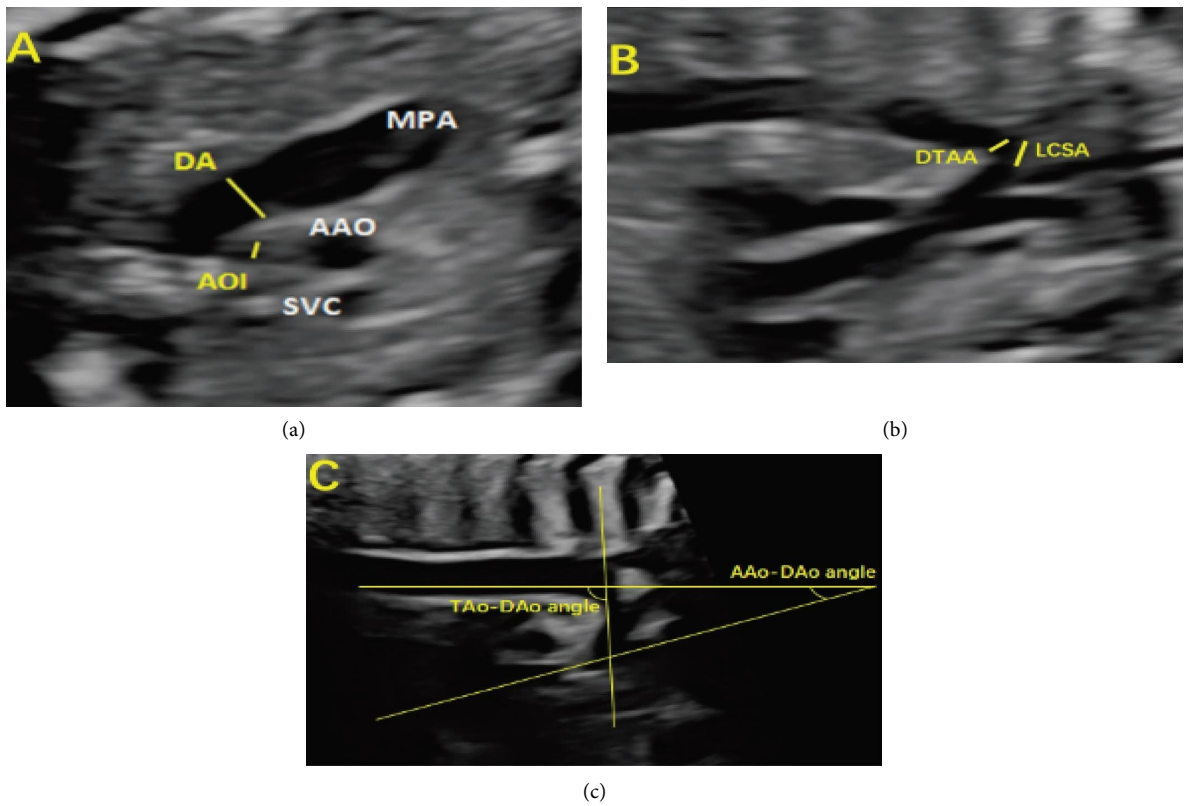

Figure 1: Fetal echocardiographic measurements. (a) Three vessel and tracheal view (b) Sagittal view for DTAA and LCSA. (c) Sagittal view for angle measurements. DA, ductus arteriosus; AOI, aortic isthmus; MPA, main pulmonary artery; AAO, ascending aorta; SVC, superior vena cava; DTAA, distal transverse aortic arch; LCSA, the distance between the left common carotid artery and left subclavian artery; AAo-DAo angle, ascending aorta-descending aorta angle; TAo-DAo angle, transverse aortic arch-descending aorta angle.

and the diameter of the distal transverse aortic arch (DTAA) measured at the takeoff of the left subclavian artery of the arch, were obtained in the sagittal view of the aortic arch as well (Figure 1(b)). To calculate the distal arch index (DAI), LCSA was divided by DTAA [16].

2.5. Neonatal Echocardiographic Measurement. Newborns suspected with coarctation of the aorta prenatally received echocardiography assessments within 24 hours after birth. An expert reviewed the imaging after an experienced sonographer had conducted the ultrasound examination [17] and submitted the images to the DICOM system. Transthoracic neonatal echocardiograms were retrospectively assessed. Birth weight and birth length were used to calculate the body surface area (BSA). According to BSA, the Z-score is calculated through the following website: https://www.parameterz.com. The LV width, RV width, TV annulus diameter, and MV annulus diameter were taken from the four-chamber view. The diameters of the ascending aorta, aortic isthmus, and transverse aortic arch were measured at the sagittal view of the aortic arch taken from the suprasternal view.

The diameters of the AoV annule and AAo were measured on the left ventricle outlet track obtained at end-systolic phase. The carotid-subclavian artery index (CSAi) was computed by dividing the distance of the LCSA by the diameter of the DTAA as previously described [18, 19]. The distance LCSA and the diameter of DTAA at the end-systole were obtained in the suprasternal view (Figure 2). Intracardiac complications such as bicuspid aortic valve (BAV), persistent left superior vena cava (PLSVC), and ventricular septal defect (VSD) were documented.

2.6. Statistical Analysis. For continuous variables, normally distributed data were expressed as mean ± standard deviation, and non-normally distributed data were expressed as median and interquartile range. Normally distributed data were analyzed using an independent sample *t* test, and non-normally distributed data were analyzed by the Mann–Whitney test. Categorical variables were expressed as frequency or rate (%), and comparison between groups was performed by the Fisher exact probability method. The factors significantly associated with neonatal surgery in the univariate logistic analysis were included in the multivariate logistic regression analysis to identify the independent predictive factors and to form the final prediction model. The model performance was assessed in terms of discrimination, calibration, and clinical utility. The area under the ROC curve (AUC) was employed to quantify the discrimination ability. The calibration performance of the model was assessed using the calibration curve and the Hosmer–Lemeshow goodness-of-fit test (H-L test). Clinical

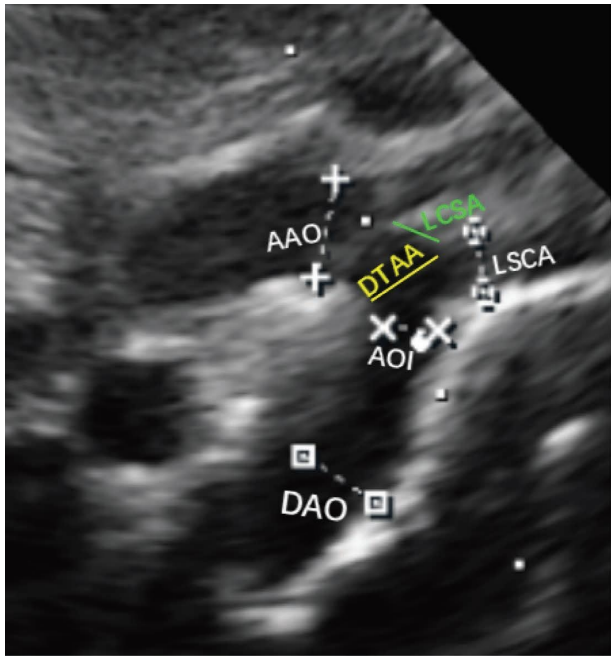

Figure 2: Neonatal echocardiography measurements. AAO, ascending aorta; DTAA, distal transverse aortic arch; LCSA, the distance between the left common carotid artery and left subclavian artery; LSCA, left subclavian artery; AOI, aortic isthmus; DAO, descending aorta.

utility was evaluated using decision curve analysis (DCA) and the clinical impact curve (CIC).

All statistical analyses were performed using R 4.2.1 (https://www.Rproject.org/) and the statistical software package IBM SPSS (version 22.0). A two-sided P value < 0.05 was considered as statistically significant.

3. Results

3.1. Clinical Characteristics. During the study period, 90 fetuses underwent echocardiographic examination which were suspected of CoA, of which 64 survived and had postnatal follow-up data. We excluded 8 fetuses with incomplete echocardiographic imaging, 5 fetuses with other major cardiac defects, and one with an extracardiac malformation. The final study population thus involved 50 neonates suspected of having CoA prenatally. Among the study population, 16 (32%) underwent CoA repair in the neonatal period, 4 (8%) received CoA repair during their infancy period, and 30 (60%) were ruled out of the diagnosis of CoA. Therefore, there were 16 patients in the neonatal CoA repair group (NCoAR group) and 34 in the non-neonatal CoA repair group (non-NCoAR group). Figure 3 shows the flowchart of population selection.

The average age of pregnant mothers was 30.06 ± 4.82 years, and the average gestational age of the included examination in the third trimester was 33.60 ± 3.02 weeks. Among the 50 cases, 31 (62%) were first suspected to be CoA before the 28th week of gestation. Among the 50 patients, 30 were males (60%) and 20 were females (40%). The median gestational age (GA) at birth was 38.4 weeks (IQR: 37.6–39.0), and the median age at surgery was 7 days (IQR: 4–13). The average birth weight was 3202.78 ± 545.86 grams, and the median birth length was 50 cm (IQR: 46.76–52). The GA of the third trimester fetal echocardiogram reviewed, the GA of the first echocardiogram suspected of CoA, or the age of pregnant women were not significantly different between two groups. There was no statistically significant difference between two groups in terms of birth weight, length, or sex.

Between the surgical cases, the technique applied for arch repair was not significantly different regarding the different surgical timings. Twelve of the neonatal surgical cases and three of the later surgery cases received extended end-to-end anastomosis; two neonatal CoA repair cases and one later surgery case underwent path augmentation. The characteristics of the study population are shown in Table 1.

Among the 50 fetuses suspected with CoA by prenatal fetal echocardiography, 3 cases were diagnosed with bicuspid aortic valves after birth, 28 cases were associated with ventricular septal defect (VSD), and 8 cases were associated with persistent left superior vena cava (PLSVC). Among the 16 children who underwent neonatal surgery, 14 cases (87.5%) were complicated with VSD, while in the non-neonatal surgery group, 14 cases (41.18%) were complicated with VSD. The difference between the two groups in the rate of patient complicated with VSD was statistically significant.

3.2. Fetal and Neonatal Echocardiographic Measurements. In fetal echocardiographic parameters, the MV Z-score, AAo Z-score, and AoV Z-score were significantly smaller in patients in the NCoAR group. Parameters concerning aortic arch dimensions and AoI Z-score, both from 3VT and sagittal view, are significantly smaller in the neonatal CoA repair group (Table 2). The DTAA diameter was significantly smaller, and the distance between the left carotid and left subclavian artery (LCSA) was significantly longer in patients in the neonatal surgery group (Table 2). The MPA/AAo diameter ratio and the AoI/DA diameter ratio demonstrated statistical significance between the NCoAR group and the non-NCoAR group (Table 2). There was no significant difference found in the TV Z-score, RV Z-score, or LV Z-score, nor were the TV/MV ratio and RV/LV ratio statistically different between groups. AoV Z-score, DA Z-score, DTAA Z-score, and LCSA were not significantly different between neonates who underwent CoA repair and those who did not. The distal arch index (DAI) did not show any statistical difference either. Table 2 demonstrates that a significantly greater proportion of neonates in the NCoAR group had a TAo-DAo angle greater than 100°, whereas the proportion of neonates with an AAo-DAo angle less than 7° did not differ statistically between the two groups.

In neonatal echocardiography, all the aortic arch structure parameters were significantly different between the two groups, including the AAo Z-score, the AoI Z-score, and the DTAA diameter. MV Z-score, TV Z-score, RV width, and LV width were not significantly different between the groups, whereas LCSA distance was statistically different

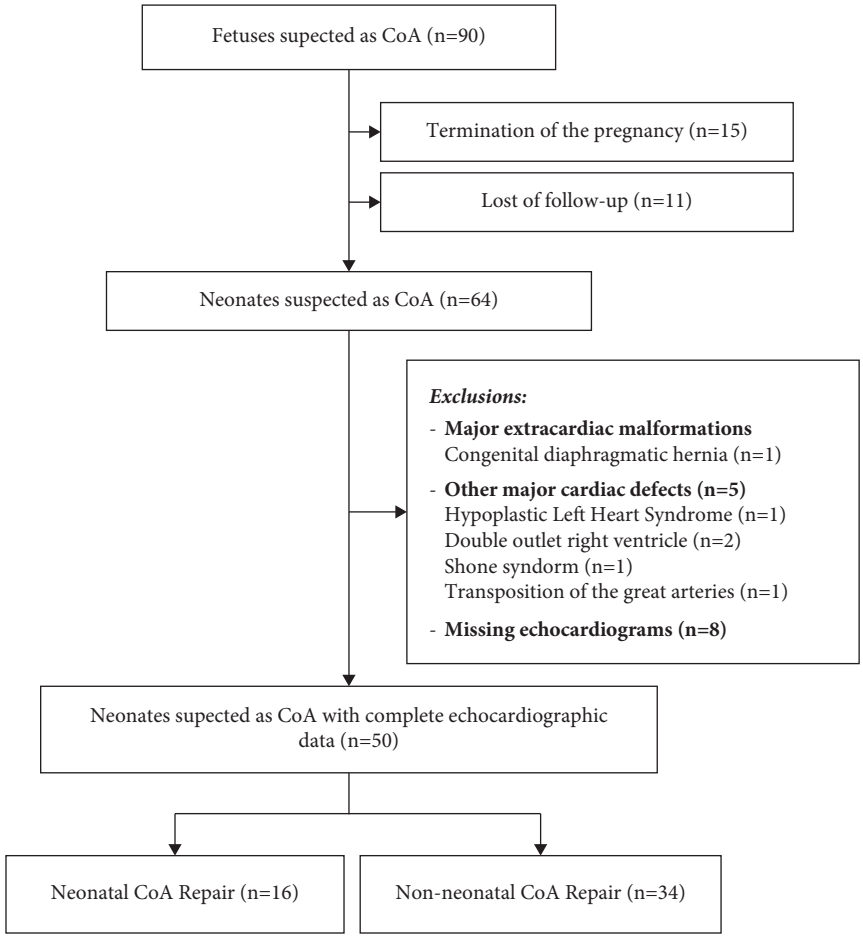

Figure 3: Flowchart of patient enrollment.

Table 1: Cohort characteristics.

	Non-neonatal CoA repair ($n = 34$)	Neonatal CoA repair ($n = 16$)	P value
Maternal age (years)	30.09 ± 5.28	30.00 ± 3.83	0.947
GA at first fetal ECHO suspected as CoA < 28 weeks (n, %)	18 (52.94%)	13 (81.25%)	0.054
GA at third trimester of fetal ECHO (weeks)	33.90 ± 3.05	32.98 ± 2.96	0.324
GA at delivery (weeks)	38.16 ± 1.65	38.16 ± 1.65	0.182
Gender			0.907
Male (n, %)	9 (60.00%)	19 (63.33%)	
Female (n, %)	6 (40.00%)	11 (36.67%)	
Birth weight (g)	3122.35 ± 591.73	3373.69 ± 396.51	0.13
Birth length (cm)	50.803 (47.3, 55.0)	49.000 (46.0, 51.0)	0.117
Age at surgery (days)	93.5 (31.0, 207.8)	15.5 (9.8, 21.5)	0.022*
Surgical repair method			1
Extended end-to-end anastomosis (n, %)	3 (75.00%)	12 (75.00%)	
Patch augmentation (n, %)	1 (25.00%)	4 (25.00%)	
Associated cardiac anomalies			
VSD (n, %)	14 (41.18%)	14 (87.50%)	0.002**
BAV (n, %)	2 (5.88%)	1 (6.25%)	0.959
PLSVC (n, %)	4 (11.76%)	4 (25.00%)	0.234

GA, gestation age; ECHO, echocardiography; VSD, ventricle septal defect; BAV, bicuspid aortic valve; PLSVC, persistent left superior vena cava.

between neonates who underwent CoA repair and those who did not (Table 3). The DAO Z-score did not show a significant difference. Shunt direction across patent ductus arteriosus (PDA), AoI/PDA diameter ratio, and CSAi were factors statistically different between the two groups. In the NCoAR group, there was a larger percentage of neonates

Table 2: Fetal echocardiographic measurements.

	Non-neonatal CoA repair ($n = 34$)	Neonatal CoA repair ($n = 16$)	P value
MV Z-score	−0.40 ± 1.35	−1.50 ± 1.55	0.013*
TV Z-score	0.59 ± 1.21	−0.05 ± 1.57	0.119
RV Z-score	0.09 ± 1.16	−0.09 ± 0.91	0.589
LV Z-score	−1.22 ± 1.54	−1.37 ± 1.20	0.735
MPA Z-score	1.510 (0.7, 2.1)	1.725 (1.3, 2.5)	0.294
AAo Z-score	−1.460 (−2.3, −0.7)	−2.005 (−3.2, −1.5)	0.027*
AoV Z-score	−0.52 ± 1.56	−1.27 ± 1.33	0.101
AoI-SAG Z-score	−3.110 (−4.3, −2.1)	−4.370 (−7.3, −3.5)	0.004**
AoI-3VT Z-score	−2.880 (−3.7, −1.9)	−4.480 (−6.1, −3.2)	0.002**
DA Z-score	−2.60 ± 2.39	−2.05 ± 2.59	0.465
DTAA (mm)	2.150 (1.6, 2.8)	2.450 (1.7, 2.9)	0.559
LCSA (mm)	2.400 (1.8, 3.5)	3.050 (2.6, 4.6)	0.157
Ratio			
TV/MV	1.30 ± 0.24	1.35 ± 0.21	0.455
RV/LV	1.216 (1.1, 1.4)	1.216 (1.1, 1.4)	0.632
MPA/AAo	1.449 (1.3, 1.6)	1.734 (1.5, 2.0)	0.004**
DAI	0.845 (0.5, 1.1)	0.593 (0.5, 1.0)	0.328
AoI/DA	0.640 (0.6, 0.8)	0.450 (0.3, 0.6)	0.000**
Angle			
TAo-DAo angel > 100°	11 (32.35%)	10 (62.50%)	0.044*
AAo-DAo angel < 7°	4 (11.76%)	2 (12.50%)	0.941

MV, mitral valve; TV, tricuspid valve; RV, right ventricle; LV, left ventricle; MPA, main pulmonary artery; AAo, ascending aorta; AoV, aortic valve; AoI, aortic isthmus; SAG, sagittal view; 3VT, three vessel and tracheal view; DA, ductus arteriosus; DTAA, distal transverse aortic arch; LCSA, the distance between the left common carotid artery and left subclavian artery; DAI, distal arch index; AAo-DAo angle, ascending aorta-descending aorta angle; TAo-DAo angle, transverse aorta-descending aorta angle.

Table 3: Neonatal echocardiographic measurements and quantitative findings.

	Non-neonatal CoA repair ($n = 34$)	Neonatal CoA repair ($n = 16$)	P value
MV Z-score	−3.11 ± 2.14	−2.80 ± 2.24	0.634
TV Z-score	−1.42 ± 1.94	−1.13 ± 1.31	0.592
RV width (mm)	12.09 ± 2.94	12.81 ± 2.82	0.417
LV width (mm)	11.56 (9.5, 14.2)	11.46 (9.6, 14.0)	0.967
AAo Z-score	−1.92 ± 2.01	−3.29 ± 1.81	0.025*
AoI Z-score	−2.64 ± 1.92	−4.37 ± 1.90	0.004**
DTAA (mm)	3.15 (2.8, 4.1)	2.40 (1.9, 3.1)	0.004**
DAO Z-score	2.98 (0.1, 4.4)	0.84 (0.0, 2.6)	0.301
PDA (mm)	3.05 ± 1.20	3.63 ± 1.38	0.137
Shunt direction across PDA			0.019*
Mostly left to right (n, %)	13 (38.24%)	1 (6.25%)	
Mostly right to left (n, %)	21 (61.76%)	15 (93.75%)	
LCSA (mm)	2.60 (1.9, 3.9)	4.20 (2.8, 5.8)	0.011*
EF (%)	70.05 (60.5, 75.3)	71.50 (59.1, 78.0)	0.983
Ratio			
MV/TV	0.893 (0.8, 1.0)	0.908 (0.8, 1.0)	0.959
RV/LV	1.004 (0.9, 1.2)	1.046 (0.9, 1.3)	0.377
CSAi > 0.7 (n, %)	11 (32.35%)	10 (62.50%)	0.044*
AoI/PDA	0.986 (0.7, 1.5)	0.700 (0.4, 1.1)	0.023*

MV, mitral valve; TV, tricuspid valve; RV, right ventricle; LV, left ventricle; MPA, main pulmonary artery; AAo, ascending aorta; AoV, aortic valve; AoI, aortic isthmus; SAG, sagittal view; 3VT, three vessel tracheal view; DA, ductus arteriosus; DTAA, distal transverse aortic arch; PDA, patent ductus arteriosus; LCSA, the distance between the left common carotid artery and left subclavian artery; EF, ejection fraction; CSAi, carotid-subclavian artery index; AAo-DAo angle, ascending aorta-descending aorta angle; TAo-DAo angle, transverse aortic arch-descending aorta angle; DAO, descending aorta.

that had a PDA with bidirectional shunting, mostly right to left (Table 3). The AoI/PDA diameter ratio was significantly smaller in neonates in the NCoAR group. Ejection fraction (EF), MV/TV diameter ratio, and RV/LV diameter ratio did not show any statistical difference in the study population (Table 3).

3.3. Independent Predictive Factors and Model Construction

3.3.1. Univariate Analysis. Univariate logistic analysis showed that there were indicators significantly associated with postnatal coarctation procedures in both fetal and neonatal ultrasound. Among fetal echocardiographic parameters, the MV Z-score, AAo Z-score, AoI-3VT-Z-score, AoI-SAG-Z-score, MPA/AAo ratio, and AoI/DA ratio were significantly relevant for predicting neonatal coarctation repair (Table 4). Among neonatal echocardiographic parameters, CSAi > 0.7, DTAA diameter, AAo Z-score, AoI Z-score, and shunt direction across PDA were significantly predictive for neonatal coarctation repair (Table 4).

3.3.2. Multivariate Analysis. To choose independent predictive factors, multivariate logistic regression analysis was further conducted. The result of multivariate analysis showed that the AoI/DA diameter ratio ($P = 0.002$, odds ratio [OR] = 0.00, 95% CI: 0.00–0.006) from fetal echocardiography, the distance of LCSA ($P = 0.008$, OR = 2.485, 95% CI: 1.27–4.862), and diameter of DTAA ($P = 0.048$, OR = 0.266, 95% CI: 0.072–0.989) from neonatal echocardiograph were independent predictors for neonatal coarctation repair (Table 4). A prediction model was established using a logistical regression model, and the predicted probability (p) for neonatal CoA repair was calculated by the equation as follows: $\ln(p/1\text{-}p) = 7.294 - 13.908^{*}\text{AoI/DA} + 0.910^{*}\text{LCSA} - 1.323^{*}\text{DTAA}$. Nomogram was generated based on the multivariate regression model (Figure 4).

3.3.3. Model Performance. Calibration ability and discriminatory power are the two metrics applied to evaluate the performance of the prediction model. The AUC of the ROC curve (Figure 5) was used to determine the discriminating capacity of the curve, which was discovered to be 0.943. The H–L test was conducted to evaluate the fitting degree of the model, and the result showed that the model fit well ($P > 0.05$). The calibration curve of the nomogram prediction mode demonstrated high agreement between the predicted and actual surgeries (Figure 6). The clinical benefit and clinical impact of the model were examined using the DCA curve and CIC. The DCA curve demonstrated strong clinical applicability of the nomogram model (Figure 7). On the CIC, the stratification of the neonatal CoA repair probability for 1,000 samples was anticipated. The predicted number of cases requiring neonatal CoA repair was close to the actual number of positive cases when the threshold probability was higher than 0.20 (Figure 8).

4. Discussion

Severe CoA is a life-threatening congenital heart disease in the neonatal period. Neonates with severe CoA who cannot be detected in time often present with poor perfusion and acidosis, increased left ventricular afterload, and eventually cardiogenic shock and end-organ damage [5], with high mortality rate. Therefore, early detection of critical coarctation of the aorta that requires surgical correction in the neonatal period has far-reaching clinical significance. Since the arch constriction is a dynamic process and obstruction may progress during the perinatal period, it is not surprising that nearly one-third of newborns with CoA were missed [20]. Therefore, a multiparameter prediction model based on prenatal and early postnatal echocardiography established in this study has significant clinical utility, and this study is the first to take both fetal and neonatal echocardiographic findings into consideration in predicting the need for neonatal CoA repair in severe cases.

Our data demonstrated that LCSA and DTAA obtained in neonatal echocardiography, and AoI/DA diameter ratio measured in fetal echocardiography were significant predictors of neonatal surgical intervention for CoA patients. These parameters are not commonly included in echocardiographic examination but easy to assess in qualified hands with good interobserver reproducibility. The prediction model, including LCSA length, DTAA diameters, and AoI/DA ratio, achieved an excellent AUC of 0.934 with 91.2% specificity and 93.8% sensitivity and demonstrated good clinical utility in DCA and CIC which were evaluated for the first time among studies aiming to improve the prediction of the CoA.

Among the research concerning multiparameter models for CoA prediction, a few studies included the AoI/DA ratio into CoA prediction models as well. The prospective study of Jowett and coworkers [21] demonstrated that the combination of AoI diameter, AoI/DA ratio, aortic arch contraductal shelf, and persistent blood flow in the isthmus of the aortic arch improved the accuracy of predicting real-fetal CoA requiring perinatal surgery (86%). Marginean and associates [22] found that 83.3% of fetuses who simultaneously meet the requirements of RV/LV > 1.5, AoI < 4.2 mm, and DA/AoI < 1.4 do not need surgical treatment of CoA after birth.

LCSA from fetal echocardiography, proposed by Arya and associates [14], had good diagnostic effectiveness, with ROC of 0.87 (sensitivity 80%, specificity 95%). Patel and associates [16] found that the average distance of LCSA for fetuses diagnosed with CoA was longer than that of people in the false-positive and control groups. During the pregnancy process, LCSA distance remained relatively unchanged in the false-positive and control groups, while it had a significant increase in the real-CoA group (average weekly change). In our study, although LCSA distance obtained from fetal echocardiography did not show significant predictive value for the need for neonatal surgery, LCSA distance obtained in neonatal echocardiography was selected into the final prediction model as a powerful predictor for neonatal CoA repair. Actually, the finding that LCSA distance was longer in neonates with coarctation compared with control cohorts was first discovered by Dodge-Khatami [23] and further verified in Vigneswaran's study [19]. It has been proposed that aberrant flow into the aortic arch during the early stages of fetal development may have an impact on the aortic arch's morphology [14]. However, in our study the LCSA distance was not independently correlated with ventricular septal defect, hypoplastic aortic arch, or the

Table 4: Univariate and multivariate analysis of the echocardiographic parameters.

	OR	OR 95% CI	*P* value	OR	OR 95% CI	*P* value
Fetal echocardiographic parameter						
MV Z-score	0.494	0.295~0.827	0.007			
TV Z-score	0.695	0.436~1.106	0.125			
LV Z-score	0.928	0.610~1.413	0.729			
RV Z-score	0.856	0.493~1.487	0.582			
MPA Z-score	1.375	0.804~2.351	0.245			
AAo Z-score	0.599	0.376~0.955	0.031			
AoV Z-score	0.697	0.450~1.080	0.106			
DA Z-score	1.046	0.813~1.344	0.728			
AoI-3VT Z-score	0.577	0.391~0.851	0.006			
AoI-SAG Z-score	0.66	0.480~0.908	0.011			
TV/MV	2.756	0.201~37.731	0.448			
RV/LV	0.264	0.011~6.322	0.411			
MPA/AAo	12.988	1.893~89.097	0.009			
AoI/DA	0	0.000~0.045	0.002	0.002	0.000	0.000–0.006
TAo-DAo Angle > 100°	3.485	1.007~12.057	0.049			
AAo-DAo Angle < 7°	1.071	0.175~6.560	0.941			
LCSA	1.154	0.599~2.224	0.669			
DTAA	1.292	0.839~1.991	0.245			
DAI	0.661	0.184~2.375	0.526			
Neonatal echocardiographic parameter						
LCSA (mm)	1.464	1.044~2.052	0.027	0.008	2.485	1.270–4.862
DTAA (mm)	0.412	0.191~0.888	0.024	0.048	0.266	0.072–0.989
RV width (mm)	1.092	0.886~1.345	0.41			
LV width (mm)	0.992	0.941~1.046	0.763			
RV/LV	5.688	0.367~88.049	0.214			
MV Z-score	1.071	0.812~1.415	0.626			
TV Z-score	1.102	0.777~1.563	0.585			
MV/TV	1.292	0.048~34.890	0.879			
AAo Z-score	0.686	0.486~0.968	0.032			
AoI Z-score	0.63	0.444~0.894	0.01			
DAO Z-score	0.851	0.641~1.131	0.266			
PDA	1.442	0.887~2.343	0.14			
AoI/PDA	0.237	0.055~1.020	0.053			
CSAi > 0.7	3.485	1.007~12.057	0.049			

MV, mitral valve; TV, tricuspid valve; RV, right ventricle; LV, left ventricle; MPA, main pulmonary artery; AAo, ascending aorta; AoV, aortic valve; AoI, aortic isthmus; SAG, sagittal view; 3VT, three vessel and tracheal view; DA, ductus arteriosus; DTAA, distal transverse aortic arch; LCSA, the distance between the left common carotid artery and left subclavian artery; DAI, distal arch index; PDA, patent ductus arteriosus; AAo-DAo angle, ascending aorta-descending aorta angle; TAo-DAo angle, transverse aortic arch-descending aorta angle; DAO, descending aorta; PDA, patent ductus arteriosus; CSAi, carotid-subclavian artery index.

disproportion of the ventricles in fetal echocardiography. There are studies examining the impact of blood flow on the elongated aortic arch which revealed differences in flow characteristics compared with normal patients [24, 25]. Higher diastolic and systolic blood pressure were found in patients with an elongated aortic arch, which can lead to remodeling and thickening of the aortic wall [26]. It also offers a hint regarding hypertension that developed in the later years of individuals with corrected CoA. But the mechanisms of this phenomenon remain to be explored in future studies.

In previous studies, DTAA was seldom regarded as a single factor for neonatal prediction but was usually included as an indispensable part of the DAI or CSA index. In our study, the CSA index derived from neonatal echocardiographic data was statistically different between research groups; however, the DAI obtained from fetal echocardiography did not demonstrate a significant difference. In 2018, Patel and associates [16] proved for the first time the predictive value of the CSA index obtained from fetal echocardiography in identifying postnatal CoA. They also found that the CSA index of patient with CoA was significantly lower than that of the false-positive group and the control group. Frickek and associates [27] further verified that using CSA index >0.78 as diagnosis criteria, the sensitivity of the fetal diagnosis of CoA was 92.3% and the specificity was 96.8%. Fujisaki and associates [28] reported that the DA index, which can be closely related with (LCCA-LSCA/DT) as it is the ratio of the distance between the origin of the left carotid artery and the origin of the left subclavian artery and the diameter of the distal aortic arch, was useful for the detection of neonatal CoA patients who need surgical intervention. The limitation of the CSA index and the DAI is that they can only be obtained from the sagittal plane of the aortic arch, which is challenging to obtain due to the position of the fetus or the shadow cast by the echo spine in the

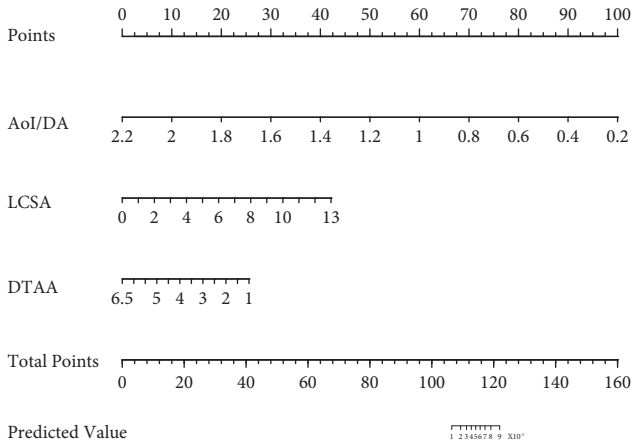

Figure 4: The nomogram for predicting the need for neonatal CoA repair. AoI/DA, aortic isthmus/ductus arteriosus diameter ratio; LCSA, the distance between the left common carotid artery and left subclavian artery; DTAA, distal transverse aortic arch.

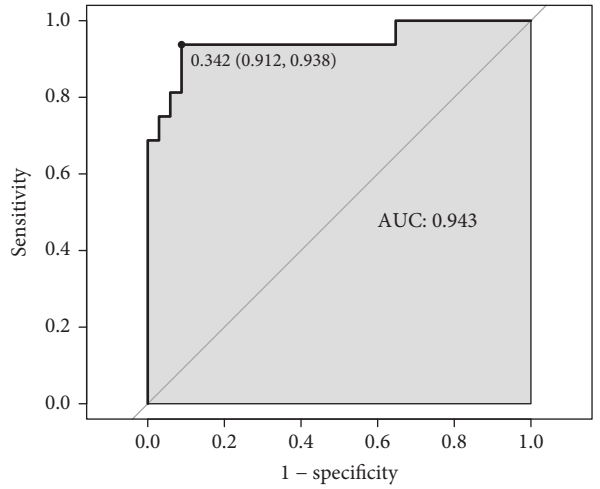

Figure 5: ROC curve of the model. The AUC was 0.943 (95% CI = 0.912–0.938). AUC, area under the ROC curve; ROC, receiver operating characteristic curve.

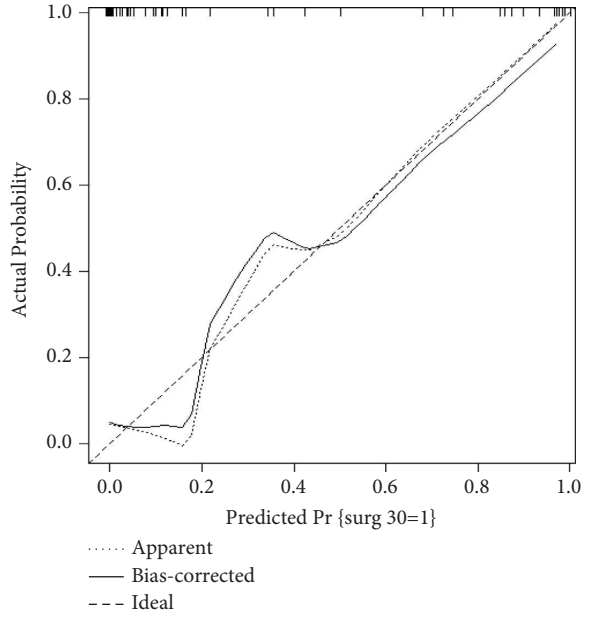

Figure 6: Calibration curve of the nomogram model.

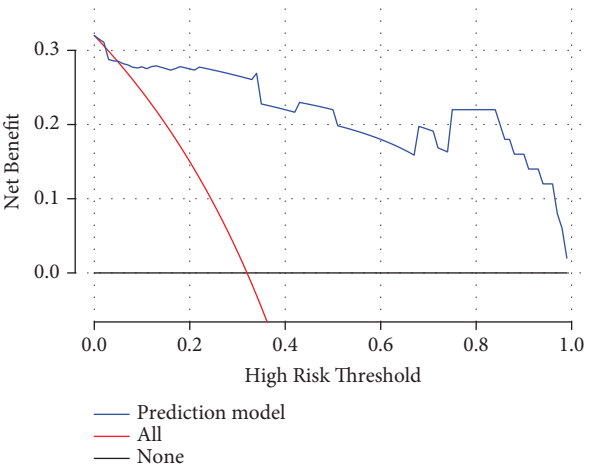

Figure 7: Decision curve of the nomogram model.

third trimester of pregnancy, and the image is relatively unclear, which may increase the measurement error [29].

In this study, angle-related indicators TAo-DAo angle and AAo-DAo angle were not selected in the final prediction model. While the AAo-DAo angle had no statistical difference between the study groups, the percentage of patients with a TAo-DAo angle > 100° was significantly higher in the NCoAR group in univariable analysis. Arya and coworkers [14] reported for the first time that the AAo-DAo angle and the TAo-DAo angle had good diagnostic efficacy as a single index in the prediction of CoA. The AUC for them to predict CoA is 0.99 and 0.98, respectively. Freeman and associates [15] later verified that the positive predictive value (PPV) and negative predictive value (NPV) of the prediction model combined AAo diameter, AAo-DAo angle, and TAo-DAo angle were 100% and 77%, respectively. The study from Benjamin and coworkers [14] proved that the AAo-DAo angle of the CoA fetus was sharper than that of the control group. While in a recent published research studyof Wang and associates [30], TAo-DAo angle and AAo-DAo angle had not shown statistically significant predictive value in multivariate regression analysis as well. Since the results of previous research study were not consistent completely yet, more studies based on larger population are needed to confirm the predictive value of TAo-DAo angle and the AAo-DAo angle.

As for intracardiac complications, our research revealed that the combination of PLSVC and BAV did not correlate substantially with the need for neonatal CoA surgery in fetuses suspected of having CoA, whereas the NCoAR group had a significantly higher proportion of patients with VSD. Results from previous studies also vary on the rate of CoA combined with PLSVC and BAV. In a previous meta-

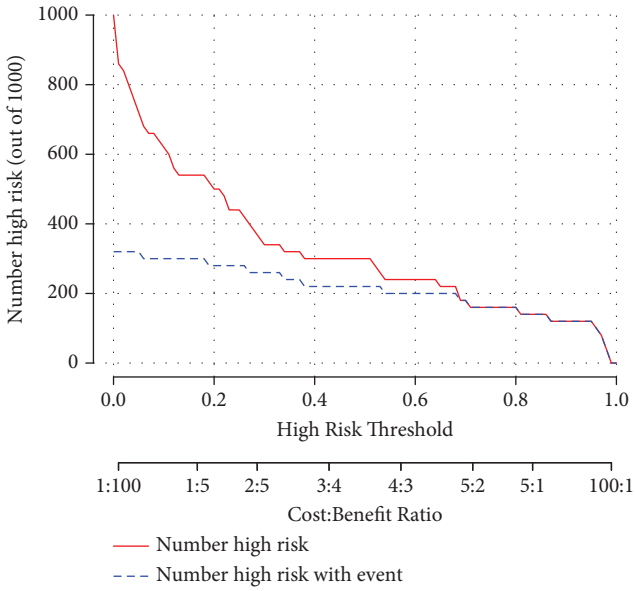

Figure 8: Clinical impact curve of the nomogram model.

analysis [6], PLSVC did not significantly increase the probability of CoA diagnosis, although the population differences in the included studies may have had an impact on this result. PLSVC was thought to be a potential independent risk factor for CoA in those who had no other troubling fetal echocardiographic findings. In addition, Gustapane and coworkers [31] thought that PLSVC was connected to the development of CoA. During the fetal period, the presence of the left superior vena cava, leading to relative right ventricular volume overload, thus leading the left and right ventricular volume imbalances, and subsequently intricates aortic coarctation. Subsequent research and postpartum follow-up may provide a clearer answer and clinically helpful conclusions. Although multiple studies [22, 32, 33] have shown a higher incidence of BAV in fetuses with a prenatal diagnosis of CoA, in this study, BAV was not significantly associated with the need for neonatal CoA repair. In the meta-analysis from Familiari and associates [6], it was confirmed that the prenatal detection of BAV was significantly correlated with the risk of postnatal CoA diagnosis, but the overall accuracy of CoA diagnosis was not good. Previous studies [28, 34, 35] reported that CoA patients often have ventricular septal defects, and this study further reported that CoA neonates with VSD are more likely to require surgical repair. Pathophysiological conditions such as shock and metabolic acidosis are the significant indicators for neonatal surgical treatment in patients with CoA. Also, left-to-right shunts of blood through the ventricular septal defect reduced the blood flow into the aorta and thus greatly reduced lower-body perfusion, making CoA children with VSD prone to suffer from systemic circulatory failure and thus need immediate surgical repair.

A large number of studies have shown that the multiparameter scoring system can reduce the occurrence of false-positive results [10]. While verifying the effectiveness of the diagnostic model in real clinical scenarios is of great significance for parental counselling, postpartum nursing planning, and clinical decision-making, most of the established prediction models, including ours, lack a prospective multicenter study to verify their effectiveness.

4.1. Limitation. This research has several limitations. First, it is a retrospective study conducted at a single center with a limited number of samples. A multicenter prospective study with larger study population is needed to support its effectiveness and clinical applicability. In addition, this study mainly focused on predicting neonatal CoA repair in patients suspected as CoA prenatally, without enrolling inpatients with false negative diagnosis but who turned out to be diagnosed with CoA, possibly yielding a selection bias.

5. Conclusions

Our research, as the first to take both prenatal and neonatal echocardiographic parameters into consideration, developed a prediction model. The model incorporating the prenatal echocardiographic parameter AoI/DA diameter ratio and the neonatal echocardiographic parameters LCSA and DTAA performed well in predicting the need for neonatal coarctation repair and showed good clinical utility in the DCA curve and CIC. Further studies focusing on the validation of the model with a larger study population and multicenter corporations are needed.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Qi Shi and Jiazhong Tang are the co-first author of this articles.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Qi Shi and Jiazhong Tang contributed equally to this manuscript.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant numbers 82170232 and 81974012).

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