

## Survival of Patients after Left-to-Right Shunt Repaired of Congenital Heart Defect: A Comparison between Baseline Pulmonary Vascular Resistances

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Received 13 March 2020 • Revised 19 May 2020 • Accepted 22 May 2020 • Published online 10 August 2020

### Abstract:

**Objective:** This study compared the survival of patients with completely repaired pulmonary hypertension-associated congenital heart disease (PH-CHD) with a left-to-right shunt based on their pulmonary vascular resistance index (PVRI).

**Material and Methods:** In this retrospective cohort study, the demographics, disease characteristics, laboratory tests, hemodynamic characteristics and survival of patients with PH-CHD in our institute between January 2004 and January 2016 were reviewed.

**Results:** Of 298 patients, 216 had a low PVRI (72.5%), 57 had a moderate PVRI (19.1%) and 25 had a high PVRI (8.4%). In the overall population, the 1-, 5- and 10-year survival rates were  $96.6 \pm 1.0\%$ ,  $94.2 \pm 1.5\%$ , and  $91.1 \pm 3.3\%$ , respectively. At 10 years after the operation, patients with a low PVRI had the best survival, but patients with a moderate PVRI didn't have significantly better survival than the patients with a high PVRI ( $98.6 \pm 0.8\%$  vs.  $81.9 \pm 5.5\%$  vs.  $76.5 \pm 11.2\%$ , respectively;  $p$ -value  $< 0.001$  in low vs. moderate or high PVRI;  $p$ -value = 0.8 in moderate vs. high PVRI). The World Health Organization functional class and PVRI were predictors of survival at 10 years after the operation.

**Conclusion:** This study supports the recent 2015 European Society of Cardiology and European Respiratory Society guideline, which says that patients with a PVRI  $< 4$  Wood units  $m^2$  have the best survival, a PVRI of 8 Wood units  $m^2$  was proposed as the limit for considering surgery, and a PVR of 4–8 Wood units  $m^2$  as the range in which the proper approach should be considered on a case by case basis.

**Keywords:** congenital heart disease, pulmonary hypertension, pulmonary vascular resistance, survival

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J Health Sci Med Res 2021;39(1):13–21  
doi: 10.31584/jhsmr.2020755  
[www.jhsmr.org](http://www.jhsmr.org)

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## Introduction

Pulmonary arterial hypertension (PAH) is caused by many conditions. In patients with congenital heart disease (CHD) with a left-to-right shunt, persistent increased blood flow and pressure to the pulmonary vasculature may result in progressive remodeling of the pulmonary arteries and increasing pulmonary vascular resistance (PVR). These lead to reversal of the shunt and cause Eisenmenger's syndrome (ES).<sup>1-4</sup>

The development of PAH in patients with CHD is associated with high morbidity and mortality. Early closure of a cardiac defect (before 2 years of age) can prevent a whole range of sequelae and can reverse a high PVR to a normal level. Conversely, if closure is delayed, the PVR may fall but not reach a normal level or may not fall and lead to right ventricular failure.<sup>5,6</sup> However, some defects may pass undetected until childhood or even adulthood. This problem is even more severe in developing countries due to a low rate of such defects being detected and dealt with in infancy, and the issue of PAH in developing countries is becoming quite problematic.<sup>7</sup>

At present, clinical examination and hemodynamic assessment are used to evaluate the operability of patients with PAH–CHD. For patients who are on the borderline, right heart catheterization hemodynamic measurements are satisfactory.<sup>8</sup> However, the decision to operate on patients with moderate increases in PVR is still difficult due to lack of an evidence-based treatment to guarantee reversibility of PVR and satisfactory long-term outcomes. This is an especially frustrating problem for physicians in the PAH-specific drug era, when unrepaired CHD and patients with ES have improving survival rates. Some studies have found that such patients have better 10-year and 20-year survival rates than completely repaired cases of CHD.<sup>1,9-12</sup>

For many years, evaluation of hemodynamics to predict operability has been performed<sup>7,13-20</sup>, yet a precise PVR level that absolutely contraindicates a surgical “point of no return” in cases of PAH–CHD has not been established. More recently, in the 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS) guideline for the diagnosis and treatment of pulmonary hypertension<sup>1</sup>, a pulmonary vascular resistance index (PVRi)  $<4$  Wood units  $m^2$  was suggested as the range in which patients were operable, a PVRi of 4–8 Wood units  $m^2$  as the range in which each patient should be discussed case by case, and a PVRi of 8 Wood units  $m^2$  was proposed as the limit above which surgery should not be considered. Our objective was to compare the survival data of three PVRi subgroups of patients with pulmonary hypertension-associated congenital heart disease (PH–CHD) to gain a better understanding of such patients and enhance disease management strategies.

## Material and Methods

In this retrospective cohort study, the data of pediatric and adult patients with PH–CHD who had been catheterized at Songklanagarind Hospital, Songkhla, Thailand, between January 2004 and January 2016 were reviewed. Following the 6<sup>th</sup> World Symposium in Pulmonary Hypertension (WSPH) proposing a major revision of the definition, the hemodynamic parameter leading to a diagnosis of PH was a resting mean pulmonary artery pressure  $>20$  mmHg. The diagnosis of PAH also included PH with a left ventricular end-diastolic pressure  $\leq 15$  mmHg and a PVRi  $>3$  Wood units  $m^2$ .<sup>1,8,21</sup> Only patients with completely repaired CHD with complete pre-operative invasive hemodynamic data were selected. Patients with unrepaired or partially repaired CHD were excluded. The selected patients were categorized

into three subgroups according to PVRI: (i) PVRI <4 Wood units  $m^2$ , (ii) PVRI 4–8 Wood units  $m^2$ , and (iii) PVRI >8 Wood units  $m^2$  (hereafter referred to as low PVRI, moderate PVRI, and high PVRI, respectively).

This study protocol was reviewed and approved by our Institutional Medical Human Research Ethics Committee (REC: 58–380–01–3), following The Declaration of Helsinki and The International Conference on Harmonization in Good Clinical Practice.

Under general anesthesia, the baseline hemodynamic measurements collected were mean right atrial pressure; right ventricular pressure; left ventricular pressure; pulmonary pressure; systemic pressure; and distal pulmonary arterial, pulmonary venous, superior vena cava (SVC), inferior vena cava (IVC) and ascending aortic oxygen saturations. A weighing of the sample one-third SVC oxygen saturation to two-thirds IVC oxygen saturation was used for the calculated mixed systemic venous oxygen saturation. When a pulmonary vein could not be reached, the pulmonary venous saturation was assumed to be 98.0%. Blood flow was estimated using Fick's method and indexed for body surface area. Oxygen consumption ( $VO_2$ ) was estimated using two methods: (i) the method of Lundell for patients  $\leq 3$  years of age and (ii) the method of Lafarge–Miettinen for patients >3 years of age. Vascular resistance indexes were calculated by dividing the arterial to venous difference by blood flow indexes (Ohm's Law)<sup>8,22</sup>

Descriptive statistics were used for subgroup comparisons, including number and percentage for categorical data and median [interquartile range (IQR)] for continuous variables that were not normally distributed.

P-values were calculated using the chi-square or Fisher's exact test for categorical data. The simple t-test was used for continuous data that were approximately normally distributed, and the Wilcoxon rank-sum test was used for continuous data not normally distributed.

The ANOVA test was used for more than two continuous data sets. All statistical tests were two-sided, and a p-value < 0.05 was considered significant.

For the survival analysis, only cardiac-related deaths were included in the Kaplan–Meier analysis (disease-specific survival analysis). Patients with non-cardiac related death were censored at the time of death. Kaplan–Meier survival curves were assessed and compared with the log-rank test according to clinical subgroups. The 1-, 5- and 10-year survival rates were estimated for PH–CHD, PAH–CHD and each of the PH–CHD subgroups. Separate stepwise multivariate survival models were estimated for all patients with PH–CHD using Cox proportional hazards regressions.

Statistical analysis was performed using R software (version 1.1.456; Prince of Songkla University, Songkhla, Thailand).

## Results

This cohort study consisted of 298 patients with PH–CHD. The median age at the time of diagnostic cardiac catheterization showing the presence of PH was 5.5 years (IQR 0.2–77.2 years) (Table 1), 209 patients (70.1%) were children <18 years of age, 196 patients (65.8%) were female, and 41 patients (13.8%) had Down syndrome. In all, 129 patients (43.3%) had patent ductus arteriosus (PDA), 207 patients (69.5%) had World Health Organization (WHO) functional class II at the time of diagnosis, and 101 patients (33.3%) had a diagnosis of PAH–CHD. The median age at operation was 5.8 years (IQR 2.4–29.5 years), and 222 patients (74.5%) had transcatheter device closure.

Among the 298 patients with PH–CHD, 216 had low a PVRI, 57 had moderate PVRI, and 25 patients had a high PVRI. Demographic and disease characteristics and pre-operative laboratory tests of the patients with PH–CHD, stratified by PVRI subgroup, are shown in Table 1.

**Table 1** Demographics, disease characteristics

Characteristic	All patients	PVR index			p-value
		<4	4–8	>8	
Patients, n (%)	298	216 (72.5)	57 (19.1)	25 (8.4)	N/A
Age at diagnosis, years	5.5 (2.1, 29.6)	5.2 (2.0, 20.7)	6.1 (2.0, 34.9)	11.4 (3.9, 38.5)	0.236
Age at operation, years	5.8 (2.4, 29.5)	5.4 (2.2, 20.7)	7.3 (2.9, 34.9)	12.2 (4.2, 38.5)	0.133
Women, n (%)	196 (65.8)	143 (66.2)	36 (63.2)	17 (68.0)	0.884
Type of defect, n (%)					0.159
Atrial septal defect	92 (30.9)	69 (31.9)	17 (29.8)	6 (24.0)	
Ventricular septal defect	58 (19.5)	39 (18.1)	14 (24.6)	5 (20.0)	
Patent ductus arteriosus	129 (43.3)	99 (45.8)	20 (35.1)	10 (40.0)	
Other	19 (6.3)	9 (4.2)	6 (10.5)	4 (16.0)	
WHO functional class, n (%)					0.015
Class I	9 (3.0)	5 (2.3)	4 (7.0)	0 (0.0)	
Class II	207 (69.5)	161 (74.5)	33 (57.9)	13 (52.0)	
Class III	80 (26.8)	49 (22.7)	19 (33.3)	12 (48.0)	
Class IV	2 (0.7)	1 (0.5)	1 (1.8)	0 (0.0)	
Down syndrome, n (%)	41 (13.8)	24 (11.1)	13 (22.8)	4 (16.0)	0.043
PAH-CHD, n (%)	101 (33.9)	30 (13.9)	50 (87.7)	21 (84.0)	<0.001
Device closure, n (%)	222 (74.5)	178 (82.4)	30 (52.6)	14 (56.0)	<0.001

All data are presented as median (IQR) unless otherwise stated

CHD=congenital heart disease, N/A=not applicable, PAH=pulmonary arterial hypertension, PVR=pulmonary vascular resistance, WHO=World Health Organization

The hemodynamic characteristics from cardiac catheterization at the time of diagnosis are listed in Table 2. The median PVRi was 2.5 Wood units  $m^2$  (IQR 1.3–4.2; mean  $\pm$  standard deviation (S.D.)  $3.5 \pm 3.3$  Wood units  $m^2$ ), median pulmonary-to-systemic vascular resistance index was 0.20 (IQR 0.10–0.30; mean  $\pm$  S.D.  $0.25 \pm 0.24$ ), and median pulmonary-to-systolic blood flow was 1.9 (IQR 1.3–2.9; mean  $\pm$  S.D.  $2.4 \pm 1.7$ ). In the three PVRi subgroups, the mean right atrial pressure, systolic blood pressure, and left ventricular end diastolic pressure had differences that were statistically insignificant. Patients with a high PVRi were significantly more likely to have a higher mean pulmonary artery pressure, systolic pulmonary artery pressure, systolic pulmonary artery pressure/systolic blood pressure ratio, and pulmonary-to-systolic vascular resistance

index. Conversely, these same patients had significantly lower pulmonary blood flow and pulmonary-to-systolic blood flow.

A total of 19 patients died during the study period; the causes of death are summarized in Table 3. In all, 15 deaths were categorized as cardiac-related deaths. Interestingly, 12 of the patients were in the moderate and high PVRi subgroups and had clinical symptoms of right and left ventricular failure, such as generalized edema, progressive dyspnea and an immediate post-operative pulmonary hypertensive crisis. But, three patients in the low PVRi subgroup died from post-operative complications, such as tension pneumothorax, ventilator-associated pneumonia and septic shock.

**Table 2** Hemodynamic characteristics from diagnostic cardiac catheterization: pre-completely repaired

Characteristic	All patients	PVR index			p-value
		<4	4-8	>8	
Patients, n (%)	298	216 (72.5)	57 (19.1)	25 (8.4)	N/A
Mean right atrial pressure, mmHg	8 (6, 11)	8 (6, 11)	8 (6, 10)	7 (6, 9)	0.569
Mean pulmonary artery pressure, mmHg	31 (25, 42)	27 <sup>a</sup> (24, 33)	46 <sup>b</sup> (35, 55)	57 <sup>c</sup> (48, 64)	<0.001
Systolic pulmonary artery pressure, mmHg	44.0 (34, 60)	39.5 <sup>a</sup> (32, 46)	65.0 <sup>b</sup> (52, 77)	81.0 <sup>c</sup> (70, 90)	<0.001
Systolic blood pressure, mmHg	91 (83, 102)	92 (82, 102)	89 (83, 102)	93 (84, 108)	0.714
Systolic pulmonary artery pressure/systolic blood pressure ratio	0.5 (0.3, 0.7)	0.4 <sup>a</sup> (0.3, 0.6)	0.7 <sup>b</sup> (0.5, 0.9)	0.9 <sup>c</sup> (0.7, 1.0)	<0.001
Right ventricular end diastolic pressure, mmHg	10 (8, 12)	9 <sup>a</sup> (8, 11)	11 <sup>b</sup> (9, 13)	10 <sup>a,b</sup> (9, 12)	0.003
Left ventricular end diastolic pressure, mmHg	12 (10, 14)	12 (11, 14)	13 (10, 15)	10 (9, 15)	0.271
Pulmonary blood flow, L/min/m <sup>2</sup>	7.4 (5.2, 11.0)	8.9 <sup>a</sup> (6.3, 13.0)	5.7 <sup>b</sup> (4.7, 7.4)	3.5 <sup>c</sup> (3.0, 4.4)	<0.001
Systolic blood flow, L/min/m <sup>2</sup>	4.1 (3.1, 5.5)	4.3 <sup>a</sup> (3.0, 4.8)	3.7 <sup>b</sup> (3.0, 4.8)	2.9 <sup>b</sup> (2.2, 4.2)	<0.001
Pulmonary-to-systolic blood flow, L/min/m <sup>2</sup>	1.9 (1.3, 2.9)	2.2 <sup>a</sup> (1.5, 3.3)	1.6 <sup>b</sup> (1.2, 1.9)	1.1 <sup>c</sup> (0.9, 1.5)	<0.001
Pulmonary vascular resistance index, Wood units m <sup>2</sup>	2.5 (1.3, 4.2)	1.8 <sup>a</sup> (1.1, 2.6)	5.3 <sup>b</sup> (4.6, 6.8)	10.9 <sup>c</sup> (9.1, 14.0)	<0.001
Systemic vascular resistance index, Wood units m <sup>2</sup>	13.5 (9.8, 20.0)	13.1 <sup>a</sup> (9.7, 18.0)	15.1 <sup>a,b</sup> (10.0, 22.0)	24.1 <sup>b</sup> (11.0, 34.0)	0.007
Pulmonary-to-systolic vascular resistance index, Wood units m <sup>2</sup>	0.20 (0.1, 0.3)	0.10 <sup>a</sup> (0.1, 0.2)	0.40 <sup>b</sup> (0.2, 0.5)	0.55 <sup>c</sup> (0.4, 0.8)	<0.001
Systemic arterial oxygen saturation, %	98 (96.0, 99.0)	98 <sup>a</sup> (97.0, 99.0)	96 <sup>b</sup> (94.0, 98.0)	95 <sup>b</sup> (92.0, 97.0)	<0.001
Mix-venous oxygen saturation, %	75 (67.0, 83.0)	76 <sup>a</sup> (69.0, 83.0)	73 <sup>b</sup> (66.0, 81.0)	69 <sup>c</sup> (59.0, 78.0)	<0.001

All data are presented as median (IQR) unless otherwise stated

L=liter; min=minute, m<sup>2</sup>=square meters, mmHg=millimeter of mercury, N/A=not applicable, PVR=pulmonary vascular resistance

<sup>a,b,c</sup>Because of multiple groups being compared, different “superscript alphabets” are a statistically significant difference.

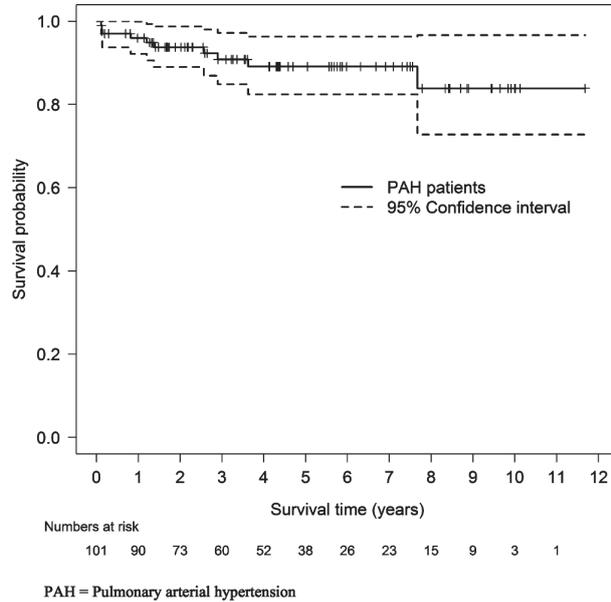
However, one death was a patient with Down syndrome with post-PDA coiling. Her PVRi was 6.87 Wood units m<sup>2</sup>. She died 3 years post-PDA coiling at home without any medical records and was categorized as unknown cause of death. Another three patients had an underlying malignancy, and they died from advanced stage malignancy.

In the overall population, the 1-, 5- and 10-year survival rates were 96.6±1.0%, 94.2±1.5%, and 91.1±3.3%, respectively (Figure 1). In patients with PAH-CHD, the 1-, 5- and 10-year survival rates were 96.0±1.9%, 89.1±3.5%, and 83.9±6.0%, respectively (Figure 2).

**Table 3** Summary of deaths among patients after repaired pulmonary hypertension associated congenital heart disease with left-to-right shunt

Description	Deaths
Total number of deaths	19
Cause of death, n (% of total deaths)	
Cardiac related	15 (78.9)
Non-cardiac related	3 (15.8)
Unknown	1 (5.3)
Categorized according to the 3 PVRI subgroups*, n (% of patients in each group)	
<4 Wood units m <sup>2</sup>	3 (1.4)
Wood units m <sup>2</sup>	9 (15.8)
>8 Wood units m <sup>2</sup>	4 (16.0)

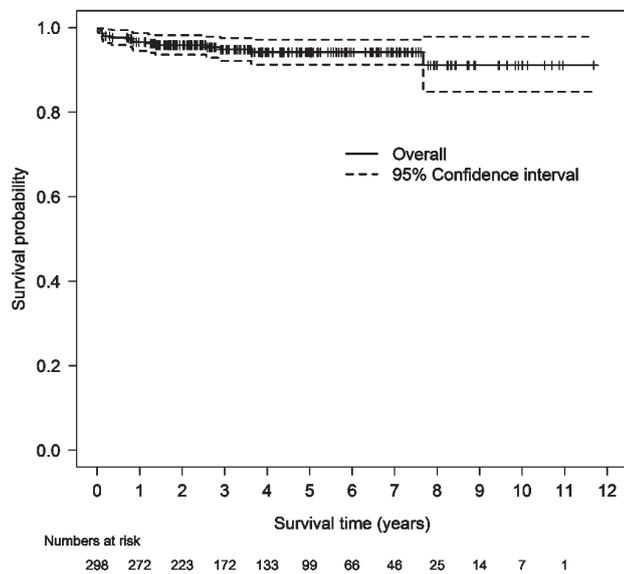
m<sup>2</sup>=square meters, PVRI=pulmonary vascular resistance index  
 \*Three patients who died from non-cardiac-related causes are not included.



**Figure 2** Kaplan–Meier survival curve (with 95% confidence interval) of 101 completely repaired patients with pulmonary arterial hypertension associated congenital heart disease

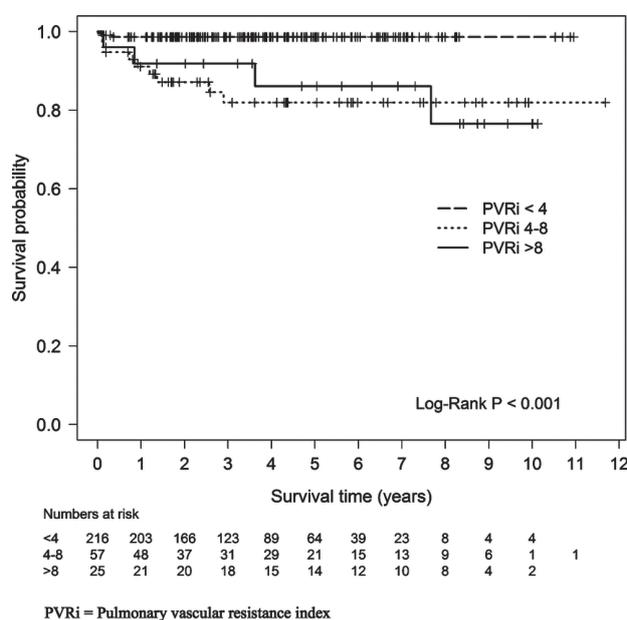
In the high PVRI subgroup, the 1-, 5- and 10-year survival rates were 91.8±5.5%, 86.1±7.6%, and 76.5±11.2%, respectively. In the moderate PVRI subgroup, the 1-, 5- and 10-year survival rates were 91.1±3.8%, 81.9±5.5%, and 81.9±5.5%, respectively (p-value 0.8 vs. high PVRI). In the last subgroup, patients with a low PVRI had the highest survival rates across three time-points, of which each time-point accounted for 98.6±0.8% (p-value <0.001 vs. high PVRI and moderate PVRI) (Figure 3).

The Cox proportional hazards regression model of survival from time of operation included six candidate variables with univariate p-values ≤0.20: Down syndrome, WHO functional class, mean pulmonary artery pressure, left ventricular end diastolic pressure, PVRI, and hemoglobin. The final stepwise multivariate model included two variables: WHO functional class (compared with the WHO



**Figure 1** Kaplan–Meier survival curve (with 95% confidence interval) of 298 completely repaired patients with pulmonary hypertension associated congenital heart disease

functional class II group, the WHO functional class III group had a hazard ratio of 2.1, 95% confidence interval (CI) 0.8 to 5.9, and the WHO functional class IV group had a hazard ratio of 42.7, 95% CI 4.7 to 92.3;  $p$ -value 0.031) and PVRI (compared with the low PVRI subgroup, the moderate PVRI subgroup had a hazard ratio of 10.2, 95% CI 3.0 to 34.3, and the high PVRI subgroup had a hazard ratio of 8.4, 95% CI 1.9 to 35.9;  $p$ -value<0.001).



**Figure 3** Kaplan-Meier survival curve of 298 completely repaired patients with pulmonary hypertension associated congenital heart disease categorized according to the 3 pulmonary vascular resistance index subgroups

## Discussion

This analysis showed that patients who underwent complete repair with a pre-repair PVRI <math>< 4</math> Wood units  $m^2$  had significantly better survival than the other PVRI ranges of the recently published 2015 ESC/ERS guideline for the diagnosis and treatment of PH.<sup>1</sup> These findings confirmed a better outcome in patients with a low PVRI who under-

went complete repair than patients who were unrepaired or patients with ES that previously presented in other studies. The 10-year survival was  $98.6 \pm 0.8\%$  in patients with a low PVRI in our study, compared with a  $89.0\%$  10-year survival of patients with ES in the study by Manes et al.<sup>12</sup> or a  $61.0 \pm 5.0\%$  7-year survival of patients who were unrepaired from the Registry to Evaluate Early And Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL).<sup>11</sup> Additionally, the survival of patients with a low PVRI didn't change over time, unlike the survival of patients who were unrepaired or patients with ES, which got worse over time.<sup>11,12</sup> This suggests that complete repair in patients with a low PVRI pre-repair confers a survival benefit.

The overall survival of patients with PAH-CHD who underwent complete repair in this study (Figure 2) was lower than patient with PAH with left-to-right shunt in the study by Manes et al.<sup>12</sup> ( $83.9 \pm 6.0\%$  vs.  $93.0\%$ , respectively). Conversely, it was much better than patients with PAH with repaired CHD from the REVEAL registry<sup>11</sup> (7-year survival  $89.1 \pm 3.5\%$  vs.  $70.0 \pm 8.0\%$ , respectively). The discrepancy of survival rates among studies may be from many reasons, such as the availability of PAH-specific therapies, type of CHD and unequal pre-operative PVRI levels. In our study, patients were treated with only an oral phosphodiesterase type 5 inhibitor drug. However, the increase of baseline PVRI may explain the differences in survival between this study and the studies by Manes et al.<sup>12</sup> and the REVEAL registry (PVRI  $6.2 \pm 3.4$ ,  $9.0 \pm 9.2$  and  $16.0 \pm 9.0$ , respectively).

A noteworthy finding of our analysis was that 10-year survival was not significantly different between the patients with moderate and high PVRI ( $81.9 \pm 5.5$  vs.  $76.5 \pm 11.2$ ,  $p$ -value 0.8). The survival curves of patients with a high PVRI gradually continuously sloped down over the time after complete repair, but the survival curve of patients with a moderate PVRI sloped down for 0 to 3 years after complete repair and did not change after that

time and started to diverge from the survival curves of patients with a high PVRI after 8-year follow-up of complete repairs. This suggests that a 10-year survival follow up is too short in studies of this situation and that much longer follow-ups of at least 20 years may be more likely to show a potential benefit of complete repair in patients with a moderate PVRI.

The main limitation of this study was the relatively small number of patients in the high PVRI subgroup who underwent surgery. However, this may be an appropriate ethical limitation. Further to this point, this study was a retrospective study, and some old incomplete data were excluded. Thus, there may have been a selection bias.

## Conclusion

We confirm that patients with a pre-repair PVRI <4 Wood units m<sup>2</sup> had better survival than other PVRI groups. Interestingly, an increase in pre-repair PVRI can cause reduced survival in patients with PH-CHD undergoing complete repair, especially patients with moderate to high PVRI, although the cardiac defect was repaired and PAH was not cured.

## Conflict of interest

The authors hereby declare no personal or professional conflicts of interest with any aspect of this study.

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