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Original Article

Systolic Blood Pressure, Cardiac Index and Eisenmenger Syndrome are Predictors of Mortality in Pulmonary Arterial Hypertension–associated with Congenital Heart Disease: An Analysis from the COHARD–PH Registry

Muflihatul Baroroh Rochmat,[1] Anggoro Budi Hartopo,[1] Budi Yuli Setianto,[1] Dyah Wulan Anggrahini,[1] Lucia Kris Dinarti.[1]

Abstract

Background: Pulmonary arterial hypertension (PAH) is a complication of left-to-right intracardiac shunt congenital heart disease (LtR-shunt CHD). There are several known predictors of mortality in PAH patients, however, predictors of mortality in LtR-shunt CHD-associated PAH need to be validated.

Objectives: We aimed to investigate the predictors of mortality among adult LtR-shunt CHD-associated PAH patients.

Methods: This retrospective cohort study included adult patients with LtR-shunt CHD-associated PAH retrieved from the COHARD-PH registry. Several baseline variables were selected as potential predictors of mortality, namely (1) clinical data: WHO-functional class, SaO2, 6-min walking distance, systolic blood pressure, and Eisenmenger syndrome; (2) laboratory data: hemoglobin and NT-pro BNP levels; (3) echocardiography data: pericardial effusion, defect size, and TAPSE; and (4) hemodynamic data: right atrial pressure, cardiac output and index, SvO2, and flow ratio. The mortality outcome was assessed from the cohort registry.

Results: A total of 124 subjects with LtR-shunt CHD-associated PAH were included. Sixteen subjects (12.9%) died during the follow-up period. The baseline variables that were significantly associated with mortality were lower systolic blood pressure, Eisenmenger syndrome, higher NT-pro BNP level, and lower cardiac output. The multivariable analysis showed that systolic blood pressure <100 mmHg (OR 10.99; 95% CI 2.54-47.51, p=0.001), cardiac index <2.5 L/min/m^2 (OR 8.13; 95% CI: 1.59-42.28, p=0.011) and Eisenmenger syndrome (OR 3.87; 95% CI: 1.06-14.07) were the independent predictors for mortality.

Conclusions: The systolic blood pressure <100 mmHg, cardiac index <2.5 L/min/m^2, and Eisenmenger syndrome were independent predictors of mortality among adults with LtR-shunt CHD-associated PAH.

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Keywords: *Congenital heart defects; pulmonary hypertension; mortality; Eisenmenger syndrome*.

[1] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Correspondence:
Anggoro Budi Hartopo, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia.
Email: a_bhartopo@ugm.ac.id

Introduction

Pulmonary arterial hypertension (PAH) is an advanced disease with ultimate morbidity as right heart failure and finally leading to cardiac arrest and death. Despite the availability of drugs and improvement in patient management, the data show that the last 3 years of survival rates among patients with PAH are still poor, with an estimate of around 55-75%.[1] Pulmonary arterial hypertension (PAH) is the most common complication faced by congenital heart disease (CHD) patients, especially those with large left-to-right intracardiac shunt (LtR-shunt CHD), which eventually leads to Eisenmenger syndrome.[2] Excessive blood flow, due to left-to-right shunts, through pulmonary circulation leads to endothelial dysfunction, vessel remodeling, raised vascular resistance, and eventually shunts flow reversal.[2] The LtR-shunt CHD-associated PAH consists of four distinctive phenotypes based on current classification all of which convey individual prognostic significance.[2,3]

The prevalence of LtR-shunt CHD-associated PAH in developing countries ranges from 1.6 to 12.5 cases per million adults, with 25-50% of patients with Eisenmenger syndrome.[2,4] The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry, the single-center hospital-based registry in Indonesia, found that more than 70% of registered patients with CHD had already developed PAH, who were mostly atrial septal defect (ASD).[5] Prognostic studies for CHD-associated PAH were limited. A current prospective study involving 91 adults (76 % with Eisenmenger syndrome) showed that the higher NT-proBNP level and reduced right ventricle function were independent predictors of mortality.[6] A retrospective study with a larger number of subjects (366 patients) showed that small defects with PAH (3 %) had the worst mortality prognostic, even as compared to Eisenmenger syndrome (26.8%), and found that WHO functional class III-IV, age at diagnosis < 10 years, elevated right atrial pressure > 15 mmHg, and baseline indexed PVR > 8 WU•m^2 were a predictor for mortality.[7] Based on the European Society of Cardiology (ESC) guideline for Pulmonary Hypertension, risk stratification for 1-year mortality has been developed,[3] however its utility in CHD-associated PAH needs evaluation. Since the Indonesian COHARD-PH registry had already collected prospective data, the prognostic study among Indonesians needs to be conducted to corroborate the previously reported data and include the ESC risk stratification model.

In the current study, we investigated the mortality outcome and its predictors among adult patients with LtR-shunt CHD-associated PAH. We retrieved the prospective data of the COHARD-PH registry, a single-center Indonesian registry. This study aimed to assess which predictors significantly predicted mortality among adult patients with LtR-shunt CHD-associated PAH.

Methods

This research was an observational study. The research design was a retrospective cohort study. The data were extracted from the COHARD-PH registry database.[5] The data of adult patients with LtR-shunt CHD-associated PAH were taken from the registry period of July 2012 – October 2020. This research protocol was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito Hospital, Yogyakarta, Indonesia with the number KE/FK/0381/EC/2021.

Subjects

The study was conducted by collecting data of demography, clinical presentation, laboratory measurement, echocardiographic result, and right heart catheterization (RHC) results at the index of diagnosis as baseline. Patients with LtR-shunt CHD-associated PAH who met the inclusion and exclusion criteria were collected from the COHARD-PH registry. The protocol of the COHARD-PH registry had been published elsewhere.[5]

The inclusion criteria were as follows: 1) patients registered in the COHARD-PH registry with complete baseline data required in this study, 2) patients with simple intracardiac LtR-shunt CHD, namely ASD, ventricle septal defects (VSD) or patent ductus arteriosus (PDA), 3) patients with uncorrected defects at the baseline, and 4) patients with PAH by hemodynamic criteria, namely mean pulmonary artery pressure (mPAP) >20 mmHg, pulmonary vascular resistance (PVR) ≥ 3 Wood unit, and pulmonary artery wedge pressure (PAWP) <15

Table 1. Baseline characteristics of subjects and their comparison between subjects who survived and subjects who died .

Characteristics	All subjects (n=124)	Survived (n=108)	Died (n=16)	P value
Age (years)*	32.5 (18-64)	33 (18-61)	28 (21-64)	0.526
Female sex, n (%)	107 (86.3)	92 (85.2)	15 (93.8)	0.696
Body mass index (kg/m2)*	17.6 (12.2-31.2)	17.7 (12.2-31.2)	16.7 (12.8-21.7)	0.125
Systolic blood pressure (mmHg)*	112.5 (80-179)	117.0 (85-179)	100.0 (80-140)	0.004
Heart rate (beat/min)*	89 (50-152)	89 (50-152)	96 (63-141)	0.602
SaO2 (%)*	95 (63-99)	95 (63-99)	93 (77-99)	0.309
WHO-fc I-II, n (%)	99 (79.8)	86 (79.6)	13 (81.3)	1.000
WHO-fc III-IV, n (%)	25 (20.2)	22 (20.4)	3 (18.8)	1.000
6 min walk distance (m)*	334 (79-580)	338 (79-580)	315 (158-420)	0.117
Haemoglobin (g/dL), mean±SD	14.47±2.27	14.47±2.28	14.49±2.32	0.976
NT-pro-BNP level (pg/mL)*	946.5 (33-35,000)	925 (33-35,000)	2,062 (237-11,674)	0.020
Pericardial effusion, n (%)	3 (2.4)	3 (2.8)	0 (0)	1.000
Defect size ≥2 cm, n (%)	94 (75.8)	80 (74.1)	14 (87.05)	0.353
TAPSE (mm)*	23.0 (9.0-39.0)	23.0 (9.0-39.0)	23.5 (15.0-34.0)	0.905
Left ventricle EF (%), mean±SD	71.19±9.59	71.24±9.75	70.81±8.71	0.868
mean PAP (mmHg), mean±SD	58.94±17.64	58.53±17.57	61.69±18.41	0.506
RA pressure (mmHg)*	8 (1.0-30.0)	9.0 (2.0-30.0)	7.0 (1.0-14.0)	0.602
Cardiac output (L/min)*	3.3 (1.6-100.67)	3.39 (1.60-100.67)	2.86 (1.95-6.10)	0.024
Cardiac index <2 (L/min/m2), n (%)	34 (27.4)	27 (25.0)	7 (43.8)	0.093
SvO2 (%)*	76 (32.0-99.0)	76.8 (32.0-99.0)	70.4 (56.0-90.0)	0.144
Flow ratio ≤1.5, n (%)	52 (41.9)	44.0 (40.7)	8.0 (50.0)	0.484
PAWP (mmHg)*	9.5 (2.0-17.0)	10.0 (2.0-15.0)	9.0 (2.0-17.0)	0.307
PVR (Woods Unit)*	12.5 (3.0-55.0)	11.8 (3.1-55.0)	16.0 (3.0-44.0)	0.188
Atrial septal defect, n (%)	113 (91.1)	98 (90.7)	15 (93.8)	0.660
Ventricle septal defect, n (%)	5 (4.0)	5 (4.6)	0 (0)	0.660
Patent ductus arteriosus, n (%)	6 (4.8)	5 (4.6)	1 (6.3)	0.660
Uncorrected defect, n (%)	112 (90.3)	96 (88.9)	16 (100)	0.362
Bidirectional shunt, n (%)	70 (56.5)	59 (54.6)	11 (68.8)	0.288
Eisenmenger syndrome, n (%)	29 (23.4)	21 (19.4)	8 (50.0)	0.012

*data presented as median (minimum and maximum values)
BP, systolic blood pressure; SaO2, arterial oxygen saturation; WHO-FC, World Health Organization class; TAPSE, tricuspid annular plane systolic excursion; RA, right atrial; SvO2, mixed veins oxygen saturation; EF, ejection fraction; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

mmHg as measured with RHC at rest.[8] The exclusion criteria were patients who did not have the required follow-up data or could not be contacted to confirm the follow-up or outcome data. Patients with Eisenmenger syndrome at baseline, with the criteria of large septal defects with dominant right-to-left shunts, presence of central cyanosis, secondary polycythemia, and chronic hypoxemia, were also included in this study.

Table 2. The bivariate analysis of variables as predictors of mortality in patients with LtR-shunt CHD-associated PAH.

Variables	Outcomes				p	QR	CI 95%	
	Survived n=108		Died n=16				Min	Max
	n	%	n	%				
Years of age					0.873	0.99	0.95	1.04
Sex					0.369	2.61	0.32	21.15
Females	92	85.2	15	93.7				
Males	16	14.8	1	6.2				
Shunt type								
Pre-tricuspid shunt	98	90.7	15	93.8	1.000	1.53	0.18	12.83
Post-tricuspid shunt	10	9.3	1	6.2				
Corrected defect								
Yes	12	11.1	0	0	0.999	0	0	∞
No	96	88.9	16	100				
Systolic blood pressure								
< 100 mmHg	12	11.1	7	43.7	0.003	6.22	1.96	19.76
≥ 100 mmHg	96	88.9	9	56.3				
WHO-functional class*								
I-II	86	79.6	13	81.3	0.880	0.90	0.24	3.44
III-IV	22	20.4	3	18.7				
6 min walk distance*								
< 165 meters	6	5.6	2	12.5	0.305	2.43	0.45	13.23
≥ 165 meters	102	94.4	14	87.5				
NT-pro BNP level*								
> 1,400 pg/mL	41	37.9	10	62.5	0.063	2.72	0.92	8.05
≤ 1,400 pg/mL	67	62.1	6	37.5				
Pericardial effusion*								
Yes	3	2.8	0	0	0.999	0	0	∞
No	105	97.2	16	100				
TAPSE								
< 18 mm	9	8,3	2	12.5	0,634	1,57	0,31	8,03
≥ 18 mm	99	91.7	14	87.5				
Right atrial pressure*								
≥ 8 mmHg	64	59.3	7	43.8	0.247	0.54	0.18	1.54
< 8 mmHg	44	40.7	9	56.2				
Cardiac index*								
< 2.5 L/min/m2	53	49.1	13	81.3	0.016	4.49	1.21	16.68
≥ 2.5 L/min/m2	55	50.9	3	18.7				
SvO2*								
≤ 65%	17	15.7	4	25.0	0.472	1.78	0.51	6.19
> 65%	91	84.3	12	75.0				
Flow ratio								
≤ 1.5	44	40.7	8	50.0	0.485	1.46	0.51	4.17
> 1.5	64	59.3	8	50.0				
Haemoglobin level								
< 12 g/dL	12	11.1	2	12.5	0.870	1.14	0.23	5.65
≥ 12 g/dL	96	88.9	14	87.5				
Defect size								
< 2 cm	28	25.9	2	12.5	0.255	0.41	0.08	1.91
≥ 2 cm	80	74.1	14	97.5				

SaO2								
< 90%	27	25.0	6	37.5	0.196	1.80	0.59	5.42
≥ 90%	81	75.0	10	62.5				
Eisenmenger syndrome								
Yes	21	19.4	8	50.0	0.007	4.14	1.39	12.32
No	87	80.6	8	50.0				

*variables derived from ESC guideline for risk stratification for prognostic of PAH3, which divided into two categories for this analysis

OR, odd ratio; CI, confidence interval; WHO-FC, World Health Organization class; 6MWD, 6-minute walk distance; TAPSE, tricuspid annular plane systolic excursion; CI, cardiac index; SvO2, mixed vein oxygen saturation; FR, flow ratio; Hb, hemoglobin; SaO2, arterial oxygen saturation.

Data collection and outcome assessment

Data collection was performed by extracting the data from the COHARD-PH registry database. Demography data were sex, age, and body mass index. Clinical data were systolic blood pressure, heart rate, WHO-functional class (WHO-fc), peripheral O2 saturation (SaO2), and 6-minute walking distance. Systolic blood pressure and SaO2 were measured from the upper extremity with a calibrated digital tensimeter and pulse oximeter respectively, during outpatient clinic visits at index of diagnosis (mean value from three measurements in the same visit). A 6-minute walking distance was derived from a 6-minute walking test performed in the hospital's Cardiac Rehabilitation Division by trained nurses. The laboratory data were hemoglobin and NT-pro BNP levels, performed with an automatic hemocytometer (Sysmex, Japan) and electrochemiluminescence immunoassay (Roche Diagnostic, Germany) respectively. The echocardiography data were collected from transthoracic (TTE) and transesophageal (TOE) echocardiography data. The hemodynamic data were collected from the RHC procedure performed in our hospital. All baseline data were collected at the index of PAH diagnosis. The index of PAH diagnosis was defined as a starting point of observation.

The outcome of this study was mortality, which was defined as death from any cause or all-cause mortality during follow-up. Subjects who underwent defect correction during follow-up were still included and analyzed in this study. The data of mortality was retrieved from the registry database. For outcome data completion, the subjects or family members were contacted by telephone or messages to confirm the outcome during the follow-up period (the end of the follow-up was October 2020). Therefore, the length of observation was ranging from 6 months to 105 months (8 years and 9 months).

Statistical analysis

The SPSS v.23 (IBM Corp., Armonk, N.Y., U.S.A) statistics software was used for analysis. The numerical data were assessed by normality test with the Kolmogorov-Smirnov test, and $p > 0.05$ indicated the data were normally distributed. Independent T-tests and Mann Whitney-U tests were applied to analyze the differences between groups among numerical data. A bivariate test with a logistic regression analysis was performed to analyze the association between predictors and mortality. The bivariate association which had a p-value < 0.25 was subsequently included in the multivariable analysis for the multiple logistic regression analysis. The independent association between predictors and mortality was deemed significant if there was a p-value < 0.05 in the multivariable analysis.

Results

Subjects and baseline characteristics

A total of 184 patients with LtR-shunt CHD-associated PAH were recorded in the COHARD-PH registry. As many as 60 patients were excluded. They were excluded due to: the absence of 6 min walking distance data (n=26), the absence of NT-pro BNP data (n=16), the absence of follow-up data (n=10), the absence of both 6 min walking distance data and NT pro-BNP data (n=6), and absence of all 6 min walking

Table 3. The multivariate analysis for predictors of mortality in LtR-shunt CHD-associated PAH.

Predictors	p-value	Adjusted OR	CI 95%	
			Min	Max
Systolic blood pressure <100 mmHg	0.001	10.99	2.54	47.51
NT-pro BNP level >1,400 pg/mL	0.271	2.01	0.58	6.95
Right atrial pressure ≥ 8 mmHg	0.139	0.36	0.09	1.38
Cardiac index < 2.5 L/min/m2	0.013	8.13	1.56	42.28
SaO2 < 90%	0.309	2.06	0.51	8.34
Eisenmenger syndrome	0.040	3.87	1.06	14.07

*OR, odd ratio; CI, confidence interval; SaO2, arterial oxygen saturation

distance, NT-pro BNP data and follow-up data (n=1). Eventually, 124 LtR-shunt CHD-associated PAH subjects were analyzed in this study. Among them, 16 subjects died during follow-up (12.9%). The range of the follow-up period was 6 months to 105 months (8 years 9 months).

The subjects had ages ranging from 18 to 64 years old. There was no age difference between subjects who died and those who survived. Females predominated in the subjects who survived (85.2%) and those who died (93.8%). Based on the type of CHD, subjects who survived consisted of ASD (90.7%), VSD (4.6%), and PDA (4.6%). In subjects who died, the CHD was ASD (93.8%) PDA (6.3%), and no VSD. Eisenmenger syndrome was significantly higher among subjects who died (50.0% vs. 19.4%, p=0.012). Twelve subjects underwent shunt correction during follow-up, and all of them were in the survivor group. The systolic blood pressure was significantly lesser in those who died (median: 117 mmHg vs. 100 mmHg, p=0.04). The level of NT-proBNP was significantly elevated in those who died as compared to survivors (median: 2,062 pg/mL vs. 925 pg/mL, p=0.020). The hemodynamic data showed that cardiac output was significantly lower in subjects who died as compared to those who survived (median: 2.86 L/min vs. 3.39 L/min). There was a trend that more subjects who died had reduced cardiac index <2 L/min/m2 as compared to subjects who survived (43.8% vs. 25.0%, p=0.093). Based on ESC risk stratification, cardiac index <2 L/min/m2 is categorized as high risk. The baseline characteristics of all subjects, and data concerning subjects who survived and died are shown in Table 1.

The analysis for predictors of mortality

For bivariate analysis, several variables derived from the ESC guideline of risk stratification and prognostic factors were converted into two categorical data, namely WHO f.c, 6 min walking distance, NT-pro-BNP level, presence of pericardial effusion, right atrial pressure, cardiac index and SvO2.[3,7] The results of the bivariate analysis for predictors of mortality are shown in Table 2. The systolic blood pressure <100 mmHg (odds ratio: 6.22; 95% CI: 1.96-19.76, p=0.003), cardiac index <2.5 L/min/m2 (odds ratio: 4.49; 95% CI: 1.21-16.68, p=0.016) and Eisenmenger syndrome (odds ratio: 4.14; 95% CI: 1.39-12.32, p=0.007) were the statistically significant predictors associated with mortality. The NT-pro-BNP level >1400 pg/mL (p=0.063), right atrial pressure ≥ 8 mmHg (p=0.247), and SaO2 <90% (p=0.196), along with systolic blood pressure, cardiac index, and Eisenmenger syndrome, were included for further analysis with multivariable logistic regression test.

The multivariable analysis showed that systolic blood pressure <100 mmHg (adjusted odds ratio: 10.99; 95% CI: 2.54-47.51, p=0.001), cardiac index <2.5 l/min/m2 (adjusted odds ratio: 8.13; 95% CI: 1.59-42.28, p=0.011) and the presence of Eisenmenger syndrome (adjusted odds ratio: 3.87; 95% CI: 1.06-14.07, p=0.040) were the independent predictors for mortality (as shown in table 3).

Discussion

The results of this study showed that there were three independent predictors for mortality of adult

patients with left-to-right intracardiac shunt CHD-associated PAH, namely systolic blood pressure <100 mmHg, cardiac index <2.5 L/min/m2 and the presence of Eisenmenger syndrome. The results highlight the importance of these three parameters at the index of diagnosis to be considered as risk modifiers for mortality, therefore the intensification of drug therapy must be emphasized.

In this study, the type of underlying shunt-defect CHD was divided into three simple defects, namely ASD, VSD, and PDA. Most subjects had ASD (pre-tricuspid shunt) followed by PDA and VSD (post-tricuspid shunt). Most subjects who died were ASD, however, this type was also observed in subjects who survived. All subjects who died had uncorrectable defects, based on RHC parameters, while in subjects who survived, 88.9% were uncorrectable defects. Therefore, all subjects who had defect correction (11.1%) survived. Supporting our study, the previous study involving a large number of patients with simple CHD, moderately complex CHD, and severely complex CHD, the mortality rate was higher than average in patients with ASD.[7,9,10]

The bidirectional shunt, detected by TTE and TOE, was more prevalent in subjects who died. Eisenmenger syndrome was an independent predictor of mortality in this study. This agrees with a previous study which showed that among patients with Eisenmenger syndrome, the location of the defect has prognostic implications between pre-tricuspid, post-tricuspid, and complex lesions.[9] It showed that the pre-tricuspid defect, such as ASD, had a lower 5-year survival rate as compared with the post-tricuspid defect and even the complex lesion group.[7] The predictors of mortality in the previous study were: WHO f.c III/IV, age < 10 years old at baseline, PAH with a small defect, right atrial pressure >15 mmHg, and PVR >8 Woods Unit at baseline measurement.[7,10] However, our study found different independent mortality predictors from a previous study in the same region.

The NT-pro-BNP level was significantly higher in subjects who died. Despite its non-statistical significance, the NT-pro-BNP level >1,400 pg/mL had a mortality risk two times greater in our study. Previous study showed that an increase in NT-pro-BNP was a predictor of PAH mortality in a single model and the multivariate model, increased NT-pro BNP remained independently associated with a higher hazard of death.[10] The NT-pro-BNP level at baseline reflects the risk stratification of patients with LtR-shunt CHD-associated PAH, and those who had higher NT-pro-BNP levels would have to intensify therapy which affected the outcome at follow-up. Therefore, the prognostic value of NT-pro BNP level may be more significant if serial measurement was performed during follow-up.

Our study showed that cardiac index value <2.5 l/min/m2, which is associated with parameters of intermediate and high-risk prognostic stratification in PAH3, had independently increased the risk of mortality in LtR-shunt CHD-associated PAH. Based on cardiac index, there are three risk categories: low risk (cardiac index ≥2.5 l/min/m2), intermediate risk (cardiac index 2.0-2.4 l/min/m2, and high risk (cardiac index <2.0 l/min/m2). Because of the insufficient number of subjects, we divided into two categories by combining intermediate and high-risk into one group (cardiac index <2.5 l/min/m2). Other previous studies indicated similar findings.[1,9,10,11] Cardiac index was measured during RHC, which is an invasive procedure not always available in non-PH centers. This measurement was usually performed only at the baseline or diagnostic level, therefore repetitive measurement is not feasible, even in several PH centers in our region. Therefore, the baseline cardiac index calculation must be performed as an important predictor for mortality in adult patients with LtR-shunt CHD-associated PAH.

Our study indicated that baseline systolic blood pressure was an independent predictor for mortality. Earlier studies showed that systolic blood pressure <100 mmHg was a significant independent risk factor for mortality in PAH patients after adjusting for age and underlying diagnosis.[12] The reduced systolic blood pressure closely correlated with lower blood sodium levels, which also posed as a significant predictor for mortality.[12] This implicated the neurohormonal activation in the setting of low cardiac output.[12] In PAH, the sympathetic activation was exaggerated and suggested to influence the hemodynamic, a process similar to left heart failure.[13] Deteriorating right ventricular function in PAH-induced sympathetic activation, which if it lasts for a long time may change the myocardial structure and function. Eventually sustained low blood pressure, along with life-threatening arrhythmias, affects the fatal outcomes in these patients.[14,15] Once reduced systolic blood pressure occurred in the index of PAH diagnosis,

it informed the future risk of mortality.

The result of our study may represent the broader population of CHD-associated PAH which is still prevalent in Indonesia. However, national data regarding the prevalence and the prognosis of different CHD-associated PAH phenotypes and the role of risk stratification in prognostication is necessary to be collected and analyzed.

There are several limitations of this study. Firstly, the study used a retrospective cohort analysis design and was based on a single-center registry. Second, there were several data that were not fully recorded in the medical records. Third, with a fairly long follow-up period from July 2012 to October 2020, there were a number of patients who were lost to follow-up so it was not known whether these patients survived or died. Fourth, for patients with PDA, the recording of the lower extremity for oxygen saturation and blood pressure was necessary to be analyzed.

Conclusions

There were three independent predictors for mortality in adult patients with left-to-right intracardiac shunt CHD-associated PAH, namely systolic blood pressure <100 mmHg, cardiac index <2.5 L/min/m2 and the presence of Eisenmenger syndrome at the index of PAH diagnosis.

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Declaration of Conflict of Interest

All the authors declare no conflict of interest.

List of Abbreviations

ASD	Atrial Septal Defect
CHD	Congenital Heart Disease
NT-ProBNP	N-Terminal Pro-B-Type Natriuretic Peptide
PDA	Patent Ductus Arteriosus
PAH	Pulmonary arterial hypertension
RHC	Right Heart Catheterization
VSD	Ventricle Septal Defects

References

1. Farber HW, Miller DP, Poms AD, Badesch DB, Frost AE, Muros-Le Rouzic E, et al. Five-Year outcomes of patients enrolled in the REVEAL Registry. *Chest*. 2015;148(4):1043-54.
2. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42(6):563-645.
3. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al.; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.
4. Ruopp NF, Cockrill BA. Diagnosis and treatment of pulmonary arterial hypertension: A review. *JAMA*. 2022;327(14):1379-91.
5. Dinarti LK, Hartopo AB, Kusuma AD, Satwiko MG, Hadwiono MR, Pradana AD, et al. The COngenital HeARt Disease in adult and Pulmonary Hypertension (COHARD-PH) registry: a descriptive study from single-center hospital registry of adult congenital heart disease and pulmonary

hypertension in Indonesia. *BMC Cardiovasc Disord*. 2020;20(1):163.
6. Schuuring MJ, van Riel AC, Vis JC, Duffels MG, van Dijk AP, de Bruin-Bon RH, et al. New predictors of mortality in adults with congenital heart disease and pulmonary hypertension: Midterm outcome of a prospective study. *Int J Cardiol*. 2015;181:270-6.
7. Vijarnsorn C, Durongpisitkul K, Chungsomprasong P, Bositthipichet D, Ketsara S, Titaram Y, et al. Contemporary survival of patients with pulmonary arterial hypertension and congenital systemic to pulmonary shunts. *PLoS One*. 2018;13(4):e0195092.
8. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Hemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913.
9. Oliver JM, Gallego P, Gonzalez AE, Garcia-Hamilton D, Avila P, Yotti R, et al. Risk factors for excess mortality in adults with congenital heart diseases. *Eur Heart J*. 2017;38(16):1233-1241.
10. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2012;39(3):589-96.
11. Leopold JA, Kawut SM, Aldred MA, Archer SL, Benza RL, Bristow MR, et al. Diagnosis and treatment of right heart failure in pulmonary vascular diseases: A National Heart, Lung, and Blood Institute Workshop. *Circ Heart Fail*. 2021;14(6):e007975.
12. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J*. 2017;50(2):1700740.
13. Thenappan T, Mark LO, John JR, Stephen LA. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ*. 2018;360:j5492.
14. Ciarka A, Doan V, Velez-Roa S, Naeije R, van de Borne P. Prognostic significance of sympathetic nervous system activation in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010;181(11):1269-75.
15. Liu RX, Luo Q, Qiao H, Yu J, Zhang QL, Wang P, et al. Clinical significance of the sympathetic nervous system in the development and progression of pulmonary arterial hypertension. *Curr Neurovasc Res*. 2017;14(2):190-8.