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A Clinical Prediction Model to Estimate the Risk of Coarctation of the Aorta in the Presence of a Patent Ductus Arteriosus

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Abstract

Objective—To create a model to help identify coarctation of the aorta (CoA) in neonates with a patent ductus arteriosus (PDA).

Background—Diagnosing CoA in the presence of a PDA may require observation until PDA closure. We created a model incorporating previously published indices to estimate the probability of neonatal CoA in the presence of a PDA.

Methods—A retrospective “investigation” cohort of 80 neonates was divided into two groups: (1) neonates with PDA and suspicion for CoA requiring observation to confirm the presence or absence of CoA and (2) neonates with PDA and confirmed diagnosis of either CoA or unobstructed aortic arch. Multivariable logistic regression was used to create the coarctation probability model (CPM), which calculates a neonate's probability of CoA. The CPM was validated internally using bootstrapping and subsequently validated prospectively using a “validation” cohort of 74 neonates with PDA.

Results—The CPM had an area under the ROC curve of 0.96 and demonstrated good clinical significance in risk stratification of neonates with a PDA and CoA. No neonate with a CPM probability of <15% had CoA after PDA closure. We classify neonates with CPM <15% as low-risk, between 15–60% as moderate-risk, and > 60% as high-risk for CoA.

Conclusion—Based on our study results, we recommend measurement of the CPM in all neonates with PDA. Those with CPM <15% no longer require observation, which could decrease observation in as many as half of neonates with unobstructed aortic arch; those with CPM between 15–60% require follow up imaging while those with CPM >60% risk should be observed as inpatients until PDA closure.

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Keywords

Coarctation of the aorta; Congenital heart disease; Patent ductus arteriosus; Neonate; Logistic regression model

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INTRODUCTION

Coarctation of the aorta (CoA) is a common congenital heart defect characterized by aortic arch obstruction, typically at the insertion point of the ductus arteriosus. Failure to diagnose CoA promptly can lead to heart failure, shock, and death. Echocardiography is the primary imaging modality used to diagnose CoA. While the diagnosis is more difficult in neonates with a patent ductus arteriosus (PDA), findings such as an elevated descending aortic velocity, posterior shelf, or markedly hypoplastic transverse arch can still help make the diagnosis. Once the diagnosis is reached in a neonate, prostaglandin E₁ (PGE) can be administered to re-open or enlarge the PDA and alleviate the obstruction prior to surgical repair. [1]

Because a PDA can normalize the descending aortic Doppler velocity and aortic arch diameters, a subset of neonates with CoA and PDA have more subtle findings that are only unmasked after PDA closure. Although these findings are subtle, the resultant aortic arch obstruction is no less critical. These neonates require close observation in the neonatal intensive care unit (NICU) without PGE to determine whether they have CoA. For the purposes of this study, we term this subset of neonates “equivocal” Neonates in this “equivocal” category who ultimately have CoA but are discharged home prior to PDA closure may present in shock or even die at home. Those “equivocal” neonates who do not develop CoA can require extended stays in the NICU that increase healthcare costs and familial stress.

Several echocardiographic indices have been developed to help diagnose CoA. These include the carotid artery to distal transverse arch (CA/DT) index, the carotid to subclavian artery (CSA) index, and the isthmus to descending aorta (I/D) index. The CA/DT is the diameter of the common carotid artery (left common carotid in a left arch and right common carotid in a right arch) divided by the diameter of the distal transverse arch (Figure 1A). [2–4] The CSA is defined as the distal transverse arch diameter divided by the distance from the common carotid artery (left common carotid in a left arch and right common carotid in a right arch) to the subclavian artery (left subclavian artery in a left arch, right subclavian artery in a right arch)(Figure 1B). [5, 6] The I/D is defined as the diameter of the aortic isthmus divided by the diameter of the descending aorta (Figure 1C). [6, 7] While these indices have demonstrated some success in diagnosing CoA in children of varying ages, none of these indices has been validated in a population of “equivocal” infants requiring observation without PGE.

The goal of this study was to create a non-invasive measure to help diagnose or rule out CoA in “equivocal” neonates requiring observation without PGE. A logistic regression model, termed the coarctation probability model (CPM), was created by incorporating the CA/DT, CSA, and I/D indices into a more comprehensive tool for diagnosis of neonatal CoA. The CPM was created using a retrospective cohort of neonates with a PDA (investigation cohort) and then validated using a prospective cohort of neonates with a PDA (validation cohort).

METHODS

Overview

This study was approved by the Vanderbilt University Medical Center Institutional Review Board. All neonates included in the study were evaluated at Vanderbilt from 2005–2011. The “investigation” cohort was retrospectively analyzed (3/2005–3/2010) to develop the logistic regression model, or CPM; the CPM was externally validated using a prospective “validation” cohort (5/2011–11/2011).

Investigation Cohort

The investigation cohort was identified by searching the echocardiographic database and consisted of 80 neonates (<1 month of age) with a PDA. Based on review of medical records, neonates with gestational age under 34 weeks, major extracardiac abnormalities, and complex congenital heart disease were excluded. This cohort was divided into 2 groups (Figure 2A): (1) equivocal and (2) control.

Equivocal Group: consisted of neonates with echocardiographic features suggestive of CoA observed in the NICU without PGE. These neonates were observed during closure of the ductus arteriosus until they could be classified as either having CoA or unobstructed aortic arch.

Control Group: consisted of neonates with a PDA, classified as having either CoA or unobstructed aortic arch on initial echocardiogram. Neonates in the control group did not require observation during closure of the ductus arteriosus.

Coarctation of the aorta was defined as an aortic arch obstruction requiring surgical intervention. Diagnosis of CoA in the investigation cohort was based on clinical assessment including presentation with shock, abnormal femoral pulses, abnormal 4-extremity blood pressures, significant arch hypoplasia by 2-dimensional (2D) echocardiography, and/or increased descending aortic velocity by pulse wave Doppler. All had operative confirmation of significant arch hypoplasia. All had retrospective, blinded review of echocardiographic images by experienced investigators (JS and DP) confirming CoA.

Unobstructed aortic arch was defined as no clinical or echocardiographic evidence of CoA after complete closure of the ductus arteriosus. All neonates in the equivocal and control groups who were classified as having an unobstructed aortic arch had a follow-up echocardiogram confirming this diagnosis after closure of the ductus arteriosus.

Neonates with inadequate echocardiographic image quality were removed from the study. Out of the 88 neonates who met inclusion criteria, 8 neonates were removed due to inadequate image quality, leaving a total of 80 neonates in the investigation cohort (Figure 2A).

Data Collection, Investigation Cohort

Four echocardiographers, blinded to clinical outcomes, reviewed the de-identified echocardiographic images from the investigation cohort. Images consisted exclusively of 2D and color Doppler views of the aortic arch obtained from the suprasternal notch. From these images, the measurements labeled in Figure 1 were performed. In addition, the echocardiographers qualitatively estimated the presence or absence of CoA in each neonate based only on 2D and color Doppler imaging.

Statistics

Descriptive statistics are presented as median (interquartile range [IQR]) or percentage (N) as appropriate. Continuous variables were compared with Wilcoxon test and dichotomous variables with Pearson test. Agreement on arch measurements among the four echocardiographers was assessed with intraclass correlation coefficient (ICC).

We fit a logistic regression model, or coarctation probability model (CPM), to estimate the probability of CoA incorporating the CA/DT, CSA, and I/D indices. These indices include five aortic arch measurements: carotid artery diameter, distal transverse arch diameter, distance from the left common carotid artery to the left subclavian artery, isthmus diameter, and descending aorta diameter (Figure 1). The nonlinear terms of the three indices were tested as a group and were removed if the result was non-significant. The CPM was internally validated and calibrated using the bootstrapping technique. [8] Descriptive statistics were used to compare CPM results with the qualitative analysis by echocardiographers. All analyses were done with the statistical programming language R, version 2.14.1 (R Development Core Team, Vienna, Austria). The level of statistical significance was set at $p < 0.05$. Study data were collected and managed using RED Cap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt. [9]

Validation Cohort

The validation cohort consisted of prospectively collected aortic arch measurements used to validate the CPM (Figure 2B). Neonates with a PDA who had echocardiograms performed between May and November 2011 were included in this cohort. Neonates with hypoplastic left heart syndrome (HLHS) were excluded because retrograde flow in the aortic arch might lead to anatomical differences that invalidate the CPM. Echocardiographers in our institution were trained to perform aortic arch measurements for the three indices described in Figure 1. These trained echocardiographers prospectively performed offline measurements in neonates with a PDA over a 6-month period (5/2011-11/2011). During that time period, 146 neonates met inclusion criteria; a full set of arch measurements was performed in 74 neonates. In these neonates, the CPM was not used for clinical decision-making. At the conclusion of the 6-month period, investigators collected demographic data and measurements for all neonates in the validation cohort. Neonates with CoA in the validation cohort were diagnosed based on clinical assessment and this diagnosis was confirmed by the surgeon at operative repair.

RESULTS

Investigation cohort

Demographics—Of the 80 neonates in the investigation cohort, there were 22 neonates in the equivocal group observed off PGE due to concerns for possible CoA, and 58 control group neonates identified by the investigators as definitively having CoA or an unobstructed aortic arch. Within the equivocal group, 9 neonates had CoA and 13 had an unobstructed aortic arch; in the control group, 33 neonates had CoA and 25 had an unobstructed aortic arch. There were no significant differences in weight, gestational age, or race between equivocal and control groups or between neonates with and without CoA (Table 1A and 1B). Comparison of neonates with CoA in the equivocal and control groups demonstrated that neonates in the equivocal group had more pre-operative echocardiograms (median of 5.1 vs 2.3, $p < 0.001$), a longer time between initial echocardiogram and surgery (median of 7.4 days vs 3.8 days, $p = 0.017$), and a longer pre-operative hospital stay (median of 7.4 days vs 4.1 days, $p = 0.023$). Associated congenital heart disease (CHD) in these neonates is categorized in Tables 2A and 2B. In addition, 11 neonates had aortic arch branching abnormalities (13.8%): 8 had brachiocephalic trunks (10%) and 3 had aberrant right

subclavian arteries (2.5%). Fifteen neonates (18.8%) had a prenatal concern for CoA. Of the 15 neonates with prenatal concern for CoA, 9 (60%) were found to have CoA postnatally.

Individual Indices and Modeling

In the control group of neonates with a definitive diagnosis of CoA or unobstructed arch, the CSA, I/D, and CA/DT indices were each statistically significant in predicting CoA ($p < 0.001$). In the equivocal group of neonates that required observation in the NICU without PGE, the CSA and CA/DT indices were statistically significant in predicting CoA ($p < 0.05$), while the I/D index did not reach statistical significance ($p = 0.209$). However, despite this statistical significance, the CSA, I/D, and CA/DT indices exhibited significant overlap in both groups (Figure 3), demonstrating poor clinical utility in discriminating between CoA and unobstructed aortic arch.

Using the investigation cohort, a multivariable logistic regression model, or CPM, was developed to estimate the probability of CoA. We selected CA/DT, I/D, and CSA DT/CA_SC) to be included in the model based on clinical relevance; the odds ratios and 95% confidence intervals (CIs) for each of the three predictors' influence on the risk of CoA are presented in Table 3. Among the three predictors, CA/DT and I/D met statistical significance at an α level of 0.05. Higher CA/DT and lower I/D were associated with increased risk of CoA.

We used bootstrapping to internally validate and calibrate the model. Figure 4A depicts the model's calibration curve, which plots the predicted vs. observed values. The plot demonstrated minimal over-fitting and good calibration. The CPM had a concordance (c) statistic of 0.96 (95% CI 0.88–0.99) (Figure 4B). The equation for the model is: $\text{Probability} = [1 + \exp(-[-2.02 + (12.5)(\text{CA/DT}) - (9.8)(\text{I/D}) - (0.601)(\text{DT/CA\_SC})])]^{-1}$ where CA = carotid artery diameter, DT = distal transverse arch diameter, I = isthmus diameter, D = descending aorta diameter, and CA_SC = distance from the left carotid artery to the left subclavian artery. Inserting each individual measurement into the CPM equation provides a probability (as a percentage) of that patient having CoA. Table 4 lists multiple cut-points and the associated sensitivity and specificity. The CPM reliably differentiated between CoA and unobstructed aortic arch in the equivocal and control groups (Figure 5A).

Validation cohort—During the 6-month period of analysis for the validation cohort, 146 neonates with a PDA had echocardiograms performed. During routine echocardiographic interpretation, the CPM was measured in 74 of these neonates (51%). In neonates with multiple echocardiograms, the earliest echocardiogram in which the CPM was calculated was included in the analysis. In this cohort, 12 neonates had CoA and 62 had an unobstructed aortic arch. Table 1C presents demographics and Table 2C presents the breakdown of associated CHD in the validation cohort. In addition, 6 neonates had aortic arch branching abnormalities (8.1%): 4 with brachiocephalic trunks (5.4%) and 2 with aberrant right subclavian arteries (2.7%). When the model was applied to the validation dataset, it showed good discrimination between neonates with CoA and unobstructed aortic arch (Figure 4C and Figure 5B).

Figure 6 demonstrates the probability of CoA for neonates from both cohorts. No neonates with a CPM $< 15\%$ had CoA. In addition, of the 56 neonates with a CPM $> 60\%$, 54 (96%) had CoA. To risk stratify neonates using the CPM, we defined those neonates with a CPM of $< 15\%$ as low-risk, those with a value of 15–60% as moderate-risk, and those with a value $> 60\%$ as high-risk (Figure 6).

Echocardiographer Prediction

In the investigation cohort, intraclass correlation for all outcome variables ranged from 0.73–0.94. When asked to differentiate between CoA and unobstructed aortic arch, the more experienced echocardiographers (>5 years experience) more accurately diagnosed CoA but were less accurate at diagnosing unobstructed aortic arches. Of note, the logistic regression model was better than all echocardiographers at risk-stratifying neonates with CoA. Figure 7 demonstrates the negative predictive value in the equivocal group of all readers compared with the CPM at a cut-off of 15%.

DISCUSSION

This study is the first, to our knowledge, to use a logistic regression model to diagnose CoA in neonates with a PDA. The CPM is based on several previously published individual indices used to predict CoA in the fetus or the newborn.[2, 4–7] These individual indices, when applied to our cohort, demonstrated statistical significance but poor clinical utility for identification of neonates with CoA in the presence of a PDA. A plausible explanation for this failure is that each index emphasizes unique anatomic differences in an aortic arch with CoA. While many patients with CoA have a long segment between the left common carotid artery and left subclavian artery, this finding is far from uniform and not diagnostic.[10, 11] Similarly, histologic specimens demonstrate that most, but not all, patients with CoA have a narrow isthmus. [12] The strength of the CPM is that it accounts for all of these anatomic differences, allowing for better risk stratification across all anatomic variations in the presence of a PDA.

Our data demonstrated that “more experienced echocardiographers” had a higher chance of correctly diagnosing CoA than their less experienced counterparts; however, even the “experienced echocardiographer” failed to consistently and accurately identify neonates with CoA in the equivocal group. An objective measurement is needed to accurately diagnose or exclude CoA. The CPM out-performed all echocardiographers in correctly identifying CoA and unobstructed aortic arch in neonates with a PDA. Although there was significant variability between echocardiographers in subjectively identifying CoA, the echocardiographers’ measurements of the aortic arch correlated well. This suggests that these measurements can be accurately reproduced. Of note, the measurements not performed routinely in our institution, such as the descending aortic diameter, had a worse correlation than those measured routinely.

The aortic arch measurements used to calculate the CPM in the validation cohort were measured prospectively by echocardiographers in our laboratory. Investigators did not re-measure or confirm these measurements. This more accurately represents clinical workflow, making this study more generalizable to other laboratories. Only 51% of the neonates who met inclusion criteria had all measurements performed, primarily due to workflow issues in the echocardiography laboratory. In addition, echocardiograms performed on nights and weekends were less likely to be interpreted by an echocardiographer and therefore the CPM was not measured in many of those neonates. Of note, the vast majority of neonates with concern for CoA during that time period had the CPM measured, likely due to the increased clinical concern.

We removed neonates with significant prematurity, significant extracardiac malformations, and complex congenital heart disease from the investigation cohort.

This allowed us to create the CPM from a more homogeneous group of neonates and prevented skewing of the model due to anatomic differences in the aortic arch. However, we included premature infants and neonates with complex extracardiac malformations and

congenital heart disease (excepting HLHS) in the validation cohort as we felt that applying the already developed CPM to a broader patient population would be more clinically useful. Because the measurements from the validation cohort were not used to create or modify the CPM, the model was not affected by anatomic variation in the validation cohort.

The CPM was more accurate in the validation cohort than in the investigation cohort. We attribute the significant improvement in CPM performance to patient selection and improved arch imaging. The model was derived from neonates in the investigation cohort, a cohort of neonates with borderline aortic arches. The validation cohort was more representative of the general population and consisted primarily of normal aortic arches with only some borderline and abnormal cases.

Fifteen neonates had prenatal concerns for CoA in the investigation cohort. Of these 15 neonates, only 9 (60%) had CoA confirmed postnatally. This percentage demonstrates the need for an objective prenatal measure. Prenatal prediction of CoA has been assessed in multiple studies, [4, 11, 13] and future studies should investigate the potential usefulness of a variant of the CPM for prenatal aortic arch evaluation.

There was one patient in the equivocal group with CoA and a PDA who was thought to have an unobstructed aortic arch and was discharged prior to ductal closure. This patient returned to our consult clinic with a murmur at 2 years of age and was found to have CoA. He underwent surgical repair the following day. The initial echocardiogram for this patient, performed at only a few days of age, was analyzed in the equivocal group of the investigation cohort. The CPM estimated a 67% probability of CoA. If this model had been applied at the time of this patient's initial echocardiogram, it would have heightened the suspicion for possible CoA and may have influenced discharge planning or follow-up.

The CPM equation can be entered into a digital PACS system as a calculation so that measurement of the five individual components (carotid artery diameter, distal transverse arch diameter, isthmus diameter, descending aorta diameter, and distance from carotid artery to subclavian artery) will automatically yield a coarctation probability as a percentage. This allows the CPM to be easily integrated into daily workflow. Alternatively, using Figure 8, the CPM can be calculated from the individual indices that comprise the model.

It is our current practice to measure the CPM on all neonates with a PDA. In those being observed off of PGE, a CPM of less than 15% is reassuring and places the neonate in a low-risk category. Based on our study results, these neonates can be safely transferred back to the newborn nursery and fed, with follow up per the clinical team's preference. This cut-point should allow approximately half of neonates with unobstructed aortic arches currently being observed without PGE to return to the newborn nursery. Those neonates with a CPM of 15–60% have a moderate-risk of developing CoA and should have follow up imaging scheduled. The majority of those with a CPM greater than 60% in our study developed CoA; we consider this group high-risk and all neonates with a CPM > 60% should undergo inpatient observation until PDA closure.

Limitations

We eliminated a small number of neonates due to inadequate arch images. In addition, some readers may have performed measurements in cases where the image quality was suboptimal. If this was the case, our data could be skewed somewhat due to poor image quality.

The model was created from a retrospective cohort of neonates; although it was validated prospectively, both cohorts were small and further prospective validation on a larger patient

population is necessary. It is possible that some neonates who met inclusion criteria were missed.

Although all neonates with unobstructed aortic arches in the investigation group had the diagnosis confirmed with repeat echocardiograms after PDA closure, the clinical follow up of these patients was variable and ranged from 2–7 years. As the progression to CoA in older children and adolescents is not well understood, it is possible that some of these patients may develop CoA in the future. Progression to CoA later in life was not evaluated, so this model can only estimate the risk for those neonates with CoA who require repair early in life. In addition, some patients continue to have a large ductal ampulla after PDA closure; in some cases, these patients can develop CoA at a later date once the ampulla regresses. In these cases, continued outpatient observation may be necessary in order to prevent a missed case of CoA. The model was calibrated to help eliminate missed cases of CoA; as such, the positive predictive value is not 100% and we do not recommend that neonates be sent for operative repair based solely on a high CPM probability.

Summary

The coarctation probability model is able to estimate the probability of CoA in the setting of a PDA and our current practice is to measure it on all neonates with a PDA. The CPM can be easily integrated into daily workflow by entering the CPM equation into a digital PACS system. Neonates with a CPM less than 15% no longer require observation in the NICU without PGE. We anticipate that using a cut-off of 15% could decrease unnecessary observation in the NICU by half. More importantly, it may help prevent a missed diagnosis of COA, with its associated morbidity and mortality, in infants falling within the moderate and high-risk categories. We recommend that a neonate with a CPM greater than 15% have follow-up imaging while a neonate with a CPM greater than 60% continue inpatient observation until PDA closure.

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Abbreviations, acronyms and calculations

CoA	coarctation of the aorta
PDA	patent ductus arteriosus
PGE	Prostaglandin E1
CHD	congenital heart disease
VSD	ventricular septal defect
DORV	double outlet right ventricle
d-TGA	d-transposition of the great arteries
CPM	coarctation probability model

$$CSA = \frac{\text{Distal Transverse Arch Diameter}}{\text{Distance from Carotid to Subclavian Artery}}$$

$$I/D = \frac{\text{Aortic Isthmus Diameter}}{\text{Descending Aorta Diameter}}$$

$$CA/DT = \frac{\text{Carotid Artery Diameter}}{\text{Distal Transverse Arch Diameter}}$$

References

1. Graham TP, Atwood GF, Boucek RJ. Use of prostaglandin E1 for emergency palliation of symptomatic coarctation of the Aorta. *Cathet Cardiovasc Diagn.* 1978; 4:97–102. [PubMed: 77192]
2. Lappen, RSMA.; Duffy, CE.; Berdussis, K.; Paul, MH. Predictability of coarctation of the aorta from the degree of transverse aortic arch hypoplasia: An echocardiographic-angiographic correlation. New York: Springer-Verlag; 1986.
3. Morrow WR, Huhta JC, Murphy DJ Jr, McNamara DG. Quantitative morphology of the aortic arch in neonatal coarctation. *J Am Coll Cardiol.* 1986; 8:616–620. [PubMed: 3745707]
4. Hornberger LK, Weintraub RG, Pesonen E, Murillo-Olivas A, Simpson IA, Sahn C, et al. Echocardiographic study of the morphology and growth of the aortic arch in the human fetus. Observations related to the prenatal diagnosis of coarctation. *Circulation.* 1992; 86:741–747. [PubMed: 1516185]
5. Dodge-Khatami A, Ott S, Di Bernardo S, Berger F. Carotid-subclavian artery index: new echocardiographic index to detect coarctation in neonates and infants. *Ann Thorac Surg.* 2005; 80:1652–1657. [PubMed: 16242433]
6. Mivelaz Y, Di Bernardo S, Meijboom EJ, Sekarski N. Validation of two echocardiographic indexes to improve the diagnosis of complex coarctations. *Eur J Cardiothorac Surg.* 2008; 34:1051–1056. [PubMed: 18824366]
7. Lu CW, Wang JK, Chang CI, Lin MT, Wu ET, Lue HC, et al. Noninvasive diagnosis of aortic coarctation in neonates with patent ductus arteriosus. *J Pediatr.* 2006; 148:217–221. [PubMed: 16492432]
8. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol.* 2001; 54:774–781. [PubMed: 11470385]
9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (RED Cap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009; 42:377–381. [PubMed: 18929686]
10. Rudolph AM, Heymann MA, Spitznas U. Hemodynamic considerations in the development of narrowing of the aorta. *Am J Cardiol.* 1972; 30:514–525. [PubMed: 4672503]
11. Hornberger LK, Sahn DJ, Kleinman CS, Copel J, Silverman NH. Antenatal diagnosis of coarctation of the aorta: a multicenter experience. *J Am Coll Cardiol.* 1994; 23:417–423. [PubMed: 8294696]
12. Ho SY, Anderson RH. Coarctation, tubular hypoplasia, and the ductus arteriosus. Histological study of 35 specimens. *British heart journal.* 1979; 41:268–274. [PubMed: 426975]
13. Quattermain MD, Cohen MS, Dominguez TE, Tian Z, Donaghue DD, Rychik J. Left ventricle to right ventricle size discrepancy in the fetus: the presence of critical congenital heart disease can be reliably predicted. *J Am Soc Echocardiogr.* 2009; 22:1296–1301. [PubMed: 19815386]

Figure 1.

Indices used to construct the coarctation probability model (CPM) include: (A) the carotid artery to distal transverse arch index (CA/DT), (B) the carotid to subclavian index (CSA), and (C) the isthmus to descending aorta index (I/D). Each echocardiographer obtained the following measurements in the investigation cohort: the distal transverse arch (DT) between the origin of the second and third head and neck vessels, the isthmus (I) just distal to the left subclavian artery (or right subclavian artery in a right arch) and proximal to the patent ductus arteriosus (PDA), descending aorta (D) distal to the PDA and above the diaphragm, left common carotid artery (CA) at its origin (or right common carotid artery in a right arch) and the distance from the carotid artery to the subclavian artery (CA_SC).

Figure 2.

Investigation Cohort: retrospective review of 88 neonates with patent ductus arteriosus (PDA) that met inclusion criteria. Eight patients were excluded due to poor image quality. Patients were divided into two groups: 1) equivocal group, or group of neonates with an unconfirmed arch diagnosis who required observation in the neonatal intensive care unit off of prostaglandin. In this group, 9 neonates had coarctation of the aorta (CoA) and 13 had unobstructed aortic arch. 2) control group, or group of neonates with a definitive diagnosis of either CoA or unobstructed aortic arch (did not require observation to reach the diagnosis). In this group, 33 neonates had CoA and 25 had unobstructed aortic arch. Validation Cohort: group of neonates with a PDA who had arch measurements prospectively measured. 146 met inclusion criteria but only 74 had all measurements performed. Of those 74, 12 neonates had CoA and 62 neonates had unobstructed aortic arch.

Figure 3.

The CSA, I/D, and CA/DT indices demonstrated statistical significance but poor clinical significance in the investigation cohort. These individual indices demonstrated overlap in both the control group and the equivocal group suggesting an inability to clinically distinguish between neonates with and without coarctation of the aorta.

Figure 4.

Results of the internal (A) and external (C) validation for the coarctation prediction model (CPM). The calibration accuracy for the original model and the bias-corrected model would be perfect if both lines fell along the ideal line. A: Internal calibration shows the apparent and the bias-corrected model performance by plotting the actual vs. predicted probabilities; B: The area under the ROC curve for the CPM is 0.96; C: External calibration using the validation cohort shows the actual vs. predicted probabilities using loess smooth function with 95% bootstrap confidence interval.

Figure 5.

Predicted probability of coarctation of the aorta (CoA) in the investigation cohort (equivocal and control group) and the validation cohort using logistic regression. The coarctation probability model (CPM) demonstrated good discrimination between neonates with and without coarctation of the aorta (CoA) in both the Control Group and the Equivocal Group. The CPM also demonstrated good discrimination between CoA and unobstructed aortic arch in the validation cohort.

Figure 6.

Risk stratification using the coarctation probability Model (CPM). Neonates with a CPM <15% are assigned a category of low-risk of developing coarctation of the aorta, those between 15–60% moderate-risk, and those above 60% high-risk.

Figure 7.

Negative Predictive Value in the Equivocal Group of Individual Readers Compared with the Coarctation Probability Model (CPM) at a Cut-Point of 15%. Neonates in the Equivocal Group required observation in the neonatal intensive care unit without prostaglandin in order to confirm or refute the diagnosis of coarctation of the aorta. Readers A & B had less than five years of experience and Readers C & D had greater than five years of experience.

Figure 8.

The nomogram allows for calculation of coarctation probability using the logistic regression model. To calculate coarctation probability, perform all measurements as in Figures 1A, 1B, and 1C. Then calculate the CA/DT, CSA, and the I/D. Find the point values for each of these indices in the nomogram by 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 coarctation of the aorta.

Table 1

Demographics of the investigation and validation cohorts

A: Demographics of investigation cohort divided into no coarctation and coarctation

	No Coarctation N=38	Coarctation N=42	p-value
Age at time of Echo (days)	2.1 ± 3.8	7.6 ± 23.3	0.018
Gender			
Male	53%	55%	0.85
Race			
Caucasian	67%	84%	0.32
African American	20%	11%	
Hispanic	10%	5%	
Asian	3%	0%	
Height (cm)	50.3 ± 4.2	49.8 ± 3.5	0.74
Weight (kg)	3.19 ± 0.66	3.07 ± 0.68	0.55
Body Surface Area (m ²)	0.202 ± 0.029	0.196 ± 0.027	0.50
Body Mass Index (kg/m ²)	12.5 ± 1.6	12.3 ± 1.8	0.66
Gestational Age (weeks)	37.9 ± 1.7	37.9 ± 1.8	0.73

B. Demographics of investigation cohort divided into equivocal and control groups:

	Equivocal N=22	Control N=58	p-value
Age at time of Echo (days)	0.91 ± 1.38	6.52 ± 20.00	0.002
Gender			
Male	41%	59%	0.16
Race			
Caucasian	74%	78%	0.85
African American	16%	14%	
Hispanic	11%	6%	
Asian	0%	2%	
Height (cm)	50.6 ± 3.6	49.9 ± 3.9	0.85
Weight (kg)	3.23 ± 0.65	3.09 ± 0.68	0.74
Body Surface Area (m ²)	0.204 ± 0.027	0.197 ± 0.028	0.66
Body Mass Index (kg/m ²)	12.5 ± 1.8	12.3 ± 1.7	0.68
Gestational Age (weeks)	38.6 ± 1.3	37.7 ± 1.8	0.066

C: Demographics of validation cohort

	No Coarctation N=62	Coarctation N=12	p-value
Age at time of Echo (days)	5.61 ± 8.90	4.75 ± 8.39	0.89
Gender			
Male	51.6%	83.3%	0.04
Race			
Caucasian	84%	60%	0.32
African American	7%	10%	
Hispanic	7%	20%	
Asian	2%	10%	
Height (cm)	47.5 ± 6.6	49.9 ± 3.2	0.18
Weight (kg)	3.17 ± 0.50	3.32 ± 0.30	0.15
Body Surface Area (m ²)	0.179 ± 0.048	0.203 ± 0.015	0.09
Body Mass Index (kg/m ²)	11.8 ± 3.1	13.4 ± 1.6	0.04
Gestational Age (weeks)	35.2 ± 4.9	38.5 ± 1.3	0.04

Table 2

Associated congenital heart disease in investigation and validation cohorts

A: Associated congenital heart disease in investigation cohort divided into no coarctation (CoA) and coarctation

	No Coarctation N=38	Coarctation N=42	Total N=80
Congenital Heart Disease	1 (2.6%)	38 (90.5%)	39 (48.8%)
Bicuspid Aortic Valve	0	26 (61.9%)	26 (32.5%)
Ventricular Septal Defect	1 (2.6%)	21 (50%)	22 (27.5%)
Left Superior Vena Cava	0	6 (14.3%)	6 (7.5%)
Aortic Stenosis	0	5 (11.9%)	5 (6.3%)
Partial Anomalous Pulmonary Venous Return	1 (2.6%)	0	1 (1.3%)

B: Associated congenital heart disease in investigation cohort divided into equivocal and control groups

	Equivocal Group N=22	Control Group N=58	Total N=80
Congenital Heart Disease	8 (36.4%)	31 (53.4%)	41 (51.2%)
Bicuspid Aortic Valve	5 (22.7%)	21 (36.2%)	26 (32.9%)
Ventricular Septal Defect	2 (9.1%)	20 (34.5%)	22 (27.5%)
Left Superior Vena Cava	0	5 (8.6%)	5 (6.3%)
Aortic Stenosis	1 (4.5%)	4 (6.9%)	5 (6.3%)
Partial Anomalous Pulmonary Venous Return	1 (4.5%)	0	1 (1.3%)

C: Associated congenital heart disease in validation cohort

	No Coarctation N=62	Coarctation N=12	Total N=74
Congenital Heart Disease	19 (30.6%)	11 (91.7%)	30 (40.5%)
Bicuspid Aortic Valve	2 (3.2%)	7 (58.3%)	9 (12.2%)
Ventricular Septal Defect	10 (16.1%)	5 (41.7%)	15 (20.3%)
Left Superior Vena Cava	0	0	0
Aortic Stenosis	0	3 (25%)	3 (4.1%)
Partial Anomalous Pulmonary Venous Return	1 (1.6%)	0	1 (1.4%)
Double Inlet Left Ventricle	0	2 (16.7%)	2 (2.7%)
d-Transposition of the Great Arteries*	2 (3.2%)	1 (8.3%)	3 (4.1%)
Double Outlet Right Ventricle	1 (1.6%)	0	1 (1.4%)

Table 3

Multivariable logistic model estimating the probability of coarctation in the investigation cohort

$$\text{Probability} = [1 + \exp(-[-2.02 + (12.5)(\text{CA/DT}) - (9.8)(\text{I/D}) - (0.601)(\text{DT/CA\_SC})])]^{-1}$$

Predictor*	Odds Ratio	95% CI	p-value
CA/DT (0.1)	3.48	(1.57–7.74)	0.002
I/D (0.1)	0.38	(0.15–0.97)	0.042
CSA (DT/CA_SC) (0.1)	0.94	(0.86–1.03)	0.193

* Odds ratio assesses the effect of 0.1 unit change in CA/DT, I/D, and CSA (DT/CA_SC) on the odds of coarctation of the aorta

Table 4

CPM Sensitivity and Specificity for Coarctation Probability Model at Different Cut Points

Cut Point	Sensitivity (95% CI)	Specificity (95% CI)
0.15	1 (0.914–1)	0.622 (0.461–0.759)
0.4	0.951 (0.839–0.987)	0.865 (0.72–0.941)
0.5	0.927 (0.806–0.975)	0.919 (0.787–0.972)
0.6	0.927 (0.806–0.975)	0.946 (0.823–0.985)