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ORIGINAL RESEARCH

Pulmonary Hypertension in Adult Congenital Heart Disease in Asia: A Distinctive Feature of Complex Congenital Heart Disease

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BACKGROUND: The epidemiology of pulmonary hypertension (PH) in patients with adult congenital heart disease in Western countries is already known. We investigate clinical characteristics of PH in adult congenital heart disease with emphasis on complex congenital heart disease (CHD) from an Asian cohort in Taiwan.

METHODS AND RESULTS: All adult patients (aged >18 years) diagnosed with CHD between January 2007 and July 2018 qualified for the study. PH was determined by cardiac catheterization data or echocardiography reports. In accord with the World Symposia on Pulmonary Hypertension, CHD was further categorized as simple, severe, or complex CHD (including pulmonary atresia-ventricular septal defect and single-ventricle anomalies).
There were 4301 patients (55.6% women), 15.7% with severe and 3.9% with complex CHD. The cumulative incidence of PH was 4.4% (95% CI, 3.8–5.0). Our multivariable regression model indicated 4.2-fold mortality increase (95% CI, 3.0–5.9) in the presence of PH, with age, female sex, and severe or complex CHD linked to higher incidence of PH. Only 49% of patients received PH-specific therapy. Five- and 10-year survival rates of patients with PH (n=190) were 72.3% (95% CI, 65.1%–78.4%) and 58.8% (95% CI, 50.1%–66.5%), respectively. Survival rates in those with Eisenmenger syndrome, PH after defect correction, and complex CHD were similar. Low oxygen saturation and high uric acid levels were associated with increased mortality.

CONCLUSIONS: In this sizable Asian adult CHD cohort, the cumulative incidence of PH was aligned with that of Western countries. Mortality proved higher in patients with PH versus without PH. Although complex CHD carried greater risk of PH compared with other adult CHD subsets, survival rate was similar.

Key Words: adult congenital heart disease ■ Asian ■ complex congenital heart disease ■ pulmonary hypertension

Congenital heart disease (CHD) is the most common cardiac ailment in children, and its prevalence in Taiwan is estimated at 13 per 1000 newborns.[1,2] Although Asian and Western countries are similar in terms of incidence, CHD subtypes vary considerably. Hypoplastic left heart syndrome, coarctation of the aorta, transposition of the great arteries (TGA), and tricuspid atresia are all less frequent in Asian populations, whereas pulmonary stenosis, tetralogy of Fallot (TOF), and atrial septal defect (ASD) occur with greater frequency.[2] Thus, it appears there are ethnic differences associated with CHD.

Modern surgical and cardiac catheterization techniques and methods of perioperative care have

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CLINICAL PERSPECTIVE

What Is New?

- In a large Asian cohort (N=4301) with adult congenital heart disease, the cumulative incidence (4.4%) of pulmonary hypertension (PH) resembled that of Western countries.
- Mortality risk increased 4.2-fold in its presence.
- Age, sex, and cyanotic or complex congenital heart disease were associated with increased incidence of PH.
- The 5-year survival rate of patients with PH was 72.3%, proving similar among patients with Eisenmenger syndrome, PH after defect correction, and complex congenital heart disease.

What Are the Clinical Implications?

- In patients with complex congenital heart disease, including pulmonary atresia-ventricular septal defect and single-ventricle anomalies, the incidence of PH may be as high as 49.7% by age 40 years. One must therefore closely monitor such patients for its onset.
- Patient response to PH-specific therapy is good, and survival across groups (complex congenital heart disease versus Eisenmenger syndrome or PH after defect correction) is similar.

Nonstandard Abbreviations and Acronyms

ACHD	adult congenital heart disease
PA-VSD	pulmonary atresia-ventricular septal defect
PH	pulmonary hypertension
SV	single-ventricle diseases
TGA	transposition of the great arteries
TOF	tetralogy of Fallot

changed the outcomes of CHD. Currently, most patients survive into adulthood, at which time late complications (especially pulmonary hypertension [PH]) become important issues.[3–5] In the Euro Heart Survey of patients (n=1877) with adult CHD (ACHD), including acyanotic (with sizeable systemic-to-pulmonary shunts) and cyanotic (with heightened pulmonary blood flow) CHD, 28% of subjects had PH, and 12% qualified as Eisenmenger syndrome.[6] Echocardiographic data from the congenital cor vitia registry, another multicenter ACHD repository, have indicated a 6.1% prevalence of PH in patients (n=1824) with ASDs or ventricular septal defects (VSDs), 3.5% displaying Eisenmenger syndrome.[7] Unlike the various extensive database studies conducted in Western countries, relevant studies in Asian populations are lacking. In addition, single ventricle disease and segmental PH, now grouped as complex CHD by the World Symposia of Pulmonary Hypertension, are seldom explored.

PH-specific therapy has been shown to improve long-term patient outcomes[8,9] and is considered standard treatment in current guidelines.[10] Our own National Health Insurance program has authorized sildenafil (2008) and bosentan (2016) for this purpose, but the long-term ramifications of these treatments in Asians is virtually unknown. Herein, we have analyzed epidemiologic factors, clinical characteristics, and PH-specific therapy in a large Asian cohort with ACHD, drawing particular attention to complex CHD.

METHODS

Data Acquisition

This retrospective database study was conducted to assess PH in the setting of ACHD, referencing all applicable health care records from the integrated medical database at National Taiwan University Hospital. This is a tertiary medical center and also the largest pediatric cardiology/ACHD center in Taiwan. We acquired all anonymized digitalized clinical, therapeutic, and laboratory data from outpatient, inpatient, and emergency departments. We also accessed death records of the Ministry of Health and Welfare in Taiwan to ascertain survival and causes of death. This study was approved by the institutional research board of our hospital, waiving informed patient consent because of data anonymity. The raw data is available at the supplemental material file Data S1.

Patient Cohort

All patients were adults (aged >18 years) and diagnosed with CHD between January 2007 and July 2018. Those with preexisting PH (n=118) upon the first visit to our hospital were excluded. Diagnoses of CHD were based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 745.0 to 747.42 or *Tenth Revision* (*ICD-10-CM*) codes Q20 to Q26. Participants were then stratified as simple, severe, or complex CHD (Table 1) using previously assigned CHD subtypes and current World Symposia of Pulmonary Hypertension recommendations,[1,11] complex CHD incorporating both pulmonary atresia-ventricular septal defect (PA-VSD), and single-ventricle disease (SV). Common forms of CHD, including ASD, VSD, endocardial cushion defect, patent ductus arteriosus, TOF, TGA, PA-VSD, and SV, were also separated for further analysis. Fontan procedures authorized by pediatric cardiologists by default signified SV. Common anomalies viewed as such were

Table 1. Distribution of Congenital Heart Disease Subtypes

Simple	n	%	Severe	n	%	Complex	n	%
ASD	1304	37.7	TOF	447	66.1	PA-VSD	44	26.2
VSD	1442	41.7	TGA	94	13.9	Single ventricle	124	73.8
PDA	206	6.0	Others	135	20.0	Heterotaxy	48	28.6
ECD	75	2.2	PA-IVS	33	4.9	Tricuspid atresia	25	14.9
Others	434	10.0	ccTGA	32	4.7	DILV	18	10.7
PS	170	4.9	DORV	31	4.6	DORV with SV	11	6.6
COA	61	1.8	TAPVR	23	3.4	Mitral atresia	7	4.2
AS	59	1.7	IAA	10	1.5	ccTGA with SV	6	3.6
Ebstein's	55	1.6						
Total	3461			676			168	

There was no significant difference among subtypes (P=0.44 by log-rank test). AS indicates aortic stenosis; ASD, atrial septal defect; ccTGA, congenital corrected transposition of great arteries; COA, coarctation of aorta; DILV, double inlet left ventricle; DORV, double outlet right ventricle; ECD, endocardial cushion defect; IAA, interrupted aortic arch; PA-IVS, pulmonary atresia with intact ventricular septum; PA-VSD, pulmonary atresia and ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary stenosis; SV, single ventricle physiology; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

heterotaxy, tricuspid atresia, double-inlet left ventricle, mitral atresia, PA with intact ventricular septum, double inlet–double outlet ventricle, and some of the double-outlet right ventricle and levo-transposition of the great arteries.

Definitions

In accord with the World Symposia of Pulmonary Hypertension, PH linked to CHD and biventricular physiology was determined at cardiac catheterization on admission, indicated by mean pulmonary artery pressure >25 mm Hg and pulmonary vascular resistance >3 Wood units.[11] Cardiac catheterization data were available for only 31.8% of our 4301 patients. In those not catheterized, we relied on echocardiographic criteria of the European Society of Cardiology, namely peak tricuspid regurgitation velocity above 3.4 m/s (pressure gradient >46 mm Hg) or a tricuspid regurgitation velocity above 2.8 m/s (pressure gradient >31 mm Hg), with signs of right heart pressure overload. Given the unique nature of CHD, patients with tricuspid regurgitation velocities above stated thresholds but with substantial valvular or peripheral pulmonary stenosis did not qualify as PH. In those with CHD and single-ventricle physiology, PH was likewise defined as mean pulmonary artery pressure ≥15 mm Hg during admission catheterization, based on past reports and current guidelines.[12–14]

Statistical Analysis

All data were expressed as mean±standard deviation values, unless otherwise specified. In sample comparisons, the Student t test was applied to numerical data, using the χ^2 test for categorical data. The Kaplan-Meier method with log-rank analysis and Cox regression were engaged for survival analyses. In assessing demographic data and for Cox regression analysis of total mortality, follow-up was from age 18 years to time of death or end of study. Patients were censored at death or when lost to follow-up. In Cox regression analysis of PH, follow-up was from age 18 years to time of PH diagnosis or end of study, censoring patients at PH diagnosis or when lost to follow-up. For Cox regression analysis of mortality in patients with ACHD and PH, follow-up was from diagnosis of PH to time of death or end of study, censoring patients at death or when lost to follow-up. The Supremum test for proportional hazards assumption was applied to each Cox model. All testing was driven by standard software (SAS version 9.4 for Windows; SAS Institute, Cary, NC), setting significance at P<0.05.

RESULTS

Patient Demographics and Outcomes of ACHD

Overall, 4301 patients (55.6% women) with ACHD qualified for the study, 15.7% with severe CHD and 3.9% with complex CHD. Itemized specific disease categories are given in Table 1, and baseline demographic data are summarized in Table 2. Overall, the most common forms of CHD were ASD and VSD, whereas TOF and TGA predominated in subjects with severe CHD, and SV prevailed in those with complex CHD. After a median follow-up of 16.0 years (interquartile range, 7.8–28.8 years) beyond age 18 years, survival rates at ages 30, 40, and 50 years were 98.9% (95% CI, 98.5%–99.2%), 97.4% (95% CI, 96.6%–97.9%), and 95.3% (95% CI, 94.1%–96.2%), respectively (Figure 1). Deaths overall were largely attributable to cardiac causes (56.6%), followed by cancer, accident, and stroke (Table 3). In multivariable Cox regression analysis, PH (hazard ratio [HR], 4.2 [95%

Table 2. Baseline Demographics and Cumulative Incidence of PH in a Large Cohort With Adult CHD

	Total, n=4301	Cumulative incidence	PH, n=190	PH with catheterization data, n=29*	No PH, n=4111
Sex					
Women	2392 (55.6)	5.6	134 (70.5)	23 (79.31)	2258 (54.9)
Men	1909 (44.4)	2.9	56 (29.5)	6 (20.69)	1853 (45.1)
CHD category					
Simple	3457 (80.4)	3.8	131 (68.9)	22 (75.86)	3326 (80.9)
Severe	676 (15.72)	3.3	22 (11.6)	2 (6.9)	654 (15.9)
Complex	168 (3.91)	22	37 (19.5)	5 (17.24)	131 (3.2)
Disease subtypes					
ASD	1304 (30.3)	5.7	74 (38.9)	14 (48.28)	1230 (29.9)
VSD	1441 (33.5)	2.9	42 (22.1)	5 (17.24)	1399 (34.0)
PDA	206 (4.8)	4.9	10 (5.3)	1 (3.45)	196 (4.8)
ECD	75 (1.7)	2.7	2 (1.1)	0 (0)	73 (1.8)
TOF	447 (10.4)	2.0	9 (4.7)	0 (0)	438 (10.7)
TGA	94 (2.2)	2.1	2 (1.1)	0 (0)	92 (2.2)
Single ventricle	124 (2.9)	19.4	24 (12.6)	2 (6.9)	100 (2.4)
PA-VSD	44 (1.0)	29.5	13 (6.8)	3 (10.34)	31 (0.8)
Others	566 (13.2)	2.5	14 (7.4)	4 (13.79)	552 (13.4)
Genetic syndrome	95 (2.21)	4.2	4 (2.1)	1 (3.45)	91 (2.2)
Mean PAP by cardiac catheterization, mm Hg†	20.3±11.5		43.3±17.3	43.3±17.3	17.8±6.4
PVR, Wood unit			7.1±4.8	7.1±4.8	1.5±1.2
PVRi, Wood unit × m^2			11.2±8.6	11.2±8.6	2.4±1.8
Follow-up, y, median (interquartile range)‡	16.0 (7.8–28.8)		30.4 (16.0–47.7)	17.42 (8.21–30.71)	15.6 (7.6–27.7)

Data are expressed as n (%) unless otherwise specified. ASD indicates atrial septal defect; CHD, congenital heart disease; ECD, endocardial cushion defect; PAP, pulmonary artery pressure; PA-VSD, pulmonary atresia- ventricular septal defect; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; TGA, transposition of great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

*No significant difference in sensitivity analysis of patients with PH±cardiac catheterization, except shorter follow-up time when data are available.

†Available data in only 325 patients overall and 29 in the PH group.

‡Follow-up from age 18 years to time of death or end of study.

CI, 3.0–5.9), male sex (HR, 2.1 [95% CI, 1.6–2.9]), genetic syndromes (HR, 5.4 [95% CI, 2.0–15]), and severe (HR, 3.0 [95% CI, 1.9–4.8) or complex (HR, 18.0 [95% CI, 10.7–30.2]) CHD were significantly associated with increased mortality (all $P<0.001$) (Table 4). Ultimately, long-term patient survival was significantly reduced in the presence of PH (Figure 1). SV (HR, 78.4 [95% CI, 44–139]), TGA (HR, 21.5 [95% CI, 7.4–62.7]), endocardial cushion defect (HR, 12.1 [95% CI, 4.7–31.1]), and PA-VSD (HR, 8.4 [95% CI, 1.1–62.2]) carried the highest risks of mortality among disease subsets, ASD serving as reference (all $P<0.01$).

PH in Conjunction With ACHD

PH was diagnosed in 190 patients, 160 (84.2%) of whom had available cardiac catheterization data. Diagnoses were otherwise based on echocardiographic data. The cumulative incidence of PH in this cohort with ACHD was 4.4% (95% CI, 3.8–5.0), women and patients with severe or complex CHD showing the highest rates (Table 5). In terms of disease subsets, we identified higher cumulative incidences in patients with PA-VSD, SV, or TGA (Table 5). In VSD, ASD, patent ductus arteriosus, TOF, and TGA subsets, cumulative incidences ranged from 1.7% to 3.5% by age 40 years and from 4.1% to 5.2% by age 50 years (Figure 2). The cumulative incidence was markedly higher in patients with complex CHD, reaching 49.7% (95% CI, 33.1%–69.2%) by age 40 years.

PH-specific therapies prescribed to these patients are shown in Table 6. Only 49% of subjects received such treatments, given more liberally to those with complex CHD. In patients with ACHD and PH, endothelin receptor antagonist use remained low (16%).

Outcomes of ACHD With PH

Among patients with PH (n=190), 5- and 10-year survival rates were 72.3% (95% CI, 65.1%–78.4%) and 58.8% (95% CI, 50.1%–66.5%), respectively. Most often, death was attributable to cardiac causes (69.7%),

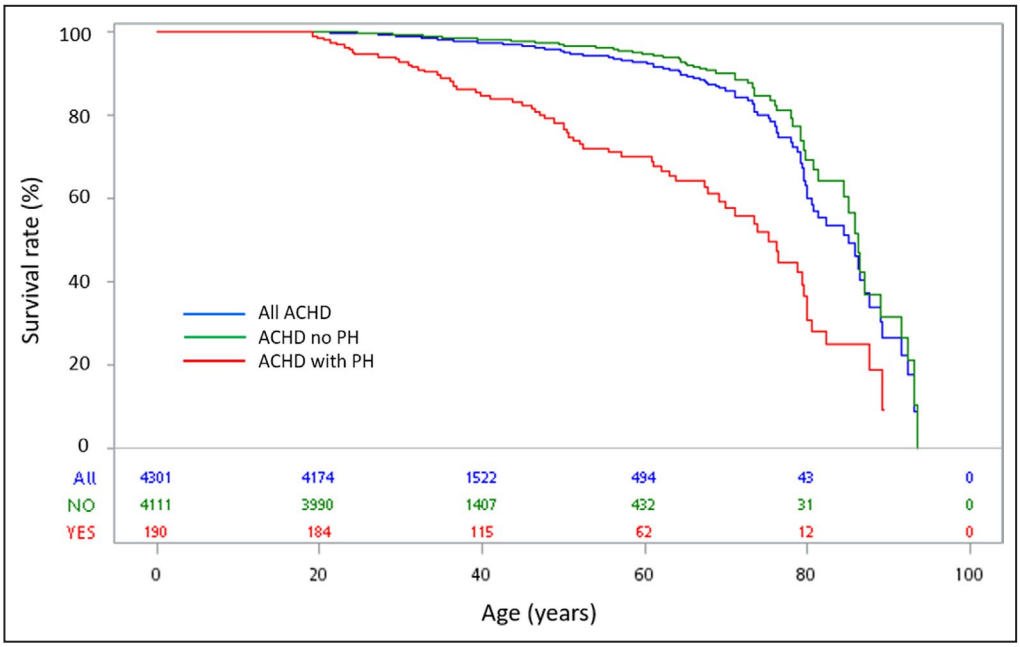

Figure 1. Kaplan-Meier survival curve for patients (n=4301) with adult congenital heart disease (ACHD), shown by presence/absence of pulmonary hypertension (PH).
There is significantly lower survival in the presence vs absence of PH (P<0.01 by log rank test).

followed by stroke (7.6%), cancer (6.1%), and diabetes (3.1%) (Table 3). Cardiac-related mortality was significantly higher in patients with versus without PH (P<0.01). Kaplan-Meier survival curves for the 5 PH subtypes are plotted in Figure 3. Corresponding mortality rates did not differ significantly. Using multivariable Cox regression analysis, we analyzed risk factors for poor outcomes in patients of ACHD with PH (Table 7). There was no association between poor long-term outcome and age at diagnosis of PH, disease category, PH category, sex, or medication use. Although pro-B-type natriuretic peptide (proBNP), uric acid, and oxygen saturation (SpO_2) were laboratory parameters signaling poor outcomes in univariate analysis, only low SpO_2 (HR, 0.93 [95% CI, 0.9–0.997]; P=0.04) and high uric acid (HR, 1.5 [95% CI, 1.1–2.2]; P=0.01) levels emerged in multivariable Cox regression analysis as parameters associated with poor long-term outcomes.

Table 3. Causes of Death Overall and With/Without PH

Cause of death	Overall, n=179	PH+, n=113	PH−, n=66
Cardiac	102 (57.0)	56 (49.6)	46 (69.7)*
Cancer	24 (13.4)	20 (17.7)	4 (6.1)
Accident	12 (6.7)	12 (10.6)	0 (0)†
Stroke	10 (5.6)	5 (4.4)	5 (7.6)
Pneumonia	5 (2.8)	4 (3.5)	1 (1.52)
Diabetes	3 (1.7)	1 (0.9)	2 (3.0)
Renal	1 (0.6)	1 (0.9)	0 (0)
Others	22 (12.3)	14 (12.4)	8 (12.1)

Data are expressed as n (%). PH indicates pulmonary hypertension.
*P<0.01.
†P<0.05.

DISCUSSION

Cumulative Incidence of PH in Patients With ACHD

Given the improved state of medical care, the life expectancy of most patients with ACHD has improved dramatically in recent decades. The majority of related deaths are now beyond age 60 years, peaking at 80 to 84 years.[15] However, PH proved to be an important cause of late mortality in this patient population. Several large-scale database studies of ACHD in Western countries have returned cumulative incidences of ~4% to 7.2% overall, with higher figures for left-to-right shunt defects (7.4%–8.3%) and the highest in those with severe CHD (13%). Even after defect closures, the incidence of PH is still ~3% to 5.7%.[7,16–20]

Unfortunately, studies of PH in Asian patients with ACHD are scarce. In one such effort undertaken by the Pediatric Pulmonary Hypertension Network, patients of Asian descent seemed prone to developing PH or PH in conjunction with CHD.[21] Likewise, the registry to evaluate early and long-term PAH disease management (REVEAL) registry analysis has indicated that enrollees with Asian origins are predisposed to CHD with PH.[22] However, both studies involved small numbers

Table 4. Cox Regression Analysis for Overall Risk of Mortality in Patients With Adult CHD

	Univariate model		Multivariable model		
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	*P* value for test*
PH	4.77 (3.45–6.61)	<0.01	4.23 (3.03–5.91)	<0.01	0.06
Sex					
Women	1		1		
Men	1.93 (1.43–2.6)	<0.01	2.12 (1.55–2.90)	<0.01	0.31
CHD category					
Simple	1		1		
Severe	3.22 (2.0–5.1)	<0.01	3.02 (1.91–4.79)	<0.01	0.61
Complex	32.12 (19.4–53.1)	<0.01	17.96 (10.7–30.2)	<0.01	0.29
Genetic	4.59 (1.67–12.6)	<0.01	5.44 (1.97–15.0)	<0.01	0.56
Disease subtypes					
ASD	1				
VSD	2.1 (1.4–3.15)	<0.01			
PDA	1.96 (1.04–3.71)	0.04			
ECD	12.1 (4.72–31.1)	<0.01			
TOF	3.90 (2.12–7.17)	<0.01			
TGA	21.5 (7.38–62.7)	<0.01			
PA-VSD	8.42 (1.14–62.23)	0.04			
Single ventricle	78.40 (44.0–139.7)	<0.01			
Others	4 (2.39–6.72)	<0.01			

ASD indicates atrial septal defect; CHD, congenital heart disease; ECD, endocardial cushion defect; HR, hazard ratio; PA-VSD, pulmonary atresia- ventricular septal defect; PDA, patent ductus arteriosus; PH, pulmonary hypertension; TGA, transposition of great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

*Supremum test for proportional hazards assumption.

of Asian participants, arriving at a percentage of CHD with PH relative to all patients with PH, rather than assessing the true incidence of PH in patients with ACHD.

Herein, the observed the cumulative incidence of PH (4.4%) was generally the same for both simple acyanotic CHD (ie, ASD, VSD, or patent ductus arteriosus) and common types of cyanotic CHD (ie, TGA or TOF). It was also aligned with figures cited by Western countries, implying no ethnic disparities.[9,10,16,23] Furthermore, the incidence increased with age (~4.1%–5.2% by age 50 years), as in a Danish nationwide registry study.[18] Women displayed a higher incidence of PH (HR, 1.47)[7,18,24] as well, and the incidence was particularly high in patients with PA-VSD or SV, now constituting complex CHD with PH (World Symposia of Pulmonary Hypertension). By age 40 years, the cumulative incidence was at 49.0%. According to findings of Schwartz and colleagues, the cumulative incidence of PH is especially high in patients with severe CHD, encompassing SV defects and complex biventricular physiology.[18] These discoveries underscore the need to address medical care and PH-targeted therapy in these vulnerable patient subsets.

Impact of PH on Long-Term Outcomes

PH is known to negatively impact mortality in patients with ACHD. In past studies of patients with CHD and PH, reported 5-year (range, 12%–24%) and 10-year (range, 21%–33%) mortality rates have been substantial. Compared with counterparts unencumbered by PH, the differences are 4- to 15-fold.[16,18,20,23,25–29] A previous multicenter registry study of ours, in which 95% of patients with CHD-PH (n=87) received PH-targeted therapy, recorded a 2-year survival of 93.2%.[30] Patients with CHD and PH (n=190) in the present analysis, however, displayed mortality rates of 27.7% at 5 years and 42.2% at 10 years, outpacing mortality in the absence of PH by 4.8-fold. These outcomes are clearly worse than the previously reported data; yet less than half of patients received PH-targeted therapy, and endothelin receptor antagonist use was exceedingly low, perhaps explaining the dismal results. Thus, optimal PH-specific therapy is imperative to improve long-term outcomes and lower cardiac mortality.

In various subtypes of ACDH with PH, published mortality rates have conflicted. Some earlier research suggests a higher mortality for Eisenmenger syndrome, compared with PH after CHD defect closure, whereas other evidence reflects comparable results for these 2 scenarios.[16,23,25] Recently, several studies have demonstrated opposite findings, showing the highest morality rate in the presence of PH after CHD defect correction.[26,28,31] Consequently, the authors discourage defect closures in patients with PH, even before Eisenmenger syndrome stage.

Table 5. Cox Regression Analysis for Overall Risk of Pulmonary Hypertension in Patients With Adult CHD

	Univariate model		Multivariable model		
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	*P* value for test*
Sex (women)	0.68 (0.48–0.97)	0.03	0.6 (0.42–0.86)	<0.01	0.94
CHD category					
Simple	1		1		
Severe	2.16 (1.33–3.51)	<0.01	2.29 (1.41–3.73)	<0.01	0.75
Complex	24.0 (14.0–41.3)	<0.01	26.53 (15.39–45.73)	<0.01	0.28
Disease subtypes					
ASD	1				
VSD	0.93 (0.63–1.37)	0.70			
PDA	0.93 (0.48–1.79)	0.82			
ECD	2.19 (0.53–8.98)	0.28			
TOF	1.03 (0.51–2.09)	0.93			
TGA	4.67 (1.11–19.57)	0.04			
PA-VSD	33.95 (15.7–73.5)	<0.01			
Single ventricle	16.98 (8.52–33.86)	<0.01			
Others	1.08 (0.57–2.04)	0.82			
Genetic	2.45 (0.6–10.02)	0.21			

ASD indicates atrial septal defect; CHD, congenital heart disease; ECD, endocardial cushion defect; HR, hazard ratio; PA-VSD, pulmonary atresia-ventricular septal defect; PDA, patent ductus arteriosus; TGA, transposition of great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.
*Supremum test for proportional hazards assumption.

In the present study, mortality was a bit higher for patients with Eisenmenger syndrome but failed to reach statistical significance. Our center has adopted a repair-and-treat strategy for most patients presenting with ASDs and PH, using transcatheter fenestrated devices to achieve closures.[32] Although totally repaired and categorized as PH after defect correction, the small fenestrations may allow right-to-left shunting in pulmonary hypertensive crises, reducing related mortality. From our previous study, where patients with ASDs and PH received such devices, mean pulmonary artery pressure, pulmonary vascular resistance, and functional class all improved, and survival analysis showed promising result.[32] This concept is also supported by data

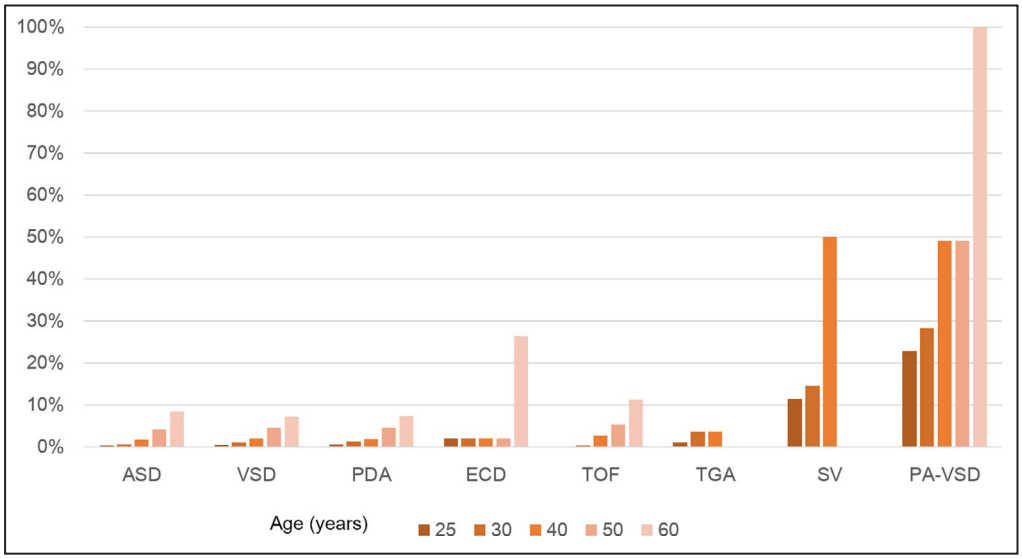

Figure 2. Cumulative incidence of pulmonary hypertension in specific subtypes of congenital heart disease shown by age group.
ASD indicates atrial septal defect; ECD, endocardial cushion defect; PA-VSD, pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; SV, single ventricle; TGA, transposition of great arteries; TOF, tetralogy of Fallot; and VSD, ventricular septal defect.

Table 6. Use of PH-Specific Therapies in Patients (n=190) With ACHD-PH

PH-specific therapy	ACHD-PH, n=190	Simple CHD, n=131	Severe CHD, n=22	Complex CHD, n=37
No drugs	97 (51.1)	77 (58.8)	12 (54.63)	8 (21.6)
PDE-5 antagonist	78 (41.1)	40 (30.5)	10 (45.5)	28 (75.7)
ERA alone or combination therapy	15 (7.9)	14 (10.7)	0	1 (2.7)

Data are expressed as n (%). ACHD indicates adult congenital heart disease; CHD, congenital heart disease; ERA, endothelin receptor antagonist; PDE-5, phosphodiesterase 5; and PH, pulmonary hypertension.

presented in Table 7, with the pretricuspid shunt (largely ascribed to ASD) displaying lower mortality relative to other disease subsets. However, this practice is still not recommended in the current guideline, and must be studied prospectively to ensure that long-term outlooks for patients with ASDs and PH are truly improved.

At present, Hjortshøj et al have analyzed cause-specific mortality in instances of Eisenmenger syndrome and found cardiac causes responsible for 50.1%, with another 10.5% of patients succumbing to thromboembolism and hemorrhage. In the REVEAL registry, Barst et al also confirmed cardiac causes in 65% of deaths attributable to CHD-PH.[25] Deaths in our patients with ACHD and PH were primarily of a cardiac nature (69.7%), accounting for 77.2% if combined with stroke; and cardiac-related mortality was significantly higher with versus without PH. Consequently, the importance of PH-specific therapy and appropriate cardiovascular medication in managing such patients cannot be overstated.

Predictors of Mortality in Patients With CHD-PH

Guidelines of the European Society of Cardiology have proposed 11 risk factors for patients with PH, specified as low, intermediate, or high risk[10]; Boucly et al have examined the usefulness of applying these factors to long-term outcomes in patients with idiopathic PH. The 3 noninvasive parameters (6-minute walk distance, proBNP level, and World Health Organization functional class) seemed to reasonably predict long-term outcomes.[33] In our previous registry study, we have also proved their merit in reliably predicting survival.[30]

Several prior studies have evaluated predictors of mortality in patients with CHD and PH. One multicenter retrospective study in Europe, based on a large cohort (n=1098) of this description, has identified older age, pretricuspid shunt, low SpO_2, absence of sinus rhythm, and pericardial effusion as mortality risk factors.[29] In the REVEAL trial, mortality risk factors included a shorter 6-minute walk distance, high right atrial pressure, elevated B-type natriuretic peptide level, and negative vasoreactivity test result.[25]

On this occasion, we used multivariable analysis to assess mortality risk in our patients with CHD and PH, identifying low SpO_2 and high uric acid as significant parameters associated with long-term mortality. Our data align well with findings of a multicenter European study,[29] although pretricuspid shunt and proBNP did not appear critical in this respect. The

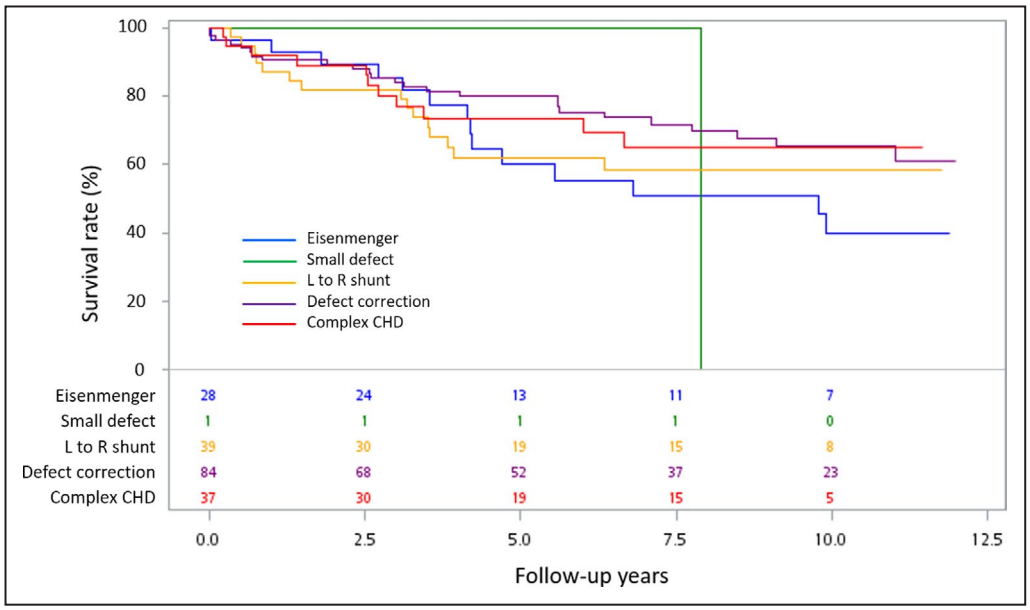

Figure 3. Kaplan-Meier survival curve for patients (n=190) with adult congenital heart disease and pulmonary hypertension, shown by subtypes of pulmonary hypertension.

Table 7. Cox Regression Analysis of Long-Term Survival in Patients (n=190) With ACHD-PH

	Univariate model		Multivariable model		
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	*P* value for test*
Age at PH onset	1.01 (1.00–1.02)	0.06			
Sex					
Men	1.37 (0.83–2.27)	0.22			
Complex CHD	0.91 (0.48–1.75)	0.79			
Pretricuspid shunt	0.71 (0.42–1.23)	0.22			
PH subclass					
Eisenmenger syndrome	1				
PH with small defects	1.54 (0.2–11.75)	0.68			
ACHD-PH+systemic-to-pulmonary shunts	0.81 (0.39–1.69)	0.58			
PH after defect correction	0.57 (0.30–1.10)	0.10			
Oxygen saturation†	0.93 (0.88–0.97)	0.01	0.93 (0.87–0.997)	0.04	0.62
Hemoglobin†	0.92 (0.83–1.02)	0.10			
Uric acid†	1.40 (1.19–1.65)	<0.01	1.54 (1.1–2.15)	0.01	0.18
ProBNP/100†	1.01 (1.01–1.02)	<0.01	1.01 (0.99–1.02)	0.26	0.29
PH drug					
No drug	1				
Sildenafil	0.69 (0.41–1.17)	0.17			
ERA/combination	0.46 (0.14–1.48)	0.19			
Genetic	0.57 (0.08–4.1)	0.58			

ACHD indicates adult congenital heart disease; CHD, congenital heart disease; ERA, endothelin receptor antagonist; HR, hazard ratio; PH, pulmonary hypertension; and ProBNP, pro-B-type natriuretic peptide.

*Supremum test for proportional hazards assumption.

†Oxygen saturation data in 126 (66.3%), hemoglobin data in 137 (72.1%), uric acid data in 107 (56.3%), and proBNP data in 134 (70.5%).

mortality associated with pretricuspid shunt was lower than rates established for other PH subsets in our study. As stated earlier, the fenestrated devices we use for ASD closures may explain the seeming contradiction. Despite the value of proBNP in predicting mortality from idiopathic PH,[33] it is not universally accepted in the context of CHD. High levels of N-terminal proBNP/B-type natriuretic peptide may conceivably be commonplace in patients with CHD and may vary considerably by subtype, weakening its predictive value.[30] However, not all patients in the present cohort had proBNP/B-type natriuretic peptide data, perhaps weakening the statistical power. Although low SpO_2 and high uric acid level offer the best means of prediction, the potential benefits of enhanced oxygen saturation via continuous O_2 or medication-induced lowering of uric acid levels have yet to be explored in this setting.

Study Limitations

As a retrospective study, control of all confounding factors implicit in regression analysis is impossible. Certain key factors, such as World Health Organization functional class and 6-minute walk distance, were not pursued at this time, and in the absence of digitalized cardiac catheterization data, echocardiography alone was insufficient to distinguish pulmonary artery hypertension from PH. Endothelin receptor antagonist use was also low in the present study, reflecting our National Health Insurance policy. Finally, low case and event numbers during subgroup analysis, especially in PA-VSD and SV defect groups, may have diminished the power of Cox regression analysis. To some degree, this limitation pertained to multivariable analysis as well (Table 7).

Because of ever-changing CHD corrective protocols (ie, earlier intervention), PH-specific therapy, and increasingly better outcomes in patients with CHD and PH, it is unrealistic to compare incidences and outcomes of PH among various studies. Hence, we cannot legitimately analyze potential differences.

CONCLUSIONS

The cumulative incidence of PH in this generous sampling of Asian patients with ACHD was comparable to that determined for Western countries. Subjects with versus without PH displayed a higher mortality rate. Medications targeting PH were underused and may account for the poor outcomes observed. Although

patients with complex CHD (SV and PA-VSD) are at the highest risk of PH, this group proved similar to other ACHD subsets in terms of survival.

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Disclosure

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Supplemental Material

Data S1

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