

Predictors of operability in children with severe pulmonary hypertension associated with congenital heart disease

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Abstract

Background: Pulmonary artery hypertension associated with congenital heart disease (PAH-CHD) occurs predominantly among patients with uncorrected CHD. Treatment of severe pediatric PAH-CHD remains a major intractability. This study evaluated the predictors and prognoses of children with PAH-CHD who underwent surgical correction.

Methods: The data for 59 children with severe PAH-CHD who underwent surgical correction, with or without postoperative medication, between May 2011 and June 2015 at the Guangdong Provincial People's Hospital were analyzed retrospectively. A regression analysis, receiver-operating characteristic (ROC) curves, and Kaplan-Meier curves were used for survival analysis.

Results: Fifty-nine children with severe PAH-CHD underwent heart catheterization and correction, with or without specific anti-PAH drugs postoperatively, were included in this study. The pulmonary pressure, heart function, and ending events were observed and median observation period was 49 ± 20 months. Twenty-eight patients (50%) received at least one additional anti-PAH drug after correction. The survival rate after 2 years was 91.5% (54/59); two patients were in a critical condition, and three were lost to follow-up. Twelve patients (29%) still received over one additional PAH-specific therapy at follow-up, whereas 42 (75%) had successfully stopped drug treatment. Two patients (3.5%) died and one underwent a second thoracotomy to remove the ventricular septal defect patch. Acute vasoreactivity test (AVT) criteria had limited efficacy in predicting pediatric PAH-CHD, whereas pulmonary vascular resistance (PVR) ≤ 6.65 Wood units (WU)/m² or PVR/systemic vascular resistance (SVR) ≤ 0.39 during AVT indicated a good prognosis after surgical correction with an AUC of 98.3% (95% confidence interval [CI]: 96.0–100%), 98.4% (95% CI: 96.0–100%) sensitivity of 100%, 100% and specificity of 82.1%, 92.9%, respectively.

Conclusions: Although the criteria for positive AVT currently used are unsuitable for pediatric patients with PAH-CHD, PVR and PVR/SVR during AVT are excellent predictors of outcome in pediatric PAH-CHD. Surgery aided by anti-PAH drugs is an effective strategy and should be recommended for severe pediatric PAH-CHD with PVR ≤ 6.65 WU/m² and PVR/SVR ≤ 0.39 after iloprost aerosol inhalation.

Keywords: Congenital heart disease; Pulmonary hypertension; Therapy; Follow-up

Introduction

Pulmonary arterial hypertension (PAH) is one of the most disastrous cardiac diseases, with high morbidity and mortality, and is characterized by progressive pulmonary vascular remodeling, heart failure, and death. PAH associated with congenital heart disease (PAH-CHD) is a common complication of CHD with an uncorrected left-to-right shunt, and is the second commonest type of PAH in children, accounting for more than 40% of cases, and even more in developing and underdeveloped areas.^[1-3]

Although guidelines for pediatric PAH-specific therapies are available, they are generally extrapolated from the clinical experience of experts and from adult clinical

trials.^[4,5] However, the management of pediatric PAH-CHD differs significantly from that of adult PAH-CHD.^[6] Previous studies have failed to improve the survival of patients with pulmonary hypertension.^[7]

Abnormal mechanotransduction secondary to congenital heart malformation is considered being the cause of PAH-CHD, so surgical repair or correction of the congenital lesions has been the most effective method of prevention and treatment. However, there are many uncertainties about the indications for and the prognosis of the surgical correction of severe PAH-CHD. Furthermore, evidence-based treatments and policies for severe pediatric PAH-CHD are still lacking or controversial. The assessment of operability and the decision to operate in these patients are

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still difficult tasks because a considerable proportion of patients are characterized by persistent or aggravated pulmonary arterial pressure abnormalities after their defects are corrected, with disastrous results.

In this study, we analyzed the data on heart catheterization (HC), treatment, and prognosis to identify indications and predictors of severe pediatric PAH-CHD in patients who underwent surgical correction.

Methods

Ethical approval

The study protocol was conducted in accordance with the *Declaration of Helsinki* and was approved by the Institutional Review Board of Guangdong Provincial People's Hospital.

Basic characteristics

This was a retrospective cohort study of 59 consecutive children (aged 2–18 years) with a diagnosis of severe PAH-CHD secondary to a simple shunt defect, who underwent surgical repair for CHD between May 2011 and June 2015 at the Guangdong Provincial People's Hospital in China (Guangzhou, Guangdong). The data were collected retrospectively from medical charts, and the last data were collected on July 31, 2017.

Heart catheterization and acute vasoreactivity test

All patients underwent general tracheal intubation, anesthesia, and right HC. Acute vasoreactivity test (AVT) was performed in accordance with a previous study,^[8] in which aerosolized iloprost (Ventavis; Bayer-Schering Pharma, Berlin, Germany) was administered at a dose of 0.5 µg/kg (the maximal dose is 20.0 µg) diluted in isotonic saline solution at a concentration of 10.0 µg/mL. It was nebulized for 15 min with the MicroDrop MasterVent Child (Vantage Pharmacy, Shephed, UK), and then with a peak effect. The effects were observed 15 min after its administration. The hemodynamic parameters were measured and calculated before and after iloprost inhalation.^[9,10]

Protocols for treatment and follow-up

The subjects underwent complete surgical repair if pulmonary vascular resistance index (PVRI) was ≤ 6 Wood units (WU)/m² or their pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) ratio was <0.3 during AVT. The patients underwent repair with a residual atrial septal defect (ASD) or ventricular septal defect (VSD) (diameter 3–5 mm) if PVRI was >6 WU/m² and PVR/SVR ≥ 0.3 . However, a lung biopsy showed that a low level of pulmonary vascular lesions indicated an opportunity for surgical repair and that the pulmonary pressure did not increase after tentative occlusion.^[11] All perioperative management was mainly in accordance with the guidelines for pediatric pulmonary hypertension and our combined experience.^[12] In brief, basic or advanced life support combined with sedatives and permissive

hypercapnia were administered. Specific drugs, such as treprostinil (United Therapeutics Corporation, Silver Spring, MD, USA), bosentan (Actelion Pharmaceuticals Ltd, Allschwil, Switzerland), Sildenafil (Pfizer, Brooklyn, NY, USA), etc, were given for pulmonary hypertension crisis or severe heart failure.

The protocol used to treat pediatric PAH-CHD post-operatively was mainly consistent with the guidelines and consensus,^[12,13] with some modifications in patients for whom no specific drug was administered, when PASP was <50 mmHg and who were in good condition in the perioperative period. Diuretics and dioxins were also given to patients to whom bosentan was administered when PASP ≥ 50 mmHg and their World Health Organization (WHO) functional class was I or II (low risk) after surgery. Diuretics and dioxins combined with bosentan were also given to patients to whom sildenafil was administered when PASP was ≥ 70 mmHg and the WHO functional class was III or IV after surgery. In brief, the initial dose of bosentan was 1 mg/kg twice a day, and the dose was increased to and maintained at 2.0 mg/kg or 62.5 mg (weight >30 kg) twice a day after 4 weeks. The therapeutic policy was adjusted in response to the patient's condition during follow-up, according to the criteria described earlier.

Prognosis assessment

The New York Heart Association (NYHA) functional class, the 6-minute walking distance (6MWD), and the cardiopulmonary hemodynamic parameters (tested with HC or echocardiography) were assessed before surgery, 1, 3, 6, and 12 months after surgery, and every year thereafter or when needed. All-cause death, hospitalization for PAH, and the requirement for additional PAH-targeting drugs were evaluated throughout the observation period.

PASP was evaluated with echocardiography or repeated HC when needed during the follow-up period, according to the guidelines.^[14] PASP was evaluated with echocardiography based on tricuspid regurgitation or the residual VSD shunt, according to the guidelines.^[15,16] The PAH class was defined as mild (PASP 41–50 mmHg), moderate (PASP 51–70 mmHg), severe (PASP 71–90 mmHg), or extremely severe (PASP >90 mmHg).^[17]

The clinical outcomes of the patients who underwent surgical repair, with or without specific drugs after the procedure, were observed and divided into favorable or unfavorable outcomes. A favorable outcome was defined as the successful cessation of specific drugs or a reduction in the NYHA functional class of more than one grade and/or in the pulmonary hypertension class of more than one degree (or a decrease in PASP of more than 20 mmHg), with no increase in the type or dose of the specific drugs administered. An unfavorable outcome was defined as the occurrence of one of the following events: death, no improvement in the WHO functional class or PAH class relative to baseline, a reduction of 15% in 6MWD compared with baseline, a requirement for intravenous epoprostenol to treat PAH deterioration based on the clinical judgment of the treating physician, or a requirement for atrial septostomy or lung transplantation.^[12]

Statistical analysis

All data were analyzed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The Wilcoxon rank sum test was used to assess the ranked data, including heart functional class and PAH class, and continuous variables such as 6MWD and the hemodynamic parameters. Fisher exact probability test and the Chi-squared test were used to analyze frequency distributions. The symmetrically distributed data were expressed as mean \pm standard deviation (SD), and the asymmetrically distributed data were expressed as interquartile range between the 25th and 75th percentile. All reported *P* values are two-sided, with statistical significance at $P < 0.05$. A receiver-operating characteristic (ROC) curve was used to evaluate the predictive values of the hemodynamic parameters at baseline or the AVT in assessing the prognosis of surgery. The area under the curve (AUC) represents the predictive value; 0.7 to 0.9 indicates a moderate predictive value and over 0.9 indicates a high predictive value. Kaplan-Meier curves

were used to demonstrate the timing of the events in the long term.

Results

In this cohort of 59 children with severe PAH-CHD (PASP ≥ 70 mmHg), the observation period was 49 ± 20 months (range, 24–78 months), and three patients were lost to follow-up (5.1%). Thus, the final study group consisted of 56 children with severe PAH-CHD, who underwent surgical repair (26 males and 30 females). The baseline demographic characteristics of the patients before surgery are summarized in Table 1.

The simple CHDs analyzed in this study included VSD ($n=28$), ASD ($n=5$), patent ductus arteriosus (PDA; $n=9$), atrioventricular septal defect (AVSD; $n=2$), aortopulmonary septal defect (APSD; $n=2$), ASD+VSD ($n=3$), ASD+PDA ($n=1$), and VSD+PDA ($n=6$). We also divided the patients into PAH-CHD with ASD

Table 1: Baseline clinical, functional, and hemodynamic characteristics of the children with severe PAH-CHD ($n=56$).

Characteristics	All	Favorable	Unfavorable	Z or χ^2	P
Age (years)	8.9 (4.0–14.0)	6.5 (3.8–13.2)	9 (7.1–14.2)	-1.54	0.120
Gender (M/F), <i>n</i>	26/30	20/22	6/8	0.10	0.760
Height (cm)	117 (95–149)	110 (93–143)	128 (115–156)	-1.82	0.069
Weight (kg)	19 (12.1–34.6)	16.2 (12.0–29.2)	20.0 (17.0–42.0)	-1.92	0.055
Type 1, <i>n</i>				7.90	0.270
VSD	28	20	8		
ASD	5	5	0		
PDA	9	6	3		
APSD	2	0	2		
VSD+PDA	6	5	1		
ASD+PDA	1	1	0		
ASD+VSD	3	3	0		
AVSD	2	2	0		
Type 2, <i>n</i>				4.48	0.049
With ASD	11	11	0		
Without ASD	45	31	14		
NYHA, <i>n</i>				5.72	<0.001
Class I	6	6	0		
Class II	39	31	8		
Class III	11	5	6		
6MWD (m)	376 (250–451)	422 (359–515)	302 (279–323)	-3.37	0.001
NT-BNP (pg/ml)	134 (68–291)	134 (66–341)	128 (75–290)	-0.21	0.835
SaPO ₂ (%)	97 (95–98)	97 (95–98)	96 (94–97)	-0.27	0.007
HC at Baseline					
mPAP (mmHg)	67 (55–74)	78 (68–87)	74 (67–84)	-2.80	0.005
BP (mmHg)	77 (70–86)	78 (68–87)	75 (73–85)		
PVR/SVR	0.35 (0.22–0.55)	0.30 (0.19–0.41)	0.67 (0.52–1.07)	-4.64	<0.001
PVRI (WU/m ²)	5.6 (4.1–9.2)	4.9 (3.5–5.9)	10.8 (9.1–14.8)	-5.01	<0.001
CO (L·min ⁻¹ ·m ⁻²)	4.5 (3.5–5.4)	4.3 (3.5–5.7)	4.7 (3.9–5.0)	-0.40	0.690
HC after AVT					
mPAP (mmHg)	57 (45–71)	52 (45–63)	74 (64–79)	-3.59	<0.001
BP (mmHg)	77 (69–85)	77 (61–84)	83 (71–86)	-1.56	0.120
PVR/SVR	0.26 (0.14–0.42)	0.19 (0.13–0.32)	0.62 (0.44–0.80)	-5.39	<0.001
PVRI (WU/m ²)	4.6 (2.7–8.1)	3.5 (2.3–4.7)	11.4 (9.6–14.1)	-5.38	<0.001
CO (L·min ⁻¹ ·m ⁻²)	4.3 (3.4–5.5)	4.3 (3.5–5.7)	4.2 (3.5–5.3)	-0.47	0.960

Data were presented by median (P₂₅, P₇₅) or *n*. APSD: Aortopulmonary septal defect; ASD: Atrial septal defect; AVT: Acute vasoreactivity test; AVSD: Atrioventricular septal defect; CO: Cardiac output; HC: Heart catheterization; PDA: Patent ductus arteriosus; PVR: Pulmonary vascular resistance; PVRI: Pulmonary vascular resistance index; M: male; F: female; SVR: Systemic vascular resistance; VSD: Ventricular septal defect.

(pretricuspid shunt; $n=11$; including ASD, AVSD, and ASD+PDA) and PAH-CHD without ASD ($n=45$; including VSD, PDA, APSD, and PDA+VSD). The patients with ASD, also called a “pre-tricuspid valve shunt,” had good prognoses [Figure 1].

The changes in PASP and the WHO functional categories during the 2 years after the operation are shown in Figure 2. PASP decreased from 93 (86–102)mmHg at baseline to 30 (30–42)mmHg two years after correction ($t=12.19$, $P<0.01$). Heart function also improved significantly ($Z=5.72$, $P<0.05$). All patients were divided into the favorable or unfavorable group according to their different outcomes, mainly involving their pulmonary pressure, heart function, and the use of specific drugs during the follow-up period. There were 42 patients in the favorable group and 14 in the unfavorable group. PASP and mean pulmonary arterial pressure (mPAP) were higher in the unfavorable group at baseline (91.5 [86.9±96.1]mmHg vs. 104.6 [97.9±111.4]mmHg, $F=9.05$, $P=0.004$ and 64.0 [60.0±67.9]mmHg vs.

74.2 [68.4±79.9]mmHg, $F=7.42$, $P=0.009$, respectively). PASP decreased from 92 (82–96)mmHg at baseline to 30 (30–30)mmHg in the favorable group ($F=27.30$, $P<0.001$), and from 107 (95–113)mmHg at baseline to 92 (87–110)mmHg in the unfavorable group ($F=1.51$, $P=0.160$). It was noteworthy that in three patients in the unfavorable group, although PASP decreased after surgery, it rebounded to severe or extremely severe levels during the withdrawal of specific drugs and in high risk condition until the end of observation although underwent anti-PH re-therapy. Heart function improved significantly in the favorable group ($Z=-6.65$, $P<0.001$), but did not improve in the unfavorable group ($Z=-0.96$, $P=0.340$).

The treatment patterns for postoperative PAH during the observation period are shown in Figure 3. The median exposure time to specific drugs between surgery and the end of data collection was 3.6 months (range 1.0–9.0 months, $n=14$) in the favorable group and 36.5 months (range 24.0–64.0 months, $n=12$) in the unfavorable group. Twelve patients in the unfavorable group were administered

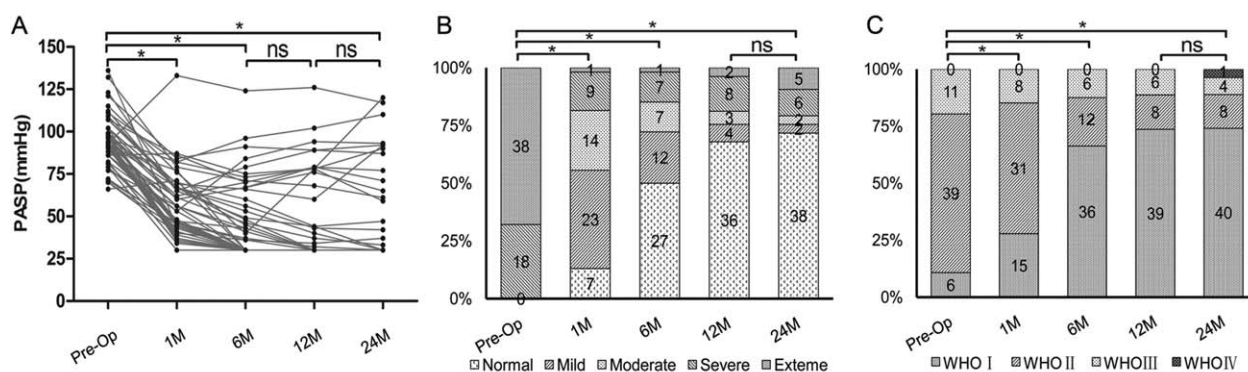


Figure 1: Pulmonary artery systolic pressure (PASP), pulmonary hypertension class, and World Health Organization (WHO) functional class improved after operation. Changes of PASP (A), pulmonary hypertension grade (B), and heart functional class (C) from baseline to 2 years after surgical correction in the total group (Pre-OP, $n=56$; 1 M, $n=54$; 6 M, $n=54$; 12 M, $n=53$; 24 M, $n=53$). PASP decreased significantly after surgery. Pulmonary pressure and heart function improved significantly after surgery in total group. M: months; OP: operation; $*P \leq 0.05$; ns: $P > 0.05$.

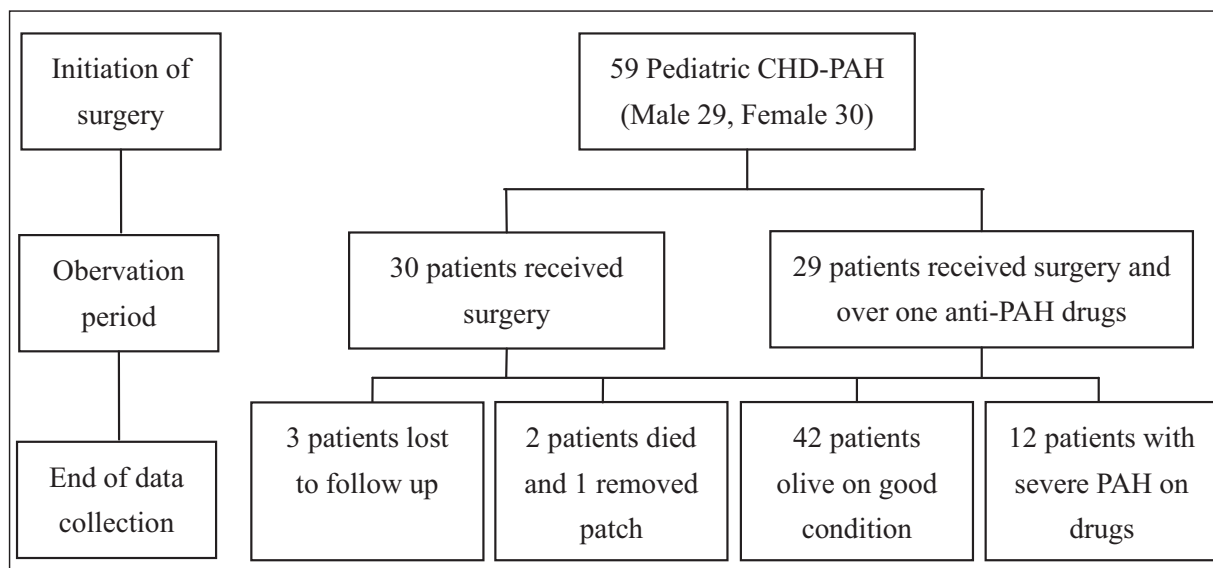


Figure 2: Flow diagram showing the retrospective study of severe pediatric PAH-CHD. PAH-CHD: Pulmonary artery hypertension associated with congenital heart disease.

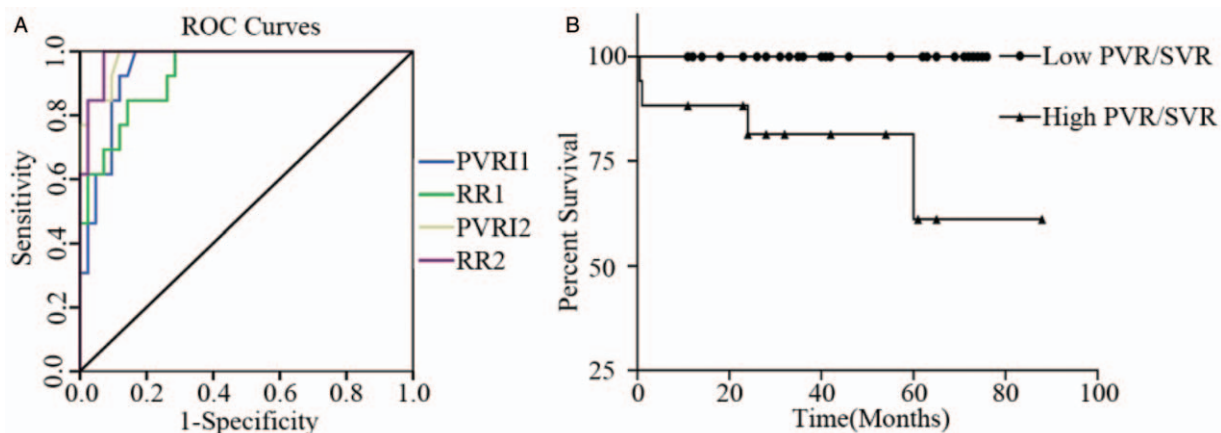


Figure 3: Receiver operating characteristic (ROC) curve of predictive values for PVRI and PVR/SVR (RR) at baseline and after AVT for predicting outcome. Kaplan-Meier curves for the first event in patients with high RR compared with those with low RR. With PVRI1 and RR1 value of 6.60 WU/m^2 or 0.48 as a cut-off value, the predictive sensitivity was 100%, 84.6%, and specificity 83.3%, 85.7%, respectively, and with PVRI2 and RR2 value of 6.65 WU/m^2 or 0.39 as a cut-off value, the predictive sensitivity was 100%, 100%, and specificity 82.1%, 92.9%, respectively (A). The patients with low RR (<0.39) had a better survival rate than those with high RR (B). AVT: Acute vasoreactivity test; PVR: Pulmonary vascular resistance; PVRI: Pulmonary vascular resistance index; SVR: Systemic vascular resistance.

bosentan and diuretics, with or without dioxins, after surgery. All patients in the unfavorable group received a combined therapy of bosentan and sildenafil, and diuretics with dioxins until the end of data collection, and two patients died during the study (one died after surgery and one died suddenly 11 months after leaving hospital). One patient underwent a secondary thoracotomy to remove the patch in response to a persistent pulmonary hypertension crisis and heart failure 7 days later, and two were hospitalized and received intravenous epoprostenol for worsening peripheral edema on their last visit during the period of data collection.

The children in the favorable group had lower PVRI, PASP, mPAP, and PVR/SVR values than those in the unfavorable group, and the differences were significant (all $P < 0.05$). According to the different criteria of Ivy *et al.*^[15] Rich *et al.*^[18] and Barst *et al.*^[19] the numbers of AVT responders were three (5.4%), six (10.7%), and nine (16.1%), respectively, in our study. The heart function of the patients in the favorable group was better than that of the patients in the unfavorable group ($Z = -2.69$, $P = 0.007$), indicated by both the WHO functional class and 6MWD (6MWD was only recommended in children older than 7 years). The differences in age, blood pressure, and the plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-ProBNP) between the favorable and the unfavorable groups were not statistically significant.

The ROC curves for PVRI and PVR/SVR at baseline and at AVT, which were used to predict the therapeutic effects of the operation with or without specific drugs, are shown in Figure 3A. The area under the ROC curve and the cut-off value for PVRI at baseline were 0.95 and 6.60 , respectively, and those for PVR/SVR were 0.93 and 0.48 , respectively. The area under the ROC curve and the cut-off value for PVRI during AVT were 0.983 and 6.65 , respectively, and those for PVR/SVR were 0.94 and 0.39 , respectively. Using the cut-off values for PVRI and PVR/SVR at baseline and at AVT to predict a favorable

prognosis for the surgical correction of severe pediatric PAH-CHD, we found that $\text{PVRI} < 6.65 \text{ WU/m}^2$ or $\text{PVR/SVR} < 0.39$ after iloprost inhalation predicted a good outcome, with high sensitivity (100% and 100%, respectively) and specificity (82.1% and 92.9%, respectively). Further analysis found that $\text{PVR/SVR} < 0.39$ after iloprost aerosol inhalation had higher specificity for predicting a favorable prognosis ($F = 45.8$, $P < 0.001$). Therefore, we used Kaplan-Meier curves to identify the first end-point event related to pH (worsening of pH, requiring intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from all causes in patients with high PVR/SVR (≥ 0.39) compared with those with low PVR/SVR (< 0.39). The Kaplan-Meier survival analysis identified a significant difference in the survival rates in the two groups: low PVR/SVR was better than high PVR/SVR ($P < 0.05$), as shown in Figure 3B [Table 2].

Discussion

PAH-CHD is a lethal condition characterized by progressive vascular remodeling, elevated vascular resistance, heart failure, and death if the abnormal shunt is not corrected.^[20] The abnormal hemodynamic environment, which enhances the shear stress from the right-to-left shunt, is the underlying cause of PAH. Abnormal mechanotransduction is the trigger of pulmonary vascular injury in PAH-CHD, and the abnormal shear stress secondary to vascular remodeling and the narrowing of the pulmonary vessel are responsible for its development.^[19,21]

All the specific first-line drugs used for PAH-CHD, including prostanoids, endothelin-receptor antagonists, and phosphodiesterase type-5 inhibitors, only ameliorate the symptoms of PAH, but do not remove the cause or stop the progression of vascular remodeling. Therefore, although advances have been made in the management of PAH, survival with this condition has not improved significantly. The pathogenesis and characteristics of pediatric pulmonary hypertension differ from those of

Table 2: ROC analysis and the cut-off values for PVRI and PVR/SVR at baseline and AVT.

Variable (s)	Area	SEM*	P	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)
PVRI at baseline	0.950	0.026	<0.001	0.89–1.00	6.60	100	83.3
RR at baseline	0.929	0.035	<0.001	0.86–0.99	0.48	84.6	85.7
PVRI after AVT	0.983	0.014	<0.001	0.96–1.00	6.65	100	82.1
RR after AVT	0.984	0.013	<0.001	0.96–1.00	0.39	100	92.9

*Under a nonparametric assumption. AVT: Acute vasoreactivity test; PVRI: Pulmonary vascular resistance index; ROC: Receiver-operating characteristic curve; RR: Pulmonary vascular resistance/systemic vascular resistance; SEM: Standard error mean.

adult pulmonary hypertension, particularly in PAH-CHD. The most significant difference from the adult condition is that most pediatric PAH-CHD is reversed completely by surgical repair. The guidelines indicate that surgical repair is recommended for PAH-CHD with $PVRI \leq 6 \text{ WU/m}^2$ or $PVR/SVR < 0.3$ during AVT. However, PAH-CHD with $6 \text{ WU/m}^2 < PVRI < 10 \text{ WU/m}^2$ or $0.3 < PVR/SVR < 0.5$ is a “gray area” because there has been no systematic study or high-quality evidence that can be used to predict a prognosis,^[4,22] so the decision to operate and the therapeutic policies for severe PAH-CHD in children aged above 2 years remain challenging and the prognosis for surgical intervention is unpredictable.^[23]

The patients included in this study had PAH complicated with simple CHD, but without confounding factors, such as functional single ventricle, persistent truncus arteriosus, double outlet of the ventricle, or hypoplasia of the pulmonary artery. This study demonstrates that pulmonary pressure and heart function improved significantly after the repair of the left-to-right shunt, indicating that a repair-and-treat strategy is an effective method for treating children with severe PAH-CHD. However, there were significant differences in the prognoses of pediatric PAH-CHD in different individuals. In the group of patients with a favorable prognosis, the pulmonary pressure decreased to below the moderate level and their heart function improved significantly with no specific drugs administered, whereas in the patients with an unfavorable prognosis, their pulmonary pressure and heart function did not improve significantly, although they were administered more than one specific drug. Consistent with previous studies, these results indicate that there is a significant difference in the prognosis of surgical correction for CHD in PAH-CHD.

A univariate analysis that compared the hemodynamic parameters and clinical characteristics of the children with different prognoses in this study showed statistically significant differences in several variables: CHD subtype, heart function, resting oxygen saturation (SpO_2), mean PAP, PVRI, and PVR/SVR at baseline, and mPAP, PVRI, and PVR/SVR during AVT. Although 6MWD is difficult to test in children younger than 7 years, the WHO functional class effectively predicted the prognoses in all children. Interestingly, 11 patients with PAH-CHD and ASD (pretricuspid shunt) all had better prognoses than those with PAH-CHD without ASD ($F=4.48$, $P=0.049$). This result is consistent with a previous report that the prognosis of surgical repair in patients with PAH secondary to a post-tricuspid shunt lesion and $PVRI <$

10 WU/m^2 is always favorable, but this conclusion requires further study. Our findings are similar to those of previous studies in that heart function, pulmonary vascular resistance, pulmonary artery pressure, and resting oxygen saturation were predictors of the prognosis of PAH-CHD.^[24] However, in contrast to the general belief, NT-ProBNP had no predicative role in the prognosis of surgery for pediatric PAH-CHD.^[25] The main reasons may be that the metabolism of brain natriuretic peptide (BNP) was affected by infection, drugs, or renal function. As mentioned in the guidelines, the lack of objective parameters and predictors of PAH-CHD in children makes matters worse.

Heart catheterization and AVT are considered the gold standard treatments for CHD and PAH. AVT has significant clinical value in selecting patients with PAH for calcium-channel blocker therapy, assessing prognosis, and evaluating operability in patients with PAH-CHD.^[26] However, the definition of an AVT responder remains inconsistent and controversial, especially in pediatric PAH. Broadly speaking, three criteria for acute vasoreactivity, defined by Kaemmerer *et al*,^[27] Rich *et al*,^[18] and Sitbon *et al*,^[21] are generally used. The Sitbon criterion, a reduction in mPAP of $\geq 10 \text{ mmHg}$, reaching $< 40 \text{ mmHg}$ with no decline in cardiac output, is generally recommended in children. The Rich criterion is a reduction in mPAP and PVR of $\geq 20\%$. The Barst criterion is a reduction in mPAP of $\geq 20\%$, with an unaltered or increased cardiac index, and a reduced or unchanged PVR/SVR ratio. In this study, the prognosis of AVT responders was good, but the positive rate and specificity were significantly lower than in other types of pediatric pulmonary hypertension. The Barst criteria have the greatest clinical sensitivity for AVT responders. These results also confirm that the currently used acute response criteria are unsuitable for pediatric patients with PAH-CHD. All current criteria include two key points: a reduction in mPAP, but no reduction in the cardiac output index. However, it is contentious whether in PAH-CHD pulmonary flow will increase when PVR is reduced with vasodilators. The relationship between pulmonary blood flow and vascular resistance is even more complex when combined with different levels of heart function. Therefore, it is difficult, but urgent, to develop new strategies for assessing the structural and dynamic characteristics of the pulmonary vasculature accurately in patients with different types of CHD.

Although the acute response criteria are unsuitable for patients with PAH-CHD, AVT can indicate the residual

pulmonary vasodilative reserve in pulmonary hypertension. In theory, pulmonary vasoconstriction and vascular remodeling are the key pathophysiologic elements of PH, and vasoactive substances, such as prostaglandin and nitric oxide, can eliminate the increase in pressure induced by pulmonary vasoconstriction. Therefore, AVT is recommended for pediatric PAH-CHD to assess whether PVR will decrease after surgical repair. Surgery is recommended for patients with post tricuspid shunt when there is reduction of PVRI is <6 to 8 WU/m^2 , or $\text{PVR/SVR} < 0.3$ after AVT. Our study identified PVRI and PVR/SVR after iloprost inhalation as excellent predictors of outcome, with high specificity and sensitivity. The cut-off values for severe pediatric PAH-CHD treated with surgical repair are $\text{PVRI} < 6.65 \text{ WU/m}^2$ and $\text{PVR/SVR} < 0.39$. Therefore, we believe that surgical intervention can be undertaken in children with a positive AVT and $\text{PVRI} < 6.65 \text{ WU/m}^2$ or $\text{PVR/SVR} < 0.39$ during AVT. The latter has higher specificity in predicting prognosis. The further Kaplan-Meier survival analysis showed that the children with low $\text{PVR/SVR} (< 0.39)$ had better survival rates than those with high PVR/SVR .

As we known, surgical repair is recommended and the children should be reassessed after the initiation of specific treatment. However, it is noteworthy that two patients who underwent repair after the initiation of specific treatment and repeated HC had poor prognoses. We attribute this to the fact that current specific first-line drugs are vasodilators, and do not reverse vascular remodeling. Therefore, they only reduce PVR by inhibiting functional vasoconstriction and do not affect pulmonary vascular remodeling. The application of a treat-and-repair strategy for pediatric PAH-CHD should be applied with care, and further research is required.^[28] The first step in the treatment of pediatric PAH-CHD should be to assess the feasibility of surgical correction.

One limitation of this study was that some specific factors affecting the prognosis could not be investigated because the specimens were too small. Another limitation was the retrospective nature of the study. However, there are few data on the factors affecting therapeutic decision-making and prognosis in severe PAH-CHD, particularly in children. Therefore, this study provides an important basis for the selection of treatment for PAH-CHD, and offers important evidence-based references for the management of PAH secondary to other complex CHDs.

In conclusion, this study demonstrates that PVRI and PVR/SVR at AVT are excellent predictors of outcome, and that repair-and-treat is an effective strategy for severe pediatric PAH-CHD. However, the management of moderate and severe PAH-CHD is complex and challenging. The ultimate decision must be made by an experienced medical team based on hemodynamic data and a thorough clinical examination. Further prospective randomized cohort studies are required to provide better evidence.

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Conflicts of interest

None.

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