East African Scholars Journal of Medical Sciences
Abbreviated Key Title: East African Scholars J Med Sci
ISSN: 2617-4421 (Print) & ISSN: 2617-7188 (Online)
Published By East African Scholars Publisher, Kenya

Volume-8 | Issue-3 | Mar-2025 | DOI: https://doi.org/10.36349/easms.2025.v08i03.002

OPEN ACCESS

Original Research Article

Factors Associated with Pulmonary Hypertension in Acynotic Congenital Heart Disease with Left to Right Shunt

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Article History
Received: 24.01.2025
Accepted: 01.03.2025
Published: 06.03.2025

Journal homepage:
https://www.easpublisher.com

Quick Response Code

Abstract: ***Background*:** The most frequent type of cardiac abnormality in childhood is left-to-right shunting in acyanotic congenital heart disease (CHD). Delays in CHD care are caused by limited access to professional health services. Limited facilities, delayed diagnosis, and family economic factors all make it difficult to close the shunt in a timely manner, increasing the patient's risk of developing pulmonary hypertension. ***Objective*:** To determine the factors that influence pulmonary hypertension in pediatric patients with left to right shunting in acyanotic congenital heart diseases. ***Materials and Methods*:** This observational study was included children with acyanotic CHD left-to-right shunting who were admitted in the Department of Pediatric Cardiology in Bangladesh Shishu Hospital & Institute (BSHI), Dhaka, from 1st January to 31st December 2024. Total 140 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. ***Results*:** Younger children are more likely to develop pulmonary hypertension ($p < 0.05$). About four-fifth 55 (78.57%) of the participants had single congenital anomaly. Out of the remaining 6 (8.57%) children ASD e PDA was 4 (5.71%), ASD and VSD was 3 (4.29%), VSD e PDA was 3 (4.29%) respectively. Heart failure was substantially higher in the pulmonary hypertension group compared to the no pulmonary hypertension group (42.86% vs. 10%, $p<0.001$). The findings revealed that heart failure was a strong predictor of pulmonary hypertension, with a hazard ratio of 4.1**.** ***Conclusion*:** Patients with acyanotic CHD and heart failure who underwent left-to-right shunting have a four-fold increased risk of developing pulmonary hypertension. Iron deficiency anemia, mitral regurgitation, and pneumonia do not substantially predict pulmonary hypertension.

Keywords: Pulmonary hypertension; congenital heart disease; predictor factors; left-to-right shunting.

INTRODUCTION

Patients with uncorrected congenital heart disease (CHD) are more likely to develop pulmonary arterial hypertension (PAH), which is diagnosed as pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) and typically results from a significant systemic-to-pulmonary shunt that is present from infancy [1]. PAH-CHD accounts for over 40% of all PAH cases and is the second most prevalent form among children. This form is also prevalent in developing and impoverished regions [2]. 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 [3].

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. 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 [4]. Limited facilities, late diagnoses, and family economic

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factors are obstacles to closing the shunt in a timely manner, increasing patient susceptibility to pulmonary hypertension. Limited access to specialized health services is a major factor contributing to delays in CHD management [5].

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 [6-10].

METHODS

This observational study was included children with acyanotic CHD left-to-right shunting who were admitted in the Department of Pediatric Cardiology in Bangladesh Shishu Hospital & Institute (BSHI), Dhaka, from 1st January to 31st December 2024. Total 140 patients aged between 1 month to 17 years with isolated atrial septal defect, or ventricular septal defect, or patent ductus arteriosus were included. Among them 70 were pulmonary hypertension group and 70 were no pulmonary hypertension group. 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. Patient data were obtained from medical history, 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. 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. 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 according to ICD-10. Heart failure was assessed based on the modified Ross criteria. Subjects were randomly selected by pairing with random numbers generated by *SPSS* ver-25. Chi-square tests were done to assess potential predictive factors of pulmonary hypertension, and analyses were continued by Chi-square result of $p<0.05$.

RESULTS

The average age was 23.79 (±5.16) in the pulmonary hypertension group and 26.84 (±6.27) in the non-pulmonary hypertension group. Younger children are more likely to develop pulmonary hypertension ($p < 0.05$). Gender, weight, height, median heart rate, median respiratory rate, mean hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and median red cell distribution width were not significantly different across the pulmonary hypertension groups (Table-1). Figure I shows about four-fifth 55 (78.57%) of the participants had single congenital anomaly. Out of the remaining 6 (8.57%) children ASD e PDA was 4 (5.71%), ASD and VSD was 3 (4.29%), VSD e PDA was 3 (4.29%) respectively. Except for iron deficiency anemia, all 140 cases were examined using Chi-square, with 22.86% having pulmonary hypertension and 20% not having pulmonary hypertension. Mitral regurgitation had 31.43% pulmonary hypertension and 20% no pulmonary hypertension, whereas pneumonia had 15.71% pulmonary hypertension and 12.86% no pulmonary hypertension. Heart failure was substantially higher in the pulmonary hypertension group compared to the no pulmonary hypertension group (42.86% vs. 10%, $p<0.001$). The findings revealed that heart failure was a strong predictor of pulmonary hypertension, with a hazard ratio of 4.28 (Table-2).

Table 1: Basic characteristics of subjects (N=140)

Characteristics	Study group		p value
	Pulmonary hypertension, n=70	No pulmonary hypertension, n=70	
Age in months	23.79 (±5.16)	26.84 (±6.27)	0.002
Sex			
Male	27 (38.57)	36 (51.43)	0.12
Female	43 (61.43)	34 (48.57)	
Median weight in kg	6.91 (±3.48)	7.68 (±4.59)	0.26
Height	97.41 (±31.7)	98.71(±31.4)	0.80
Median heart rate (IQR), times/minute	115.26 (±37.25)	114.93 (±29.67)	0.95
Median respiratory rate (IQR), times/minute	31.25(±17.9)	29.31(±11.6)	0.45
Mean hemoglobin (IQRSD), g/dL	11.92(±1.85)	11.78(±1.63)	0.63
Mean corpuscular volume (SD), fL	79.16(±10.97)	80.24(±10.13)	0.54
Mean corpuscular hemoglobin (SD), pg	27.13(±3.82)	26.97(±3.71)	0.80
Median red cell distribution width (IQR), %	16.17(±3.24)	15.93(±3.76)	0.68

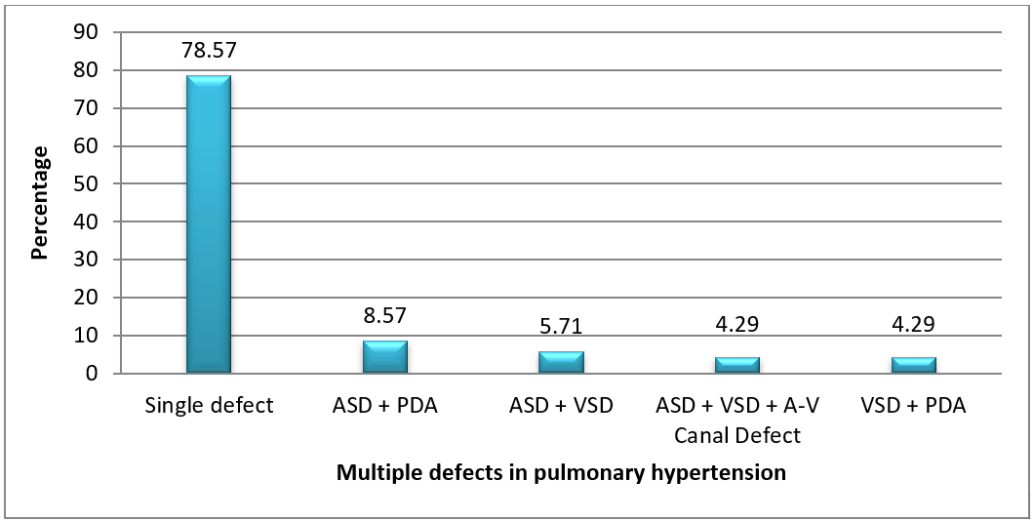

Figure I: Distribution of the children by the presence of multiple defects in pulmonary hypertension group (n=70)

Table 2: Predictors of pulmonary hypertension in children with acyanotic CHD (N=140)

Characteristics	Study group		95% CI	Relative risk	p value
	Pulmonary hypertension, n=70	No pulmonary hypertension, n=70			
Iron deficiency anemia	16 (22.86)	14 (20.0)	0.604 to 2.159	1.1429	0.68
Mitral regurgitation	22 (31.43)	14 (20.0)	0.877 to 2.813	1.5714	0.12
Pneumonia	11 (15.71)	9 (12.86)	0.540 to 2.764	1.2222	0.63
Heart failure	30 (42.86)	7 (10.00)	2.018 to 9.1006	4.2857	<0.001

DISCUSSION

In this study observed that the mean age was 23.79 (±5.16) in the pulmonary hypertension group and 26.84 (±6.27) in the non-pulmonary hypertension group. Younger children are more likely to develop pulmonary hypertension ($p < 0.05$). Gender, weight, height, median heart rate, median respiratory rate, mean hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and median red cell distribution width were not significantly different across the pulmonary hypertension groups. Gunawijaya and Yantie study found that age at presentation were correlated with the correctability of pulmonary hypertension. Infants had more severe pulmonary hypertension than older children. Females were more prevalent in populations with pulmonary hypertension due to any cause (59%) and in those with PAH-CHD (62%) [11]. Barua *et al*., [12] reported the mean ± SD of age was calculated to be, (3.1912 ±3.94387) and age ranged from 25 days to 14 years. About half of the participants [24 (48.0%)] were Males. Male: Female ratio was about 1:1.08 and female were proportionately higher in count [12].

Current study showed that about four-fifth 55 (78.57%) of the participants had single congenital anomaly. Out of the remaining 6 (8.57%) children ASD e PDA was 4 (5.71%), ASD and VSD was 3 (4.29%), VSD e PDA was 3 (4.29%) respectively. Similar observation was found Barua *et al*., [12] 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 [12]. In general, conditions that occur with pressure overload and high flow, such as VSD, increase the possibility of pulmonary hypertension [13]. 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 [14].

Present study showed Except for iron deficiency anemia, all 140 cases were examined using Chi-square, with 22.86% having pulmonary hypertension and 20% not having pulmonary hypertension. Mitral regurgitation had 31.43% pulmonary hypertension and 20% no pulmonary hypertension, whereas pneumonia had 15.71% pulmonary hypertension and 12.86% no pulmonary hypertension. Heart failure was substantially higher in the pulmonary hypertension group compared to the no pulmonary hypertension group (42.86% vs. 10%, $p<0.001$). The findings revealed that heart failure was a strong predictor of pulmonary hypertension, with a hazard ratio of 4.2. Weny Inrianto *et al*., [3] reported

heart failure was the one independent factor predictive of pulmonary hypertension (P=0.001). 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 [15]. 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% [16]. This difference may have been due to the classification of anemia in the basic health survey Riskesdas by Ministry of Health Republic of Indonesia as that report included all anemia cases without distinguishing the cause [17]. Previous studies have shown an association between iron deficiency and the incidence of pulmonary hypertension, including increasing pulmonary arterial pressure [18, 19].

CONCLUSION

Patients with acyanotic CHD and heart failure who underwent left-to-right shunting have a four-fold increased risk of developing pulmonary hypertension. Iron deficiency anemia, mitral regurgitation, and pneumonia do not substantially predict pulmonary hypertension. We advise giving defect closure a priority for acyanotic CHD patients with left-to-right shunts since heart failure is an independent predictor of pulmonary hypertension in these patients.

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Cite This Article: Shayla Afroze, Mahmudul Huq Chowdhury, Meherdad Yousuf Ahmed (2025). Factors Associated with Pulmonary Hypertension in Acynotic Congenital Heart Disease with Left to Right Shunt. *East African Scholars J Med Sci*, *8*(3), 96-100.