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Original Article

Predictors of pulmonary hypertension in children with left-to-right shunting in acyanotic congenital heart disease

Weny Inrianto, Indah K. Murni, Ida Safitri

Abstract

Background Left-to-right shunting in acyanotic congenital heart disease (CHD) is the most common type of defect in childhood heart disease. Limited access to specialist health services causes delays in CHD management. In limited resource settings, identification of factors that influence the occurrence of pulmonary hypertension is important in order to decide which patients should be prioritized for defect closure to prevent further complications.
Objective To determine predictive factors of pulmonary hypertension after a left-to-right shunt CHD diagnosis.
Methods This retrospective cohort study included children aged 1 month to 17 years with isolated atrial septal defect, or ventricular septal defect, or patent ductus arteriosus. Potential predictors studied were iron deficiency anemia, mitral regurgitation, pneumonia, and heart failure. Bivariate analysis was done with Chi-square test and multivariate analysis was done with Cox regression to determine the hazard ratio.
Results Pulmonary hypertension occurred in 68 of 176 subjects. Iron deficiency anemia, mitral regurgitation, and pneumonia were not predictive factors of pulmonary hypertension. However, heart failure was a significant predictive factor for pulmonary hypertension, with a hazard ratio of 4.1 (95%CI 2.2 to 7.5; P=0.001).
Conclusions Heart failure is a predictive factor of pulmonary hypertension in children with left-to-right shunting in acyanotic CHD. **[Paediatr Indones. 2021;61:119-24 ; DOI: 10.14238/pi61.3.2021.119-24**].

Keywords: *pulmonary hypertension; congenital heart disease; predictor factors; left-to-right shunting*

Left-to-right shunting in acyanotic CHD, such as atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA) are the most common types of abnormalities in pediatric heart disease. Delayed defect closure results in pulmonary hypertension. The 5-year survival rate of pulmonary hypertension among children with CHD is 74%.[1] Increased pulmonary blood flow causes stretching of the pulmonary vasculature, which in turn stimulates vasoconstriction, ultimately leading to thickening of the vascular walls and narrowing of the pulmonary vascular lumen. These vascular changes persist if adequate intervention is not done. As changes occur in the shunting from right to left, the patient may become cyanotic. Eisenmenger's syndrome increases mortality four times higher than that of a healthy population.[2] Limited facilities, late diagnoses, and family economic factors are obstacles to closing the shunt in a timely manner, increasing patient susceptibility to pulmonary hypertension.

From the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada/Department of Pediatrics Dr. Sardjito Hospital, Yogyakarta, Central Java, Indonesia.

Corresponding author: Indah K. Murni. Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Department of Pediatrics Dr. Sardjito Hospital. Jl Kesehatan No. 1 Sekip Sinduadi, Yogyakarta, DIY 55284, Indonesia. Phone: (0274) 587333/631190 ext. 546. Email: indah.kartika.m@ugm.ac.id.

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Limited access to specialized health services is a major factor contributing to delays in CHD management.[3] Identification of factors that influence the occurrence of pulmonary hypertension can be useful in deciding which patients should be prioritized for defect closure to prevent further complications, especially in limited resource settings. Factors related to pulmonary hypertension in previous studies were inflammation, lower respiratory tract infection (bronchiolitis, pneumonia, episodic wheezing), gene mutation, iron deficiency, mitral regurgitation, and increased pulmonary blood flow in congestive heart failure.[4-8] We aimed to determine the predictors of pulmonary hypertension in children with acyanotic CHD with a left-to-right shunt.

Methods

This retrospective cohort study included children with acyanotic CHD left-to-right shunting who were recruited from the Pediatric Cardiology Clinic of Dr. Sardjito Hospital, Yogyakarta, from January to December 2017. Patients aged between 1 month to 17 years with isolated atrial septal defect, or ventricular septal defect, or patent ductus arteriosus were included. Patients who had abnormalities that limited blood flow to the lungs, such as pulmonary stenosis, disorders that limited systemic blood flow such as aortic stenosis, aortic coarctation, mitral stenosis, as well as patients with rheumatic heart disease, cardiomyopathy, and infective endocarditis were excluded. The minimum required sample size for a prognostic study with 30% pulmonary hypertension incidence and four predictive factors was 170 subjects.[9-11] Patients were followed up for 5 years beginning from the time of diagnosis, based on echocardiography. Patient data were obtained from medical records, which included the following possible predictors of pulmonary hypertension: iron deficiency anemia, mitral regurgitation, pneumonia, and heart failure.

Subjects who had peak tricuspid regurgitation velocity >2,8 m/s were considered to have pulmonary hypertension.[12] Iron deficiency anemia was defined as low hemoglobin level according to *World Health Organization* (WHO) criteria with microcytic, hypochromic, and red cell distribution width (RDW) >14.[13-15] Mitral regurgitation was the backflow of blood from the left ventricle to the left atrium through the mitral valve based on echocardiography. Pneumonia was a documented period of lower respiratory tract infection coded J12-J18 according to ICD-10 in the medical record. Heart failure was assessed based on the modified Ross criteria.[16]

Subjects were randomly selected by pairing with random numbers generated by *MS Office Excel*. The normality of data distribution was tested by Kolmogorov-Smirnov test. Chi-square tests were done

Table 1. Basic characteristics of subjects

Characteristics	Pulmonary hypertension (n = 68)	No pulmonary hypertension (n = 108)
Male, n (%)	25 (36.8)	59 (54.6)
Median age at diagnosis (IQR), months*	16 (73)	14.5 (56)
Median weight (IQR), kg*	7.2 (9.3)	8.7 (10)
Height (SD), cm†	96.6 (33.7)	99.3 (31.4)
Median heart rate (IQR), times/minute*	115 (35)	113 (24)
Median respiratory rate (IQR), times/minute*	30 (18)	28 (10)
Mean hemoglobin (IQRSD), g/dL†	11.7 (1.7)	11.8 (1.4)
Mean corpuscular volume (SD), fL†	78.8 (11.1)	80.1 (9.5)
Mean corpuscular hemoglobin (SD), pg†	26.5 (3.8)	26.9 (3.3)
Median red cell distribution width (IQR), %*	15.5 (3)	15 (2.6)
Defect type, n (%)		
Atrial septal defect	26 (38.2)	25 (23.1)
Ventricular septal defect	22 (32.4)	58 (53.7)
Patent ductus arteriosus	20 (29.4	25 (23.2)

*Median (interquartile range) for data whose distribution was skewed
†Mean (standard deviation) for data whose distribution was normal

to assess potential predictive factors of pulmonary hypertension, and analyses were continued by multivariable Cox regression for predictors that had a Chi-square result of P<0.25, to determine adjusted hazard ratios (HR). The study protocol was approved by the Medical and Health Research Ethics Committee of the Universitas Gadjah Mada, Faculty of Medicine, Public Health and Nursing.

Results

The basic characteristics of subjects are shown in **Table 1**. Of 176 study subjects, 41 subjects (23.3%) had mitral regurgitation, which of that one subject (0.6%) had severe mitral regurgitation, 51.2% had mild mitral regurgitation, 4.9% had moderate mitral regurgitation, 22% had trivial mitral regurgitation, and 19.5% had an unknown degree of mitral regurgitation . Twenty three subject had iron deficiency anemia which mean hemoglobin was 10.1 g/dL and the median age was 15 months. Heart failure occurred at a median age of 17 months. Pulmonary hypertension occurred at a median age of 27 months.

All 176 subjects were analyzed in Chi-square, except for iron deficiency anemia; there were 59 missing data due to no record of hemoglobin concentration, thus Chi-square analysis of this variable was calculated in a total of 117 subjects. We calculate the hazard ratio adjusted with variables that have a P value <0.25. The result showed that heart failure was a significant predictive factor for pulmonary hypertension, with a hazard ratio of 4.1 (**Table 2**). Pulmonary hypertension in both groups with and without heart failure mostly occurred within 3 years of age. In subjects with heart failure, the survival of pulmonary hypertension decreased from about 70% in the first year to 40% within three years. Whereas in subjects without heart failure, the survival of pulmonary hypertension was about 80% in three years (**Figure 1**).

Table 2. Predictors of pulmonary hypertension in children with acyanotic CHD

Variables	Pulmonary hypertension (n=68)	No pulmonary hypertension (n=68)	HR† (95%CI) (n=108)	P value
Iron deficiency anemia, n (%)	11‡ (21.6)	12§ (18.2)		0.65
Mitral regurgitation, n (%)	20 (29.4)	21 (19.4)	1.3 (0.7 to 2.6)	0.13
Pneumonia, n (%)	10 (14.7)	13 (12)		0.61
Heart failure, n (%)	29 (42.6)	10 (9.3)	4.1 (2.2 to 7.5)	0.001

*Chi-square; †Cox regression with adjusted hazard ratio; ‡n=11/51, 17 missing; §n=12/66, 42 missing

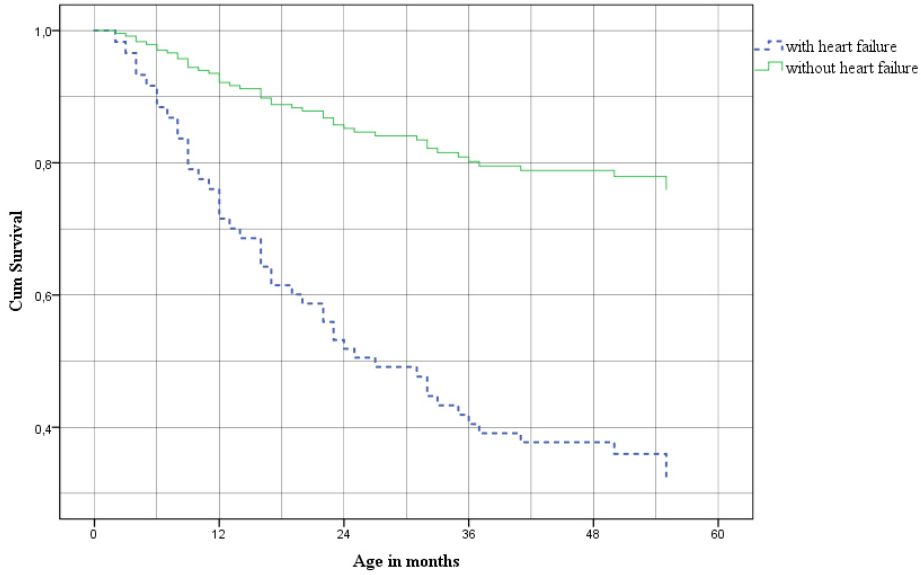

Figure 1. Survival analysis for pulmonary hypertension with regards to heart failure

Discussion

There was a similar proportion of males and females among our subjects. The most common type of defect was VSD (45.5%), similar to the epidemiological profile of acyanotic CHD at the same hospital in 2014. At that time, 47.6% of CHD defects were VSD.[17] Pulmonary hypertension occurred in 38.6% of subjects, greater than the incidence of pulmonary hypertension in the entire population of ASD, VSD, Eisenmenger syndrome, and other cyanotic CHDs (28%).[18] Heart failure was the one independent factor predictive of pulmonary hypertension in our subjects (P=0.001).

Iron deficiency anemia was found in 23/117 (19.7%) of subjects, smaller than the prevalence of anemia in children aged 1-14 years, which was between 26-28%.[19] This difference may have been due to the classification of anemia in the basic health survey (*Riskesdas 2013*) by Ministry of Health Republic of Indonesia as that report included all anemia cases without distinguishing the cause.[14] In addition, there may have been differences in the diagnostic criteria for anemia. Chi-square analysis revealed no significant difference in iron deficiency anemia between the with and without pulmonary hypertension groups. Previous studies have shown an association between iron deficiency and the incidence of pulmonary hypertension, including increasing pulmonary arterial pressure.[8,20-24] Differences in determining the parameters of iron deficiency in the previous studies that might have affected the results. We used an erythrocyte index showing hypochromic microcytic anemia with red distribution width of more than 14% to determine the presence of iron deficiency. Moreover, serum iron levels were not routinely examined in our patients with CHD. Hypochromic microcytic anemia is a late manifestation of iron deficiency, meaning that the erythrocyte index and hemoglobin levels can be normal at the early onset of iron deficiency. Thus, there was possible bias as some subjects may have been iron deficient, but not yet anemic. Hence, iron deficiency could have been present in more than the number of subjects with iron deficiency anemia.

Mitral regurgitation was found in 23.3% of subjects. The proportions of mitral regurgitation in the pulmonary hypertension and non-pulmonary hypertension groups did not differ significantly. Pulmonary hypertension among children with mitral regurgitation may have been caused by backward fluid overload, leading to left atrial enlargement and left ventricular hypertrophy. As a maladaptive response to the left ventricle deterioration, left ventricular contractility decreases, while the systolic and the right atrial pressures increase. Increased right atrial pressure is passively delivered to the pulmonary vein, which causes interference with the alveolar capillaries resulting in capillary leakage and pulmonary edema. Pulmonary hypertension reportedly occurs in 23% of patients with severe mitral regurgitation.[25] Mitral regurgitation in this study was mostly trivial (22%) and mild (51.2%), thus possibly not high enough to affect pulmonary vein pressure.

Pneumonia occurred in 14.8% of subjects, of whom 50% had pulmonary hypertension. The incidence of pulmonary hypertension in our study was lower than reported by the pediatric intensive care unit (PICU) of Santa Clara Hospital in Bogota, Colombia, in which 72.7% of subjects with pneumonia had pulmonary hypertension. Their pneumonia with pulmonary hypertension patients had a 7.5 times higher risk of death compared to pneumonia without pulmonary hypertension.[26] Differences in pneumonia severity may have affected the result, which has yet to be investigated.

Pulmonary arterial pressure increased in patients with acyanotic CHD with the advancement of age. All the children above 5 years of age had moderate to severe pulmonary arterial hypertension.[9] In general, conditions that occur with pressure overload and high flow, such as VSD, increase the possibility of pulmonary hypertension.[27] Diuretics (furosemide or spironolactone) are one of the main therapies for patients with pulmonary hypertension who have symptoms of right heart failure.[27,28] Pulmonary hypertension in acyanotic CHD with left-to-right shunting occurs at various ages depending on the location of the lesion. In pre-tricuspid lesions, such as ASD, shunting causes volume overload to the right atrium and pulmonary circulation, but does not immediately increase pulmonary arterial pressure. Pulmonary hypertension usually occurs in the fourth decade of life. In post-tricuspid lesions, such as VSD and PDA, shunts occur at high pressure, causing volume overload in the left ventricle and volume overload or pressure in the pulmonary circulation. This condition usually causes pulmonary hypertension

in the first year of life.[29] The principle of congestive heart failure in children is that of volume overload in the pulmonary circulation. Therefore, if heart failure is not well controlled, pulmonary hypertension will occur. This pathomechanism is consistent with our results, which showed that the presence of heart failure was associated with four times higher incidence of pulmonary hypertension. The optimal time to close the defect is before two years of age, in order to avoid permanent pulmonary vascular remodeling.[30] In Dr. Sardjito Hospital, Yogyakarta, the median age of defect closure was two years. Our results reinforce the idea that closing the defect sooner for patients with symptoms of heart failure, then the survival of pulmonary hypertension decreases from 70% in the first year to 40% within three years. Unfortunately, in low- and middle-income countries with limited resources, defect closure is often delayed for several months to years. Some real-world concerns in developing countries such as Indonesia related to cardiac defect closure include competing priorities, poor organizational structural, limited financial resources, and lack of trained human resources which may contribute to delays in treatment. Also, major adverse events and mortality following cardiac surgery are high.[31] Other challenges for Indonesia involve long distances between the major inhabited islands, with only six institutions with comprehensive facilities to care for children with CHD.[32] Thus, defect closure should be prioritized for patients with symptoms of heart failure that cannot be controlled with medication, in order to prevent further complications.

In conclusion, left-to-right shunting in acyanotic CHD with heart failure has four times increased risk of pulmonary hypertension. Iron deficiency anemia, mitral regurgitation, and pneumonia are not significant predictors of pulmonary hypertension. Since heart failure is an independent predictor of pulmonary hypertension in acyanotic CHD patients with left-to-right shunts, we recommend prioritizing defect closure for these particular patients.

Conflict of Interest

None declared.

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References

1. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125:113-22. DOI: 10.1161/CIRCULATIONAHA.111.026591.
2. Frank DB, Hanna BD. Pulmonary arterial hypertension associated with congenital heart disease and Eisenmenger syndrome: current practice in pediatrics. Minerva Pediatr. 2015;67:169-85. PMC: 4382100.
3. Adatia I, Kothari SS, Feinstein JA. Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. Chest. 2010;137:52-61. DOI: 10.1378/chest.09-2861.
4. Bardi-Peti L, Ciofu EP. Pulmonary hypertension during acute respiratory diseases in infants. Mædica. 2010;5:13-9. PMC: 3150087.
5. Dimopoulos K, Wort SJ, Gatzoulis MA. Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J. 2014;35:691-700. DOI: 10.1093/eurheartj/eht437.
6. Pan X, Zheng Z, Hu S, Li S, Wei Y, Zhang Y, *et al.* Mechanisms of pulmonary hypertension related to ventricular septal defect in congenital heart disease. Ann Thorac Surg. 2011;92:2215-20. DOI: 10.1016/j.athoracsur.2011.07.051
7. Rahayuningsih SE. Hubungan antara hipertensi pulmonal pada defek septum atrium sekundum dan mutasi gen. Sari Pediatr. 2009;11:113-7. DOI: 10.14238/sp11.2.2009.113-7
8. Rhodes C, Howard L, Busbridge M, Ashby D, Kondili E, Gibbs J, *et al.* Iron deficiency and raised hepcidin in idiopathic pulmonary arterial hypertension: clinical prevalence, outcomes, and mechanistic insights. J Am Coll Cardiol. 2011;58:300-9. DOI: 10.1016/j.jacc.2011.02.057.
9. Barua C, Barua SK, Hossain MZ, Karim T. Pulmonary

hypertension in children with congenital left to right cardiac shunt anomalies. Chattagram Maa-O-Shishu Hosp Med Coll J. 2015;14:31-7. DOI: 10.3329/cmoshmcj.v14i2.25714.

10. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. J Clin Epidemiol. 1995;48:1503-10. DOI: 10.1016/0895-4356(95)00048-8.
11. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis I. Background, goals, and general strategy. J Clin Epidemiol. 1995;48:1495-501. DOI: 10.1016/0895-4356(95)00510-2.
12. Parasuraman S, Walker S, Loudon BL, Gollop ND, Wilson AM, Lowery C, *et al.* Assessment of pulmonary artery pressure by echocardiography-A comprehensive review. IJC Hear Vasc. 2016;12:45-51. DOI: 10.1016/j.ijcha.2016.05.011
13. Ozdemir N. Iron deficiency anemia from diagnosis to treatment in children. Turk Pediatr Ars. 2015;50:11-9. DOI: 10.5152/tpa.2015.2337
14. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. World Health Organization. 2011. [cited 2021 April 28]. Available from: http://www.who.int/vmnis/indicators/haemoglobin.pdf.
15. Wu AC, Lesperance L, Bernstein H. Screening for iron deficiency. Pediatr Rev. 2002;23:171-8. DOI: 10.1542/pir.23-5-171
16. Ross RD. The Ross classification for heart failure in children after 25 years: A review and an age-stratified revision. Pediatr Cardiol. 2012;33:1295-300. DOI: 10.1007/s00246-012-0306-8
17. Ismail MT, Hidayati F, Krisdinarti L, Noormanto, Nugroho S, Wahab AS. Epidemiological profile of congenital heart disease in a national referral hospital. Acta Cardiol Indones. 2015;1:66-71. DOI: 10.22146/aci.17811.
18. Mulder BJM. Changing demographics of pulmonary arterial hypertension in congenital heart disease. Eur Respir Rev. 2010;19:308-13. DOI: 10.1183/09059180.00007910.
19. Badan Penelitian dan Pengembangan Kesehatan. Riset kesehatan dasar (RISKESDAS) 2013. Jakarta: Kemenkes RI; 2013.
20. Soon E, Treacy CM, Toshner MR, MacKenzie-Ross R, Manglam V, Busbridge M, *et al.* Unexplained iron deficiency in idiopathic and heritable pulmonary arterial hypertension. Thorax. 2011;66:326-32. DOI: 10.1136/thx.2010.147272
21. Sutendra G, Bonnet S. The iron paradigm of pulmonary arterial hypertension: Popeye knows best. Circ Res. 2015;116:1636-8. DOI: 10.1161/circresaha.115.306440.
22. Ruiter G, Lankhorst S, Boonstra A, Postmus PE, Zweegman S, Westerhof N, *et al.* Iron deficiency is common in idiopathic pulmonary arterial hypertension. Eur Respir J. 2011;37:1386-91. DOI: 10.1183/09031936.00100510
23. Plesner LL, Schoos MM, Dalsgaard M, Goetze JP, Kjøller E, Vestbo J, *et al.* Iron deficiency in COPD associates with increased pulmonary artery pressure estimated by echocardiography. Heart Lung Circ. 2017;26:101-4. DOI: 10.1016/j.hlc.2016.04.020.
24. Cotroneo E, Ashek Ac, Wang L, Wharton J, Dubois O, Bozorgi S, *et al.* Iron homeostasis and pulmonary hypertension: iron deficiency leads to pulmonary vascular remodeling in the rat. Circ Res. 2015;116:1680-90. DOI: 10.1161/circresaha.116.305265.
25. Patel H, Desai M, Tuzcu EM, Griffin B, Kapadia S. Pulmonary hypertension in mitral regurgitation. J Am Heart Assoc. 2014;3:1-9. DOI: 10.1161%2FJAHA.113.000748.
26. Guzmán MC, Izquierdo LM, Carvajal D, Duque B, Rodriguez-Martinez MC. Clinical outcomes of pulmonary hypertension in children with pneumonia and respiratory failure. J Resp Dis. 2017;1:107.
27. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, *et al.* Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015;132:2037-99. DOI: 10.1161/CIR.0000000000000329.
28. Maxwell AJ, Bridges ND. Pediatric primary pulmonary hypertension. Curr Treat Options Cardiovasc Med. 2001;3:371-83. DOI: 10.1007/s11936-001-0027-4.
29. Hansmann G. Pulmonary hypertension in infants, children, and young adults. J Am Coll Cardiol. 2017;69:2551-69. DOI: 10.1016/j.jacc.2017.03.575.
30. Kozlik-Feldmann R, Hansmann G, Bonnet D, Schranz D, Apitz C, Michel-Behnke I. Pulmonary hypertension in children with congenital heart disease (PAH-CHD, PPHVD-CHD). Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart. 2016;102:ii42-8. DOI: 10.1136/heartjnl-2015-308378.
31. Murni IK, Djer MM, Yanuarso PB, Putra ST, Advani N, Rachmat J, et al. Outcome of pediatric cardiac surgery and predictors of major complication in a developing country. Ann Pediatr Cardiol. 2019;12:38-44. DOI: 10.4103/apc.APC_146_17
32. Murni IK, Musa NL. The need for specialized pediatric cardiac critical care training program in limited resource settings. Front Pediatr. 2018;6:59. DOI: 10.3389/fped.2018.00059.