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# A clinical prediction model to estimate the risk for coarctation of the aorta: From fetal to newborn life

Hui-Hui Wang[1], Xi-Ming Wang[2], Mei Zhu[1], Hao Liang[1], Juan Feng[1], Nan Zhang[1], Yue-Mei Wang[3], Yong-Hui Yu[4] and An-Biao Wang[5]

[1]*Department of Echocardiography, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China*
[2]*Department of Radiology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China*
[3]*Department of Echocardiography, Jinan Maternity and child care Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China*
[4]*Department of Neonatal Intensive Care Unit, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China*
[5]*Department of Cardiovascular Surgery, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China*

## Abstract

***Aim:*** A prenatal diagnosis of coarctation of the aorta (CoA) is challenging. This study aimed to develop a coarctation probability model incorporating prenatal cardiac sonographic markers to estimate the probability of an antenatal diagnosis of CoA.

***Methods:*** We reviewed 89 fetuses as an investigation cohort with prenatal suspicion for CoA and categorized them into three subgroups: severe CoA: symptomatic CoA and surgery within the first 3 months; mild CoA: surgery within 4 months to 1 year (29); and false-positive CoA: not requiring surgery (45). Logistic regression was used to create a multiparametric model, and a validation cohort of 86 fetuses with suspected CoA was used to validate the model.

***Results:*** The prediction model had an optimal criterion >0.25 (sensitivity of 97.7%; specificity of 59.1%), and the area under the receiver operator curve was 0.85. The parameters and their cut-off values were as follows: left common carotid artery to left subclavian artery distance/distal transverse arch (LCCA-LSCA)/DT Index >1.77 (sensitivity 62%, specificity 88%, 95% confidence interval [CI]: 0.6–0.8), and z-score of AAo peak Doppler > −1.7 (sensitivity 77%, specificity 56%, 95% CI: 0.6–0.8). The risk assessment demonstrated that fetuses with a model probability >60% should have inpatient observation for a high risk of CoA, whereas fetuses with a model probability <15% should not undergo clinical follow-up.

***Conclusion:*** The probability model performs well in predicting CoA outcomes postnatally and can also improve the accuracy of risk assessment. The objectivity of its parameters may allow its implementation in multicenter studies of fetal cardiology.

**Key words:** coarctation of the aorta, congenital heart disease, logistic regression, prediction model, prenatal diagnosis.

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**Correspondence:** Xi-Ming Wang, Shandong Provincial Hospital, Shandong University, #324, Jingwu Road, Jinan, Shandong 250021, China.
Email: wenddywang0903@163.com

 

## Introduction

Coarctation of the aorta (CoA) accounts for 5%–7% of all congenital heart disease (CHD) cases in the infant population.[1] The diagnosis of CoA prenatally is difficult for fetal cardiologists. The catheter organization theory states that the narrowing of the aorta is due to the displacement of smooth muscle cells growing in the aorta, the hemodynamic theory states that the narrowing of the aorta is due to the decrease in blood flow through the aortic arch during the fetal period, and these were responsible for the false negative and false positive diagnoses at fetal echocardiography.[2] Once the newborn is diagnosed with CoA, prostaglandin E1 (PGE1) can be administered immediately to maintain the patent ductus arteriosus (PDA), and surgery can be performed electively.[3,4] During the patency of the ductus arteriosus, severe constriction in the flow of the descending aorta will not occur antenatally, which leads to potential lethal consequences, such as a premature closure of the PDA during the postnatal life.[5–7] Findings and advances in imaging trends toward detailed morphology of the fetal aortic arch and isolated CoA may still avoid prenatal screening[8]; therefore, how to avoid abortion due to overdiagnosis and how to avoid excessive rates of mortality and morbidity due to omission remain unclear. An increasing number of ultrasound indirect indicators have been proposed in fetuses in addition to ventricular asymmetry to potentially improve the detection rate of prenatal diagnosis for CoA.[9–11] Multiple criteria-prediction diagnostic models that integrate different ultrasound signs to replace isolated parameters for the detection of CoA have already been described, and these especially include fetal echocardiographic scoring models, which have also been suggested descriptive indices for the shape of the aortic arch have been demonstrated to be successful in the diagnosis of CoA in children[12–14]; however, none of these indices has been validated in fetuses with equivocal findings that require observation.

This study primarily evaluated whether there are any novel parameters associated with the diagnostic accuracy of CoA and created a noninvasive model to help rule out or screen out CoA in a fetus with equivocal findings. The secondary aim was to calculate the probability of CoA procedurally and then validate it using a prospective validation cohort of fetuses, and this model can help clinicians classify patients with unconfirmed CoA and allows for risk profiling and decision making.

## Methods

### Study design investigation cohort and validation cohort population

Institutional review board approval was obtained for this study, and the need for patient consent was waived. A total of 89 fetuses that were suspected to have CoA and who underwent prenatal and postnatal echocardiography examinations in Shandong Provincial Hospital Central Campus and Shandong Maternity and Child Care Hospital from May 2015 to May 2020 were enrolled as the investigation cohort in this retrospective study. Based on their postnatal outcomes, the fetuses were further subdivided into the following groups: the true-positive group, which included those fetuses who subsequently required arch surgical repair. According to the operation time, the patients were divided into a severe group ($n = 15$); a mild group ($n = 29$); and a false-positive group ($n = 45$). To analyze the morphological differences of the aortas between the groups, 90 patients who had unobstructed aortic arches after birth were included as a control group. The validation cohort consisted of 86 fetuses from Shandong Provincial Hospital East Campus (November 2019 to May 2021) who were suspected to have CoA, and we prospectively collected the valuable parameters used to validate the model as a prospective study. The clinical decision was not made with the model. The fetuses were divided into the true CoA group ($n = 30$) and false CoA group ($n = 56$) according to whether they required surgical intervention (Figure 1). This study was performed at a tertiary first-class hospital. True CoA was defined as aortic arch coarctation requiring surgical intervention, which was based on clinical assessment,[15] as well as echocardiography and aortic computed tomography angiography (CTA) examinations. Prostaglandin dependence, an arm-leg blood pressure gradient >20 mm Hg, weak/absent femoral pulses, and decreased LV function are indications for surgical repair at our institution.[6] False CoA was defined as no clinical or echocardiographic evidence of CoA after PDA complete closure or after surgical ventricular septal defect (VSD) closure during follow-up. The exclusion criteria included pregnancy termination, fetal death in utero, difficulty in obtaining clear images, unavailable postnatal follow-up data, and other major extracardiac abnormalities, such as large VSDs (>4 mm), interruption of the aortic arch, transposition of the great arteries, a double outlet right ventricle, and atrioventricular septal. All fetuses

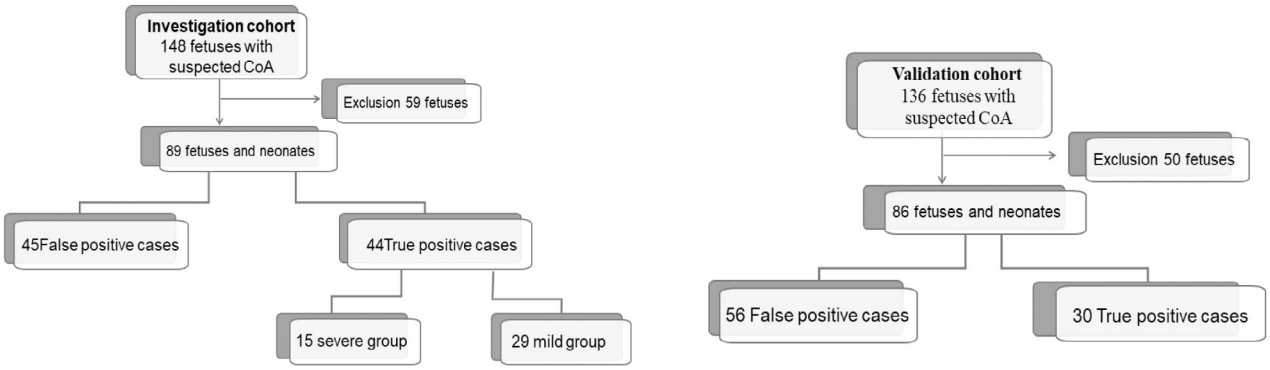


**FIGURE 1** Investigation cohort: retrospective review of 89 fetuses and neonates who met the inclusion criteria. Patients were divided into two groups: (1) the equivocal group, neonates with unconfirmed arch diagnoses who required observation in the NICU off of PGE, of whom 44 had CoA and 45 had unobstructed aortic arches, in the false-positive cases, 11 neonates with biventricular repair. Validation cohort: 136 met the inclusion criteria, but only 86 had all measurements performed. Of those 86, 30 neonates had CoA and 56 had unobstructed aortic arches

were assessed in our department, and most neonates were treated in our department. However, we obtained all follow-up information. The demographic and clinical data are shown in Table 1.

### Echocardiographic assessment

Fetal echocardiography was performed using a Philips IE33 or GE Vivid E9 ultrasound machine. All fetal echocardiogram data were analyzed offline from stored images and reports. In the standard section, measurements of the ascending aorta (AAo), main pulmonary artery (MPA), aortic isthmus (AoI), right ventricle end-diastolic dimensions (RVEDD), left ventricle end-diastolic dimensions (LVEDD), and mean AAo peak Doppler were obtained. The gestational age of the fetus was combined to calculate the z-score of these variables.[16,17] After blinding of the clinical outcomes, the characteristics of the investigation cohort were measured. From the sagittal aortic arch view during systole, we obtained the left common carotid artery to left subclavian artery distance/distal transverse arch (LCCA-LSCA)/DT (Figure 2a).[17–19] The ascending aorta to descending aorta (AAo-DAo) angle and transverse aorta to descending aorta (TAo-DAo) angle were measured as described in Figure 2b and c. All measurements were performed retrospectively by two blinded and experienced observers (Hui-Hui Wang and Feng Juan), who independently confirmed the presence of CoA. A single investigator (Nan Zhang) reviewed all of the measurements from the archived records.

Postnatal echocardiography was implemented using a Phillips IE33, Phillips CX50, or GE Vivid E9 device. The first echocardiogram was evaluated for the presence or absence of CoA within 24 h of birth. The diagnosis of CoA relied on the presence of a localized narrowing of the descending aorta just beyond the origin of the LSCA, together with high flow velocity (>2 m/s), complicated with a loss of pulsatility of the abdominal aorta. The presence or absence of a VSD, a bicuspid aortic valve (BAV), a left superior vena cava (LSVC), and a PDA were also noted. The decision to start prostaglandin E1 after birth was decided during the last assessment and was reviewed following the initial postnatal echocardiography. In inconclusive cases or when a PDA precludes a confirmation or an exclusion of the presence of CoA, clinical monitoring and subsequent echocardiographs were performed until such a diagnosis could be established, and then the patients were grouped according to the operation time. All of this information was recorded in each patient's file.

Analysis of the validation cohort was focused on the evaluation of the z-score of AAo, mean AAo peak Doppler, AoI, and the ratios of LCCA-LSCA/DT and TAO-DAO/AAO-DAO, which were obtained from previous investigative cohort research as prospective studies. After one and a half years, the demographic data and arch measurements for all of the fetuses and their outcomes were collected.

All statistical analyses were performed in SPSS 20.0 software (SPSS, Chicago, IL, USA) and MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium). Continuous variables are expressed as the mean values ± SD, whereas categorical variables are expressed as numbers or percentages.

 

**TABLE 1** Baseline characteristics of study participates

| Variables | Investigation cohort | | | | Validation cohort | | | Normal | |
|---|---|---|---|---|---|---|---|---|---|
| | Group | | | | Group | | | | |
| | Severe CoA ($n = 15$) | Mild CoA ($n = 29$) | False-positive CoA ($n = 45$) | $p$-Value | True CoA ($n = 30$) | False-positive CoA ($n = 56$) | $p$-Value | $n = 90$ | $p$-Value |
| GA at first echo, median (range) | 29.3 ± 3.9 | 28.5 ± 3.5 | 29.0 ± 3.7 | 0.746 | 28.1 ± 3.8 | 29.0 ± 3.7 | 0.266 | 26.7 ± 3.9 | 0.125 |
| ≤28 weeks (%) | 7 (47) | 14 (48) | 21 (26) | | | | | | |
| >28 weeks (%) | 8 (53) | 15 (52) | 34 (74) | | | | | | |
| GA at birth | 38 ± 1.4 | 38.5 ± 0.99 | 38 ± 1.3 | 0.627 | 38.6 ± 1.0 | 39 ± 1.3 | 0.354 | | |
| Gender | | | | | | | | | |
| F (%) | 7 (47) | 13 (45) | 21 (47) | | 14 (46) | 29 (52) | | | |
| | | | | | | 90 | | | |
| | | | | | | 90 | | | |
| M (%) | 8 (53) | 16 (55) | 24 (53) | | 16 (54) | 27 (48) | | | |
| AAo peak Doppler Z-score | −0.66 ± 1.3[a] | −1.4 ± 0.9 | −1.6 ± 0.9[a] | 0.042 | −0.81 ± 1.2[a] | −1.2 ± 1.1 | 0.149 | | |
| AAo Z-score | −0.34 ± 0.4[a] | −0.18 ± 0.6 | 0.15 ± 1.15[a] | 0.065 | −0.42 ± 1.0 | −0.18 ± 1.4 | 0.40 | | |
| MPA Z-score | 2.47 ± 0.8 | 2.41 ± 1.1 | 2.31 ± 1.1 | 0.477 | 2.80 ± 1.2 | 1.96 ± 0.97 | 0.001 | | |
| Mean RVEDD Z-score | 0.26 ± 1.5 | 0.24 ± 1.5 | −0.85 ± 2.0 | 0.520 | | | | | |
| Mean LVEDD Z-score | −3.89 ± 1.4 | −2.7 ± 1.5 | −2.5 ± 1.9 | 0.965 | | | | | |
| Mean RVEDD/ LVEDD | 1.67 ± 0.5[a] | 1.46 ± 0.5 | 1.34 ± 0.2[a] | 0.003 | 1.77 ± 0.9[a] | 1.21 ± 0.2[a] | 0.02 | | |
| Aortic isthmus Z-score | −4.68 ± 2.1[a] | −2.95 ± 2.3 | −2.43 ± 2.5[a] | 0.412 | −4.65 ± 2.0 | −2.32 ± 2.18 | 0.005 | | |
| VSD (%) | 7 (47) | 14 (48) | 11 (24.4) | 0.07 | 11 (36.7) | 16 (28.5) | 0.07 | 3 (3.3) | |
| LSVC (%) | 4 (27) | 6 (20.7) | 7 (15.5) | 0.584 | | | | 2 (2.2) | |
| BAV (%) | 3 (20) | 3 (10.3) | 2 (4.4) | 0.12[b] | | | | | |
| PFO restricted shunt (%) | 5 (33.3) | 4 (13.8) | 12 (26.7) | 0.296[b] | | | | | |
| AoI-R (%) | 5 (33.3) | 5 (17.2) | 7 (15.6) | 0.41[b] | | | | | |
| AAo-DAo/ TAo-DAo angle ratio | 0.39 ± 0.1 | 0.38 ± 0.4 | 0.33 ± 0.1 | 0.089 | 0.25 ± 0.4 | 0.29 ± 0.9 | 0.101 | 0.2 ± 0.05 | 0.089 |
| LCCA-LSCA/ DT diameter ratio | 2.1 ± 0.8[a] | 1.4 ± 0.8[a] | 1.3 ± 0.4[a] | <0.001 | 1. 8 ± 0.4[a] | 1.3 ± 0.3[a] | <0.001 | 1.0 ± 0.8[a] | .<0.001 |

(*Continues*)

**TABLE 1** Continued

| Variables | Investigation cohort | | | | Validation cohort | | | Normal | |
|---|---|---|---|---|---|---|---|---|---|
| | Group | | | | Group | | | | |
| | Severe CoA ($n = 15$) | Mild CoA ($n = 29$) | False-positive CoA ($n = 45$) | *p*-Value | True CoA ($n = 30$) | False-positive CoA ($n = 56$) | *p*-Value | $n = 90$ | *p*-Value |
| AAo-DAo angle | 39.1 ± 14.8[a] | 34.3 ± 19.1[a] | 31.0 ± 15.1[a] | 0.001 | | | | 17.9 ± 4.2 | <0.001 |
| TAo-DAo angle | 100.6 ± 11.7 | 100.8 ± 21.8 | 95.5 ± 16.9 | 0.057 | | | | 92.4 ± 6.4 | 0.057 |

*Note*: Data is described as mean ± SD unless otherwise stated.; Abbreviations: AAO, ascending aorta; AoI-R, aortic isthmus retrograde; BAV, bicuspid aortic valve; DAO, descending aorta; GA, gestational week; LCCA-LSCA/DT, Left Common Carotid Artery to Left Subclavian Artery distance/Distal Transverse Arch; LSCA, left subclavian artery; LCCA, left common carotid artery; LSVC, left superior vena cava; LVEDD, left ventricle end-diastolic dimensions; MPA, main pulmonary artery; PFO, patent foramen ovale; RVEDD, right ventricle end-diastolic dimensions; TAO, transverse aorta; VSD, ventricular septal defect.; [a]Statistical significance was set at a $p < 0.05$. and [b]Fisher's exact test for all pair-wise differences is not significant at $\alpha = 0.017$.




**FIGURE 2** (a) ① Distal transverse arch diameter (between LCCA and LSCA); ② DT transverse arch diameter; (b) (AAo-DAo) angle ①: defined as the angle between two straight lines: Along the internal boundary, a straight line from the proximal to the distal in the AAo; and the second line was drawn distal (distal thoracic aorta) to proximal (just prior to the isthmus) of the DAo. (c) (TAo-DAo) angle ②: formed by two straight lines: a straight line was drawn from the proximal (from the first head vessel) to the distal (to the third head vessel) of aortic arch and the second line was drawn along the DAo as described in the preceding text

The continuous variables were compared between the groups using the unpaired *t* test. The *t* test or analysis of variance was used for normally distributed and nonnormally distributed data using the Mann–Whitney *U* test. The categorical variables were compared using the Pearson $\chi^2$ test or Fisher's exact test. Statistical significance was established at $\alpha = 0.017$, and the Bonferroni correction method was used for the three between-group comparisons. One-way ANOVA tests were performed to assess the factors

 

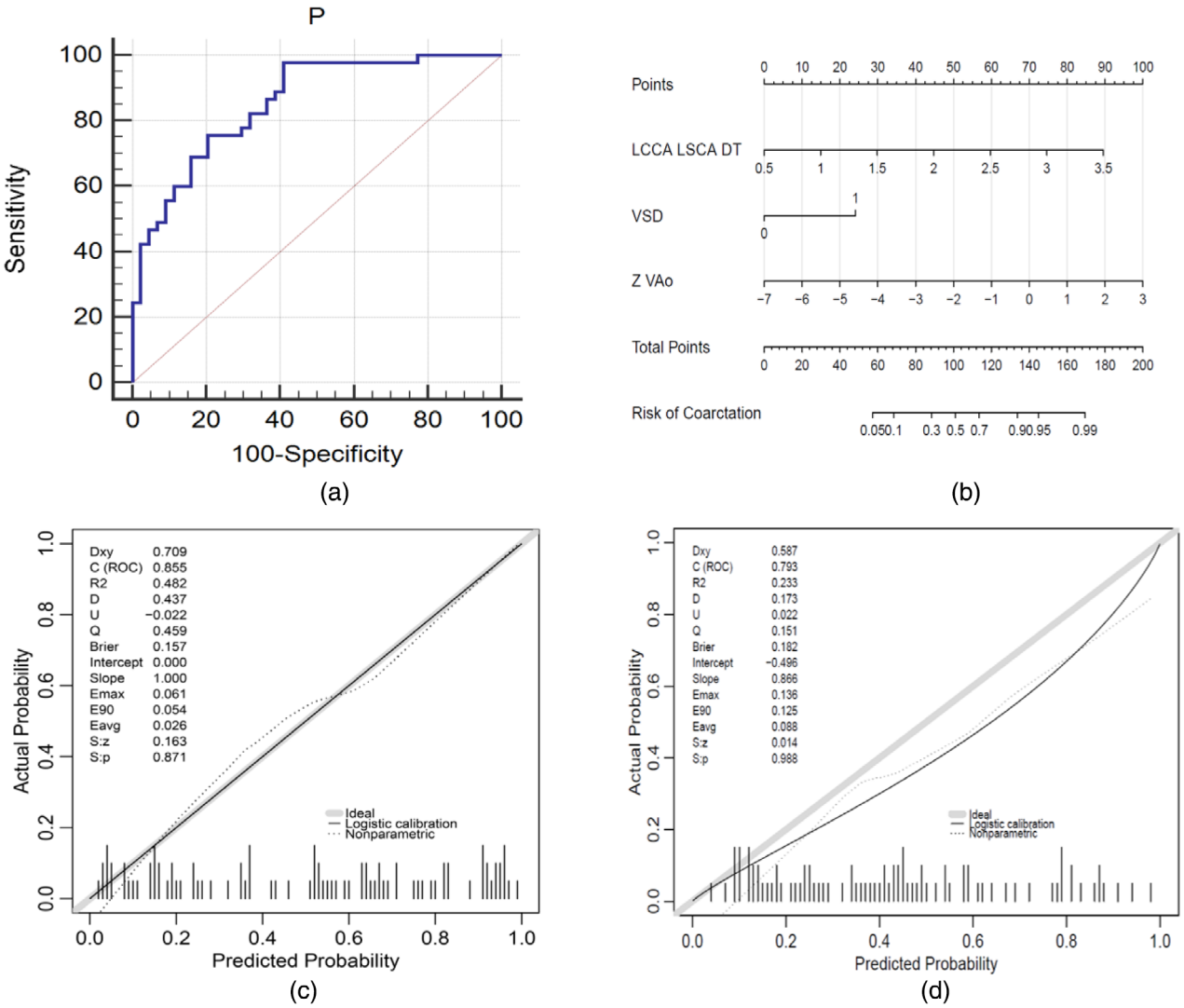


**FIGURE 3** (a) The area under the receiver operating characteristic curve (AUC) for the model was 0.85. (b) The nomogram allows the calculation of coarctation probability using the logistic regression model. Calculate the LCCA-LSCA/DT, VSD, and Z value of VAo indices, find the point values for each of these indices in the nomogram, drawing a vertical line from the values measured for each index to the "points" scale at the top of the nomogram. Add up the points for all three indices to obtain the total points for that patient. Find the total number of points on the "total points" scale, then draw a vertical line down to the "risk of coarctation" scale to find the predicted probability of CoA. (c) Results of internal validation for the model. (d) External calibration using the validation cohort shows the actual versus predicted probabilities using loess smooth function with 95% bootstrap confidence interval (CI)

associated with coarctation. A receiver operating characteristic (ROC) curve was generated to compare the diagnostic performance of the model and to determine the cut-off values of the discriminative parameters. We fitted an equation for our model using logistic regression analyses to estimate the probability of CoA, which characterized the discriminative parameters to assess their interdependence and to select the best combination. The model was internally validated and calibrated using bootstrapping. R version 4.0.5 (Shake and Throw) was used to generate a nomogram for the binary logistic regression predictive models (Figure 3b). The level of statistical significance was set at $p < 0.05$.

## Results

### The patient population of the investigation cohort

There were 148 fetuses included who were suspected to have CoA during the study period in the investigation cohort; 59 fetuses were excluded. We excluded 13 fetuses with inadequate fetal imaging, 15 fetuses with insufficient postnatal follow-up data, and 8 patients died (3 fetuses died in utero and 5 patients died perioperatively). Fetal karyotyping was performed in 80 cases, and 23 of the fetuses were miscarried (2 miscarriages due to trisomy 18, 3 miscarriages due to trisomy 21, 1 miscarriage due to urinary malformation, 3 miscarriages due to nervous system malformations). This left 89 fetuses included for the analysis. The median follow-up was 4.2 years, with a maximum follow-up of 6.8 years. Coarctation of the aorta was confirmed postnatally in 44 (49%) patients. Fifteen (16.8%) patients had CoA and underwent surgery within 3 months of birth (median 52 days), and 29 patients underwent aortic arch surgery within 3 months to a year after birth (median 297 days); the remaining 45 (50.6%) patients (false-positive group) were not confirmed to have coarctation after clinical and echocardiographic assessment during the initial assessment or during subsequent follow-up. Eleven of them only underwent VSD closure surgery without coarctation intervention. None of the controls had any additional defects.

### Fetal echocardiographic findings and modeling of the investigation cohort

The fetal echocardiographic characteristics are outlined in Table 1. In the investigation cohort, patients in the severe group had a higher RVEDD/LVEDD ratio and a higher z score of the ascending aorta peak velocity (z-VAo), whereas they had smaller z scores of AAo and aortic ischemus. The gestational age (GA), the main pulmonary artery (MPA) z-score, retrograde blood flow in the aortic isthmus (AoI-R), BAV, a patent foramen ovale (PFO)-restricted shunt, or LSVC were not associated with the postnatal intervention. Small VSDs were observed more frequently in the severe group than in the other groups, but this was not statistically significant between the three subgroups. The indicators of LCCA-LSCA/DT, AAo-DAo angle, and TAo-DAo angle were compared between 90 control fetuses and the investigation cohort. The LCCA-LSCA/DT diameter ratio and AAo-DAo angle demonstrated statistical significance in predicting CoA compared within the four study groups; the severe group demonstrated a higher LCCA-LSCA/DT diameter ratio toward the false-positive CoA group ($2.12 \pm 0.86$ vs. $1.31 \pm 0.47$, $p < 0.001$). The AAo-DAo angle was also larger in the severe group. The differences in the TAo-DAo angle and TAo-DAo/AAo-DAo angle ratio between the four groups were not statistically significant ($p > 0.05$). The interobserver agreement achieved satisfactory results, with intraclass correlation coefficients (ICCs) for all variables ranging from 0.7 to 0.9 in this investigation cohort.

The model was created using the investigation cohort. The equation is $p = (1 + \exp[-1.423 + 1.969*(\text{LCCA-LSCA/DT}) + 1.62*\text{VSD} + 0.665*(\text{z-VAo})])^{-1}$. Among the three predictors, higher LCCA-LSCA/DT (OR = 7.1, CI: 2.6–19.3), VSD (OR = 5.0,CI:1.6–15.8), and z-VAo (OR = 1.9, CI: 1.3–3.1) were related to an increased risk for CoA. With the ROC curve, we determined the cut-off value for these predictors (LCCA-LSCA/DT >1.77, z-VAo > −1.7). For the predictive model, the area under the receiver operating characteristics (AUROC = 0.85, 95% CI: 0.76–0.92) with performance metrics (a sensitivity of 0.97 and a specificity 0.59) has good predictability for detecting CoA (Figure 3a). Among all the variables studied, the LCCA-LSCA/DT diameter ratio from the model had the highest sensitivity (62%) and specificity (88%) for detecting CoA (AUROC = 0.76, 95% CI: 0.65–0.86). Bootstrapping was used to validate and calibrate the model internally (Figure 3c). Figure 3d depicts the calibration curve of the model, which predicted and observed the data fitting effect. The plot demonstrates good calibration and minimal overfitting.

### The patient population of the validation cohort

The validation cohort consisted of the echocardiographic characteristics of 136 eligible fetuses that were prospectively collected, and these characteristics were used to validate the model. The median follow-up time was 2.1 years, with a maximum follow-up of 6.3 years, and only 86 patients had all measurements performed. In this cohort, 30 patients developed CoA that required intervention, and 56 patients did not develop stenosis at the last follow-up. The model was applied to all 86 fetuses echocardiographic data sets, and it showed good discrimination between patients with CoA and patients without CoA. Figure 4 demonstrates the risk stratification of CoA for fetuses among all of the groups. As we can see from this output, no

 

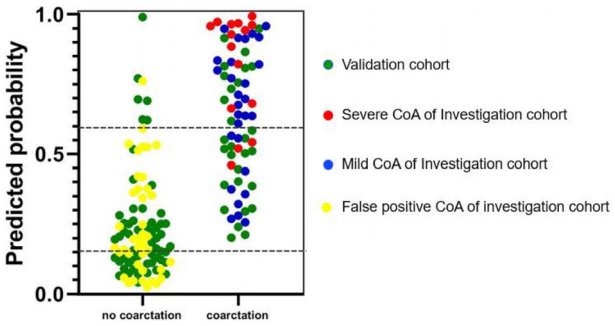


**FIGURE 4** Risk stratification using the model. Fetus with probabilities <15% were assigned to the category of low risk for CoA, those with probabilities of 15% to 60% to the moderate-risk category, and those with probabilities >60% to the high-risk category

fetuses with a model probability <15% had CoA, while 58 fetuses with a probability >60% had CoA.

## Discussion

Our study highlights the prenatal echocardiographic variables comprised of LCCA-LSCA/DT, small VSD and z-VAo that were associated with the intervention whether needed in fetuses suspected of CoA. In the present collaborative study, the diagnosis of CoA is possible and is best facilitated by the observation of quantitative distal aortic arch hypoplasia.[4,20] The morphological characteristics of the aortic arch indices, such as the LCCA and LSCA diameter of the DT arch, have already been applied to postnatal echocardiograms.[11,20–24] Our study examined the fetal echocardiographic arches and applied these characteristics as indicators in order to identify CoA prenatally. Compared with postnatal echocardiography, the evaluation of the fetal aortic arch added the benefit of permitting simultaneous visualization of the AAo-TAo and AAo-DAo angles.[10]

Among the true-positive coarctation fetuses, a surprising finding was that neither a narrow measurement at the isthmus nor a retrograde blood flow of the isthmus (AoI-R) was seen more often; in addition, bidirectional flow was observed in a fair number of fetuses who did not develop coarctation postnatally. The LSVC, ventricular size disproportion, and PFO restricted shunt did not help in diagnosing true coarctation. VSD was more common in the true-positive group, which clearly illustrates that aortic coarctation is often associated with VSD. The defect should be an insufficient increase in aortic flow that produces severe obstructive lesions to the aortic arch under the influences of hemodynamics and embryology. We found that many patients achieved rather satisfactory flow velocity after undergoing BV repair. In conclusion, we feel that it is important for clinicians dealing with VSDs to be aware of CoA and to select an opportune operation time for infants with both VSD and CoA.

The measurement of the morphology of the aortic arch showed a very clear pattern; at the very least, we can say that as the ratio of LCCA-LSCA/DT increases, the degree of constriction also increases. We suggest that a higher LCCA-LSCA/DT (>1.7) can be used as an indicator of coarctation throughout pregnancy. The higher the ratio is, the higher the specificity of the diagnosis whereas with a reduced sensitivity to the constriction. The same conclusion applies to a higher z-VAo, which leads to lower flow resulting in abnormal narrow growth of the vessels of the aortic arch, which is, not surprisingly, a common fact in fetal cardiology. Although the angle of the aortic arch was not included in the model, compared with the normal group, the AAo-DAo angle was still meaningfully distinguished in the true-positive group compared to the false-positive group. The angle between AAo-DAo and TAo-DAo in the diseased group was more obtuse, which is different from the results of the study by Bhawna et al.[23]

We analyzed the Spearman correlation coefficient between LCCA-LSCA/DT and AAo-DAo/TAo-DAo and found that there was a weak negative correlation between the two in the normal group. As the degree of constriction increased, the two parameters showed an improved positive correlation; that is, as the distance between LCCA-LSCA increased, the morphology of the entire arch tended to be more obtuse. We theorize that during the early embryological development of the aorta arch with coarctation, the course of insertion of the descending aorta into the proximal descending aorta leads to the loss of its original soft shape and is replaced by isthmus collapse, which demonstrates that the anatomy of the descending aorta itself has a factor in the occurrence of CoA and especially illustrates the potential impact on the shape of the arch. Our opinion is identical to Benjamin, who demonstrated that the AAo-DAo angle was more acute in fetuses with CoA.[25] This also explains why the ratio of AAo-DAo/TAo-DAo angles in the real CoA group was greater than that in the false-positive group in this study.

Although more experienced echocardiographers had a higher accuracy in diagnosing CoA, the measurements of the aortic arch that were recorded by the echocardiographers correlated well. The measurements of the aortic arch parameters that were used to calculate the prediction model in the validation cohort were performed prospectively without any remeasures to confirm these data, which makes it more intuitive and accurately improves the overall clinical workflow. By entering the three individual components, namely, the LCCA-LSCA/DT, z-VAo, and VSD, into a digital picture archiving or by using Figure 3b, the probabilities can be calculated against the index data constituting our model. The calibration accuracy of our original model was perfect through the internal calibration. It is almost the same as the external validation, which performs good fitting degrees with very low actual prediction probabilities. Perhaps ultrasonographers and obstetricians could help to improve fetal echocardiography and could avoid high abortion rates.

Figure 4 demonstrates the risk stratification of CoA for fetuses among all of the groups. As we can see from this output, no fetuses with a model probability <15% had CoA, while 58 fetuses with a probability >60% had CoA. There was one fetus from the investigation cohort and in the mild group with PFO-restricted shunts whose aortic arch was thought to be unobstructed with PDA after the postpartum echocardiography was carried out; however, this patient returned to our hospital due to heart failure 6 months after birth and had a surprising finding of CoA. After immediate surgical repair, her left ventricular ejection fraction returned to normal within a month. The antenatal echocardiogram of this patient was analyzed in the investigation cohort, and the model estimated a 43% probability of CoA. Although it belongs to the moderate-risk category, we recommend that fetuses with probabilities above 15% should undergo follow-up imaging until PDA closure.

As in our previous study,[26] women pregnant with fetuses suspected to have CoA presented with heightened levels of anxiety and depression compared with women pregnant with fetuses having serious heart disease. Our model can provide more effective counseling for pregnant women who are shocked and scared, thereby helping them to be better prepared for their delivery.

The model possesses high accuracy and can be applied for an antenatal diagnosis of CoA simply and efficiently. We recommend that fetuses with model probabilities<15% do not need to be observed or hospitalized, while fetuses with model probabilities>60% need inpatient observation until PDA closure. We suggest that the time frame of this follow should be 7 years. The fetal ultrasound parameters of the (LCCA-LSCA)/DT, (AAo-DAo) angle, (TAo-DAo) angle and a higher peak AAo Doppler velocity may allow the implementation of the model in fetal cardiology research centers.

### Limitations

We were unable to further investigate the association between the AAo peak velocity and VSD with aortic arch dysplasia because of inadequate patient numbers. Future large prospective studies and multiparametric diagnostic models are needed to quantify the diagnostic performance of ultrasound in detecting CoA prenatally.

In conclusion, the variables associated with postnatal CoA intervention comprised LCCA-LSCA/DT, z-VAo, and VSD. The model performed well in predicting the need for surgical intervention in postpartum CoA and could be used to evaluate the risk stratification of postpartum CoA. It could also be a basis for pilot surgeries for this disease in the fetal multidisciplinary diagnosis and treatment model.

## Author contributions

All measurements were collection retrospectively and blinded by reviewers (Hui-Hui Wang, Juan Feng and Nan Zhang) to the outcomes by experienced investigators (Mei Zhu, Hao Liang and Yue-Mei Wang) confirming CoA. Xi-Ming Wang is assigned as corresponding author edited this manuscript and as advisor of Hui-Hui Wang. Neonatal monitoring and surgery were carried out by An-Biao Wang and Yong-Hui Yu.

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## Conflict of interest

All authors declared that they have no conflicts of interest to this work.

## Data availability statement

Original data that support the findings of this study have been deposited using this link: https://datadryad.org/stash/share/1lR9LEwS3aoBMYUYb3VsV5A2S6jpHOXmckJ_rICXrIw. Our dataset has also been assigned a DOI https://doi.org/10.5061/dryad.vdncjsxvf. This statement will be published alongside our manuscript if it is accepted for publication.

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