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Survival comparison in adults with congenital systemic to pulmonary shunt and borderline elevated pulmonary vascular resistance versus Eisenmenger syndrome

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Pulmonary arterial hypertension (PAH) associated with congenital heart disease (PAH-CHD) is a consequence of unrepaired large systemic-to-pulmonary shunts. The long-term data of adult patients who have PAH-CHD with elevated pulmonary vascular resistance (PVR) are limited. We aimed to investigate the survival of adults who had PAH-CHD with predominantly left-to-right (L-R) shunts with (1) borderline-to-high PVR and (2) treat-and-repair compared with those with Eisenmenger syndrome (ES). From 1995 to 2021, 99 adults with ES (age 34.1 ± 11.2 years) and 118 adults with PAH-CHD with predominantly L-R shunts (age 39.1 ± 13.7 years) were eligible. The PVR in the ES group was 21.0 ± 13.1 WU. Most ES patients (97%) received pulmonary vasodilator therapy. Among the 118 patients with PAH-CHD with predominantly L-R shunts, the baseline PVR was 7.6 ± 4.6 WU, and 78 patients (66.1%) had borderline to high PVR (≥ 5 WU). In the group, 105 patients (88.9%) underwent repair; 84 had defect closure, and 21 had fenestrated closure. Treat-and-repair was used to treat 53 patients with a preoperative final PVR of 3.58 ± 2.63 WU. No early postoperative deaths were reported. At a median follow-up time of 5.4 years (range 0.1–23.6 years), the 10- and 15-year survival rates of adults with borderline PVR were 82.3% and 82.3%, respectively, which were not inferior to the rates for patients with ES, which were 77.8% and 71.2%, respectively ($p = 0.41$). The survival rate of patients who underwent treat-and-repair was slightly better than that of patients who underwent ES, although the difference was not statistically significant ($p = 0.19$). Independent mortality risk factors were functional class III-IV at initial presentation (hazard ratio 5.7, 95% CI 1.2–26.6; $p = 0.02$) and oxygen saturation < 94% at the most recent visit (hazard ratio 9.4, 95% CI 2.1–42.9; $p = 0.004$).

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Keywords Pulmonary arterial hypertension (PAH), Congenital heart disease (CHD), Eisenmenger, Predominantly systemic-to-pulmonary shunt, Treat-and-repair

Recent advances in the diagnosis and management of congenital heart disease (CHD) have significantly improved the survival of patients, allowing young patients to grow to adulthood. The increasing number of patients with adult congenital heart disease (ACHD) now accounts for two-thirds of the CHD population[1,2]. Pulmonary hypertension (PH) is a common complication in patients with CHD and is related to the type and

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size of the defect and the repair history. PH burdens 10–28% of adults with CHD and predisposes them to adverse symptoms and further clinical deterioration[1,3–5]. PH is currently defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg at rest by heart catheterization, according to the 6th World Symposium of Pulmonary Hypertension (WSPH), which was updated in 2018. Most patients with CHD are classified into Group I pulmonary arterial hypertension (PAH), which is hemodynamically characterized by precapillary PAH (pulmonary vascular resistance, PVR ≥ 2 Wood units (WU), and pulmonary artery wedge pressure ≤ 15 mm Hg)[6–8]. PAH associated with CHD (PAH-CHD) is a consequence of unrepaired moderate-to-large systemic-to-pulmonary shunts and pulmonary overcirculation and induces shear stress with arterial endothelial damage and pulmonary vascular remodeling. The after-effects of long-standing high pulmonary artery pressure (PAP) with elevated PVR may lead to pulmonary vascular disease (PVD) with subsequent reversal of shunting and cyanosis, so-called Eisenmenger syndrome[1,5,8].

The clinical classification of PAH-CHD typically applies to both adults and children and can be further classified as Eisenmenger syndrome (ES), PAH-CHD associated with predominantly left-to-right (L-R) shunts, PAH with coincidental CHD or a small defect, or PAH after defect correction[7–10]. ES represents the most severe form of PAH-CHD, with reversal of the shunt direction from systemic to pulmonary predominant versus pulmonary to systemic circulation. PAH with coincidental CHD or a small defect has a poor clinical course and is known as idiopathic PAH (IPAH), similar to persistent PAH after defect correction, which is even worse than ES[11,12]. In the pediatric population, PAH-CHD shunts, predominantly L-R shunts, most often involve a posttricuspid systemic-to-pulmonary shunts with mildly elevated PVR, which has excellent prognosis, as complete resolution typically occurs after early shunt elimination in early life[13]. The criteria for operability that incorporate baseline hemodynamics, including an indexed PVR and response to acute vasodilator testing (AVT), have been proposed for pediatric patients, but AVT is not convincing in the ACHD guidelines[8,14–16]. In the 2018 AHA/ACC ACHD guidelines, Qp: Qs > 1.5 is required for a recommended closure (AHA/ACC Class I: symptomatic, significant shunt, no cyanosis, and PA systolic pressure (PASP)/systemic artery systolic pressure (SASP) < 50% or PVR/systemic vascular resistance (SVR) < 0.33; Class IIa: asymptomatic; Class IIb: PVR/SVR = 0.34–0.66 or PASP/SASP > 50% but less than 66% of systemic)[17]. The 2020 ESC ACHD guidelines use right heart enlargement as a marker of significant L-R shunts in patients with atrial septal defect (ASD) and use the same cutoff PVR as for ventricular septal defects (VSDs) and patent ductus arteriosus (PDA). The Class I recommendation in the 2020 ESC guidelines is recommended only for patients without PAH (PVR < 3 WU) and with a significant L-R shunt (RV volume overload), regardless of symptoms. For PVR 3–5 WU and a significant shunt (Qp: Qs > 1.5), closure should be considered (ESC, Class IIa). Patients with PVR > 5 WU may be considered for fenestrated closure if the PVR falls to < 5 WU and significant L-R shunting occurs after treatment with PAH therapies [i.e., the so-called treat-and-repair strategy (ESC, Class IIb)][18]. The most challenging decision to be made concerns the treatment of borderline PVR or the gray zone group (PVR/SVR > 0.33 or PASP > 50% SASP in the 2018 AHA/ACC ACHD guidelines or PVR > 5 WU in the 2020 ESC). AHA guidelines suggest that these patients should be evaluated by an ACHD and the PAH team to treat PAH before considering closure, whereas ESC has an option for fenestrated closure of septal defects if the PVR decreases to less than 5 WU after targeted PAH treatment and if a significant L-R shunt is present (Class IIb indication)[8,17–19]. Individual decisions should be based on the specific lesion, age of the patient, and comorbidities[8,18]. The treat-and-repair strategy has allowed for a reconsideration of reversibility and operability in some PAH-CHD patients[20,21]. Nevertheless, the outcomes and prognosis in adults who have PAH-CHD with borderline to high PVR are still debated. Fenestrated closure or treat-and-repair may be beneficial and are needed for long-term follow-up[8,22]. We hypothesized that the survival of these borderline PVR patients who underwent treat-and-repair/fenestrated closure is not inferior to that of ES patients, who are classified at the severe end of the spectrum. The aims of this study were to assess the survival of adults who had PAH-CHD with predominantly L-R shunts with (1) borderline-to-high PVR and (2) the treat-and-repair strategy in comparison to patients with ES and to investigate the mortality risks in adults with PAH-CHD with predominantly L-R shunts.

Results

Demographics

Between 1995 and 2021, a total of 99 adults with ES and 118 adult patients with PAH-CHD with predominantly L-R shunts were eligible for analysis. The flow of the study is shown in Fig. 1. Patient characteristics are listed in Table 1. The age of patients with cardiac catheterization-confirmed ES was 34.1 ± 11.2 years (median age of 31.7; range 18.4–69.1 years), and that of patients with PAH-CHD with predominantly L-R shunts was 39.1 ± 13.7 years (median age of 36.2; range 18.1–72.3 years). The most common anatomical defects were pretricuspid shunts, comprising 39% of ES and 57% of PAH-CHD with predominantly L-R shunts. Hemodynamic data revealed that PAP, PVR, and PVR/SVR were significantly greater in ES patients than in PAH-CHD with predominantly L-R shunt patients, even after AVT was performed. Initial N-terminal brain natriuretic peptide data was obtained in only 15 patients with ES and in 13 patients with PAH-CHD with predominantly L-R shunts. The median levels were 1089 (range 63–6396) pg/mL in the ES group and 374 (range 28–2585) pg/mL in the PAH-CHD with predominantly L-R shunt group. Initial right ventricular-to-pulmonary artery coupling (RV-PA coupling), which was obtained in 14 patients with ES and 39 patients with PAH-CHD with predominantly L-R shunts, showed reduced RV-PA coupling in both groups (median 0.17; range 0.19–0.33, and median 0.25; range 0.07–0.64, respectively).

Management and outcomes

Among the 99 ES patients, 95 patients (96%) received pulmonary vasodilator therapy as PAH-targeted therapy, 74 patients received monotherapy, and 21 patients received combined therapy. The initial therapy was mostly sildenafil (58.3%), followed by an oral prostacyclin analog (32.3%). During the median follow-up (8.1 years,

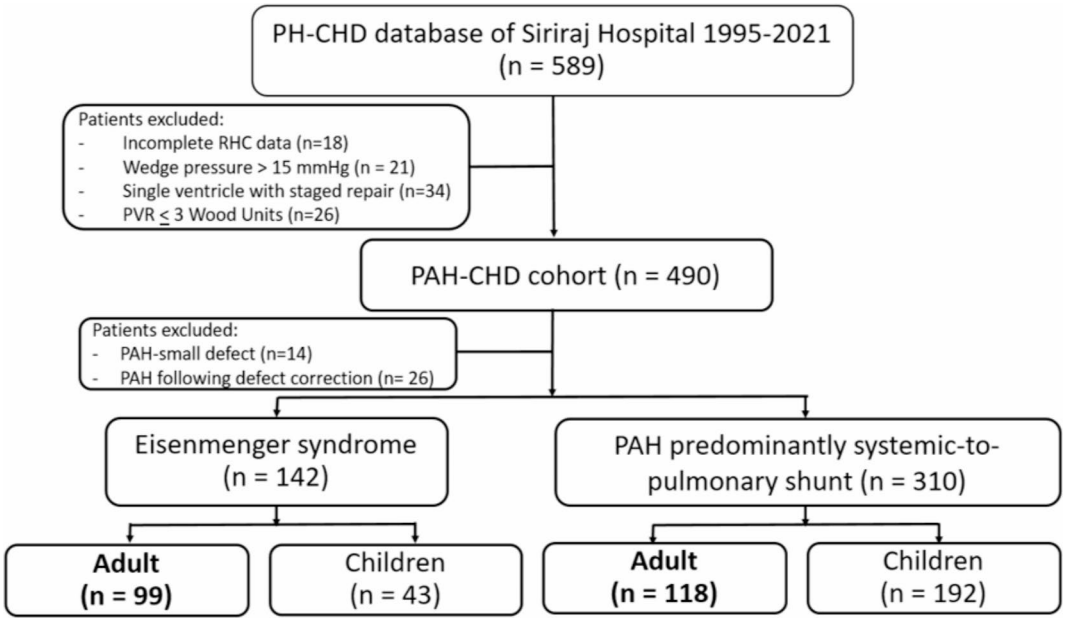


Fig. 1. Flow of the study ($n=217$) (PH, pulmonary hypertension; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; RHC, right heart catheterization).

ranging from 0.1 to 16.4 years), 23 patients experienced right heart failure, and 15 patients died due to a cardiovascular event (15.1%).

Among the 118 patients with PAH-CHD with predominantly L-R shunts, 78 patients (66.1%) had borderline to high PVR (> 5 WU). The demographics of the 118 patients classified by PVR < 5 WU and > 5 WU are shown in Table 2. Hemodynamic data from post-AVT patients were included, which revealed some response to AVT in both groups. Pulmonary vasodilators were given as pretreatment to targeted therapy in 61 patients; 17 patients had mildly elevated PVR, and 44 patients had borderline-to-high PVR. Among the 118 patients, 105 patients (88.9%) underwent repair, 84 had complete closure, and 21 had fenestrated closure. Among the 105 patients, 53 patients received pretreatment with pulmonary vasodilators, which constituted a treat-and-repair strategy. Pretreatment with monotherapies such as sildenafil (62.2%) was mainly prescribed, followed by oral prostacyclin analogs and bosentan. The profiles of the 53 patients who received the treat-and-repair strategy are shown in Table 3. Notably, 44 patients (37%) were referred from outside hospitals and had already received pulmonary vasodilators such as sildenafil before visiting our center. Consequently, their cardiac catheterizations at our center were performed after pretreatment prior to closure. Patients who underwent treat-and-repair at our center underwent cardiac catheterization both before and after pretreatment. Overall, all patients in the study underwent complete cardiac catheterization prior to defect closure. The median time interval for pretreatment therapy prior to the intervention was 9.2 months (range 1.7–69.8 months). The median age of the 105 patients who underwent interventional closure was 36.5 years (range 18.9–72.3 years). No in-hospital mortality was reported. Late mortality was noted in 7 patients at a median time of 69 months (range 13–195 months). During the median follow-up (5.6 years; range 0.1–23.6 years), almost half ($n=52$) of the patients experienced persistent PAH following defect closure, and 17 patients experienced right heart failure. Persistent PAH following defect correction in 52 patients was diagnosed via echocardiography performed at the most recent follow-up, and 11 patients were confirmed by cardiac catheterization. Importantly, these adverse cardiac events were more often reported in patients with borderline to high PVR than in patients with PVR < 5 WU ($p=0.009$ and 0.037, respectively) (Table 2). Oxygen saturation at a recent visit was $97.3 \pm 2.5\%$. A total of 13 patients did not undergo defect correction because of denial of surgery, being on a waiting list, or being lost to follow-up. Two patients died while waiting for surgery.

Survival

At the median follow-up (8.1 years; range 0.1–16.4 years), the survival rates of adult patients with ES at 5, 10, and 15 years were 93.2%, 77.8%, and 71.2%, respectively. For patients with PAH-CHD, predominantly L-R shunts, at the median follow-up (5.6 years; range 0.1–24.3 years), the survival rates at 5, 10, and 15 years were 93.6%, 86.1%, and 86.1%, respectively (Fig. 2). For the borderline PVR group (> 5 WU), the survival rates at 5, 10, and 15 years were 92.6%, 82.3%, and 82.3%, respectively (Fig. 3). Overall, the survival rate of patients with PAH-CHD with predominantly L-R shunts with borderline PVR was greater than that of ES patients, although the difference was not statistically significant (log rank $p=0.41$).

In addition, the survival of patients who received treat-and-repair was slightly better than that of ES patients, though the difference was not statistically significant ($p=0.19$). The survival rates of patients who received treat-and-repair at 5, 10, and 15 years were 94.1%, 88.2%, and 88.2%, respectively (Fig. 4). When the survival rates of 105 patients with interventional closure (84 total repairs and 21 fenestrated closures) were compared with

	ES ($n=99$)	Adult with PAH-CHD with predominantly L-R shunt ($n=118$)	p value
Age at diagnosis (years)	34.15 ± 11.22	39.09 ± 13.68	0.002*
Male gender	22 (22.2%)	36 (30.5%)	0.169
WHO functional class III-IV at diagnosis	31 (31.3%)	19 (16.1%)	0.008*
CHF at presentation	48 (48.5%)	95 (80.5%)	< 0.001*
Trisomy 21	2 (2.0%)	3 (2.5%)	1.000
Oxygen saturation (%)	87.78 ± 7.03	94.58 ± 4.30	< 0.001*
Hematocrit (%)	47.22 ± 7.63	40.48 ± 6.17	< 0.001*
Home oxygen therapy	8 (8.1%)	2 (1.7%)	0.046*
Type of shunt Pretricuspid shunts Posttricuspid shunts Combined shunts Complex shunts	39 (39.4%) 35 (35.4%) 8 (8.1%) 17 (17.2%)	68 (57.6%) 37 (31.4%) 10 (10.5%) 3 (2.5%)	0.001*
Cardiac catheterization			
mRAP (mmHg)	8.46 ± 3.37	9.68 ± 6.69	0.104
RVEDP (mmHg)	11.51 ± 4.15	11.28 ± 3.68	0.369
mPAP (mmHg)	75.60 ± 17.59	56.92 ± 16.85	< 0.001*
PAWP (mmHg)	11.69 ± 2.78	11.51 ± 2.58	0.217
DPG (mmHg)	42.86 ± 15.95	28.28 ± 14.42	0.595
Qp: Qs	1.01 ± 0.55	1.96 ± 0.86	< 0.001*
PVR (WU)	21.01 ± 13.15	7.66 ± 4.56	< 0.001*
PVRi (WU m^2)	29.86 ± 18.25	10.85 ± 6.02	< 0.001*
PVR/SVR	1.02 ± 0.71	0.41 ± 0.24	< 0.001*
Post AVT mPAP (mmHg)	72.27 ± 18.71	51.83 ± 14.10	0.024*
Post AVT Qp: Qs	1.74 ± 1.38	3.90 ± 2.50	< 0.001*
Post AVT PVR (WU)	13.82 ± 10.40	3.50 ± 2.53	< 0.001*
Post AVT PVRi (WU m^2)	19.23 ± 14.17	5.08 ± 3.49	< 0.001*
Post AVT PVR/SVR	0.72 ± 0.63	0.22 ± 0.14	< 0.001*
Follow-up time from diagnosis (years)	7.60 ± 5.98	6.47 ± 5.64	0.153
Persistent PAH post intervention	0 (0%)	52 (44.1%)	-
RVSP on the recent TTE (mmHg)	92.89 ± 24.11	60.87 ± 23.77	< 0.001*
Experience of right heart failure	23 (23.2%)	17 (14.4%)	0.095
Oxygen saturation at recent visit (%)	84.05 ± 10.01	97.31 ± 2.53	< 0.001*
Mortality	15 (15.2%)	9 (7.64%)	0.078

Table 1. Patient characteristics ($n=217$). The data are presented as the means ± SDs, medians (interquartile ranges), and n (% within columns). * Statistical significance at p value < 0.05. ES = Eisenmenger syndrome; PAH-CHD with predominantly L-R shunt = pulmonary arterial hypertension associated with congenital heart disease with predominantly left-to-right shunt; WHO = World Health Organization; CHF = congestive heart failure; mRAP = mean right atrial pressure; RVEDP = right ventricular end diastolic pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; DPG = diastolic transpulmonary gradient (= difference between PA diastolic pressure and pulmonary arterial wedge pressure); Qp: Qs = flow to pulmonary and systemic ratio; PVR = pulmonary vascular resistance; WU = Wood units; PVRi = pulmonary vascular resistance index; SVR = systemic vascular resistance; AVT = acute pulmonary vasodilator testing; RVSP = right ventricular systolic pressure; TTE = transthoracic echocardiography.

those of patients with no interventional closure by any means ($n=13$) and ES ($n=99$), the survival curve of the interventional closure group was higher than those of the ES group or the group without any interventional closure (log rank $p=0.12$ and <0.001, respectively). In fact, the survival curve of the group without any interventional closure was significantly lower than that of the ES group or the interventional closure group (log rank $p=0.008$ and <0.001, respectively) (Fig. 5).

Mortality risks

The patients' characteristics were reviewed to evaluate their mortality risks in adults with PAH-CHD with predominantly L-R shunts (Table 4). A multivariate analysis identified two predictors of death: functional class III-IV at initial presentation (hazard ratio 5.7, 95% CI 1.2–26.6, $p=0.02$) and oxygen saturation < 94% at the most recent visit (hazard ratio 9.4, 95% CI 2.1–42.9, $p=0.004$).

	PVR < 5 WU (*n* = 40)	PVR ≥ 5 WU (*n* = 78)	*p* value
Age at diagnosis (years)	46.23 ± 13.11	35.40 ± 12.51	< 0.001*
Male gender	16 (40%)	20 (25.6%)	0.109
WHO functional class III-IV at diagnosis	4 (10%)	15 (19.2%)	0.197
CHF at presentation	38 (95%)	57 (73.1%)	0.004*
Trisomy 21	1 (2.5%)	2 (2.6%)	1.00
Complex CHD	0 (0%)	3 (3.8%)	0.209
Initial cardiac catheterization			
Baseline mPAP (mmHg)	44.68 ± 12.81	63.20 ± 15.17	< 0.001*
Baseline Qp: Qs	2.33 ± 0.92	1.77 ± 0.75	< 0.001*
Baseline PVR (WU)	3.50 ± 1.08	9.79 ± 4.17	< 0.001*
Baseline PVRi (WU m^2)	5.26 ± 1.99	13.72 ± 5.33	< 0.001*
Baseline PVR/SVR	0.25 ± 0.10	0.49 ± 0.24	< 0.001*
Post AVT mPAP (mmHg)	40.25 ± 8.64	57.76 ± 12.59	< 0.001*
Post AVT Qp: Qs	3.91 ± 2.45	3.85 ± 2.53	0.947
Post AVT PVR (WU)	2.08 ± 1.30	4.20 ± 2.75	< 0.001*
Post AVT PVRi (WU m^2)	3.39 ± 2.05	5.95 ± 3.75	< 0.001*
Post AVT PVR/SVR	0.17 ± 0.11	0.23 ± 0.14	0.012*
Final preoperative cardiac catheterization			
Final PVR (WU)	2.04 ± 1.18	4.21 ± 2.71	< 0.001*
Final PVRi (WU m^2)	3.42 ± 1.91126	5.91 ± 3.82	< 0.001*
Final AVT PVR/SVR	0.16 ± 0.10	0.24 ± 0.14	< 0.001*
Pretreatment with pulmonary vasodilator	17 (42.5%)	44 (56.4%)	0.152
Treat and repair	15 (37.5%)	38 (48.7%)	0.246
Interventional closure Total repair Fenestrated closure Denied surgery or being on the list for intervention	37 (92.5%) 31 (77.5%) 6 (15%) 3 (7.5%)	68 (87.2%) 53 (67.9%) 15 (19.2%) 10 (12.8%)	0.526
Age at intervention (years) (*n* = 105)	47.23 ± 13.18	35.57 ± 11.32	< 0.001*
Follow-up time from diagnosis (years)	6.14 ± 5.31	6.63 ± 5.83	0.658
Persistent PAH postoperation/at the recent visit	11 (27.5%)	41 (52.6%)	0.009*
RVSP on the recent TTE (mmHg)	50.46 ± 21.19	66.07 ± 23.44	0.004*

Table 2. Treatment outcomes of adults with PAH-CHD with predominantly L-R shunt with different initial pulmonary vascular resistances (*n* = 118). The data are presented as the means ± SDs, medians (interquartile ranges), and n (% within columns). * Statistical significance at *p* value < 0.05. PAH-CHD with predominantly L-R shunt = pulmonary arterial hypertension associated with congenital heart disease with predominantly left-to-right shunt; WHO = World Health Organization; CHF = congestive heart failure; mPAP = mean pulmonary arterial pressure; Qp: Qs = flow to pulmonary and systemic ratio; PVR = pulmonary vascular resistance; WU = Wood units; SVR = systemic vascular resistance; AVT = acute pulmonary vasodilator testing; PAB = pulmonary artery banding; PAH = pulmonary arterial hypertension. RVSP = right ventricular systolic pressure; TTE = transthoracic echocardiography.

	PVR < 5 WU (*n* = 40)	PVR ≥ 5 WU (*n* = 78)	*p* value
Experience of right heart failure post repair	2 (5%)	15 (19.2%)	0.037*
Mortality	2 (5%)	7 (9%)	0.441

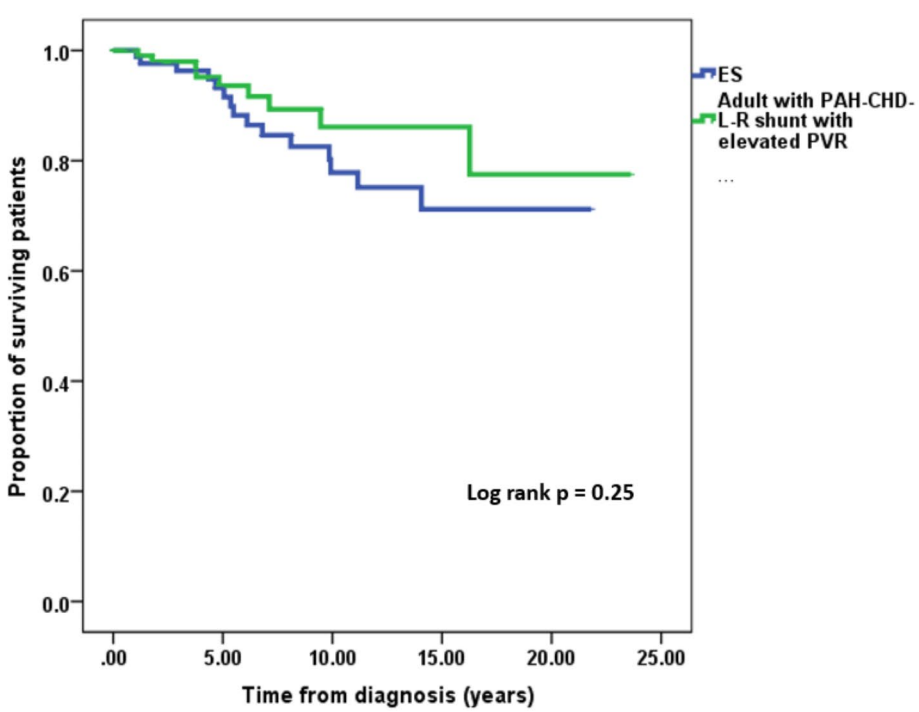
Discussion

The present study used a 25-year CHD database from a large referral cardiac center in Thailand to assess the survival rates and outcomes of 118 adults with PAH-CHD with predominantly L-R shunts compared with 99 adults with ES. Among the 118 patients, 78 patients (66.1%) had borderline-to-high PVR (> 5 WU). Most patients (88.9%) underwent repair, which included 17.7% fenestrated closures. The treat-and-repair strategy was performed safely in 53 patients (42.4%). The 10- and 15-year survival rates for adults with borderline PVR tended to be higher than those for patients with ES ($p = 0.41$). The survival rate of patients who received treat-and-repair was slightly better than that of patients who received ES, although the difference was not statistically significant

	ES ($n=99$)	Adults with treat-and-repair ($n=53$)	p value
Age at diagnosis (years)	34.15 (11.22)	38.25 (13.73)	< 0.01*
Male gender	22 (22.2%)	13 (24.5%)	0.748
WHO functional class III-IV at diagnosis	31 (31.3)	6 (11.3%)	0.006*
CHF at presentation	48 (48.5%)	42 (79.2%)	< 0.001*
Trisomy 21	2 (2%)	1 (1.9%)	0.955
Home oxygen therapy	8 (8.1%)	1 (1.9%)	0.123
Oxygen saturation (%)	87.35 ± 7.06	91.50 ± 6.61	0.003*
Hematocrit (%)	47.22 ± 7.63	41.37 ± 4.2147	< 0.001*
Complex CHD	17 (17.2%)	1 (1.9%)	0.005*
Initial cardiac catheterization			
mRAP (mmHg)	8.46 ± 3.37	10.00 ± 8.88	0.05*
mPAP (mmHg)	74.73 ± 16.72	60.52 ± 13.82	0.819
RVEDP (mmHg)	11.51 ± 4.15	11.25 ± 4.21	0.968
PAWP (mmHg)	11.69 ± 2.78	11.43 ± 2.73	0.422
DPG (mmHg)	42.86 ± 15.95	30.11 ± 15.04	0.920
Qp: Qs	1.01 ± 0.55	1.72 ± 0.77	0.01*
PVR (WU)	21.02 ± 13.15	8.39 ± 4.86	< 0.001*
PVRi (WU m^2)	29.86 ± 18.25	11.94 ± 6.11	< 0.001*
PVR: SVR	1.03 ± 0.71	0.46 ± 0.24	< 0.001*
Post AVT mPAP (mmHg)	72.27 ± 18.72	52.94 ± 13.75	0.055
Post AVT Qp: Qs	1.74 ± 1.38	3.99 ± 2.74	< 0.001*
Post AVT PVR (WU)	13.81 ± 10.40	3.65 ± 2.65	< 0.001*
Post AVT PVRi (WU m^2)	19.23 ± 14.17	5.22 ± 3.65	< 0.001*
Post AVT PVR/SVR	0.72 ± 0.64	0.23 ± 0.15	< 0.001*
Final preoperative cardiac catheterization			
Final PVR (WU)	-	3.58 ± 2.63	-
Final PVRi (WU m^2)	-	5.06 ± 3.57	-
Final AVT PVR/SVR	-	0.22 ± 0.15	-
Interventional closure Total repair Fenestrated closure	0 (0%)	36 (67.9%) 17 (32.1%)	< 0.001*
Follow-up time from diagnosis (years)	7.60 ± 5.98	6.52 ± 4.98	0.239
Persistent PAH post procedure	0 (0%)	29 (54.7%)	-
RVSP on the recent TTE (mmHg)	92.89 ± 24.11	58.48 ± 23.24	< 0.001*
Experience of right heart failure	23 (23.2%)	8 (15.1%)	0.235
Mortality	15 (15.2%)	3 (5.7%)	0.084

Table 3. Patient characteristics and outcomes of adults with PAH-CHD with predominantly L-R shunts treated with the treat-and-repair strategy ($n=53$) and patients treated with ES ($n=99$). The data are presented as the means ± SDs, medians (interquartile ranges) and n (% within columns). * Statistical significance at p value < 0.05. ES = Eisenmenger syndrome; PAH-CHD with predominantly L-R shunt = pulmonary arterial hypertension associated with congenital heart disease with predominantly left to right shunt; WHO = World Health Organization; CHF = congestive heart failure; mPAP = mean pulmonary arterial pressure; Qp: Qs = flow to pulmonary and systemic ratio; PVR = pulmonary vascular resistance; WU = Wood units; SVR = systemic vascular resistance; AVT = acute pulmonary vasodilator testing; PAB = pulmonary artery banding; PAH = pulmonary arterial hypertension; RVSP = right ventricular systolic pressure; TTE = transthoracic echocardiography.

($p=0.19$). These findings indicate that surgical/interventional repair should be considered for patients with PAH-CHD with predominantly L-R shunts and borderline PVR, especially for those who respond to pulmonary vasodilators or pretreatment targeted therapy, because their survival rates tend to be better than those of patients with ES. In this study, 2 mortality cases were noted among 13 patients who did not undergo interventional repair, which significantly decreased the survival rate of this group compared with patients with ES or patients who underwent interventional repair. This finding highlights the risk that is present when adult patients with PAH-CHD with predominantly L-R shunts and borderline PVR are unable to receive timely intervention. To our knowledge, this is the first retrospective cohort study on the survival of adults with PAH-CHD with predominantly L-R shunts with borderline PVR compared with patients with ES in a developing country.

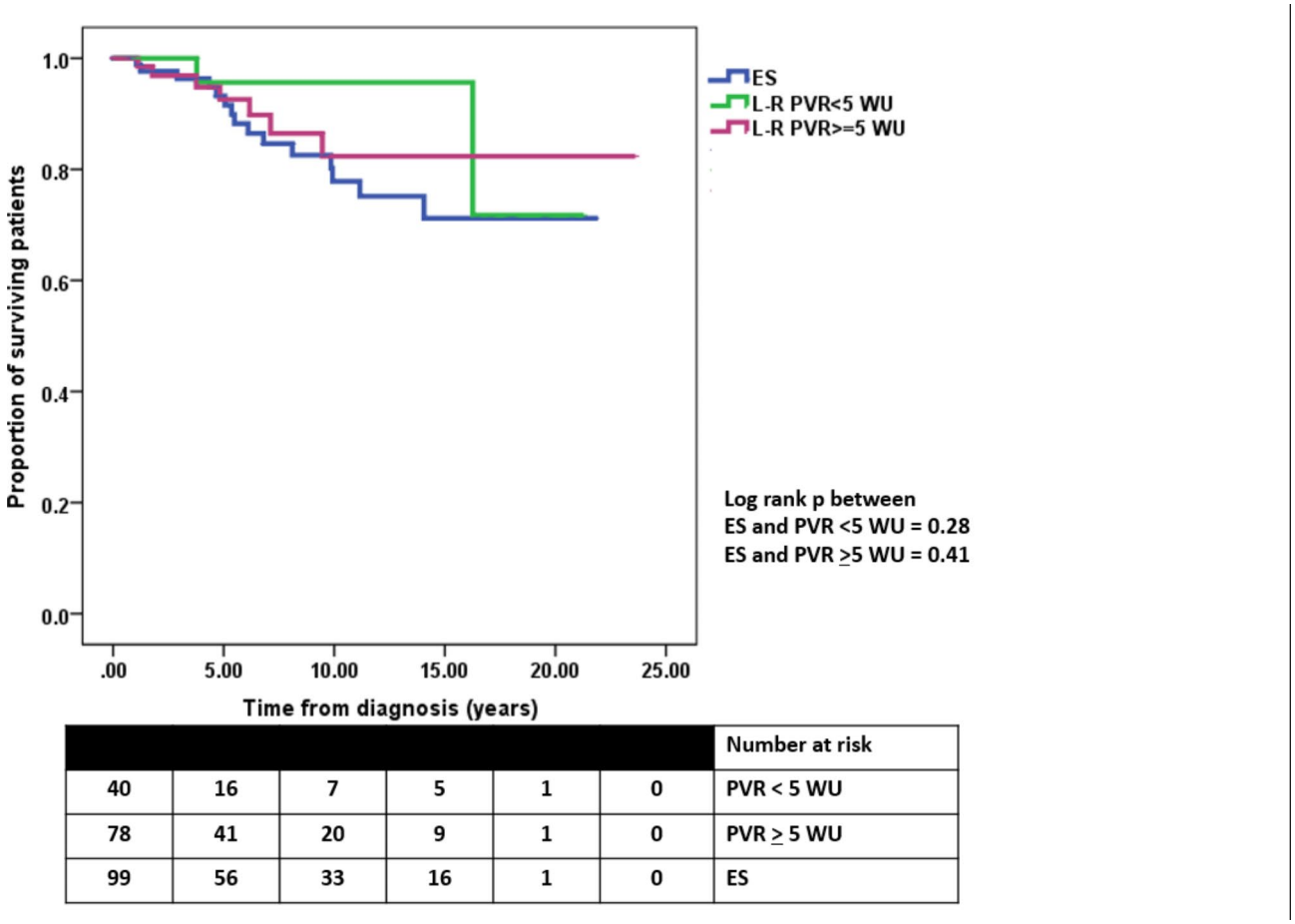


						Number at risk
118	57	27	14	2	0	Adult with PAH-CHD-L-R shunt with elevated PVR
99	56	33	16	1	0	ES

Fig. 2. Cumulative survival of adult patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) with predominantly left to right (L-R) shunts with elevated pulmonary vascular resistance (PVR) and Eisenmenger syndrome (ES): (1) ES (blue), (2) PAH-CHD with predominant L-R shunts with elevated PVR (green).

Assessing the reversibility of PAH-CHD has long been a subject of debate. Currently, the operability criteria are largely based on expert opinions incorporating patient age, type of defect, comorbidities, and baseline and exertional saturations, including hemodynamic data from cardiac catheterization[8]. Recent pediatric guidelines suggest that PVRi < 4–6 WU·m^2 and PVR/SVR < 0.3 are safe for shunt closure and that PVRi 4–8 WU m^2 plus PVR/SVR 0.3–0.5, with evidence of reactivity with AVT, is relatively safe for shunt closure or fenestrated closure[8,14–16]. Data from the study of inhaled nitric oxide as a preoperative test (INOP) support the usefulness of AVT and increase the accuracy of the inoperability criteria from 46 to 88% when PVRi > 8 WU m^2 or PVR/SVR < 0.3 with AVT is used[23]. Alternatively, baseline Qp: Qs, PVR, PVR/SVR, and improved PVR after treat-and-repair have been recommended in the ACHD guidelines for shunt closure or fenestrated closure[8,18]. AVT is not recommended in adult guidelines when deciding whether to close an ASD in patients with PVR > 5 WU[18,24]. Thomaz et al. reported that 15% of patients who were defined as nonresponders showed improvement in the Qp: Qs following surgery and PAH-targeted therapy[24]. Our present retrospective study included adult participants with PAH-CHD from 1995 to 2021, when the knowledge of operability criteria and guidelines was not well established. Patient age, type of defect, comorbidities, oxygen saturation, baseline Qp: Qs, PVR, PVRi, PVR/SVR, a positive response to AVT, and response to pretreatment targeted therapy that required final preoperative hemodynamic values were used for the decision to perform shunt closure. The final decision for surgical candidacy was settled by cardiologists and cardiac surgeons in conference. Fenestrated closure, which was recently introduced to our center, is reserved for patients with borderline elevated PVR. Overall, 68 patients with borderline-to-high PVR (≥ 5 WU) in the cohort underwent repair, including complete closure ($n = 53$) or fenestrated closure ($n = 15$). From baseline, the PVR and PVR/SVR ratios of 9.79 ± 4.17 WU and 0.49 ± 0.24, respectively, were reduced to 4.21 ± 2.71 WU and 0.24 ± 0.14, respectively, in the final preoperative RHC after targeted therapy or AVT, suggesting that most patients responded to pulmonary vasodilators.

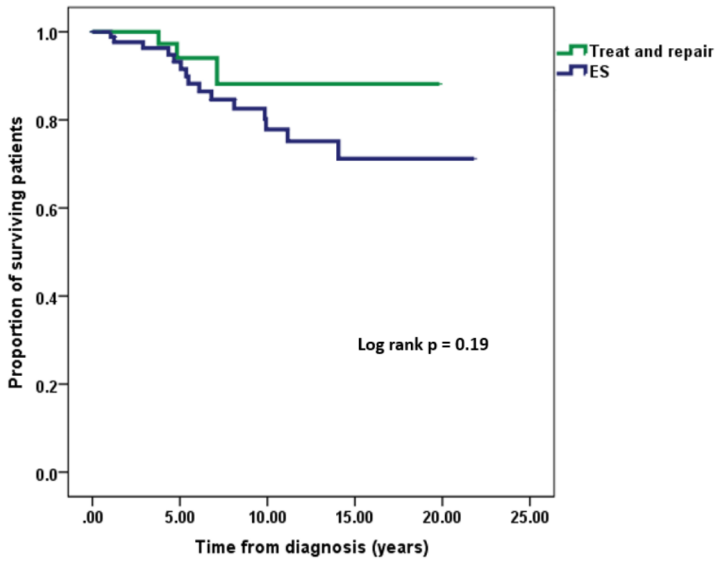
The treat-and-repair strategy and fenestrated/partial closure have been adopted in our center, and several studies have reported favorable short-term outcomes[20–22,25,26]. The North American ASD-PAH (NAAP) Multicenter Registry conducted a retrospective study of 69 patients with atrial septal defects (ASDs) with elevated PVRs of 8.7 ± 4.9 WU. A total of 19 patients responded to pretreatment targeted therapy, and their final



						Number at risk
40	16	7	5	1	0	PVR < 5 WU
78	41	20	9	1	0	PVR ≥ 5 WU
99	56	33	16	1	0	ES

Fig. 3. Cumulative survival of adult patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) with predominantly left to right (L-R) shunts with elevated pulmonary vascular resistance (PVR) and Eisenmenger syndrome (ES): (1) ES (blue), (2) PAH-CHD with predominant L-R shunts with PVR > 5 WU (purple), and (3) PAH-CHD with predominant L-R shunts with PVR < 5 WU (green).

PVR was reduced to < 6.5 WU, after which they safely underwent ASD closure[20]. In a large study of 56 patients with ASD and severe PAH by Yan et al., the effectiveness of combined treat-and-repair with ambrisentan plus tadalafil for three months was demonstrated, and repair was accomplished by fenestrated ASD closure without mortality. The median follow-up time was 10 months. Initially, the median PVR declined from 8.6 WU to 4.7 WU prior to the fenestrated procedure; however, at the one-year follow-up, the PAH data revealed that 11 of 19 patients had persistent PAP, and 5 of 8 patients who had normalized PAP had recurrent PAH after targeted therapy was discontinued[25]. Similarly, a recent retrospective study by Linder et al. revealed that pretreatment with targeted therapy led to improved hemodynamics in 30 patients who had PAH-CHD with predominant L-R shunts. Initially, one-third of the patients had a baseline PVRi > 8 WU·m^2, but no patients in the preoperative final RHC had PVRi > 8 WU·m^2, and favorable outcomes were reported at the midterm follow-up[26]. Practical considerations were also proposed for fenestrated closure, including the need for dual or triple PAH-targeted therapy preoperatively, intravenous prostanoids preoperatively, the presence of right ventricular dysfunction, and PVRi > 5 WU·m^2 at the time of diagnosis[26]. In our study, 53 patients were treated with monotherapy with sildenafil, mostly because of the national coverage policy. Nevertheless, the decision about operability, which was based on the PVR at presentation, varied throughout the study and was made individually by experts (the average final PVR was 3.5 ± 2.6 WU for the treat-and-repair group in this cohort). Among the 105 patients who underwent shunt closure, 23 patients had a preoperative final PVR > 5 WU. No early postoperative deaths were noted; however, at the median follow-up (5.6 years; range 0.1–24.3 years), late mortality was reported in 7 patients. Among these patients, four had a preoperative final PVR > 5 WU. Fenestrated closure was performed in 21 patients; 15 patients had a baseline PVR > 5 WU, and a majority of the patients had ASD (Table S1). The baseline and preoperative final PVRs in the 21 patients were 8.8 ± 4.4 and 4.3 ± 3.2 WU, respectively. One patient died one year after fenestrated closure of the ASD due to pulmonary emboli and persistent PAH. Data concerning fenestrated closure in the cohort are presented in the supplementary file. Following defect correction, 52 of the 105 patients had a different clinical classification from predominant L-R shunt to persistent PAH. Among the 52 patients, 28 patients had right ventricular systolic pressure > 50 mmHg on their recent echocardiography, suggesting that moderate pulmonary hypertension continued to occur even in those who received pulmonary



						Number at risk
53	28	11	3	0	0	Adult with PAH-CHD and received treat and repair
99	56	33	16	1	0	ES

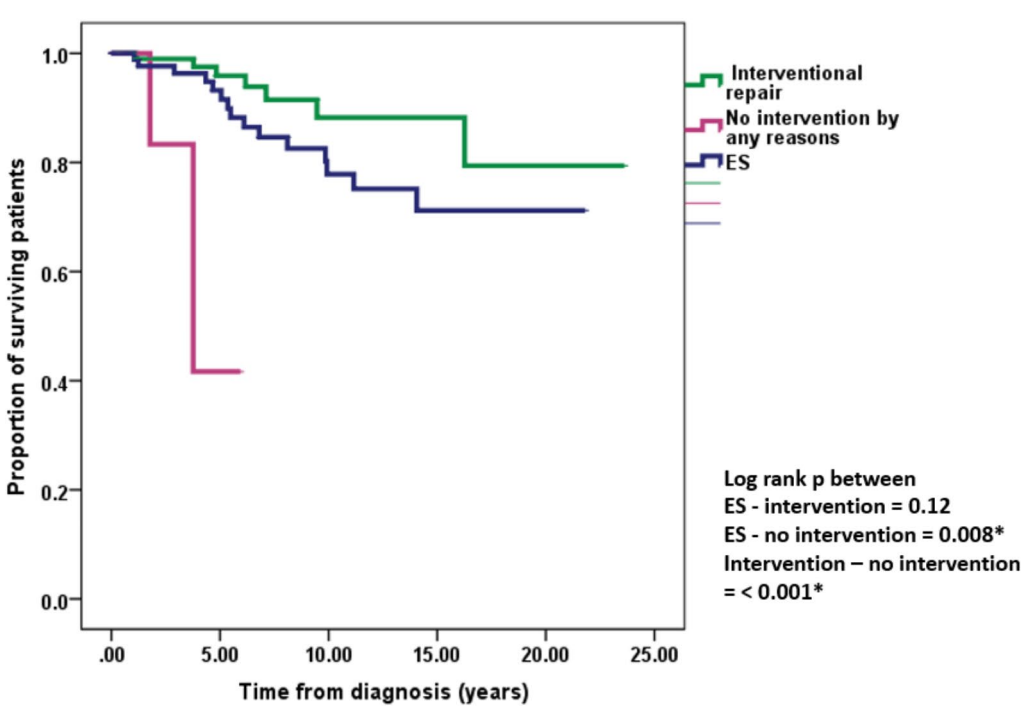
Fig. 4. Cumulative survival of adult patients who had pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) with predominantly left to right (L-R) shunts and received treat-and-repair with Eisenmenger syndrome (ES): (1) ES (blue), (2) PAH-CHD and received treat-and- repair (green).

vasodilators. Despite the incomplete data for the right ventricular-to-pulmonary artery coupling and the 6-minute walk test at the recent visit, patients with persistent PAH following defect correction tended to have lower values than patients without correction. At the recent visit, most patients (90.5%) who underwent defect correction were still in WHO functional classes I-II, including some patients who had persistent PAH (49.5%). The independent mortality risk factors for patients with PAH-CHD with predominantly L-R shunts were functional class III-IV at initial presentation and oxygen saturation < 94% at the recent visit. Hemodynamic data such as RAP > 15 mmHg and post-AVT PVR > 5 WU were nearly statistically significant (p value 0.06) according to the multivariate model.

Our results revealed that the survival of adults with congenital systemic-to-pulmonary shunts with borderline-to-high PVR tends to be better than that of those with ES, although the difference was not statistically significant. The treat-and-repair strategy combined with fenestrated closure seems to offer an expanded window of operability for patients with PAH-CHD with predominantly L-R shunts and elevated PVR. In turn, this may increase the number of patients with persistent PAH following defect correction. Considerations for candidates for shunt closure or fenestrated repair in our center have been recently updated. On the basis of current guidelines and the mortality risks identified in this study, adult patients who respond to AVT or pretreatment therapy are defined as having a final PVR < 5 WU and PVR/SVR ratio < 0.3 with Qp: Qs > 1.5. Practitioners must also be aware of possible subsequent persistent PAH after defect correction. The follow-up protocol included clinical outcomes, functional class, echocardiographic data, a 6-minute walk test, and NT-proBNP to assess the risk and management of postoperative PAH. Further research with a more robust entry protocol, larger numbers of eligible patients, and longer follow-up periods is warranted.

Study limitations

Because this was a retrospective cohort observational study at a single center, selection bias is inevitable. We attempted to select only patients with PAH-CHD who had been newly diagnosed and had undergone cardiac catheterization to confirm that their diagnoses of PAH were in accordance with the current PAH definition. We excluded patients who had a staged, repaired single ventricle due to the unique characteristics of this group. Pediatric patients were also excluded because of differences in the use of PVRi and AVT in terms of their operability criteria. Our retrospective data also lacked specific measurements that could have been used for prognostication, such as the brain natriuretic peptide level, 6-minute walk test, and tricuspid annular plane systolic excursion. In any case, complete cardiac catheterization data were provided for the baseline characteristics. To address immortal time bias, all patients who fulfilled the criteria were included, and for survival analysis, the time of cardiac catheterization diagnosis was considered time 0. The survival endpoint was either the date of mortality or censoring. All patients were contacted in 2022 to confirm their functional class and their status as deceased or alive. We were unable to contact 46 patients with ES and 52 patients with PAH-CHD with predominantly L-R shunts in 2022, and for survival analysis, censoring was considered the last date of follow-up. The median time



						Number at risk
105	56	27	14	2	0	Interventional repair
13	1	0	0	0	0	No intervention
99	56	33	16	1	0	ES

Fig. 5. Cumulative survival of adult patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) with predominantly left to right (L-R) shunts who underwent interventional repair with Eisenmenger syndrome (ES): (1) ES (blue), (2) PAH-CHD and interventional repair (green), and (3) PAH-CHD without interventional repair by any means (purple).

for follow-up in these patients was 2.6 years (range 0.1–21.8 years). Furthermore, a low event rate (< 10%) can affect the power of survival analysis. As a result, significant differences between groups may be difficult to detect.

Conclusion

Adults with PAH-CHD with predominantly L-R shunts have had a fairly good survival rate for the past decade. The overall survival rates at 5, 10, and 15 years were 93.6%, 86.1%, and 86.1%, respectively. The survival of patients with PAH-CHD with predominantly L-R shunts, including the borderline-to-high PVR group, tended to be better than that of patients with ES, although the difference was not statistically significant. Nevertheless, mortality can occur if a patient does not undergo repair, which significantly worsens the survival curve for this group. Treat-and-repair therapy combined with fenestrated or partial closure is safe and expands the options for operability. In any case, the selection of patients with systemic-to-pulmonary shunts and elevated-to-borderline PVR must be carefully scrutinized for their operability. If the threshold is too high, an increase in postoperative adverse events is more likely. Independent predictors of death in patients with PAH-CHD with predominantly L-R shunts are functional class III-IV at initial presentation and oxygen saturation < 94% at the recent visit.

Materials and methods

The present study was a single-center, observational, retrospective cohort study using a hospital database from a large referral cardiac center in Thailand. The study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (SIRB protocol no. 116/2565(IRB1), COA Si265/2022). The requirement for informed consent from patients was waived with the approval of the Ethics Committee of the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University. Multiple steps were taken to ensure patient confidentiality. All research methods were performed according to Good Clinical Practice (GCP) guidelines and regulations.

The records of 589 patients with PH-CHD who had undergone cardiac catheterization to assess their hemodynamic data or transcatheter closure of the defects at Siriraj Hospital from January 1, 1995 to December 31, 2021 were retrieved from the database. All patients with evidence of PAH on cardiac catheterization, including

Variables	Crude hazard ratio (95% CI)	*p* value	Adjusted hazard ratio (95% CI)	*p* value
Age at diagnosis > 35 years	1.791 (0.447–7.181)	0.411		
Complex shunt	0.042 (0-3503.420)	0.583		
Trisomy 21	0.046 (0–3545.861)	0.704		
WHO functional class III-IV at initial presentation	5.417 (1.447–20.281)	0.012*	5.750 (1.243–26.601)	0.025*
Initial oxygen saturation < 90%	1.633 (0.907–7.92)	0.543		
RAP > 15 mmHg	6.153 (1.231–30.749)	0.027*	7.010 (0.913–53.841)	0.061
Baseline PVR > 5 WU	1.703 (0.352–8.236)	0.501		
Baseline PVR/SVR > 0.66	0.324 (0.065–1.611)	0.168	0.815 (0.132–5.045)	0.826
Post AVT PVR > 5 WU	4.685 (1.257–17.468)	0.126	4.330 (0.907–20.670)	0.066
Post AVT PVR/SVR > 0.20	5.271 (1.093–25.417)	0.038*	3.322 (0.476–23.187)	0.226
Persistent PAH post procedure	1.223 (0.326–4.581)	0.766		
Oxygen saturation < 94% at the recent visit	8.456 (2.211–32.337)	0.002*	9.438 (2.077–42.899)	0.004*

Table 4. Predictors of mortality in adults with PAH-CHD with predominantly L-R shunts and elevated pulmonary vascular resistance ($n = 118$). Univariate analysis and multivariate analysis via Cox regression. * Statistical significance at p value < 0.05. PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; L-R = left to right; Qp = pulmonary blood flow; Qs = systemic blood flow; PVRi = pulmonary vascular resistance index; WU = Wood units; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; AVT = acute pulmonary vasodilator testing; PAH = pulmonary arterial hypertension; RAP = right atrial pressure.

mPAP > 20 mmHg, PAWP ≤ 15 mmHg, and calculated PVR ≥ 2 WU on the basis of the current definition of PAH, were included[6]. Patients who had a single ventricle following staged surgery were excluded from the study. Patients with PAH-CHD clinical classifications of 1 (ES) and 2 (predominantly L-R shunts) were selected. A total of 452 patients (142 ES; 310 PAH-CHD with predominantly L-R shunts) were identified from the database. All children (43 with ES and 192 with PAH-CHD with predominantly L-R shunts) were excluded. A total of 99 adults with ES [median age (IQR) of 31.7 (13.8) years] and 118 adults with PAH with predominantly L-R shunts (median age (IQR) of 36.2 (23.5) years) were identified for the analysis (Fig. 1). Demographic information, including date of birth, sex, presenting symptoms, functional class, hematocrit (%), oxygen saturation (%), anatomical–pathophysiological classification (pretricuspid, posttricuspid, combined, complex shunt), history of home oxygen therapy prior to diagnosis, date of diagnosis (i.e., date of first confirmatory cardiac catheterization), cardiac catheterization hemodynamic data [including mean right atrial pressure (mRAP), right ventricular end diastolic pressure (RVEDP), PAP, mPAP, PAWP, left ventricular end diastolic pressure (LVEDP), diastolic transpulmonary gradient (DPG) (= PA diastolic pressure minus PAWP), Qp: Qs, PVR, PVRi, and PVR/SVR] at baseline in room air and following acute vasodilator testing (AVT) were obtained from the retrospective chart review. The data collection method was previously described in our prior study and has been updated[12]. Adults with PAH-CHD with predominantly L-R shunts were categorized into two groups on the basis of their baseline PVR: mildly elevated PVR (< 5 WU) or borderline-high PVR (≥ 5WU), and the outcomes and survival rates were compared to those of patients with ES. Patients who received the treat-and-repair strategy were recorded and reported in terms of survival.

Follow-up and outcome measurements

The primary endpoint of the study was all-cause mortality. Survival time was estimated from the date of cardiac catheterization-confirmed PAH-CHD diagnosis to the survival endpoint, which was taken either as the date of mortality or censoring. Patients were censored if they were lost to follow-up in 2022.

The clinical outcomes of adults with PAH-CHD with predominantly L-R shunts, including recent PAH classification, persistent PAH after defect correction, right heart failure, and recent functional class, were recorded from chart reviews and telephone interviews.

Statistical analyses

The patients' baseline characteristics and outcomes were summarized via descriptive statistics. The normally distributed data are presented as the means ± SDs or, in cases where the distribution was not normal, as medians with interquartile ranges. Categorical data are presented as numbers and percentages (%). Differences in

categorical data were assessed via Pearson's chi-square test or Fisher's exact test. One-way analysis of variance with Bonferroni correction was used to determine differences between data for greater than two groups for continuous variables. Cumulative survival from the date of diagnosis to the endpoint was calculated via the Kaplan–Meier method. The relationships between baseline characteristics and mortality were evaluated via Cox regression and multivariate analyses. The covariates, which represented p values < 0.2 in the crude regression analysis, were chosen for the multivariate analysis via the enter method in the Cox regression model. SPSS 20.0 for Windows (SPSS. Inc., Chicago, IL, USA) was used for all analyses, and all the statistical tests were two-tailed, with the significance level set to a p value < 0.05.

Data availability

Data sets generated during the current study are available from the corresponding author on reasonable request.

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Author contributions

C.V. conceptualized the study, collected and analyzed the data for this research, and wrote the manuscript. J.S., N.C., and D.B. collected and analyzed the data. K.D. and J.So. provided meaningful comments and substantial edits to the manuscript. P.C., P.W.C., S.K., P.T., T.P., T.T, E.N., Kr.T., and T.S. edited the manuscript. All authors contributed to the manuscript, and read and approved the final submission.

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Declarations

Competing Interests

The authors declare that they have no competing interests.

Additional information

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