Mortality risk factors in pneumonic children with congenital heart disease left to right shunt: A case-control study

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Abstract

Children with Congenital Heart Disease (CHD) left to right shunt is closely related to the incidence of respiratory tract infections, especially pneumonia. In resource-limited settings, the mortality rate in children with left-to-right shunt CHD with pneumonia is tremendous. This study aims to evaluate and investigate mortality risk factors for left-to-right shunt CHD children with pneumonia during admission. This study is an analytic observational study with a case-control design. We used medical records from January 2016 – December 2021 at Dr. Soetomo General Hospital. Inclusion criteria included children aged six months – five years, diagnosed with pneumonia, had echocardiography results proving a left-to-right shunt CHD, and the outcome at discharge died and/or recovered. Patients with sepsis and septic shock, incomplete medical records, and down syndrome or cerebral palsy were excluded. A total of 96 pneumonia children with left-to-right shunt CHD were included consisting of 48 children who survived and died at discharge. The median age of the children was 6 [IQR 3-12] months. The most common type of CHD was Atrial septal defect (ASD), 44.8%, followed by Ventricular Septal Defect (VSD), 20.8%. Those who died were younger, with a median of 4 [IQR 3 – 11.7] months. In multivariate analysis, defect size, desaturation, first antibiotic replacement, and pulmonary hypertension were the risk factors that affected the mortality in pediatric patients with left-to-right shunt CHD and pneumonia with p-values of 0.011, 0.012, 0.004, and 0.008; OR 8.135, 4.95, 6.13, and 6.45 respectively. Mortality risk factors in children with left-to-right shunt CHD and pneumonia are affected by defect size, desaturation, first antibiotic replacement, and pulmonary hypertension. Monitoring the patient's condition based on these underlying factors in order to prevent respiratory complications and improve the patient's survival rate is needed.

Keywords: *Congenital Heart Disease, Left-to-Right Shunt CHD, Pneumonia, Mortality.*

1. Introduction

Pneumonia is one of the most common diseases and the most significant cause of death in children worldwide, followed by the prevalence of congenital heart disease (CHD) [1]. Pneumonia and CHD have a reciprocal relationship. CHD can be the underlying disease for pneumonia and vice versa [2]. Pneumonia increases CHD mortality. Pneumonia without CHD has a mortality of 1.5%, while pneumonia with CHD has a mortality of 37% [3]. Increased mortality in children with CHD who have pneumonia has its risk factors but has not been widely studied. Identifying these risk factors can be helpful in the management and preventive efforts, with the primary goal of preventing death [4]. In addition, the introduction of risk factors can predict the current and future condition of children [5].

The prevalence of pneumonia in children with CHD from a study in Indonesia reached 35% [6]. Research in North America showed that 9% of 2952 children hospitalized for severe pneumonia had CHD [7]. According to Indonesia's health profile in 2017, pneumonia sufferers in Indonesia amounted to 447,431 children under the age of 1 year, as many as 149,944 patients and ages 1-4 years, as many as 297,487 patients and the most deaths were caused by very severe pneumonia with CHD [8]. Research conducted in 2005 on pneumonia in children with CHD showed that the average episode of pneumonia in left-to-right shunt CHD was 9-10 times/year and in cyanotic CHD 15-16 times/year [9].

World Health Organization, through the Millennium Development Goals (MDGs) program targets reducing child deaths from preventable diseases, including pneumonia. In Indonesia, the strategy for controlling and preventing pneumonia is the implementation of Integrated Management of Sick Toddlers (IMCI), measles immunization, Diphtheria Pertussis Tetanus (DPT), Haemophilus influenzae type b (Hib), and Pneumococci, as well as control of risk factors that need immediate intervention. While the control and prevention strategies for CHD are prematurity and Low Birth Weight Babies (LBW).

Previous studies identified age, sepsis, impaired renal function, need for invasive ventilation, use of ECMO, pericardiocentesis, and cardiopulmonary resuscitation during treatment as the highest risk factors for death in children with heart disease with pneumonia with adenovirus etiology. However, it was conducted on all types of heart disease (acquired and congenital) [10]. Other studies in adult patients have also confirmed that pneumonia-related deaths in patients with CHD are associated with the incidence of heart failure, arrhythmias, the need to take heart medications, or the presence of comorbid diseases other than CHD and pneumonia [11].

We noticed that data on mortality rates and risk factors for mortality in children with CHD treated for pneumonia in Indonesia are still limited. Most studies only revealed the risk factors for pneumonia in children with CHD. In addition, the incidence of pneumonia in children with CHD is relatively high in RSUD dr. Soetomo and it risks becoming severe pneumonia, leading to death. Therefore, a study on the risk factors for childhood mortality with CHD with pneumonia is considered necessary.

2. Materials and Methods

Research Type and Design

This research is a case-control study examining risk factors for pneumonia mortality in children with left-to-right shunt CHD. This type of research is analytically observational (Figure 1). We noted the incidence of pneumonia-related deaths in children with CHD left-to-right shunts. We retrospectively analyzed the history of exposure to the risk factor for pneumonia-related death in children with CHD left-to-right shunts.

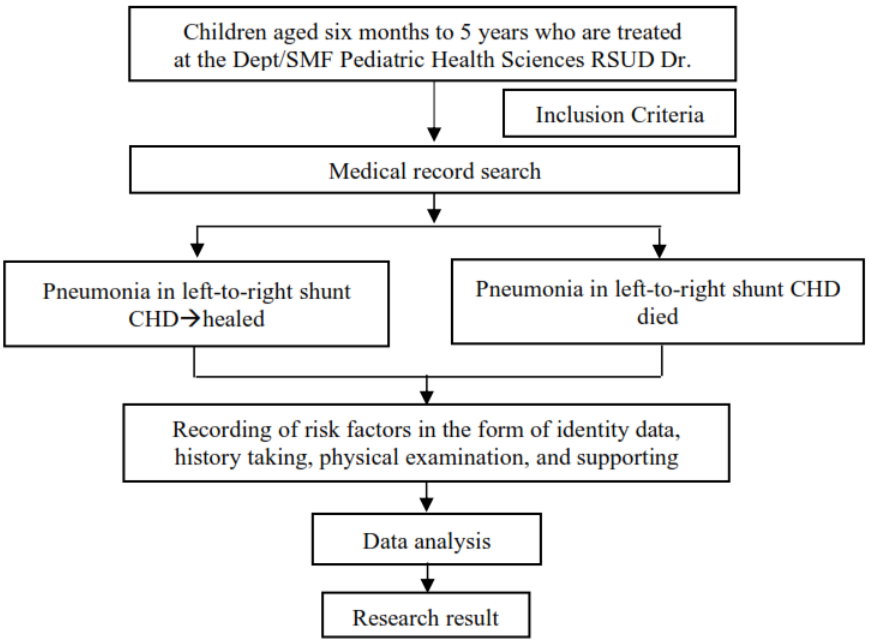

Figure 1. Research flow conducted in this study

Population, Sample Size, and Sampling Technique

Research population

Two population were recorded including the case and control population. The case population refers to children with left-to-right shunt CHD who suffered from pneumonia and died. The control population was defined as children with left-to-right shunt CHD who suffered from pneumonia and lived until the end of the treatment period. Samples were taken by consecutive sampling from medical records, not random, but those who met the inclusion and exclusion criteria (Table 1).

Table 1. Inclusion and exclusion criteria on subjects

Criteria	Case	Control
Inclusion	1. Children aged six months – 5 years 2. Diagnosed with pneumonia 3. The outcome is death 4. Have a heart echo result that proves CHD left-to-right shunt	1. Children aged six months – 5 years 2. Diagnosed with pneumonia 3. The outcome is healed 4. Have a heart echo result that proves CHD left-to-right shunt
Exclusion	1. Patients with sepsis and septic shock 2. Incomplete medical record 3. Patients with comorbid diseases such as Down syndrome or cerebral palsy	1. Patients with sepsis and septic shock 2. Incomplete medical record 3. Patients with comorbid diseases such as Down syndrome or cerebral palsy

Sample size

Children aged six months to 5 years with pneumonia and left-to-right shunt CHD were sampled. The sample size is calculated using the following formula:

$$n = \frac{\left[Z_{\propto}\sqrt{2PQ} + Z_{1-\beta}\sqrt{P_1Q_1 + P_2Q_2}\right]^2}{(P_1 - P_2)^2}$$

n = The required sample size for each population
Z = The standard value at 0.05, which is 1.96
Z1-β = The standard value at 0.05, which is 1.28
P1 = The proportion of left-to-right shunt CHD is 0.14 based on previous studies.
P2 = The proportion of pneumonia in left-to-right shunt CHD is 0.08 based on previous studies

Based on the above formula, the required number of samples is 48 pneumonia subjects with left-to-right shunt CHD who died and 48 pneumonia subjects with left-to-right shunt CHD who lived until the end of treatment.

Sample technique

Sampling was carried out by collecting data from medical records of patients under five years diagnosed with pneumonia and left-to-right shunt CHD treated at the Pediatric Respirology Inpatient Installation (IRNA), Department of Pediatrics, RSUD Dr. Soetomo Surabaya. Patient data regarding identity, history taking, physical examination, and supporting examinations will be recorded on the data collection sheet.

Table 2. Variable Operational Definition

Variable	Definition	How to measure	Measurement result	Scale
Pneumonia	Cough and difficulty breathing	Based on clinical and confirmed by radiological examination results, plain chest X-ray	1=pneumonia 0=no pneumonia	Nominal
Child's age	The patient's age at the time of initial examination, expressed in months	By date of birth	Moon, grouped 1=2-5 months old 2=age 6-59 months	Nominal
Nutritional status	Anthropometrically evaluated by measuring weight and height	2006 WHO curve is upheld SD BB/U < -3SD = Poor nutrition -3SD to -2SD = Undernourished -2SD to +2SD = Good Nutrition > 2SD = More Nutrition	Grouped 1 = children with poor nutrition / less 2 = children with good nutrition / more	Nominal
History of gestational age	The duration of pregnancy from the formation of the fetus to birth	Based on the first day of the mother's last menstrual period, which is listed in the Maternal and Child Health (MCH) book	Moon, grouped 1=premature, gestational age <37 weeks 2=term, gestational age≥37 weeks	Nominal
Low birth weight baby	Infants with birth weight <2500 grams	Based on the records of the midwife/doctor who assisted in childbirth, which is listed in the Maternal and Child Health (MCH) book	Grams, grouped 1=LBW 0=no LBW	Nominal

Anemia	Hb level less than 5th percentile according to age	Complete blood counts were carried out at the Diagnostic Center Center, RSUD Dr. Soetomo Surabaya	g/dl, grouped 1=anemia 0=no anemia	Nominal
Type of CHD	Abnormalities in the structure and function of the heart that are present from birth	Enforcement is based on the relevant Consultant Pediatrician listed on the echocardiography examination result sheet.	Grouped 1=USD 2=VSD 3=PDA	Nominal
Pulmonary hypertension	Increased pulmonary vascular resistance until pulmonary arterial pressure can exceed systemic blood pressure.	Enforcement based on the relevant Consultant Pediatrician	Grouped 1=pulmonary hypertension 0=no pulmonary hypertension	

Data collection, processing, and analysis

Secondary data from Dr. Soetomo General Academic Hospital, Surabaya were recorded. These include anamnesis, physical examination, and supporting medical record examinations during treatment at the Pediatric Respirology Inpatient Unit, Department of Child Health Sciences, Dr. Soetomo hospital, Surabaya.

All data from each examination result is ensured to be complete and relevant before further processing and classified based on the variables described in the operational definition. Data analysis was carried out using Statistical Package for the Social Science (SPSS) software, in the following order:

1) The descriptive analysis presents mean and standard deviation data for interval or ratio scale data (continuous data) and frequency distribution for categorical data. Data are presented in tabular form.
2) Bivariate analysis to determine the relationship between variables with pneumonia mortality in patients with left-to-right shunt CHD was carried out by logistic regression using the bootstrap method because of the small sample and the incidence of toxicity.
3) Multivariate analysis was performed using multiple logistic regression using the bootstrap method to simultaneously determine the effect of several variables.

Research Ethics

The ethical feasibility of the research was obtained from the Health Research Ethics Committee (KEPK) RSUD Dr. Soetomo Surabaya. Confidentiality of research subjects is maintained by writing initials.

3. Results

We used medical patient records from Medical Record Installation and IRNA Pediatric Respirology, Department of Pediatrics, RSUD Dr. Soetomo from January 2016 to December 2021. A total of 348 pediatric patients with left-to-right shunt CHD, who were treated with pneumonia and met the inclusion criteria. Around 98 patients were excluded due to incomplete medical record data or experiencing sepsis in the course of the disease. Sampling was done consecutively and found 48 patients with left-to-right shunt CHD with pneumonia who managed to survive and 48 patients who died.

Characteristics of children with CHD left to right shunt with pneumonia

Characterisation of children with left-to-right shunt CHD with pneumonia was performed (Table 3). This data described the clinical and socioeconomic characteristics of children with left-to-right shunt CHD with pneumonia. A total of 51% of the samples were male. The median age of children with left-to-right shunt CHD with pneumonia during the treatment period was 4.9 years old. Around 47.9% of the sample had a history of MRS within the last year. The first antibiotics used for pneumonia therapy were Ceftriaxone and Ampicillin Gentamicin, as much as 48% and 40.7%, respectively. As many as 22% have a poor response to antibiotics, so it is necessary to replace antibiotics to support pneumonia therapy in children with left-to-right shunt CHD. There are 5 (five) children who have HIV, and around 21.9% of children got left-to-right shunt CHD. Almost 23% of children suffer from pulmonary hypertension.

Socioeconomic condition of the majority family as much as 60.4% have an income of less than Rp. 2.000.000,- and the number of people living in the same room with the child is more than 2 (two) people. As many as 82.3% of pediatric patients had a house with adequate ventilation, while the rest (17.7%) had limited ventilation. The condition of children's homes with left-to-right shunt CHD accompanied by pneumonia has residents who smoke as much as 55.2%. In addition, almost 70% of PJB children with left-to-right shunts with pneumonia consume PAM water as drinking water.

Table 3. Characteristics of children with left-to-right shunt CHD with pneumonia

Characteristics	Score
Age (months), mean ± SD; median [IQR]	18.40 ± 33.31; 6 [3-12]
Gender Woman	 47 (49)

Characteristics	Score
Man	49 (51)
Birth weight (grams), mean ± SD; median [IQR]	2726.82 ± 585.49; 2800 [2400-3100]
LBW (grams)	
2500	67 (69.8)
< 2500	29 (30.2)
Type of child delivery	
Spontaneous	63 (65.6)
Sectio Caesarea (SC)	33 (34.4)
Prematurity	
term	83 (86.5)
premature	13 (13.5)
Breast milk history	
Not	14 (14.6)
Yes	82 (85.4)
Maternal age (years), mean ± SD; median [IQR]	31.43 ± 6.78; 30 [27-37.75]
Mother's Education	
Not a Bachelor/Diploma	82 (85.4)
Undergraduate diploma	14 (14.6)
Family income	
IDR 2.000.000,-	58 (60.4)
> IDR 2,000,000,-	38 (39.6)
Home Ventilation	
Enough	79 (82.3)
Limited	17 (17.7)
Type of drinking water	
Commercial mineral water	19 (19.8)
PAM (Municipal water supply)	66 (68.8)
Well	10 (10,4)
River water	1 (1)
Number of people living in the same room (person)	
2	22 (22.9)
> 2	74 (77.1)
Smokers	
Not	43 (44.8)
Yes	53 (55.2)
Body weight (kg), mean ± SD; median [IQR]	44.24 ± 358.45; 4.9 [3.5-7]
Height (cm), mean ± SD; median [IQR]	65.03 ± 21.96; 62 [52-69]
Nutritional status	

Characteristics	Score
Good/normal nutrition	28 (29.2)
Malnutrition/poor	68 (70.8)
Type of CHD	
ASD	43 (44.8)
VSD	20 (20.8)
PDA	15 (15.6)
ASD, PDA	6 (6.3)
ASD, VSD	8 (8.3)
VSD, PDA	3 (3,2)
ASD, VSD, PDA	1 (1)
Defect size	
Small	37 (38.6)
Currently	44 (45.8)
Big	15 (15.6)
Anemia	
Not	44 (45.8)
Yes	52 (54.2)
Hemoglobin (g/dL), mean ± SD; median [IQR]	10.91 ± 2.11; 10.55 [9.32-12]
Desaturation	
Not	75 (78.1)
Yes	21 (21.9)
First antibiotic prescription	
Ceftriaxone	46 (48)
Ampicillin	5 (5,3)
Gentamycin	1 (1)
Erythromycin	1 (1)
Chloramphenicol	1 (1)
Ampicillin, Gentamycin	39 (40.7)
Ampicillin, Cotrimoxazole	1 (1)
Ampicillin, Cefoperazone Sulbactam	1 (1)
Ampicillin, Gentamycin, Cefo sulbactam	1 (1)
Antibiotic replacement	
Not	75 (78.1)
Yes	21 (21.9)
Hematology	
Not	80 (83.3)
Yes	16 (16.7)
Neuromuscular	
Not	51 (53.1)
Yes	45 (46.9)

Characteristics	Score
HIV	
Not	91 (94.8)
Yes	5 (5,2)
Pulmonary hypertension	
Not	74 (77.1)
Yes	22 (22.9)
Medical admission records (MRS) in the last one year	
Not	50 (52.1)
Yes	46 (47.9)
Length of stay (days), mean ± SD; median [IQR]	9.15 ± 8.05; 7 [4-11]
Mortality	
Life	48 (50)
Die	48 (50)

*Data are displayed as mean ± standard deviation; median [interquartile range]; n(%).

Clinical risk factors for children with left-to-right shunt CHD with pneumonia based on mortality

Clinical risk factors for children with left-to-right shunt CHD with pneumonia based on mortality were also recorded (Table 4). We performed the bivariate test to see which clinical risk factors are associated with mortality in pediatric patients with left-to-right shunt CHD with pneumonia. The above results found that birth weight, pulmonary hypertension, history of desaturation, and response to first antibiotic change were risk factors associated with the risk of mortality by bivariate analysis. The p-values of these risk factors include 0.000, 0.004, 0.026, and 0.007, respectively.

Table 4. Clinical risk factors for children with left-to-right shunt CHD with pneumonia based on mortality

Variable	Mortality		*p*	OR	95% CI *Lower - Upper*
	Life (N=48)	Die (N=48)			
Age (months)	18.46±31.68 8.50 [4 – 14.5]	18.33±35.20 4 [3 – 11.75]	0.071c	-	-
Nutritional status					
Good/normal nutrition	13 (27.1)	15 (31.3)	0.653b	0.817	0.338 – 1.974
Malnutrition/poor	35 (72.9)	33 (68.8)			

Prematurity					
term	41 (85.4)	42 (87.5)	0.765b	0.837	0.259 – 2.702
premature	7 (14.6)	6 (12.5)			
Birth weight (grams)	2801.56±576.03 2900 [2425 – 3200]	2652 ± 591.33 2650 [2300 – 3000]	0.000a*		
LBW (grams)					
2500	36 (75)	31 (64.6)	0.266b	1,645	0.681 – 3.972
< 2500	12 (25)	17 (35.4)			
Anemia					
Not	23 (47.9)	21 (43.8)	0.682b	1.183	0.530 – 2.642
Yes	25 (52.1)	27 (56.2)			
Type of CHD					
ASD	26 (54.2)	17 (35.4)			
VSD	12 (25)	8 (16.7)			
PDA	5 (10,4)	10 (20.8)	0.096b	-	-
ASD, PDA	3 (6.3)	3 (6.3)			
ASD, VSD	1(2.1)	7 (14.6)			
VSD, PDA	1(2.1)	2 (4,2)			
ASD, VSD, PDA	0 (0)	1(2.1)			
Defect size					
Small	20 (41.7)	17 (35.4)	0.057b	-	-
Currently	17 (35.4)	27 (56.3)			
Big	11 (22.9)	4 (8.3)			
Pulmonary hypertension					
Not	43 (89.6)	31 (64.6)	0.004b*	4,716	1.572 – 14,152
Yes	5 (11)	17 (35.4)			
Desaturation					
Not	42 (87.5)	33 (68.8)	0.026b*	3.182	1,113 – 9,100
Yes	6 (12.5)	15 (31.3)			
Antibiotic replacement					
Not	43 (89.6)	32 (66.7)	0.007b*	4,300	1,426 – 12,964
Yes	5 (10,4)	16 (33.3)			
Length of stay (days)	7.60±4.89 7 [4.25 – 9]	10.69 ± 10.12 6.50 [3 – 15.75]	0.597c	-	-

Data are displayed as mean ± standard deviation; median [interquartile range]; n(%); aTest T, for normally distributed variables; b Pearson Chi-square or Fisher Exact test; c Test Mann-Whitney U; * p value <0.05, which means the variable is statistically significant. CI = Confidence Interval. OR = Odd Ratio.

Children's socioeconomic risk factors for left-to-right shunt CHD with pneumonia based on mortality

the socioeconomic risk factors associated with child mortality with left-to-right shunt CHD with pneumonia were analyzed using the bivariate test (Table 5). We showed that No risk factors were significant or statistically associated with child mortality with left-to-right shunt CHD with pneumonia. However, home ventilation showed an OR value of 2.867, which means that limited house ventilation increased the risk of death by 2.8 times in children with left-to-right shunt CHD with pneumonia.

Tabel 5. Socioeconomic risk factors for children with left-to-right shunt CHD with pneumonia based on mortality

Variable	Outcome		*p*	OR	95% CI *Lower - Upper*
	Life (N=48)	Die (N=48)			
Mother's Education			0.247	0.504	0.155 – 1.633
Not a	39 (81.2)	43 (89.6)			
Bachelor/Diploma	9 (18.8)	5 (10.4)			
Undergraduate diploma					
Family income			0.676	0.840	0.370 – 1.905
IDR 2,000,000,-	28 (58.3)	30 (62.5)			
> IDR 2,000,000,-	20 (41.7)	18 (37.5)			
Home Ventilation			0.061	2,867	0.923 – 8.904
Enough	43 (89.6)	36 (75)			
Limited	5 (10.4)	12 (25)			
Type of drinking water			0.789	-	-
Commercial mineral water	10 (20.8)	9 (18.8)			
Municipal water supply (PAM)	33 (68.8)	33 (68.8)			
Well	5 (10.4)	5 (10.4)			
River water	0 (0)	1(2.1)			
Number of people living in the same room (person)			0.627	1,267	0.487 – 3.292
2	12 (25)	10 (20.8)			
> 2	36 (75)	38 (79.2)			

Smokers			0.538	0.776	0.347 –
Not	20 (41.7)	23 (47.9)			1.739
Yes	28 (58.3)	25 (52.1)			

Data is displayed in the form of mean ± standard deviation; median [interquartile range]; n(%); Pearson Chi-square or Fisher Exact test; * p value <0.05, which means the variable is statistically significant. CI = Confidence Interval. OR = Odd Ratio.

Multivariate analysis of risk factors affecting mortality in children with left-to-right shunt CHD with pneumonia

Multivariate analysis was performed on the risk factors from tables 4 and 5 with $p < 0.25$ (Table 5). The risk factors in the multivariate analysis included the child's age, birth weight (grams), type of CHD, defect size, pulmonary hypertension, history of desaturation, first antibiotic replacement, mother's education, and home ventilation. Based on the multivariate analysis in Table 5.4, the risk factors that have a significant influence on the incidence of mortality in children with left-to-right shunt CHD with pneumonia include the size of the defect, pulmonary hypertension, desaturation, and antibiotic replacement with p values of 0.011, 0.008, 0.012, and 0.004 respectively. Sequentially. The size of the defect affects the incidence of mortality in children with left-to-right shunt CHD with pneumonia, with an OR value of 8.

Pediatric patients with left-to-right shunt CHD with pneumonia who do not have pulmonary hypertension significantly influence the incidence of mortality. This is proved by the value of OR < 1,000, which indicates a protective risk. For this reason, the interpretation must be reversed to (OR, 1/0.155 = 6.45) so that it means that pediatric patients with left-to-right shunt CHD with pneumonia who have pulmonary hypertension have a 6.45 times greater risk of suffering from mortality events compared to those who do not have pulmonary hypertension. A history of desaturation in pediatric patients with left-to-right shunt CHD with pneumonia also had a 4.9 times greater risk (OR, 1/0.202 = 4. 95) of suffering incident mortality compared to unsaturated pediatric patients at the time of admission. The first antibiotic change in pediatric patients with left-to-right shunt CHD with pneumonia had a 6.13 times greater risk (OR, 1/0.163 = 6.13) for mortality compared to pediatric patients who did not change antibiotics or had an excellent first antibiotic response at the time of treatment.

Tabel 6. Multivariate analysis of mortality risk factors in children with left-to-right shunt CHD with pneumonia

Risk factors	***p***	***Adjusted OR***	**95% CI *Lower – Upper***
Defect size	0.011*	8.135	1,626 – 40,692
Desaturation	0.012*	0.202	0.058 – 0.704

No [(1)]			
Yes			
Antibiotic replacement	0.004*	0.163	0.048 -0.552
No [(1)]			
Yes			
Pulmonary hypertension	0.008*	0.155	0.039 – 0.620
No [(1)]			
Yes			

Logistic regression test; * p value <0.05 means statistically significant. CI = Confidence Interval. OR = Odd Ratio. [(1)]Adjusted OR value *references*.

4. Discussion

Characteristics of CHD Children Left to Right Shunt with Pneumonia

Pneumonia is the most common cause of death in children under five. Epidemiological factors and disease burden differ in developing and industrialized countries. Left-to-right shunts are the most common type of CHD found in cases diagnosed with pneumonia, with VSD in at least 20% of all defects, ASD in up to 2%, and patent ductus arteriosus in about 10% [12]. This theory supports the number of children with left-to-right shunt CHD cases with pneumonia most often found in RSUD Dr. Soetomo Surabaya, namely ASD 44.8%, VSD 20.8%, and PDA 15.6%. These results are supported by the same research conducted at the RSUPN dr. Cipto Mangunkusumo from 2015-2019 with a sample of 333 children with left-to-right shunts, 162 of whom had pneumonia (50.2%) with the type of CHD with the highest incidence of pneumonia being VSD [13]. A 2013 study in Turkey that examined 242 patients with a mean age of 61.6 ± 51.2 months showed that children with a diagnosis of VSD were most at risk for developing pulmonary artery hypertension among those diagnosed with a sizeable left-to-right CHD shunt. Pulmonary arterial hypertension developed in 12.3% of isolated left-to-right shunts [14].

Specifically, a study in Portland, United States, in 2021 found that adult patients with CHD had a two-fold more significant risk of being hospitalized due to pneumonia compared to the general population of the same age and sex [15]. More than 60% of pediatric patients with left-to-right shunt CHD accompanied by pneumonia have moderate and significant defects. Pediatric patients with left-to-right shunt CHD with pneumonia often have many risk factors that can contribute to the occurrence and severity of pneumonia, including abnormal lung physiology, altered immune function, congestive heart failure, anemia, splenomegaly, and others [16-18]. This study found that the median age of children with left-to-right shunts accompanied by pneumonia was 6 (six) months old. Nearly 35% of children were delivered by cesarean section, and 13.5% had a history of prematurity. Looking at the characteristics of these pediatric patients, in developing countries such as Indonesia, child mortality with CHD and pneumonia increases over time.

Clinical Risk Factors for Children with CHD Left to Right Shunt with Pneumonia Based on Mortality

The clinical risk factors for left-to-right shunt CHD children with pneumonia on mortality are shown in Table 5.2. Through bivariate analysis, it was found that birth weight had a significant relationship with the mortality incidence of left-to-right CHD children with pneumonia ($p<0.001$). Age in this study did not significantly correlate to mortality risk in children with left-to-right shunt CHD with pneumonia. Research conducted by Baseer et al. (2021) also reported no significant difference between pediatric patients with pneumonia and those without pneumonia. The history of prematurity and LBW did not provide a significant relationship in this study ($p>0.05$) [19].

Pulmonary hypertension contributes 4.7 times greater risk for left-to-right shunt CHD pediatric patients with pneumonia to experience mortality than those without pulmonary hypertension. Pulmonary hypertension that occurs in left-to-right shunts, such as VSD, ASD, and PDA, will cause high-flow pulmonary hypertension. However, if this continues, it will cause damage to the intima-media of the lung tissue. It will be replaced by fibrosis which will cause pulmonary hypertension resistance and a poor prognosis [20]. The estimated survival rate for patients with CHD with pulmonary arterial hypertension at 5 (five) years is only 76% but is significantly better than for patients with idiopathic pulmonary arterial hypertension. However, the overall survival of pediatric patients with CHD with pulmonary hypertension remains dependent on the underlying diagnosis and treatment status [21].

Nutritional status in this study did not have a significant relationship with the incidence of mortality in children with left-to-right shunt CHD with pneumonia. It is different from a previous study conducted in Bangladesh in 2014 that examined 405 children with pneumonia and severe malnutrition at the time of inpatient admission (OR 3.64 [95% CI 1.66-7.97], $p = 0.001$) and age <12 months (OR 2.54 [95% CI]). CI 1.1-8.8], $p = 0.03$) was significantly associated with post-discharge mortality. Those who die after discharge from the hospital are also significantly more malnourished than those who survive [22]. However, a study in China reported malnutrition as a common complication in children with CHD symptoms. Approximately 25% of children with CHD suffer from malnutrition. Hospitalization, mechanical ventilation, pulmonary hypertension, cyanotic heart disease, and age at the surgery are associated with preoperative malnutrition [23].

In pediatric patients with left-to-right shunt CHD with pneumonia who suffered desaturation at hospitalization, the risk was 3.1 times greater for mortality. Substitution of antibiotics in pneumonia therapy also significantly impacts the risk of mortality in children with left-to-right shunt CHD with pneumonia. Table 4 displayed the bivariate analysis of pediatric patients with left-to-right shunt CHD with pneumonia who change the antibiotic in the first prescription have a 4.3 times greater risk of experiencing mortality compared to pediatric patients who do not change the type of antibiotic. In general, many difficulties in antimicrobial resistance surveillance are due to limited laboratory capacity, harmonized diagnostic procedures, and lack of a surveillance network [24].

Socio-Economic Risk Factors of PJB Children Shunt Left to Right with Pneumonia Based on Mortality

This study did not find socioeconomic risk factors such as maternal education, family income of house ventilation, type of drinking water, number of people living in one room, and the presence of smoking residents at home in children with left-to-right shunt CHD with pneumonia on the incidence of mortality (Table 5). The results of this study are supported by Chisti et al. in 2014. They reported that socioeconomic risk factors such as family income per month did not affect the incidence of death in children with left-to-right shunt CHD with pneumonia [22].

However, there are some findings regarding the ventilation of the house, and the number of people living in one room has a relatively large risk. Limited home ventilation increases the risk of death by 2.8 times in children with left-to-right shunt CHD with pneumonia. Some literature shows that many socioeconomic factors contribute to a person being infected with pneumonia. Research in India in 2020 reported that a total of 270 children were hospitalized. Environmental factors had a significant influence, such as poor ventilation of the house, number of families in one house, air population in the house, and contact with suspected Tuberculosis (TB). While in line with this study, the type of drinking water and smoking occupants did not have a significant relationship with the risk of pneumonia and death [25].

Risk Factors Affecting Mortality in Children with CHD Left to Right Shunt Accompanied by Pneumonia

The risk factors that influence mortality in children with left-to-right shunt CHD with pneumonia have been presented in table 6 using multivariate analysis. The factors that significantly affect the incidence of mortality in children with left-to-right shunt CHD with pneumonia include the size of the defect, desaturation, first antibiotic replacement, and pulmonary hypertension. In this study, children with left-to-right shunt CHD with pneumonia who had medium and large defects were eight times more likely to experience mortality than children with minor defects. This study also found that a history of desaturation in pediatric patients with left-to-right shunt CHD with pneumonia also had a risk 4.

Pulmonary hypertension in the multivariate analysis had a 6.45 times greater risk for children with left-to-right shunt CHD with pneumonia to experience mortality than those without pulmonary hypertension. In 2017, a study suggested that minor defects (generally ventricular septal defects <1 cm or atrial septal defects <2 cm) are not considered a major cause of pulmonary arterial hypertension. It may even benefit patients with pulmonary arterial hypertension by allowing right-to-toe shunts. -occasionally left, thereby decompressing the right ventricle and maintaining systemic cardiac output. Pulmonary arterial hypertension alone is relatively common in CHD, affecting the quality of life and survival [26].

The first antibiotic change in pediatric patients with left-to-right shunt CHD with pneumonia had a 6.13 times greater mortality risk than in pediatric patients who did not change antibiotics or had an excellent first antibiotic response when treated. The first antibiotics used in this study were ceftriaxone and ampicillin-gentamicin, at 48% and 40.7%, respectively. In the study, 160 pediatric patients with pneumonia received intravenous ceftaroline fosamil or ceftriaxone in a randomized, active-controlled, blinded-by-observer clinical trial. The effectiveness of ceftaroline fosamil is similar to that of ceftriaxone, with high clinical cure rates on cure tests in the modified intention-to-treat population (94/107, 88%, and 32/36; 89%, respectively) [27,28]. The WHO Revision on Classification and Treatment of Pneumonia in Children in Health Facilities: Summary of Evidence was published in 2014 (WHO, 2015). Prior to the 2014 revision, four treatment categories were defined for community-acquired pneumonia (CAP). Children with 'rapid breathing' pneumonia were treated with oral cotrimoxazole. Children with 'chest retraction' pneumonia are referred to health facilities and treated with injectable penicillin/ampicillin [28,29].

The 2014 revision favors oral amoxicillin over oral cotrimoxazole for the treatment of rapid respiratory pneumonia and is equivalent to injectable penicillin/ampicillin in cases of chest retraction pneumonia. Because both rapid respiratory pneumonia and chest retraction are now best treated with amoxicillin, the classification was also revised. The new classification was revised to include only two categories of pneumonia: 'pneumonia' with rapid breathing and/or chest retractions, which requires home treatment with oral amoxicillin, and 'severe pneumonia,' pneumonia with any general danger sign, which requires referral and treatment. injection antibiotics [27,28]. Optimal dose recommendations for amoxicillin remain unclear, with limited pharmacological and clinical evidence. There is limited evidence from surveillance to show whether amoxicillin or a broader spectrum antibiotic (e.g., third-generation cephalosporin) is most commonly used for pediatric pneumonia in various WHO regions. Further pragmatic trials are needed to optimize the management of hospitalized children with severe and very severe pneumonia [27].

Research Strengths and Limitations

In research on risk factors for mortality in children with pneumonia with left-to-right shunt CHD, several literatures have examined the same in several centers in Indonesia. However, the mortality factor itself is still rarely found. This study found any supporting factors at the time of treatment that affects the survival rate of pediatric pneumonia patients with left-to-right shunt CHD. Based on the findings of this study, a multidisciplinary approach is needed to prevent respiratory complications that can lead to death. Although the study sample data is retrospective, the investigators believe this study has an essential contribution to managing pneumonia in children with left-to-right shunt CHD.

This study has several weaknesses, including adding various supporting factors, such as culture results in patients undergoing the first antibiotic replacement and the number of samples. In addition to mortality factors, we also support researching the condition of

patients with pulmonary hypertension, considering that these conditions have a relatively large risk. Mortality in pediatric pneumonia patients with left-to-right shunt CHD.

5. Conclusion

Our data demonstrated that 48 children with left-to-right shunt CHD treated with pneumonia and experienced mortality, 56.2% had moderate-size defects, and 35.4% died with Atrial Septal Defect CHD. We also noticed that some factors including age of the patient, nutritional, history of premature birth, low birth weight, anemia, type of CHD and period of stay in hospital were not a risk factor for mortality in children with left-to-right shunt CHD treated with pneumonia. However, the incidence of mortality in children with left-to-right shunt CHD treated with pneumonia was influenced by the degree of defect size (small, medium, large), pulmonary hypertension, history of desaturation and response to the first antibiotic therapy. These risk factors were demonstrated by the OR values of 8.135; 6.45; 4.95; 6.13, respectively.

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Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

References

[1]. I. Adatia, S. S. Kothari, J. A. Feinstein. “Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective”. Chest. Vol. 137, no. 6, **(2010)**, pp. 52s-61s. doi: 10.1378/chest.09-286.

[2]. K. A. Baseer, H. Sakhr. “Clinical profile and risk factors of recurrent pneumonia in children at Qena governorate, Egypt”. International Journal of Clinical Practice. Vol. 75, no. 4, **(2021)**, pp. e13695. doi: 10.1111/ijcp.13695.

[3]. J.L Blumer, T. Ghonghadze, C. Cannavino, T. O'Neal, A. Jandourek, H. D. Friedland, and J. S. Bradley. “A Multicenter, Randomized, Observer-blinded, Active-controlled Study Evaluating the Safety and Effectiveness of Ceftaroline Compared With Ceftriaxone Plus Vancomycin in Pediatric Patients With Complicated Community-acquired Bacterial Pneumonia”. Pediatr Infect Dis J. Vol. 35, no. 7, **(2016)**, pp. 760-6. doi: 10.1097/INF.0000000000001160.

[4]. M. Brida, M. A. Gatzoulis. “Pulmonary arterial hypertension in adult congenital heart disease”. Heart. Vol 104, no. 19, **(2018)**, pp. 1568-1574. oi: 10.1136/heartjnl-2017-312106.

[5]. A. K. Cabalka. “Physiologic risk factors for respiratory viral infections and immunoprophylaxis for respiratory syncytial virus in young children with congenital heart disease". Pediatr. Infect. Dis. J. Vol. 23, no. 1, **(2004)**, pp. 41–5. doi: 10.1097/01.inf.0000108220.94201.

[6]. H. G. Cabezuelo, M. S. Vidal, G. A. Abeledo, and I. P. Frontera. “Underlying causes of recurrent pneumonia”. An. Pediatr. Vol. 63, no. 5, **(2005)**, pp. 409–12. doi: 10.1157/13080405.

[7]. A. Cevik, R. Olgunturk, S. Kula, B. Saylan, A. Pektas, D. Oguz, and S. Tunaoglu. “Left-to-right Shunt with Congenital Heart Disease: Single Center Experience”. Cardiology. Vol. 2013, **(2013)**, pp. 1-5. doi: 10.1155/2013/301617.

[8]. M. J. Chisti, S. M. Graham, T. Duke, T. Ahmed, A. S. Faruque, H. Ashraf, P. K. Bardhan, A. D. Shahid, K. M. Shahunja, and M. A. Salam. “Post-discharge mortality in children with severe malnutrition and pneumonia in Bangladesh”. PLoS One. Vol. 9, no. 9, **(2014)**, pp. e107663. doi: 10.1371/journal.pone.0107663.

[9]. C. A. Crawford, C. E. Vujakovich, L. Elmore, E. Fleming, B. J. Landis, K. G. Spoonamore, and S. M. Ware. “Adolescents with congenital heart defects: a patient and parental perspective of genetic information and genetic risk”. Cardiol Young. Vol. 30, no.2, **(2020)**, pp. 219-226. doi: 10.1017/S1047951119002646.

[10]. M. R. Dewi, R. R. Windi P, M. Imanto. “Karakteristik bronkopneumonia pada anak balita dengan penyakit jantung bawaan asianotik di bangsal alamanda Rumah Sakit Abdul Moeloek Bandar Lampung”. Med. J. Lampung Univ. Vol. 8, no. 1, **(2019)**, pp. 102–7.

[11]. G. P. Diller, D. Enders, A. E. Lammers, S. Orwat, R. Schmidt, R. M. Radke, J. Gerss, F. De Torres Alba, G. Kaleschke, and U. M. Bauer, U. Marschall, H. Baumgartner. “Mortality and morbidity in patients with congenital heart disease hospitalised for viral pneumonia”. Heart. Vol. 107, no. 13, **(2020)**, pp. 1069–76. doi: 10.1136/heartjnl-2020-317706.

[12]. M. M. Djer, E. Osmardin, B. Hegar, and D. B. Setyanto. “Increased Risk of Recurrent Acute Respiratory Infections in Children with Congenital Heart Disease: A Prospective Cohort Study”. Indones. Biomed. J. Vol. 12, no. 4, **(2020)**, pp. 355-60. doi: 10.18585/inabj.v12i4.1262.

[13]. P. D. Evers, D. K. Farkas, M. Khoury, M. Olsen, and N. L. Madsen. “Risk factors and lifelong impact of community-acquired pneumonia in congenital heart disease”. Cardiol Young. Vol. 31, no, 3, **(2021)**, pp. 446-451. doi: 10.1017/S1047951120004254.

[14]. B. M. Farr, C. L. Bartlett, J. Wadsworth, and D. L. Miller. Risk factors for community-acquired pneumonia diagnosed upon hospital admission. British Thoracic Society Pneumonia Study Group”. Respir Med. Vol. 94, no. 10, **(2000)**, pp. 954-63. doi: 10.1053/rmed.2000.0865.

[15]. J. M. Geskey, S. E. Cyran. “Managing the morbidity associated with respiratory viral infections in children with congenital heart disease”. Int J Pediatr. Vol. 2012, **(2012)**, pp. 1–8 doi: 10.1155/2012/646780.

[16]. F. Healy, B. D. Hanna, R. Zinman. “Pulmonary complications of congenital heart disease. Paediatr Respir Rev”. Vol. 13, no. 1, **(2012)**, pp. 10-5. doi: 10.1016/j.prrv.2011.01.007.

[17]. I. Iliopoulos, D. P. Nelso. “Cardiopulmonary interactions in adults and children with congenital heart disease”. Progress in Pediatric Cardiology. Vol. 39, no. 2, **(2015)**, pp. 151-156. doi: 10.1016/j.ppedcard.2015.10.017.

[18]. H. Kaemmerer, M. Gorenflo, D. Huscher, D. Pittrow, C. Apitz, H. Baumgartner, F. Berger, L. Bruch, E. Brunnemer, W. Budts, M. Claussen, G. Coghlan, I. Dähnert, M. D'Alto, M. Delcroix, O. Distler, S. Dittrich, D. Dumitrescu, R. Ewert, M. Faehling, I. Germund, H. A. Ghofrani, C. Grohé, K. Grossekreymborg, M. Halank, G. Hansmann, D. Harzheim, A. Nemes, K. Havasi, M. Held, M. M. Hoeper, M. Hofbeck, W. Hohenfrost-Schmidt, E. Jurevičienė, L. Gumbienė, H. J. Kabitz, H. Klose, T. Köhler, S. Konstantinides, M. Köestenberger, R. Kozlik-Feldmann, H. H. Kramer, C. Kropf-Sanchen, A. Lammers, T. Lange, P. Meyn, O. Miera, K. Milger-Kneidinger, R. Neidenbach, C. Neurohr, C. Opitz, C. Perings, B. A. Remppis, G. Riemekasten, L. Scelsi, W. Scholtz, I. Simkova, D. Skowasch, A. Skride, G. Stähler, B. Stiller, I. Tsangaris, C. D. Vizza, A. Vonk Noordegraaf, H. Wilkens, H. Wirtz, G. P. Diller, E. Grünig, and S. Rosenkranz. “Pulmonary Hypertension in Adults with Congenital Heart Disease: Real-World Data from the International COMPERA-CHD Registry”. J Clin Med. Vol. 9, no. 5, **(2020)**, pp. 1456. doi: 10.3390/jcm9051456.

[19]. S. K. Kasundriya, M. Dhaneria, A. Mathur, and A. Pathak. “Incidence and Risk Factors for Severe Pneumonia in Children Hospitalized with Pneumonia in Ujjain, India”. Int J Environ Res Public Health”. Vol. 17, no. 13, **(2020)**, pp. 4637. doi: 10.3390/ijerph17134637.

[20]. B. R. Manopo, E. D. Kaunang, and A. Umboh. “Gambaran penyakit jantung bawaan di Neonatal Intensive Care Unit”. e-Clinic. Vol. 6, no. 2, **(2018)**, pp. 87–93. doi: 10.35790/ecl.v6i2.22124.

[21]. S. Mathur, A. Fuchs, J. Bielicki, J. Van Den Anker, and M. Sharland. “Antibiotic use for community-acquired pneumonia in neonates and children: WHO evidence review”. Paediatr Int Child Health. Vol. 38, no. 1, **(2018)**, pp. S66-S75. doi: 10.1080/20469047.2017.1409455.

[22]. C. Medrano, L. Garcia-Guereta, J. Grueso, B. Insa, F. Ballesteros, J. Casaldaliga, V. Cuenca, F. Escudero, L. G. de la Calzada, M. Luis, M. Luque, A. Mendoza, F. Prada, M. Del Mar Rodríguez, P. Suarez, C. Quero, and M. Guilera; CIVIC Study Group from the Spanish Society of Pediatric Cardiology and Congenital Heart Disease. “Respiratory infection in congenital cardiac disease. Hospitalizations in young children in Spain during 2004 and 2005: the CIVIC Epidemiologic Study”. Cardiol Young. Vol. 17, no. 4, **(2007)**, pp. 360-71. doi: 10.1017/S104795110700042X.

[23]. E. Muthumbi, B. S. Lowe, C. Muyodi, E. Getambu, F. Gleeson, and J. A. G. Scott. “Risk factors for community-acquired pneumonia among adults in Kenya: a case-control study”. Pneumonia (Nathan). Vol. 9, no. 17, **(2017)**, pp. 1-9. doi: 10.1186/s41479-017-0041-2.

[24]. O. Y. Şahan, K. Erhan, and Z. U. Tutar. "Evaluation of children with congenital heart disease hospitalized with the diagnosis of lower respiratory tract infection". J. Pediatr. Res. Vol. 5, no. 1, **(2018)**, pp. 32–6. doi:10.4274/jpr.90532.

[25]. P. K. Singh, P. K. Chaudhuri, and A. K. Chaudhary. "Incidence of congenital heart disease in children with recurrent respiratory tract infection". IOSR J. Dent. Med. Sci. Vol. 16, no 9, **(2017),** pp. 89–94. e-ISSN: 2279-0853.

[26]. G. Vernet, C. Mary, D. M. Altmann, O. Doumbo, S. Morpeth, Z. A. Bhutta, and K. P. Klugman. "Surveillance for antimicrobial drug resistance in under-resourced countries". Emerg Infect Dis. Vol. 20, no. 3, **(2014)**, pp. 434-41. doi: 10.3201/eid2003.121157.

[27]. D. S. Waworuntu. "Pneumonia pada anak dengan penyakit jantung bawaan pirau kiri ke kanan = Pneumonia in children with left to right shunt congenital heart disease in developing country". (**2020)**.

[28]. World Health Organization. "Pocket book of hospital care for children: Guidelines for the management of common illness with limited resources". WHO Press. Vol. 2, **(2013)**, pp. 75-86. ISBN-13: 978-92-4-154837-3.

[29]. M. Zhang, L. Wang, R. Huang, C. Sun, N. Bao. and Z. Xu. "Risk factors of malnutrition in Chinese children with congenital heart defect". BMC Pediatr. Vol. 20, no. 1, **(2020)**, pp. 213. doi: 10.1186/s12887-020-02124-7.