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Model for screening adult congenital heart disease surgery eligibility with echocardiography parameters

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KEYWORDS:
congenital heart disease;
echocardiogram;
pulmonary artery hypertension;
pulmonary to systemic flow ratio;
pulmonary to systemic vascular resistance ratio

OBJECTIVES: This study aimed to screen for the eligibility of correction in cases of adult congenital heart disease (CHD). Pulmonary to systemic flow ratios (Qp/Qs) > 1.5 and pulmonary to systemic vascular resistance ratios (Rp/Rs) < 1/3, acquired by right heart catheterization (RHC), are two essential parameters. Nonetheless, performing RHC at every follow-up is impractical and even harmful. Thus, it is important to establish a model to predict Qp/Qs and Rp/Rs status before a RHC confirmation, using echocardiography parameters.

METHODS: A total of 1,785 patients with adult CHD were enrolled and randomly assigned to the derivation or validation groups. Echocardiogram parameters of the 974 patients in the derivation group were considered candidate predictors for surgery eligibility (Qp/Qs > 1.5 and Rp/Rs < 1/3). Binary logistic regression analyses were performed to identify the independent predictors and establish a scoring system. The scoring system was further examined in the validation group using a receiver operating characteristic (ROC) analysis.

RESULTS: Estimated pulmonary artery systolic pressure, velocity through the pulmonary valve, and diameters of the left and right atria were identified as independent predictors. The area under the ROC curve of the predictive value in the validation group and its pre- and post-tricuspid valve malformation subgroups were 0.87 (95% confidence interval [CI]: 0.84−0.90, $p < 0.01$), 0.86 (95% CI: 0.82−0.91, $p < 0.01$), and 0.85 (95% CI: 0.79−0.90, $p < 0.01$), respectively.

CONCLUSIONS: This scoring system could augment flexibility and convenience for pre-screening CHD patients' eligibility for surgery, before RHC.

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Abbreviations: CHD, congenital heart disease; CI, confidence interval; ePASP, estimated pulmonary artery systolic pressure; LA, left atria anterior-posterior diameters; OR, odds ratio; PAH, pulmonary artery hypertension; PV, highest blood flow velocity through pulmonary valve; Qp/Qs, pulmonary to systemic flow ratio; RA, Right atrial diameter; RHC, right heart catheterization; Rp/Rs, pulmonary to systemic vascular resistance ratio; ROC, receiver operating characteristic

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Congenital heart disease (CHD) is a common cause of congenital malformations in newborns, with an incidence of approximately 0.8%.[1] Due to advancements in cardiac surgery, most patients with CHD can survive to adulthood.[2] In America and Europe, the number of adult patients with CHD exceeded that of children in this century.[3,4] Nonetheless, approximately 20% of CHD patients will require heart surgery in their adult years, and approximately 70% of these surgeries are first-time operations.[5] In less developed areas that lack adequate cardiac screening for newborns, the proportion of first-time surgeries in adults might be even larger.

To screen for eligibility for surgery or percutaneous intervention, pulmonary artery pressure, pulmonary vascular resistance (PVR), pulmonary to systemic flow ratio (Qp/Qs), and pulmonary to systemic vascular resistance ratio (Rp/Rs) are essential parameters. Although the detailed standard for PVR is still debatable, Qp/Qs > 1.5 with Rp/Rs < 1/3, are two critical terms for eligibility, according to the existing guidelines.[6,7] Right heart catheterization (RHC) is the gold standard for acquiring Qp/Qs, Rp/Rs, and other hemodynamic parameters in patients with CHD. Nevertheless, performing RHC at every follow-up can be impractical and even harmful due to X-ray exposure. To avoid unnecessary invasive measurements, a pre-screening for patients' eligibility for surgery before RHC is needed. Currently, the prediction of surgery eligibility and the decision of RHC confirmation are mainly based on the experiences of CHD specialists. If a scoring system based on echocardiography parameters were available, it would provide greater usability to patients and physicians. There are several methods now available to estimate pulmonary circulation hemodynamics by echocardiogram.[8-13] However, there is no existing model or formula for Qp/Qs and Rp/Rs in patients with CHD. Thus, we intended to establish a model to predict whether CHD patients had Qp/Qs > 1.5 and Rp/Rs < 1/3 using echocardiogram parameters.

Methods

Patient selection criteria

This retrospective single-center study was conducted in the Department of Adult Congenital Heart Disease of the Guangdong Provincial People's Hospital, Guangzhou, Guangdong, China. Patients diagnosed with CHD with shunt(s) who received RHC from January 1, 2010 to December 31, 2020 were initially included. Exclusion criteria were as follows: 1) Single ventricle, single atrium, and/or complete atrioventricular septal defects; 2) anomalous great artery connection, such as transposition of the great arteries, double outlet right ventricle; 3) residual shunt due to previous surgery or intervention; 4) echocardiogram received more than three months before RHC; 5) missing echocardiogram data; and 6) age < 18 years. Two-thirds of the patients were randomly assigned to the derivation group by systematic sampling and the rest were placed in the validation group.

Echocardiogram

Complete two-dimensional Doppler echocardiography was performed by unspecified operators at our center. All operators were trained and supervised by the consultant doctors. The echocardiographic equipment was all commercially available, including GE VIVID E9, GE VIVID 7(GE Vingmed, Horten, Norway), Philips IE 33, Philips IE ELITE (Philips Medical Systems, Boston, MA, USA), Siemens SC2000, and Siemens Acuson Sequoia 512 (Siemens Medical Solutions USA, Inc., Mountain View, CA, USA). All Doppler-echocardiographic images were recorded in native DICOM format and centralized, after anonymization, at the Echo Laboratory at Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences. A minimum of three cardiac cycles were recorded for analysis. Using the parasternal short axis view, the pulmonary artery diameters were measured at end-diastole, between the pulmonary valve annulus, and the highest blood flow velocity through the pulmonary valve (PV) was recorded (Figure S1). Using the parasternal long axis view, the left atria anterior-posterior diameters (LA), ascending aortic diameters and left ventricular end-diastolic diameters were measured at end-diastole (Figure S2). The right atria diameters (RA) and right ventricular longitudinal diameters were assessed at end-systole, by measuring the superior-inferior axes from the apical four-chamber view (Figure S3). From the apical five-chamber view, the highest blood flow velocity through the aortic valve was recorded (Figure S4). The estimated pulmonary artery systolic pressure (ePASP) was calculated by adding the right atrial pressure to the transtricuspid pressure gradient. The right atrial pressure was estimated to be 5, 10, or 15 mm Hg, based on the inferior vena cava diameter variation.[14] The transtricuspid pressure gradient was calculated from the velocity of tricuspid regurgitation using the simplified Bernoulli equation.[11] The left ventricular ejection fraction was also calculated using the Teicholz method.[15]

Transtricuspid pressure gradient
$= 4*(\text{Tricuspid regurgitation Velocity})^2$

Right heart catheterization

The RHC procedure has been described in detail in our previous study.[16] Before RHC, weight and height were routinely measured and recorded. RHC was performed in the catheter laboratory under electrocardiographic monitoring. After local anesthesia, a 6-French MPA 2 catheter (Cordis Inc., Miami, FL, USA) was inserted into the right heart system through the right femoral vein by placement of a 6-French vascular sheath. The catheter was manipulated to the correct position under fluoroscopy. We measured the pressure in the right atrium, pulmonary artery, and wedged pulmonary artery. Before measuring the pressure, the transducers were calibrated to zero at atmospheric pressure. At the same time, blood from the superior vena cava, inferior vena cava, pulmonary artery, and systemic circulation were aspirated for blood gas assays. After oxygen saturation was measured, cardiac output and pulmonary output were calculated using the indirect Fick method. Vascular resistance was derived using the following formula: vascular resistance = pressure gradient/blood flow. Subsequently, Qp/Qs and Rp/Rs were calculated, where patients with a Qp/Qs > 1.5 and Rp/Rs < 1/3, were considered eligible for CHD closure or repair.

Statistical analyses

Data was analyzed using SPSS 22 software (IBM Corp., Armonk, NY, USA) and presented as number (percentage) or mean ± standard deviation. Descriptive data analysis was conducted to examine the data distribution. Proportions were compared using chi-square (χ^2) tests. Continuous data was compared using the Kolmogorov–Smirnov test. The relationships between the parameters and eligibility were initially evaluated using univariate binary logistic regression. Further, multivariate binary logistic regression was performed on parameters with statistical significance. Independent predictors were further identified through the multivariate analysis and only parameters with statistical significance were selected for the final model. After categorizing the independent predictors based on their quartiles, these categorical parameters were entered into the final multivariable binary logistic regression model. Scores applied to different independent predictors were determined by the relative size of β coefficient from the final model, and the predictive values for each patient were the sum of their scores. Receiver operating characteristic (ROC) curves of the predictive values were used for validation. A stratified scoring system of surgery eligibility were further constructed based on the positive predictive value. All tests were 2-tailed, and statistical significance was set at $p < 0.05$.

Missing data

Since < 5% of the data were missing in the analyzed variables in this study, we used complete case analysis in the main analysis. To confirm the robustness of the data set, we repeated our analysis, where missing data was imputed and replaced with the according average value.

Ethics

This study was approved by the Research Ethics Committee of Guangdong Provincial People's Hospital, Guangdong, China, on July 24, 2015 (No. GDREC2015254H[R1]). Data from all participants were de-identified, and informed consent was waived for this study. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Patient population and clinical characteristics

A flowchart of the enrollment process is presented in Figure 1. Based on the study criteria, 1,461 patients were included in the study. Among them, 974 and 487 patients were included in the derivation and validation groups, respectively. The diagnoses and hemodynamic and echocardiographic parameters are shown in Tables 1 and 2, respectively. The diagnosis distribution and clinical characteristics indicated no statistical difference between the derivation and validation groups ($p > 0.05$).

Model derivation

The parameters univariately associated with surgery eligibility are presented in Table 3. In the multivariate regression analysis, the ePASP, LA, RA, and PV remained independent significant predictors associated with surgery eligibility (Table S1). The variance inflation factors were 1.03, 1.37, 1.39, and 1.07, respectively. As they were all within the permissible range, the multicollinearity effect was negated. After categorizing these predictors based on quartiles, a scoring system was developed through the final multivariate analysis (Table 4). Using an arithmetic sum of the scores of ePASP, LA, RA, and PV presented in Table 4, a predictive value was calculated.

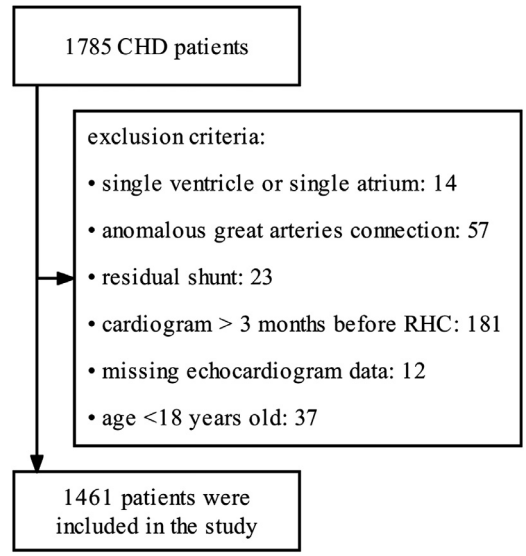


Figure 1 Flow chart of the enrollment process. his figure illustrates the patient enrollment process. Each box includes the criteria and the related patient number. CHD: congenital heart disease; RHC: right heart catheterization.

Model validation

The ROC curves of the predictive value for screening eligibility in the validation group are presented in Figure 2 and Table 5. The area under the curve (AUC) was 0.87 (95% confidence interval [CI]: 0.84-0.90, $p < 0.01$), demonstrating that the prediction model had high accuracy. We also

Table 1 Types of CHD in Participants

Type	Derivation	Validation
Total, n	974	487
Pre-tricuspid valve		
ASD, n (%)	580 (59.5%)	286 (58.7%)
APVC, n (%)	2 (0.2%)	4 (0.8%)
Post-tricuspid valve		
VSD, n (%)	197 (20.2%)	99 (20.3%)
PDA, n (%)	142 (14.6%)	67 (13.8%)
AVSD, n (%)	48 (4.9%)	27 (5.5%)
RASV, n (%)	5 (0.5%)	4 (0.8%)

APVC: anomalous pulmonary venous connection; ASD: atrial septal defect; AVSD: atrioventricular septal defect; CHD: congenital heart disease; PDA: patent ductus arteriosus; RASV: ruptured aneurysm of the sinus of Valsalva; VSD: ventricular septal defect.

Table 2 Patient Clinical Characteristics

	Derivation	Validation
Sample Size, n	974	487
Eligible, n (%)	544 (55.9%)	260 (53.4%)
Sex: Men, n (%)	293 (30.1%)	158 (32.4%)
Age (years)	39.49±14.01	39.21±14.07
BSA (m^2)	1.49±0.16	1.51±0.18
sPAP (mmHg)	78.42±34.33	80.75±33.52
dPAP (mmHg)	28.59±17.92	30.00±18.17
mPAP (mmHg)	47.13±23.38	49.08±23.46
PAWP (mmHg)	10.22±3.86	10.21±4.13
SAP (mmHg)	122.28±20.53	122.44±21.19
DAP (mmHg)	71.79±12.42	72.22±12.51
MAP (mmHg)	89.88±13.27	90.39±14.49
SaO_2 (%)	93.75±5.10	93.75±5.42
Qp (L/min)	9.90±5.55	9.86±5.28
Qs (L/min)	5.11±1.8	4.98±1.51
PVR (WU)	5.94±6.6	6.23±6.45
SVR (WU)	17.95±6.27	18.23±6.04
Qp/Qs	2.02±1.09	2.05±1.06
Rp/Rs	0.34±0.39	0.36±0.38
ePASP (mmHg)	79.26±28.77	82.55±27.99
LA (mm)	37.23±9.12	36.76±8.46
LVEDD (mm)	43.30±10.77	42.84±10.67
RA (mm)	57.94±13.72	57.54±13.15
RV (mm)	62.10±9.92	61.87±9.79
LVEF (%)	64.98±8.21	64.97±8.68
PV (m/s)	1.31±0.59	1.27±0.52
AV (m/s)	1.15±0.36	1.15±0.35
PA (mm)	35.38±9.37	35.71±8.72
AO (mm)	25.27±3.80	25.27±3.93

Values of parameters are presented as mean ± standard deviation.

AO: aortic diameter; AV: highest blood flow velocity through the aortic valve; BSA: body surface area; DAP, diastolic artery pressure; dPAP: diastolic pulmonary artery pressure; ePASP: estimated pulmonary artery systolic pressure; LA: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; MAP, mean artery pressure; mPAP, mean pulmonary artery pressure; Qp/Qs: pulmonary blood flow to systemic blood flow ratio; PA: pulmonary artery diameter; PAWP: pulmonary arterial wedge pressure; PV: highest blood flow velocity through the pulmonary valve; PVR: pulmonary vascular resistance; Qp: quantity of pulmonary blood flow; Qs: quantity of systemic blood flow; RA: right atrial diameter; Rp/Rs: pulmonary to systemic vascular resistance ratio; RV: right ventricular longitudinal diameter; SaO_2: arterial oxygen saturation; SAP: systolic artery pressure; sPAP: systolic pulmonary artery pressure; SVR: systemic vascular resistance.

confirmed that, the final model had a similar performance to the models without categorizing parameters or applying integral scores (Table S2). In subgroup analyses, the AUC of the pre-tricuspid valve and post-tricuspid valve malformation both reached 0.85, indicating that the model was compatible with different kinds of CHD, without the complex malformations mentioned in the exclusion criteria.

Positive predictive value stratifying

After the validation, we stratified patients' possibility of eligibility based on the positive predictive value for better use (Table 6). An example using the scoring system is presented in Figure 3. We further confirmed that, when PVR < 5 wood units was also taken into the eligibility standard, the positive predictive value of the predictive score fitted in the according range.

Table 3 Univariate Binary Logistic Regression Analysis of Factors for Surgery Eligibility

	Unit	OR	95% CI	*p*
Sex (Men)		1.09	0.83−1.44	0.54
Age	1 years	1.05	1.04−1.06	<0.01
BSA	0.1 m^2	1	0.92−1.08	0.97
ePASP*	1 mmHg	0.97	0.96−0.98	<0.01
LA	1 mm	1.09	1.07−1.11	<0.01
LVEDD	1 mm	1.00	0.99−1.01	0.96
RA	1 mm	1.07	1.06−1.09	<0.01
RV	1 mm	1.05	1.03−1.06	<0.01
LVEF	1%	0.99	0.98−1.01	0.27
PV	0.1 m/s	1.22	1.17−1.26	<0.01
AV	0.1 m/s	1.01	0.98−1.05	0.46
PA	1 mm	1	0.99−1.02	0.68
AO	1 mm	1.01	0.98−1.04	0.58

*Patients without tricuspid valve regurgitation or those with minimal regurgitation were not included.

AO, ascending aortic diameter; AV: highest blood flow velocity through the aortic valve; BSA: body surface area; ePASP: estimated pulmonary artery systolic pressure; LA: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; OR: odds ratio; PA: pulmonary artery diameter; PV: highest blood flow velocity through the pulmonary valve; RA: right atrial diameter; RV: right ventricular longitudinal diameter.

Robustness confirmation

The results from the imputed dataset were similar to the results from the primary analysis, and the scoring system had a similar performance when predictive scores were ≤ 6 or ≥ 12 (Table S3 - 6).

Discussion

In this study, we established a model based on echocardiogram parameters to predict Qp/Qs and Rp/Rs status in patients with CHD. Among the independent significant predictors in the final model, ePASP and PV have greater weight in the scoring system. In pulmonary artery hypertension (PAH), significantly elevated pulmonary artery pressure represents a later stage of the disease course, and ePASP is already widely used in PAH assessment.[17] As for PV, it is highly related to the real-time pulmonary circulation volume,[18] while the pulmonary blood flow volume is positively related to Qp/Qs and negatively related to Rp/Rs. The other two parameters included in this scoring system are LA and RA. RA would be enlarged due to a left-to-right shunt,[19] and LA could represent the return blood volume from the pulmonary veins, which are related to the Qp/Qs and Rp/Rs status. In the validation group, and its two subgroups, the AUC all reached 0.85, indicating high reliability.

To our knowledge, this is the first model to predict Qp/Qs and Rp/Rs in patients with CHD based on

Table 4 Multivariable Binary Logistic Regression Analysis of Independent Predictors for Surgery Eligibility

		Score	OR	95% CI	*p*	β coefficient
ePASP	≤60	5	6.89	4.73−10.03	<0.01	1.93
(mmHg)	61-80	4	5.29	3.63−7.72	<0.01	1.67
	81-100	1	1.830	1.28−2.63	<0.01	0.61
	>100	0	1 (reference)			
RA	≤48	0	1 (reference)			
(mm)	49-56	2	1.89	1.31−2.72	<0.01	0.64
	57-64	3	3.28	2.2−4.89	<0.01	1.19
	>64	3	3.53	2.37−5.26	<0.01	1.26
LA	≤30	0	1 (reference)			
(mm)	31-36	1	1.7	1.18−2.46	<0.01	0.53
	37-42	2	2.86	1.89−4.32	<0.01	1.05
	>42	3	3.35	2.19−5.14	<0.01	1.21
PV	≤0.9	0	1 (reference)			
(m/s)	0.91-1.20	3	3.76	2.57−5.51	<0.01	1.33
	1.21-1.50	5	8.41	5.53−12.8	<0.01	2.13
	>1.5	6	10.73	7.1−16.24	<0.01	2.37

*Score=β coefficient*2.35, rounded to the nearest integer.

ePASP: estimated pulmonary artery systolic pressure; LA: left atrial diameter; OR: odds ratio; PV: highest blood flow velocity through the pulmonary valve; RA: right atrial diameter.

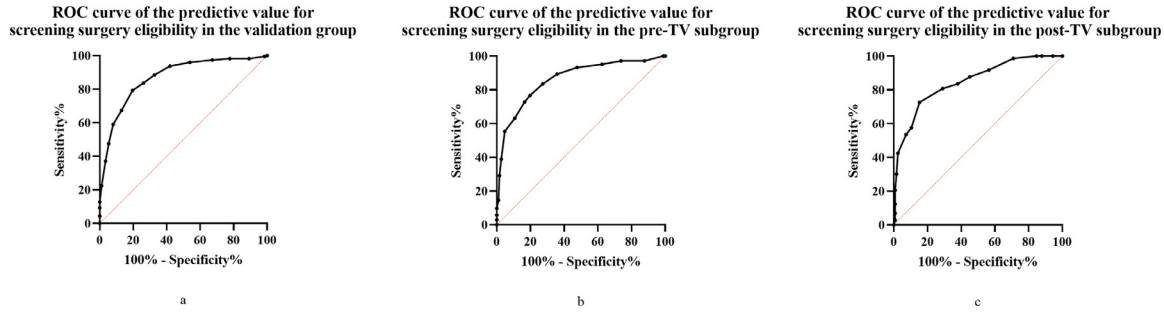


Figure 2 Predictive values for screening surgery eligibility in the validation group. (A) ROC curve of the predictive value for screening surgery eligibility in the validation group. (B) ROC curve of the predictive value for screening surgery eligibility in the pre-TV subgroup. (C) ROC curve of the predictive value for screening surgery eligibility in the post-TV subgroup. These figures present the ROC curves of the predictive values in the validation group and its subgroups. Each point on the curve represents different threshold settings and shows the sensitivity and specificity for screening surgery eligibility. ROC: receiver operating characteristic; TV: tricuspid valve.

Table 5 Area Under the ROC Curve of Predictive Values for Screening Surgery Eligibility in Validation Group

Malformation type	AUC	95% CI	*p*
All	0.87	0.84−0.90	<0.01
Pre-tricuspid valve	0.86	0.82−0.91	<0.01
Post-tricuspid valve	0.85	0.79−0.90	<0.01

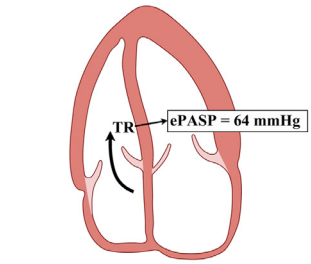
AUC: Area under the curve.

Table 6 Eligible Possibility Between Different Predictive Value Cut-Points

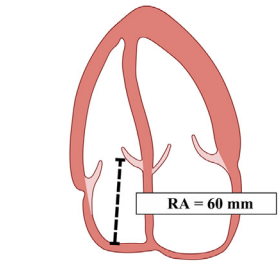
Predictive value	Possibility*	Class
≤ 6	< 20%	Low
7−8	20%−50%	Medium low
9−11	50%−80%	Medium high
≥ 12	> 80%	High

*Derived from positive predictive value.

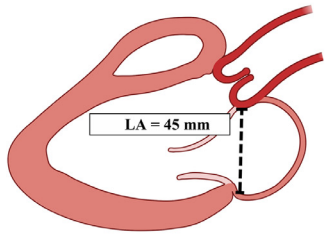
echocardiograms. In patients with PAH but without shunts, several pulmonary hemodynamic parameters can be estimated using ultrasound, including ePASP,[11] mean pulmonary artery pressure,[8-10,12] cardiac output,[11] and PVR.[20-23] Regardless, estimating pulmonary circulation volume and resistance in patients with CHD-PAH is challenging due to the irregular shape of the right heart. In addition, to achieve high reproducibility and usability, the parameters in this model are widely used in clinical practice, and the predictive value could be easily calculated. Although other echocardiogram data also had a high accuracy in assessing PAH hemodynamics, such as time-velocity integral and pulmonary artery acceleration time, their strength in assessing CHD hemodynamics, especially Qp/Qs, might need further evaluation due to the shunt interference.[20,24] Moreover, when patients are transferred to a CHD center, these advanced parameters might not be available, as they were



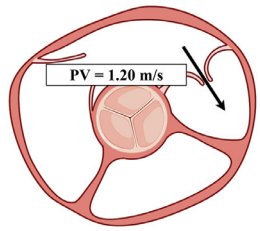
ePASP (mmHg)	Score
≤ 60	5
61 - 80	4
81 - 100	1
> 100	0



RA (mm)	Score
≤ 48	0
49 - 56	2
> 56	3



LA (mm)	Score
≤ 30	0
31 - 36	1
37 - 42	2
> 42	3



PV (m/s)	Score
≤ 0.9	0
0.91 - 1.20	3
1.21 - 1.50	5
> 1.5	6

Score	Possibility
≤ 6	Low
7 - 8	Medium low
9 - 11	Medium high
≥ 12	High

Total score = 13, high possibility for surgery eligibility

Figure 3 Example of using this scoring system. This figure provides an example of how to use this scoring system. Each box with black border provides the value of ePASP, RA, LA and PV. The boxes with red border indicate the scores, arithmetic sum and the according eligible possibility. ePASP: estimated pulmonary artery systolic pressure, RA: Right atrial diameter, LA: left atria anterior-posterior diameters, PV: highest blood flow velocity through pulmonary valve.

not mandatory measurements. Thus, we established this model using the fundamental elements of the echocardiogram for better generalization.

In real-world clinical practice, physicians could use this scoring system to have an initial prediction of patients' eligibility for surgery at their first visit, which could allow the medical team to better prepare treatment plans after RHC confirmation. In addition to the feasibility at the baseline evaluation, this scoring system could also be helpful during the follow-up. Currently, patients who were ineligible for surgery at first RHC were prescribed targeted PAH vasodilators during the follow-up, and considered for CHD correction surgery, after another RHC confirmed that patient hemodynamics reached standards. Nonetheless, the timing for reassessment could be challenged: a premature RHC could lead to a failure of eligible hemodynamics and result

in unnecessary incisions and X-ray exposure, while a delayed RHC might increase the possibility of adverse events before CHD correction. With this scoring system, doctors might be able to pre-screen for patients with a high possibility of eligibility for surgery and better decide the RHC timing. Lastly, it should be once again noted that, this scoring system should not be used as a substitute for RHC, as it is the gold standard to confirm CHD surgery eligibility. Moreover, even in patients who were ineligible for surgery due to severe CHD-PAH, RHC is indispensable when accurate hemodynamics data is needed, such as for monitoring or changing prescriptions.

This study has some limitations. First, more than half of the diagnoses were atrial septal defects, which might have limited the effectiveness of post-tricuspid valve malformation. Other complex CHDs with single atria, single ventricle, complete atrioventricular septal defects, and/or abnormal great artery connection were not included, as the valve velocity was difficult to define. Second, this was a retrospective study and did not undergo strict inspections during echocardiogram examinations, RHC, data collection, and randomization. However, this might be more similar to real-world practices. Under this study design, accuracy was still satisfactory, which indicates that this model might be practical in real clinical settings. Third, the model was not externally verified. As mentioned above, this was a retrospective study, did not have a unified protocol, and the systemic error might have already been limited. Lastly, this model did not include critically ill patients who were unable to receive an echocardiogram or RHC and this might have weakened the predictive accuracy for these patients.

Author contributions

This study was mainly undertaken by Dr. Yang Zi-yang and Dr. Li Hezhi and supervised by Dr. Zhang Caojin and Dr. Fei Hongwen. Dr. Zhou Yin and Dr. Xie Nanshan helped with hemodynamic data collection and analysis. Dr. Luo Dongling provided assistance with the statistical analysis.

Declaration of Competing Interest

The authors declare no other potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Financial conflict of interest statement

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2022.08.016.

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