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RESEARCH ARTICLE

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Therapeutic effects of treat and repair strategy in pediatric patients with pulmonary arterial hypertension and simple congenital heart defects

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Abstract

Surgical indications for patients with pulmonary arterial hypertension (PAH) and congenital heart defects are controversial. The treat and repair strategy has demonstrated efficacy in adult populations, but there have been no studies on pediatric patients. This study included pediatric patients with PAH and simple congenital heart defects who underwent corrective repair between 2012 and 2021. According to the preoperative treatment strategies, the patients were divided into a regular strategy group (Group 1) and a treat-and-repair strategy group (Group 2). Postoperative recovery and follow-up results were compared between the two groups. A total of 33 patients were included in this study. Group 1 consisted of 19 patients, whereas Group 2 consisted of 14 patients. The pulmonary vascular resistance index in Group 2 was higher than that in Group 1 (10.9 ± 4.1 vs. 8.2 ± 1.6 WU, $p = 0.031$). There were no differences in postoperative recovery between the two groups ($p > 0.05$). During follow-up, five patients were lost (three in Group 1 and two in Group 2). The median follow-up period was 59 months. One patient died in Group 1, and two patients died in Group 2. There was no significant difference in the survival curve ($p = 0.39$). At the last follow-up, another seven patients had experienced a non-low-risk condition, with a total of three non-low-risk patients in Group 1 and seven in Group 2, including one patient in each group who had a history of ICU admission. According to the ROC curve, a preoperative PVRi <8.2 WU×m^2 can predict postoperative persistent low-risk state, PVRi <5.2 WU×m^2 can avoid postoperative death and/or ICU administration. In pediatric patients with PAH and simple congenital heart defects, the treat and repair strategies may provide surgery opportunities, PVRi should be <8 WU×m^2, and <5.2 WU×m^2 is the best choice.

KEYWORDS
congenital heart disease, follow-up, pediatric patients, pulmonary arterial hypertension, treat and repair strategy

Xiaofeng Wang and Shilin Wang contributed equally as co-first authors.

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital malformation, with an incidence of 1%.[1] Due to the increase in pulmonary blood flow and the shear force injury caused by the large left-to-right shunt type CHD, pulmonary arterial hypertension (PAH) occurs in patients who miss the recommended repair time. In these patients, corrective repair is controversial because even if the operation is successful, PAH may still occur during long-term postoperative follow-up.[2] Postoperative PAH affects approximately 10% of CHD patients.[3] The follow-up data indicate that the postoperative long-term survival is comparatively lower than that of Eisenmenger syndrome.[4]

For patients with CHD-PAH, early research suggests that a pulmonary vascular resistance index (PVRi) <4 WU×m^2 is an ideal indication for corrective repair. If PVRi is >8 WU×m^2, surgical treatment is not recommended. Patients with a PVRi between 4 and 8 WU×m^2 should be evaluated individually.[5] Only medical treatment and follow-up can be performed for inoperable patients. Consequently, these patients inevitably deteriorate to the Eisenmenger syndrome stage. Although the life expectancy of Eisenmenger syndrome is acceptable, it can cause multisystem complications and reduce quality of life. With the development of targeted drugs for PAH, many types of targeted drugs in different pathways have been put to clinical application. As a result, the prognosis of PAH has improved significantly. A large Chinese multicenter registry study on Eisenmenger syndrome proved the total of 1060 patients have significantly impaired exercise tolerance and right ventricular function at diagnosis, which are closely associated with long-term survival. PAH-targeted therapy including combination therapy showed a favorable effect on survival. However, the long-term survival of Chinese patients remains to be improved.[6] A recent study suggested that patients with postoperative PAH have similar survival curves to those with Eisenmenger syndrome.[7] Therefore, there has been a progressive shift in surgical indications. PVRi <6 WU×m^2 is the optimal surgical indication, while PVRi 6–8 WU×m^2 belongs to the gray area. If PVRi exceeds 8 WU×m^2, it is considered inoperable or requires reassessment after targeted therapy for PAH.[8] This practice is called the treat-and-repair strategy. However, owing to the short history of this strategy, only a limited number of studies have provided corroborative findings. Most of these studies have focused on adult patients with atrial septal defects who received interventional therapy after targeted treatment. This study aimed to investigate the effects of treat and repair strategy in pediatric patients who underwent corrective surgical repair.

METHODS

Study design and data collection

This study was a single-center retrospective cohort analysis of pediatric patients (aged <18 years) with simple shunt defects who underwent corrective repair at FuWai Hospital from 2012 to 2021. We included patients whose PVRi exceeded 6 WU×m^2. Patients with a high PVRi are allowed to maintain an atrial septal defect after the procedure. The exclusion criteria were complex CHD, high PVRi with small defects, and fenestrated VSD repair.

Patients were divided into a regular strategy group (Group 1) and a treat-and-repair strategy group (Group 2) according to whether they received standard targeted therapy before surgical repair. Targeted therapy was defined as the regular use of targeted drugs for at least 3 months before the final right heart catheterization to determine the surgical indication. preoperative treatment was determined by different surgeons based on the evaluation of the right heart catheterization data and their own experience. In terms of targeted drug selection, our center preferred bosentan combined with sildenafil treatment, but bosentan monotherapy was administered to adolescent males, and patients with obvious liver injury after the application of bosentan were discontinued.

Age, sex, cardiac lesions, cardiopulmonary bypass, and preoperative PVRi in both groups were recorded. In Group 2, the types of targeted drugs, duration of treatment, and changes in PVRi were recorded. Pulmonary hypertension crisis, inhaled nitric oxide therapy, mechanical ventilation hours, ICU days, length of postoperative stay, reintubation, renal replacement therapy, delayed thoracotomy/bedside thoracotomy, ECMO (Extracorporeal Membrane Oxygenation) assistance, and death were recorded in both groups for short-term postoperative recovery. The mid-to long-term follow-up data included the duration of follow-up and all-cause mortality.

Right heart catheterization

Right heart catheterization was performed under general anesthesia. Local anesthesia was administered when the femoral vein and artery were perforated. The Indirect Fick method was used for data computing. The body surface area was generated by automatic calculation of height and weight. PVRi was the main indication for corrective repair. A PVRi <8 WU×m^2 was usually used as the surgical standard, which could be extended to 10 WU×m^2 for individual patients. If the above indications were not

achieved, targeted therapy should be administered for a minimum duration of 3 months, and the right cardiac catheter should be re-examined. Corrective repair was performed if the above surgical indications were met or if there was a considerable decrease in PVRi compared with the previous outcome (>20%).

Surgical treatment

Different qualified surgeons performed the surgeries. Patch closure of the ventricular septal defect was performed using cardiopulmonary bypass and aortic cross-clamping. The patent ductus arteriosus can be cured through direct closure or cardiopulmonary bypass without cardioplegic arrest. The pulmonary artery catheter was not routinely inserted in the operating room. All patients were transferred to the ICU under general anesthesia and mechanical ventilation to facilitate ongoing medical care.

ICU management

Sedative and analgesic treatment with midazolam and fentanyl was prescribed to patients with an unstable hemodynamic status. The prescription of muscle relaxants (pancuronium bromide or cisatracurium besilate) was based on hemodynamic conditions induced by continuous infusion or bolus infusion. The aim of oxygen therapy during mechanical ventilation was to achieve a PaO2 of 100–150 mmHg measured by arterial blood gas analysis. The objective of mild hyperventilation during mechanical ventilation was to achieve a pCO2 of 30–35 mmHg (arterial blood gas). The aim of the alkalemia was arterial blood gas (pH 7.4). Vasoactive drugs included dopamine 3–8 μg/kg/min, dobutamine 3–8 μg/kg/min, milrinone 0.3–1 μg/kg/min, epinephrine 0.03–0.1 μg/kg/min, and vasopressin 0.005–0.03 μg/kg/h depending on the hemodynamic status. Continuous intravenous infusion of torsemide 0.1–0.2 mg/kg/h was prescribed as diuretic treatment. In patients with acute kidney injury or kidney disease (improving global outcomes criteria were used for diagnosing and staging acute kidney injury), renal replacement therapy was initiated at urine volume <0.5 mL/kg/h for 6–12 h. Renal replacement therapy included peritoneal dialysis or continuous venovenous hemofiltration. After tracheal extubation, patients were provided with noninvasive assistance in the case of dyspnea/respiratory failure. Reintubation was performed in cases with an unstable circulatory status.

Pulmonary hypertension crisis and postoperative targeted therapy

The pulmonary hypertension crisis was defined as an increase in central venous pressure combined with a decrease in blood pressure of more than 20% and/or percutaneous oxygen saturation <90%.[9] The treatment of pulmonary hypertension crisis included the following aspects: (1) Ceasing all possible causes of pulmonary hypertension crisis; (2) administration of inhaled 100% oxygen, and (3) administration of inhaled nitric oxide, (4) Sedation and analgesia treatment; (5) In cases of refractory pulmonary hypertension crisis, bedside open-chest and ECMO assistants were selected. The administration of nitric oxide gas was administered using a delivery and monitoring system (SLE3600 INOSYS). At our center, the concentration of inhaled nitric oxide concentration was 20 ppm. When inhaled nitric oxide therapy was withdrawn, oral sildenafil (0.25 mg/kg/dose, QID) and bosentan (2 mg/kg/dose, BID) were prescribed sequentially. Single-drug therapy or combined-drug therapy was selected based on the severity of PAH and preoperative drug regimen.

Follow-up

All patients continued the targeted medical therapy during the follow-up period. The patients underwent postoperative follow-up 1, 3, 6, and 12 months after surgery. Subsequently, they were monitored for PAH at intervals of 6–12 months for PAH. Various diagnostic procedures were performed during the follow-up period, including clinical evaluation, electrocardiography (ECG), radiography, echocardiography, blood routine, and blood biochemistry. Based on the above results, risk stratification of the patients was carried out.[5,8] Children were classified into low-risk and high-risk conditions based on the 2019 Updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The EPPVDN, endorsed by AEPC, ESPR, and ISHLT, whereas adults were classified into low-risk, medium-risk, and high-risk conditions based on the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the ESC and the ERS: Endorsed by: AEPC, ISHLT. The goal of follow-up was to maintain a low-risk condition with an upgrade of targeted drugs and an increase in the frequency of follow-up. Unexpected hospital readmissions were recorded during follow-up.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 25.0; IBM Corp.). Because the sample size of the study is limited, to avoid sample loss as much as possible, imputation (expectation maximization) is considered for continuous variables. When the proportion of missing variables is greater than 20%, we exclude them. The Shapiro–Wilk test was used to evaluate the distribution of continuous variables and determine whether they followed a normal or nonnormal distribution. Continuous data following a normal distribution are typically represented using means and their corresponding standard deviations. Conversely, nonnormally distributed variables were defined as medians and their related interquartile ranges (IQRs). Categorical variables are represented numerically, together with their respective proportions. The statistical analyses involved paired *t* tests and independent *t* tests for continuous variables following a normal distribution. The Wilcoxon rank-sum test was used to analyze nonnormally distributed variables. Categorical variables were analyzed using Fisher's exact test. The probability of survival was evaluated using the Kaplan–Meier method and visualized using the Kaplan–Meier curve. The Mantel–Cox log-rank test was also used to assess any disparities in event rates between the two groups. Binary logistic regression was used to determine the correlation between the variables and outcomes. The ROC curve was used to show the sensitivity, specificity, area under the curve, and cutoff point of the variables. Statistical significance was set than 0.05.

Ethical review

Approval from the FuWai Hospital Ethics Committee was obtained in October 2022 (ID: 2022-1859. The ethical principles followed the 1975 Declaration of Helsinki. This retrospective analysis was based on anonymized data collected for routine clinical care and administrative purposes. Consequently, the requirement for individual informed consent was waived.

RESULTS

A total of 33 pediatric patients were enrolled, including 19 in Group 1 and 14 in Group 2. Among the 14 pediatric patients in Group 2, the duration of preoperative targeted therapy ranged from 3 to 28 months, with a median course of 9 months. The types of targeted drugs included bosentan in five patients, sildenafil in one patient, and bosentan combined with sildenafil in eight patients. The PVRi decreased from 13.2 ± 3.7 to 10.9 ± 4.1 WU×m^2. The results of the pre-post treatment PVRI for each patient were shown in Figure 1. The basic data for the two groups are shown in Table 1.

The early-term postoperative recovery

In the early postoperative recovery period, there was no statistical difference between the two groups for any of the indicators. All patients in both groups were discharged successfully, with no serious complications such as reintubation, renal replacement therapy, delayed or bedside thoracotomy, and ECMO support. The details of early postoperative recovery are shown in Table 2.

The midterm to long-term postoperative recovery

The final follow-up period in the trial was May 2023. Five patients (15%) were lost to follow-up. Specifically, three

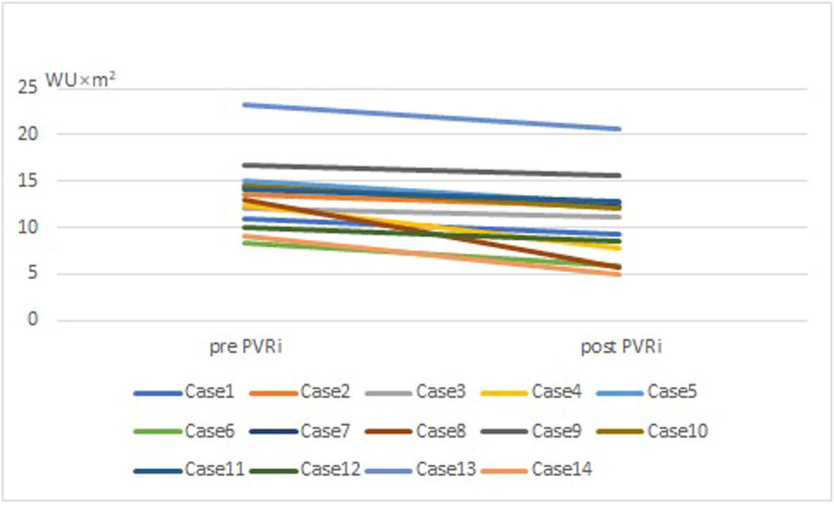

FIGURE 1 The results of the pre-post treatment PVRI for each patient.

TABLE 1 The basic data of the two groups.

	Group1 ($n = 19$)	Group2 ($n = 14$)	p Value
Age (years)	4.4 (3.1, 10)	7 (4, 12.5)	0.27
Gender			0.72
Male	6 (32)	6 (43)	
Female	13 (68)	8 (57)	
Cardiac lesion			0.024
Ventricular septal defect	19 (100)	10 (71)	
Patent ductus arteriosus	0 (0)	4 (29)	
Cardiopulmonary bypass	19 (100)	11 (79)	0.067
PVRi (WU×m^2)[a]	8.2 ± 1.6	10.9 ± 4.1	0.031
Rp/Rs	0.44 ± 0.13	0.54 ± 0.15	0.042

Abbreviations: PVRi, pulmonary vascular resistance index; Rp/Rs, pulmonary vascular resistance/systemic vascular resistance ratio.
[a]Posttreatment PVRi.

TABLE 2 The early-term postoperative recovery data.

	Group1 ($n = 19$)	Group2 ($n = 14$)	p Value
Inhaled nitric oxide	4 (21)	6 (43)	0.26
Pulmonary hypertension crisis	1 (5)	2 (14)	0.56
Mechanical ventilation hours	20 (14, 22)	9 (6, 23)	0.23
Intensive care unit days	2 (2, 5)	1.5 (1, 3)	0.177
Length of postoperative stay (days)	8 (7, 15)	8 (7, 10)	0.63
Reintubation	0 (0)	0 (0)	NA
Renal replacement therapy	0 (0)	0 (0)	NA
Delayed/bedside thoracotomy	0 (0)	0 (0)	NA
ECMO	0 (0)	0 (0)	NA

Abbreviation: ECMO, extracorporeal membrane oxygenation.

cases in Group 1 and two in Group 2. The follow-up duration ranged from 3 to 125 months, with a median of 59 months. Among the remaining 28 cases, there were three deaths during follow-up, resulting in an all-cause mortality rate of 10.7%. One patient in Group 1 died, resulting in an all-cause mortality rate of 6%. This occurred approximately 3 months after the operation. In Group 2, two patients died at 3 and 20 months after the operation. The overall all-cause mortality rate was 17%. The cumulative survival analysis of the two groups is shown in Figure 2; there was no statistically significant difference ($p = 0.395$). The characteristics of the deceased patients were analyzed, revealing the presence of two prevailing commonalities. First, all patients underwent surgical treatment in the early stages (before December 2014), and the last death occurred in June 2016. Second, the PVRi of all the patients exceeded 8 WU×m^2 (8.5, 9.1, and 9.3, respectively). At the last follow-up, another seven patients had experienced a non-low-risk condition, with a total of three deaths and non-low-risk patients in Group 1 (19%) and seven in Group 2 (58%), including one patient in each group who had a history of ICU admission. The proportion of patients with persistent low-risk conditions in Group 2 was lower than that in Group 1 ($p = 0.05$). The preoperative PVRi in patients with persistent low-risk was lower than that in those in whom the treatment goal was not achieved (7.6 ± 2.0 vs 11.6 ± 3.9 WU×m^2, $p = 0.011$). Univariate regression suggested that the treat and repair strategy significantly increased the risk of postoperative deaths and non-low-risk conditions (RR 6.067, $p = 0.038$, 95% CI 1.107–33.238). Preoperative low PVRi was protective for postoperative death and non-low-risk conditions (RR 0.536, $p = 0.017$; 95% CI 0.321–0.895). Multivariate regression results suggested that PVRi alone was an independent risk factor. According to the ROC curve, the sensitivity and specificity of preoperative PVRi <8.2 WU×m^2 in predicting postoperative persistent low-risk condition were 0.722 and 1.0, with the area under curve 0.867. The ROC curve results are shown in Figure 3.

For the five cases of serious complications (three deaths and two ICU admissions) during follow-up, although there was no statistical difference, we still drew the ROC curve to find the recommended PVRi value to avoid life-threatening postoperative complications. According to the ROC curve, the preoperative PVRi <5.2 WU×m^2 can avoid life-threatening postoperative complications with the area under curve 0.583. The ROC curve results are shown in Figure 4.

DISCUSSION

At present, a lot of studies and guidelines established a correlation between postoperative PAH and high mortality, which imposed strict criteria for surgical repair.[5,8,10,11] In recent years, with the development of targeted drugs for PAH in different pathways, the drug regimens (combined therapy for high-risk patients) and the definition of treatment goals (maintaining patients in a low-risk state), life span, and quality of life of PAH patients have significantly improved.[12]

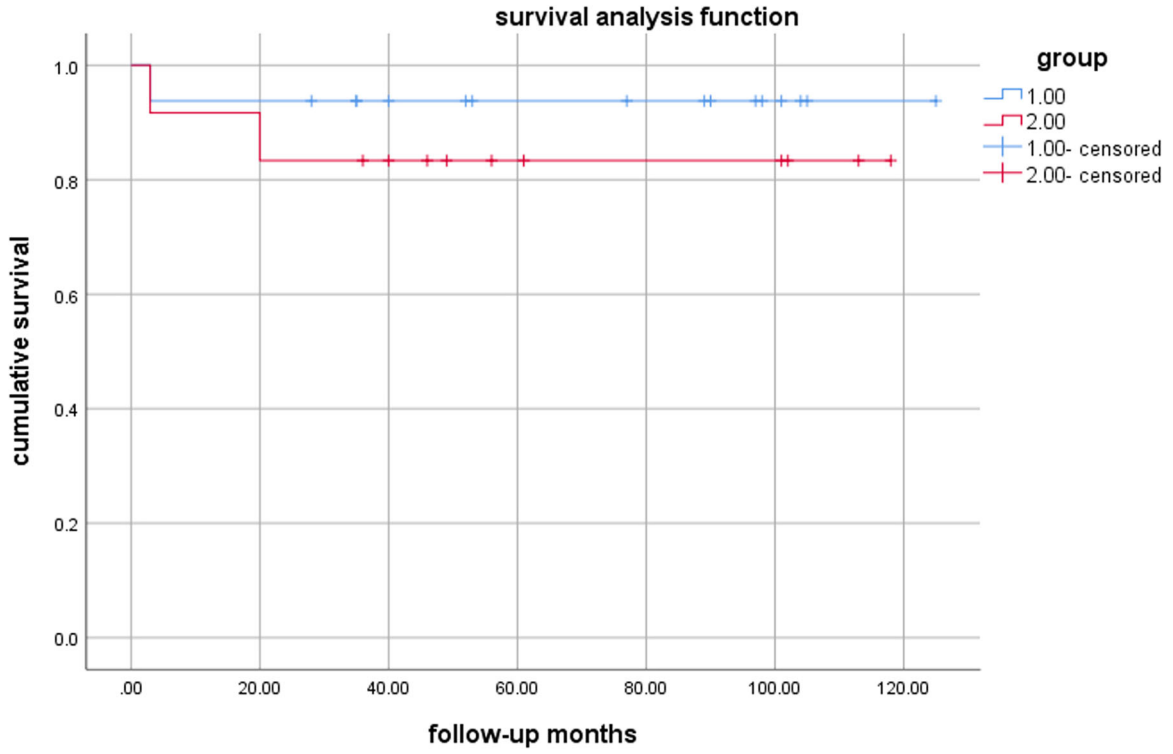

FIGURE 2 The midterm to long-term postoperative follow-up survival rate between the two groups.

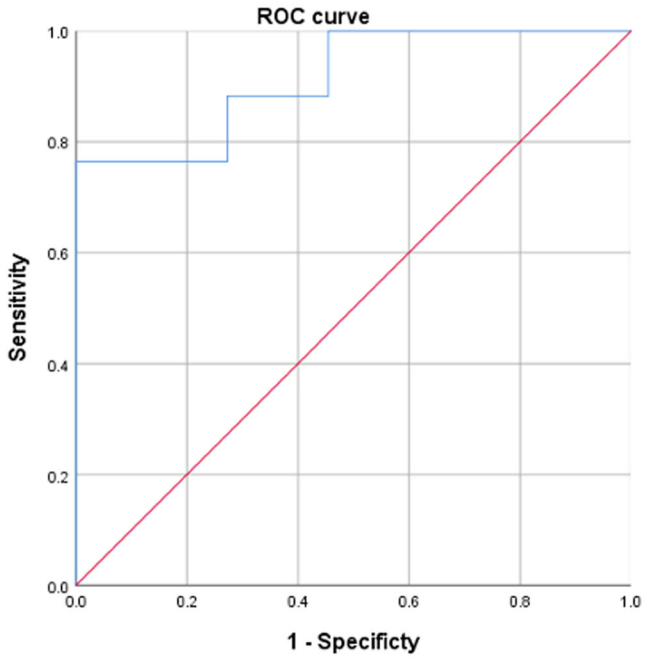

FIGURE 3 The ROC curve of PVRi in predicting persistent low-risk patients.

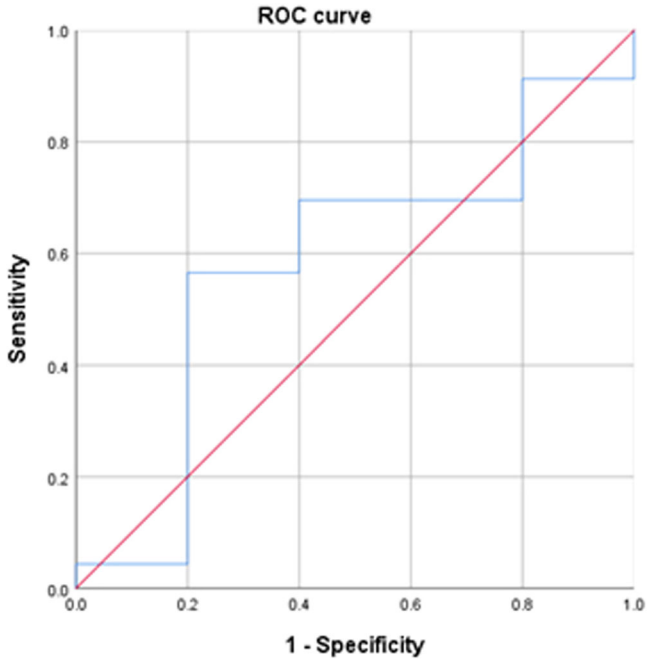

FIGURE 4 The ROC curve of PVRi in avoiding death and/or ICU admission.

Owing to the advancements in medical therapy, a treat and repair strategy has been proposed with the aim of obtaining surgical indications for CHD-PAH patients in the gray zone. This strategy has provided evidence-based support for adult patients. Bradley et al.[13] included 69 adult patients with PAH and atrial septal defects from nine centers in North America, 19 of whom underwent atrial septal defect intervention. After 4.4 years of follow-up, they

found that compared with drug therapy alone, patients in the treat and repair groups had better 6-min walking distance performance and more noticeable improvement in right heart function assessed by echocardiography. Takaya et al.[14] included 42 adult patients with PAH and atrial septal defects from 13 centers in Japan. All patients underwent treat and repair treatments. After an average follow-up of 33 months, only one elderly patient died after surgery for uncertain reasons. In the remaining patients, NYHA classification and pulmonary arterial pressure significantly improved compared with themselves before interventional repair.

In terms of surgical repair of ventricular septal defects, Akagi et al.[15] conducted a case series of three adult patients in Japan, all of whom underwent successful ventricular septal defect repair. At the midterm to long-term follow-up, there was a significant reduction in the mean pulmonary artery pressure measured using right heart catheterization. Hu et al.[16] included 41 adult patients with PAH and ventricular septal defects in a single center who underwent repair treatment. In this study, two patients died early after surgery. The remaining 39 patients were followed-up for an average of 37 months, and there were no deaths during follow-up.

Apart from our study, there are no reports of pediatric patients receiving treat and repair strategies. At present, only Golovenko et al. in Ukraine[17] have reported their surgical techniques ($n = 89$). In their study, pediatric patients who received sildenafil treatment for 3 months before surgery ($n = 33$) experienced more significant benefits than those who did not receive targeted drug therapy ($n = 56$). The duration of mechanical ventilation was shorter, but no mid-to long-term follow-up data were reported.

In this study, for the first time, we included pediatric patients with CHD-PAH and divided them into groups based on different preoperative strategies. The early- and midterm to long-term follow-up results of the two groups were provided to support the efficacy of the treat and repair strategy in managing gray zone patients with CHD-PAH. In the present study, the administration of targeted medications resulted in an improvement in PVRi. However, it is noteworthy that the PVRi and pulmonary vascular resistance/systemic vascular resistance ratio in Group 2 remained significantly higher than that in Group 1. Based on the available evidence, it may be inferred that the severity of PAH was greater in Group 2 than in Group 1.

In addition, the proportion of patients in Group 2 who required nitric oxide was double that of Group 1. It may simply be underpowered by the relatively low sample size, but this difference deserves mention. Patients in Group 2 had a higher PVRi and were indeed more at risk, which is worthy of attention. There were no serious complications during the postoperative hospital stay in Group 2, which is likely the result of receiving more advanced targeted drugs, and does not mean that patients receiving treatment and repair strategies can change the standard of corrective repair.

The total mortality rate of 10.7% is extremely high for simple cardiac defects repairs. The three deceased patients had two characteristics. First, all patients underwent surgical repair in the early stage. Second, the preoperative PVRi was >8 WU×m^2. Based on these characteristics, we infer the possible causes of death. Before 2015, the accessibility of targeted PAH drugs in China was lower than that in developed countries. Meanwhile, the high cost of targeted drugs poses a significant barrier for patients in their need to select combination therapy. In recent years, China has witnessed significant advancements in its healthcare system and medical security coverage, resulting in the emergence of many new drugs in the market. Consequently, doctors can choose medication based on disease severity rather than on financial circumstances. Nevertheless, we still do not recommend surgical treatment for patients with significantly elevated PVRi because of the increased postoperative mortality and complications.

According to the results of the risk stratification, 18 patients were able to maintain a low-risk condition after surgery. We analyzed preoperative PVRi and found that all patients maintained a low-risk condition in the group with PVRi <8 WU×m^2. Through ROC curve, a preoperative PVRi <8.2 WU×m^2 could predict postoperative persistent low-risk and act as the minimum surgical indication.

However, this study also found that patients with treat and repair strategies had a higher probability of postoperative complications, which is worthy of attention. Through the data of this study, we found that to avoid major postoperative complications (such as death, ICU admission), surgical indications should be strictly controlled, and PVRi <5.2 WU×m^2 may be the recommended value. This is more in line with current recommendations in the guidelines for adult CHD (PVRi <5 WU is recommended in the latest guideline).[10]

STUDY LIMITS

First, right heart catheterization, magnetic resonance imaging, and cardiopulmonary exercise tests[18] were not performed during the routine follow-up. These items should be added in the future to obtain adequate postoperative follow-up data. Second, some studies have suggested that the mortality of patients with postoperative PAH can be

significantly increased 10 years after surgery.[19] The duration of follow-up in this study was only 5 years, which requires an extension of the follow-up period to yield long-term outcomes.

CONCLUSION

In pediatric patients with PAH and simple congenital heart defects, treat and repair strategies may provide patients with surgery opportunities, but PVRi should be at least <8 WU×m^2, and <5.2 WU×m^2 is the best choice. Future studies with larger sample sizes and longer follow-up periods are needed to provide more evidence.

AUTHOR CONTRIBUTIONS

Xiaofeng Wang and Shilin Wang contributed to the article writing, data collection, and statistical analysis. Zhongyuan Lu and Wenlong Wang contributed to the drafting and critical review of the article. Xu Wang contributed to the study design and the review of the final article. All authors have contributed to the manuscript and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request with the corresponding author.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Fuwai Hospital (ID: 2022-1859). Because this was a retrospective study, the requirement for informed consent was waived. The ethical principles of the 1975 Declaration of Helsinki were followed in this study.

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