Cardiology in the Young

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Original Article

Cite this article: Lozano-Espinosa DA, Huertas-Quiñones VM, and Rodríguez-Martínez CE (2020) Impact of pulmonary hypertension and congenital heart disease with hemodynamic repercussion on the severity of acute respiratory infections in children under 5 years of age at a pediatric referral center in Colombia, South America. *Cardiology in the Young* **30**: 1866–1873. doi: 10.1017/S1047951120002991

Received: 1 July 2020
Revised: 9 August 2020
Accepted: 26 August 2020
First published online: 30 September 2020

Keywords:
Acute respiratory infection; congenital heart disease; pulmonary hypertension; respiratory syncytial virus; echocardiography; children

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Impact of pulmonary hypertension and congenital heart disease with hemodynamic repercussion on the severity of acute respiratory infections in children under 5 years of age at a pediatric referral center in Colombia, South America

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Abstract

Background: Acute respiratory infection is one of the main causes of morbidity in children. Some studies have suggested that pulmonary hypertension and congenital heart disease with haemodynamic repercussion increase the severity of respiratory infections, but there are few publications in developing countries. *Methods:* This was a prospective cohort study evaluating the impact of pulmonary hypertension and congenital heart disease (CHD) with haemodynamic repercussion as predictors of severity in children under 5 years of age hospitalised for acute respiratory infection. *Results:* Altogether, 217 children hospitalised for a respiratory infection who underwent an echocardiogram were evaluated; 62 children were diagnosed with CHD with haemodynamic repercussion or pulmonary hypertension. Independent predictors of admission to intensive care included: pulmonary hypertension (RR 2.14; 95% CI 1.06–4.35, p = 0.034), respiratory syncytial virus (RR 2.52; 95% CI 1.29–4.92, p = 0.006), and bacterial pneumonia (RR 3.09; 95% CI 1.65–5.81, p = 0.000). A significant difference was found in average length of hospital stay in children with the cardiovascular conditions studied (p = 0.000). *Conclusions:* Pulmonary hypertension and CHD with haemodynamic repercussion as well as respiratory syncytial virus and bacterial pneumonia were predictors of severity in children with respiratory infections in this study. Early recognition of cardiovascular risks in paediatric populations is necessary to lessen the impact on respiratory infections.

Acute respiratory infections are one of the main causes of morbidity and mortality in children under 5 years of age, with respiratory syncytial virus being the most frequent causative agent.[1] There are associated clinical conditions that increase morbidity from this disease,[2] including cardiovascular factors such as increased pulmonary vascular resistance and congenital heart disease (CHD) with haemodynamic repercussion. This is probably explained by airway compression due to dilated pulmonary vessels, the growth of heart chambers and increased pulmonary vascular resistance, which leads to a lower alveolar reserve and a greater risk of pulmonary edema, in addition to a lower ability to compensate for the impaired oxygen distribution produced by respiratory infections.[2–4]

We know today that CHD is a public health problem, especially in less developed countries; the global incidence is 9 cases per 1000 newborns[5] and in Colombia, South America, CHDs are the number one congenital malformation, with an incidence of 15.1 events per 10,000 newborns.[6,7] Previous studies have shown the impact of CHD with haemodynamic repercussion on the severity of acute respiratory infections, especially when accompanied by respiratory syncytial virus and a history of prematurity.[8,9] Likewise, the impact of pulmonary hypertension on the severity of acute respiratory infections (especially those due to respiratory syncytial virus) has been studied, an impact explained by changes in lung volume, atelectasis or hyperinflation, hypoxic vasoconstriction, endothelin activation, and Th2-mediated immune response.[10–14]

Local studies (in Colombia) evidence the impact of pulmonary hypertension and CHD on a longer hospital stay and admission to the intensive care unit (ICU) in children hospitalised for respiratory infections.[15,16] The timely diagnosis and treatment of these diseases, the administration of palivizumab against respiratory syncytial virus in this population, and preventive measures against

respiratory infections represent the main pillars for decreasing morbidity in children with cardiovascular risk conditions.[17,18]

There are few studies investigating the role of these cardiovascular conditions on the severity of respiratory infections in children from low and middle income countries like ours; in addition, the few described have been developed mostly as retrospective study models. The objective of the present study was to determine the epidemiology and severity (understood as admission to ICU, need for mechanical ventilation, and longer hospitalisation) of acute respiratory infections in children under 5 years of age with pulmonary hypertension or CHD with haemodynamic repercussion at HOMI-Fundación Hospital Pediátrico de la Misericordia (Bogotá, Colombia, South America), between August 2017 and June 2018.

Methods

Study site

Bogotá is the capital and main economic centre of Colombia. It lies approximately 2.650 m above sea level, being the third highest city in South America (after Quito and La Paz). It is located in the centre of Colombia on the Bogotá savanna in the eastern Andes. Temperatures range from 5 to 19°C, with an average of 13°C. It has two rainy and two dry seasons. According to the last national survey in 2018, Bogotá has a population of 7,200,000 people, and it is estimated that by 2032, it will have reached 8,374,333. The Fundación Hospital Pediátrico de la Misericordia (HOMI) is located in Bogotá and is the national paediatric reference centre with the highest complexity level, serving children with all types of health insurance, including the paediatric population of neighbouring countries. It is also the health institution with the most experience and capacity to care for children with hematological and oncological diseases, nationwide.

Pulmonary hypertension and congenital heart disease detected by echocardiography

Pulmonary hypertension interpreted by echocardiography was assessed indirectly using the peak tricuspid regurgitation gradient, geometric changes in ventricular curvature, and the diastolic pulmonary insufficiency gradient.[19–21] The pressure gradient between the right ventricle and the right atrium was identified using the modified Bernoulli equation. In this study, pulmonary hypertension was defined as pulmonary artery pressure one-third or more of the systemic blood pressure. Furthermore, CHD refers to alterations in the structure and function of the heart, the circulatory system, and the great vessels which begin with embryogenesis and are present at birth. Echocardiography is the test used to detect anatomical alterations and represents the least invasive and most cost-effective method for cardiac evaluation.[22] The haemodynamic repercussion criteria for CHD were defined based on the echocardiographic findings; for ventricular and interatrial defects, these included ventricular dysfunction, pulmonary hypertension, right heart chamber volume overload and dilation, the size of the heart defects, the interdependence of the defects, interventricular septal displacement, and left ventricular geometric changes and systolic dysfunction.[23] In the particular case of patent ductus arteriosus, the relationship between the left atrium and the aorta, the size of the defect, pulmonary over-circulation, and left ventricular systolic and diastolic dysfunction were taken into account.[24] All echocardiograms were performed by paediatric cardiologists at the researchers' institution.

Study design and patient population

This was a prospective cohort study in which children under 5 years of age hospitalised for acute respiratory infection were evaluated in a paediatric healthcare reference centre in Colombia, South America (HOMI-Fundación Hospital Pediátrico de la Misericordia in the city of Bogotá) between August 2017 and June 2018. The patients admitted to the study were divided into two groups. Group 1 included children with CHD with haemodynamic repercussion or pulmonary hypertension, and Group 2 included patients without these conditions.

For the selection of patients with respiratory infection who required an echocardiogram, the paediatrician or paediatric intensivist evaluated whether there was a known history of CHD or pulmonary hypertension that could have explained the patient's clinical deterioration. Another criterion for performing the echocardiogram was abnormalities found on cardiovascular examination (heart murmurs, a loud second heart sound, or signs of heart failure) or abnormalities on the chest X-ray (such as an enlarged cardiac silhouette or alterations in the pulmonary flow) that would lead to a suspicion of CHD or pulmonary hypertension.

Data collection

Through the institutional program (HIS-ISIS), echocardiograms on hospitalised children under 5 years of age with a diagnosis of acute respiratory infection ordered due to confirmed or suspected CHD or pulmonary hypertension were identified daily; the study variables were entered in an Excel program. Once the patients were identified, follow up was performed throughout their respective hospitalisations.

After selecting the children for the cohort, the following demographic and clinical variables were collected: age, gender, and the type of acute respiratory infection that required hospitalisation (such as croup, bronchiolitis, wheezing episodes, viral or bacterial pneumonia), as well as viral microorganisms such as respiratory syncytial virus, adenovirus, influenza and parainfluenza 1, 2, and 3 (detected in nasopharyngeal aspirate by indirect immunofluorescence), medical risk-related health history such as respiratory diseases, syndromic diagnoses, anthropometric measures, history of prematurity (birth before 37 weeks), type of CHD, and classification of pulmonary hypertension (by indirect echocardiographic detection of vascular resistance in the pulmonary circulation). Likewise, the variables related to healthcare were evaluated and severity was defined as ICU admission, days of hospitalisation in a regular hospital ward, and prolonged hospitalisation (defined as a stay of 7 or more days, taking into account the average length of stay for respiratory infections in the researchers' hospital and comparative studies[15]). The ICU admission criteria in the researchers' institution were: hypoxemia, hypercapnia, apnea, or respiratory distress requiring mechanical ventilation (invasive or non-invasive).

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median, as appropriate. Categorical variables were presented as numbers (%). A bivariate analysis was used to determine the statistical relationship between the predictor variables and the outcome variables using the chi-square test. A logistic regression model was used for multivariate analysis, with an entry probability of the variables of 0.1 and an exit probability of 0.05, using the Wald forward selection method. Serious illness was defined as:

https://doi.org/10.1017/S1047951120002991 Published online by Cambridge University Press

admission to the ICU, need for mechanical ventilation, and prolonged hospital stay (defined as 7 or more days). The predictor variables included in the models were: age less than 12 months, malnutrition, respiratory syncytial virus, bronchiolitis, bacterial pneumonia, history of prematurity, bronchopulmonary dysplasia, CHD with heamodynamic repercussion, pulmonary hypertension, and respiratory syncytial virus + pulmonary hypertension. The result of the multivariate analysis was presented as relative risk (RR) with its 95% confidence interval (CI). All statistical tests were two tailed, and the significance level used was $p < 0.05$. A Student's t-test was performed to find a difference in mean days of hospitalisation. The data were analysed with the SPSS version 24.0 statistical package.

Results

Patient description

Between August 2017 and June 2018, 217 patients under 5 years of age who required hospitalisation for an acute respiratory infection and an echocardiogram due to a history or suspicion of CHD or pulmonary hypertension were identified. Sixty-two children had CHD with haemodynamic repercussion or pulmonary hypertension; of these, 35 only had CHD with haemodynamic repercussion (16.1%), 48 only had pulmonary hypertension (22.1%), and 21 had both conditions (10%). The group of patients without these risk conditions consisted of 155 patients; it should be noted that 19 children with some type of CHD but without haemodynamic compromise were found in this last group. The average age in the cohort was 9.8 months. Most of the children were between 1 and 12 months old (76%). Male sex was the most prevalent (63.6%).

Regarding related comorbidities, malnutrition was highly prevalent in the entire cohort (91/217, 41.9%) and even more frequent in patients with CHD and pulmonary hypertension (32/62, 51.6%). Altogether, 11.1% had some history of respiratory disease: bronchopulmonary dysplasia (19/217, 8.8%), asthma (4/217, 1.8%), and obstructive sleep apnea-hypopnea syndrome (1/217, 0.5%). A total of 28.1% of patients had a history of prematurity, and 9.7% had some type of syndrome: 7.4% had Down syndrome (16/217), 0.46% had Noonan syndrome (1/217), 0.46% had VACTER association (1/217), and 1.38% were being tested for a dysmorphic syndrome (3%).

Regarding the cohort's acute respiratory infections, bronchiolitis (80/217, 36.9%) and bacterial pneumonia (61/217, 28.1%) were the most frequent. In most patients, no microorganism was isolated (65.9%); respiratory syncytial virus was the most frequent microorganism (58/217, 26.7%). In total, 54 of the 217 patients had CHD (25%); 35 of these had haemodynamic repercussion, with 54 heart defects, and 19 did not have haemodynamic repercussion, with 21 heart defects. Atrial septal defect was the most frequent heart disease in the cohort (44%), followed by patent ductus arteriosus (29.3%), and ventricular septal defect (13.3%). Acyanotic CHD with increased pulmonary flow made up the majority of the study cases (88%). A total of 48 children with pulmonary hypertension were found in this study, of whom 39.6% represented Group I of the 2018 Nice classification (Group 1.4.4 includes patients with simple operable and inoperable CHD) and 60.4% were in Group III (due to lung diseases and/or hypoxia).[21]

The average length of hospitalisation was 11.2 days, with a minimum of 1 and a maximum of 79 days; 60.3% of the patients had a hospital stay of 7 or more days (prolonged). Of the 217 patients, 67 required ICU admission (30.9%) and 48 required some type of mechanical ventilation (22.1%), with an average stay of 7.2 and 6.1 days, respectively. The average days in hospitalisation, ICU, and mechanical ventilation were 16.3, 9.7, and 8.6 days, respectively, in children with a CHD with haemodynamic repercussion or pulmonary hypertension, compared to 9.1, 5.4, and 4.5 days in children without these conditions. In the group of patients with CHD with haemodynamic repercussion or pulmonary hypertension, there were six hospital readmissions for respiratory symptoms during the 11-month follow-up, while in the groups of patients without theses conditions, there were eight readmissions. In this last group, one patient died. The main frequencies of the studied cohort are described below (see Table 1).

Variable analysis

The bivariate analysis results with a p-value less than 0.05 for the ICU admission variable were: prematurity ($p = 0.019$), bronchopulmonary dysplasia ($p = 0.032$), respiratory syncytial virus ($p = 0.007$), bacterial pneumonia ($p = 0.000$), pulmonary hypertension ($p = 0.004$), and pulmonary hypertension with respiratory syncytial virus ($p = 0.002$) (see Table 2). For the mechanical ventilation requirement variable they were: prematurity ($p = 0.018$), respiratory syncytial virus ($p = 0.003$), bacterial pneumonia ($p = 0.000$), pulmonary hypertension ($p = 0.034$), and pulmonary hypertension with respiratory syncytial virus ($p = 0.004$) (see Table 3). Regarding the prolonged hospital stay (7 or more days) variable: respiratory syncytial virus ($p = 0.002$), bronchiolitis ($p = 0.004$), bacterial pneumonia ($p = 0.000$), and pulmonary hypertension ($p = 0.011$) (See Table 4). Children who only had CHD with haemodynamic repercussion did not have a significant association with the variables of ICU admission ($p = 0.2$), mechanical ventilation requirement ($p = 0.741$), or prolonged hospitalisation ($p = 0.716$). We found a statistically significant relationship between the subgroup of children with pulmonary hypertension and respiratory syncytial virus and admission to the ICU ($p = 0.002$), but this was not the case for the prolonged ICU stay outcome variable ($p = 0.154$).

In the multivariate analysis, a logistic regression model was employed with an input probability of the model variables of 0.1 and an exit probability of 0.05, using the Wald forward selection method. Reduced model number 3 better explained the relationship of respiratory syncytial virus (RR 2.52; 95% CI 1.29–4.92, $p = 0.006$), bacterial pneumonia (RR 3.09; 95% CI 1.65–5.81, $p = 0.000$), and pulmonary hypertension (RR 2.14; 95% CI 1.06–4.35, $p = 0.034$) to the variable ICU admission. Reduced model number 2 explained the relationship of respiratory syncytial virus (RR 3.20; 95% CI 1.51–6.75, $p = 0.002$) and bacterial pneumonia (RR 6.20; 95% CI 3.006–12.81, $p = 0.000$) to the variable mechanical ventilation. Reduced model number 2 explained the relationship of respiratory syncytial virus (RR 3.81; 95% CI 1.71–8.49, $p = 0.001$) and bacterial pneumonia (RR 10.89; 95% CI 4.609–25.75, $p = 0.000$) to the variable prolonged hospitalisation. The average days of hospitalisation, days in ICU and days of mechanical ventilation in the group with pulmonary hypertension or CHD with haemodynamic repercussion were 16.3, 9.7, and 8.6, compared to 9.1, 5.4, and 4.5 days in children without these risk conditions, indicating a significant difference in means ($p = 0.000$; $p = 0.000$; and $p = 0.001$, respectively).

An analysis of the interactions between other variables was performed: in the 48 children with only pulmonary hypertension, a more frequent relationship was found with CHD with

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Table 1. Description of children under 5 years of age with acute respiratory infections

Variable	Group 1 With CHD with haemodynamic repercussion/pulmonary hypertension (62 children)	Group 2 Without CHD with haemodynamic repercussion/without pulmonary hypertension (155 children)	TOTAL 217
Gender			
Male	30 (48.4%)	108 (69.7%)	138 (63.6%)
Female	32 (51.6%)	47 (30.3%)	79 (36.4%)
Age group			
1–12 months	41 (66.1%)	124 (80%)	165 (76%)
13–24 months	11 (17.7%)	17 (11%)	28 (12.9%)
25–36 months	1 (1.6%)	9 (5.8%)	10 (4.6%)
37–48 months	4 (6.5%)	4 (2.6%)	8 (3.7%)
49–60 months	5 (8.1%)	1 (0.6%)	6 (2.8%)
Microorganism			
Not detectable	40 (64.5%)	103 (66.4%)	143 (65.8%)
Respiratory syncytial virus	17 (27.5%)	41 (26.5%)	58 (26.72%)
Influenza	0 (0%)	5 (3.2%)	5 (2.3%)
Adenovirus	1 (1.6%)	1 (0.6%)	2 (0.92%)
Others	4 (6.4%)	5 (3.3%)	9 (4.26%)
Type of acute respiratory infection			
Bronchiolitis	15 (24.2%)	65 (41.9%)	80 (36.9%)
Bacterial pneumonia	28 (45.2%)	33 (21.3%)	61 (28.1%)
Atypical/viral pneumonia	3 (4.9%)	13 (8.4%)	16 (7.4%)
First wheezing episode	1 (1.6%)	1 (0.6%)	2 (0.9%)
Second wheezing episode	1 (1.6%)	8 (5.2%)	9 (4.1%)
Recurrent wheezing	5 (8%)	6 (3.9%)	11 (5.1%)
Croup	0 (0%)	2 (1.3%)	2 (0.9%)
Bronchiolitis/bacterial superinfection	5 (8%)	14 (9%)	19 (8.8%)
Laryngotracheobronchiolitis	4 (6.5%)	13 (8.4%)	17 (7.8%)
Pulmonary hypertension			
Group I	19 (39.6%)		
Group III	29 (60.4%)		
TOTAL	48 (100%)		
Congenital heart disease			
Atrial septal defect	19 (35.1%)	14 (66.7%)	33 (44%)
Patent ductus arteriosus	18 (33.3%)	4 (19%)	22 (29.3%)
Ventricular septal defect	8 (15%)	2 (9.5%)	10 (13.34%)
Pulmonary stenosis	2 (3.7%)	1 (4.8%)	3 (4%)
Aortic stenosis	2 (3.7%)	0 (0%)	2 (2.7%)
Coarctation of the aorta	1 (1.85%)	0 (0%)	1 (1.33%)
Single ventricle	3 (5.5%)	0 (0%)	3 (4%)
Atrioventricular canal (Rastelli A)	1 (1.85%)	0 (0%)	1 (1.33%)
TOTAL	54 (100%)	21 (100%)	75 (100%)
Average length of stay	16.3 days	9.1 days	11.2 days
Prolonged hospitalisation (7 or more days)			
TOTAL	47 (75.8%)	84 (54.2%)	131 (60.4%)
Intensive care unit			
TOTAL	29 (46.8%)	38 (24.5%)	67 (30.9%)
Mean	9.7 days	5.4 days	7.2 days
Mechanical ventilation			
TOTAL	19 (30.6%)	29 (18.7%)	48 (22.1%)
Mean	8.6 days	4.5 days	6.1 days

https://doi.org/10.1017/S1047951120002991 Published online by Cambridge University Press

Table 2. Bivariate analysis. Clinical conditions associated with admission to ICU

Variables	Admitted to ICU	Not admitted to ICU	RR (95% CI)	p
Bacterial pneumonia	38	42	2.24 (1.509–3.33)	0.000
Pulmonary hypertension and respiratory syncytial virus	9	4	2.43 (1.59–3.71)	0.002
Pulmonary hypertension	23	25	1.84 (1.24–2.71)	0.004
Respiratory syncytial virus	26	32	1.73 (1.17–2.56)	0.007
Prematurity	26	35	1.62 (1.09–2.40)	0.019
Bronchopulmonary dysplasia	10	9	1.82 (1.13–2.95)	0.032
CHD with haemodynamic repercussion	14	21	1.37 (0.86–2.18)	0.2
Bronchiolitis	30	81	0.77 (0.51–1.15)	0.209
Malnutrition	31	60	1.19 (0.80–1.17)	0.387
Down syndrome	4	12	0.79 (0.33–1.9)	0.597
Less than 12 months	50	115	0.92 (0.58–1.45)	0.745

Table 3. Bivariate analysis. Clinical conditions associated with mechanical ventilation

Variables	Mechanical ventilation	Without mechanical ventilation	RR (95% CI)	p
Bacterial pneumonia	33	47	3.76 (2.18–6.49)	0.000
Respiratory syncytial virus	21	37	2.13 (1.31–3.46)	0.003
Pulmonary hypertension and respiratory syncytial virus	7	6	2.67 (1.51–4.75)	0.004
Prematurity	20	41	1.82 (1.11–2.98)	0.018
Pulmonary hypertension	16	32	1.76 (1.05–2.92)	0.034
Bronchopulmonary dysplasia	7	12	1.77 (0.93–3.4)	0.106
Bronchiolitis	20	91	0,.68 (0.41–1.13)	0.136
Less than 12 months	34	131	0.77 (0.44–1.31)	0.339
Down syndrome	3	13	0.83 (0.29–2.39)	0.736
CHD with haemodynamic repercussion	7	28	0.88 (0.43–1.81)	0.741
Malnutrition	20	71	0.98 (0.59–1.64)	0.966

Table 4. Bivariate analysis. Clinical conditions associated with a prolonged stay

Variables	7 or more days of hospitalisation	Fewer than 7 days of hospitalisation	RR (95% CI)	p
Bacterial pneumonia	73	7	1.78 (1.94–2.13)	0.000
Respiratory syncytial virus	48	10	1.38 (1.16–1.64)	0.002
Bronchiolitis	63	48	0.75 (0.61–0.91)	0.004
Pulmonary hypertension and respiratory syncytial virus	13	0	1.56 (1.41–1.74)	0.007
Pulmonary hypertension	39	9	1.32 (1.10–1.58)	0.011
Bronchopulmonary dysplasia	16	3	1.31 (1.05–1.63)	0.078
Less than 12 months	104	61	0.84 (0.69–1.02)	0.112
Down syndrome	9	7	0.84 (0.54–1.31)	0.398
Prematurity	42	19	1.06 (0.86–1.305)	0.566
CHD with haemodynamic repercussion	24	11	1.04 (0.81–1.34)	0.716
Malnutrition	61	30	1.03 (0.85–1.24)	0.765

https://doi.org/10.1017/S1047951120002991 Published online by Cambridge University Press

haemodynamic repercussion (n = 21/35, 60%), bronchopulmonary dysplasia (n = 9/19, 47.4%), malnutrition (n = 23/91, 25.3%), Down syndrome (n = 10/16, 62.5%), and bacterial pneumonia (n = 27/80, 33.8%); with a significant association with bacterial pneumonia (RR 2.2; 95% CI 1.33–3.62, p = 0.002), CHD with haemodynamic repercussion (RR 5.28; 95% CI 2.91–9.57, p = 0.000), Down syndrome (RR 5.9; 95% CI 2.24–15.3, p = 0.000), and bronchopulmonary dysplasia (RR 3.1; 95% CI 1.36–7.35, p = 0.006). However, it was not significant for respiratory syncytial virus (RR 1.01; 95% CI 0.58–1.78, p = 0.95). Similarly, children with bronchopulmonary dysplasia had a significant association with bacterial pneumonia (RR 1.89; 95% CI 1.28–2.50, p = 0.03). Patients who only had CHD with haemodynamic repercussion were found to frequently have malnutrition (n = 21/91, 23.1%), respiratory syncytial virus (n = 11/58, 18.9%), bronchiolitis (n = 18/111, 16.2%), bacterial pneumonia (n = 11/80, 13.8%), prematurity (n = 12/61, 19.7%), Down syndrome (n = 7/16; 43.8%), and bronchopulmonary dysplasia (n = 4/19, 21%); with a significant association with malnutrition (RR 2.07; 95% CI 1.11–3.81, p = 0.018) and Down syndrome (RR 3.14; 95% CI 1.63–6.03, p = 0.002). When the 51 patients who had CHD with and without haemodynamic repercussion were combined, it was observed that they frequently presented with bronchiolitis (n = 29/111, 26.1%), respiratory syncytial virus (n = 14/58, 24.1%), Down syndrome (n = 8/16, 50%), bacterial pneumonia (n = 16/80, 20%), prematurity (n = 20/61, 32.8%), and bronchopulmonary dysplasia (n = 4/19, 21%); with a significant association with Down syndrome (RR 2.18; 95% CI 1.25–3.79, p = 0.016).

Discussion

In the present study, of the 217 children with acute respiratory infections, pulmonary hypertension was detected in 48 (22.1%), CHD with haemodynamic repercussion in 35 (16.1%), and both conditions in 21 (10%). We found that pulmonary hypertension and CHD with haemodynamic repercussion were predictors of severity for acute respiratory infections in children under 5 years of age in Colombia and, most likely, in low-income countries in the region with similar conditions. Likewise, respiratory syncytial virus, bronchiolitis, and bacterial pneumonia were important factors in predicting the severity of acute respiratory infections in the children studied. The current results have allowed us to better understand the predictors of severity in these patients. This may have implications for planning interventions to prevent respiratory infections, especially during the rainy seasons, such as the reinforcement of hand washing techniques, the adequate use of personal protective elements, nutrition assurance, and policies to guarantee passive immunisation with palivizumab against respiratory syncytial virus in children with cardiovascular risk factors. In addition, in the particular case of CHD and pulmonary hypertension, this would include encouraging caregivers to recognise symptoms and related signs early, and health professionals to diagnose promptly.

We were able to determine that, in our study centre, children under 5 years old hospitalised for acute respiratory infections had 2.1 times more risk of ICU admission when they had pulmonary hypertension compared to those who did not have this condition. Children with CHD with haemodynamic repercussion and pulmonary hypertension did not have a longer stay (understood as 7 or more days) than those who did not have these conditions, taking into account comparative studies[15] and the time established in our institution. However, a significant difference was found in the average number of days in ICU and total hospitalisation when they were evaluated together. Children with respiratory syncytial virus had 2.5, 3.2, and 3.8 times greater risk of ICU admission, mechanical ventilation requirement, and prolonged hospitalisation, respectively, compared to children without respiratory syncytial virus. Likewise, children with bacterial pneumonia had 3.09, 6.2, and 10.8 times the risk of admission to ICU, mechanical ventilation requirement, and prolonged hospitalisation, respectively.

In our study, the most frequent microbiological agent was respiratory syncytial virus (26.7%), and bronchiolitis and bacterial pneumonia were the most prevalent respiratory infections (36.8 and 28.1%, respectively). These findings are consistent with those reported by Medrano C, et al,[8] who evaluated the epidemiological behaviour of acute respiratory infections in 167 children under 24 months of age who had CHD with haemodynamic repercussion. This prospective, multicentre study found that the most frequent microbiological agent was respiratory syncytial virus, and bronchiolitis and pneumonia were the most frequent lower respiratory tract infections (54.1 and 19.1%, respectively). It also showed a significant frequency of children with Down syndrome (OR 1.89), 22q11 deletion (OR 4.31), and prematurity (OR 1.54). These latter findings are related to what was found in our study, where prematurity occurred in 28.1% of the entire cohort and in 20% of the 54 children with CHD. In addition, Down syndrome was significantly associated with CHD (RR 2.18; 95% CI 1.25–3.79, p = 0.016). In our study, the ICU admission percentage was 30.9% (20.9% in children with CHD), a higher figure than the 18.1% described by Medrano C, et al.[8] The high percentage of ICU admissions in our study is probably explained by the fact that most children with acute respiratory infections who needed an echocardiogram had a more marked deterioration or a more complicated disease course that required ruling out an underlying cardiac risk condition. The increased severity of acute respiratory infections in children with CHD, especially those with haemodynamic impact, is due to the severely restricted ability of cardiac function to increase cardiac output and oxygen supply, associated with compromised oxygen uptake due to increased respiratory effort and the inflammatory effect on the airway. Furthermore, the compressive effect of the dilated chambers on the bronchi and the greater pulmonary venous return lead to a lower alveolar reserve.[3,4]

A local study by Rodríguez DA, et al[15] described the epidemiological behaviour of the predictor variables in children who had acute respiratory infections due to respiratory syncytial virus. This retrospective cohort study described the following as severity (ICU admission) variables: a history of prematurity (RR 1.61; 95% CI 1.20–2.17, p = 0.001), age less than 6 months (RR 2.01; 95% CI 1.70–2.38, p < 0.001), and CHD (RR 2.03; 95% CI 1.16–3.54, p = 0.013). In their study, 43% of the patients were younger than 12 months, bronchiolitis was the most frequent infection (74.6%) and 22.1% were admitted to the ICU with a significant association (p < 0.001). Comparing this to our study, we found that prematurity was a risk variable for ICU admission (p = 0.019), and the prevalence of children younger than 12 months was 76%, and 20% for children in this age group with respiratory syncytial virus. Although children with CHD with haemodynamic repercussion were not significantly associated with ICU admission (p = 0.02), they did have a significantly higher average length of stay, together with those with pulmonary hypertension, than those without these conditions (p = 0.000). Children younger than 12 months and children with a history

https://doi.org/10.1017/S1047951120002991 Published online by Cambridge University Press

of prematurity are at greater risk due to immunological immaturity and incomplete development of their lung function, making these patients more susceptible to the harmful effect of respiratory pathogens.[25]

Dai Kimura, et al[10] showed a higher frequency of pulmonary hypertension during respiratory syncytial virus infection with: CHD, paediatric chronic lung disease, prematurity, and Down syndrome, having a significant association with ICU admission (OR: 6.4; 95% CI 2.2–18.8, p = 0.0007), intubation (OR: 4.7; 95% CI 1.8–12.3, p = 0.002), high frequency ventilation (OR: 8.4; 95% CI 2.95–23.98, p < 0.0001), and prolonged hospitalisation in ICU (OR: 4.9; 95% CI 2.0–11.7, p = 0.0004). These findings are consistent with those in our study, in which both pulmonary hypertension and pulmonary hypertension plus respiratory syncytial virus infection were risk factors for ICU admission (p = 0.004 and p = 0.007, respectively), although this was not true for the outcome variable "prolonged hospitalisation in ICU (10 or more days)" (p = 0.154). The above is probably explained by the impact of the respiratory syncytial virus on the airway, which has a lower baseline alveolar reserve. In our study, prolonged hospitalisation in ICU was not significant due to the limited number of cases with these conditions, unlike Dai Kimura, et al´s study.[10] In their study, Bardi-Peti and Ciofu EP[11] found that, for infants with bronchoobstructive disease, hospitalisation was significantly higher when they had pulmonary hypertension (p = 0.04 in the 1–2 months subgroup and p = 0.005 in the 2–12 months subgroup), compared to the representative prolonged hospitalisation results in our children with pulmonary hypertension (p = 0.011), although the subgroup of infants younger than 12 months did not have a significant association (p = 0.112). Pulmonary hypertension is a risk factor in children with acute respiratory infections; in contrast to what was found in our study, Pedraza AM's[10] study reported a history of recurrent wheezing (RR 1.77; 95% CI 1.12–2.79, p < 0.015) and a history of pulmonary hypertension (RR 3.62; 95% CI 2.38–5.52, p < 0.001) as independent predictors of severity (increased ICU admission) in children younger than 5 years with acute lower respiratory tract infection. The greater severity of respiratory infections in children with CHD with haemodynamic repercussion or pulmonary hypertension demonstrated in related studies and found in our research could be explained by the lower alveolar reserve, the greater risk of pulmonary edema and a lower ability to compensate for the impaired oxygen distribution caused by respiratory infections.[3,4]

The authors recognise at least three limitations of this study. First, the patients studied did not represent all admissions for respiratory infections in the research period, since the selected children were those who, due to greater deterioration or cardiovascular history, required an echocardiographic study. Also, a sample size was not formally calculated. This could represent a selection bias that may have overestimated the results. Secondly, it is important to mention that the study was carried out in a tertiary referral hospital, which could limit the generalisation of the results to other settings. Finally, other important variables, such as the administration of palivizumab, were not included since not all patients for whom it was indicated had received it, or the parents did not provide vaccination records. Thus, as is the case in other observational epidemiological studies, residual confounding cannot be excluded, and these results must be interpreted with caution. As far as we know, this is the first prospective study at the local level to evaluate the impact of CHD and pulmonary hypertension on the severity of respiratory infections in children under 5 years of age, which represents the main strength to be highlighted.

In conclusion, the present study demonstrates that, in our paediatric reference centre, cardiovascular conditions understood as CHD with haemodynamic repercussion or pulmonary hypertension are risk conditions that increase morbidity in children with respiratory infections, although we also found predictors of severity such as bacterial pneumonia and respiratory syncytial virus. Echocardiography is the most cost effective and non-invasive method of detecting pulmonary hypertension and cardiac abnormalities and should be routinely implemented, especially in children with rapid and torpid acute respiratory infection deterioration, and even more so if they have a history of prematurity and bronchopulmonary dysplasia. Pulmonary hypertension could be a poor prognostic marker in children with acute respiratory infections, especially if there is a CHD with haemodynamic repercussion. Therefore, its timely diagnosis and treatment, as well as primary prevention against respiratory syncytial virus in at-risk populations and education regarding protective measures against respiratory infections are important strategies to reduce morbidity in children under 5 years of age in our setting and in countries of the region with low or middle incomes and similar social and demographic characteristics.

Acknowledgements. We would like to thank the Department of Paediatric Cardiology of HOMI-Fundación Hospital Pediátrico de la Misericordia directed by Dr. Roy Sanguino Lobo and the Universidad Nacional de Colombia for their support, as well as Germán E. García Laverde for his methodological support throughout this project.

Financial Support. This research study received no specific grants from any funding agency, commercial, or not-for-profit sectors.

Conflicts of Interest. None.

Ethical Standards. The research protocol was presented to the Research Committee of the HOMI-Fundación Hospital Pediátrico de la Misericordia for review and approval. The present study is classified as "without risk".

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