Asian Jr. of Microbiol. Biotech. Env. Sc. Vol. 26, No. (1) : 2024 : 163-167

ISSN-0972-3005

DOI No.: http://doi.org/10.53550/AJMBES.2024.v26i01.027

THE DUAL RISK OF MORTALITY AND MORBIDITY IN INFANTS WITH CONGENITAL HEART DISEASE AND PNEUMONIA INFECTION AND VIRAL AETIOLOGY

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(Received 24 June, 2023; Accepted 26 August, 2023)

***Key words**: Respiratory syncytial virus, Congenital heart disease, Pneumonia, Congestive heart failure, Pulmonary hypertension*

Abstract– Infants with congenital heart disease (CHD) are at an elevated risk for severe respiratory illness, with pneumonia infection posing a particular threat. CHD patients hospitalized with pneumonia have mortality and morbidity rates higher compared to those without pneumonia infection. However, it remains unclear whether viral pneumonia infection determine recent morbidity and mortality rates from pneumonia infection in a paediatric CHD population and the prevalence of viral aetiology in the pneumonia infection. We enrolled 100 infants with congenital anomalies of these 64 with CHD, including those with (n=32) and without (n=32) pneumonia, remaining 36 with different congenital anomalies with Upper and Lower Respiratory Tract Infection were excluded. We collected nasopharyngeal swab samples and recorded demographic data and clinical history. The samples were then processed for Respiratory Syncytial Virus (RSV) A and B specific RNA using a real-time PCR kit. All infants enrolled in this study were aged between 0-12 months, with 37 males and 27 females. Among the infants with pneumonia, one male and one female were infected with both RSV A and B, and died during treatment due to Congestive Heart Failure. Our results indicate that CHD patients with pulmonary hypertension is associated with increased mortality rates compared to the children without pneumonia. The RSV viral aetiology is observed as 6.25% in children with pneumonia with 100% mortality. These findings underscore the importance of careful monitoring and timely intervention in CHD patients with pulmonary hypertension, particularly those with RSV infection. Further studies are needed to investigate the underlying mechanisms contributing to the elevated mortality risk associated with RSV infection in this vulnerable population.

INTRODUCTION

Pneumonia is a significant respiratory condition that poses a considerable health burden, particularly among newborns and young children. Among the various etiological agents responsible for pneumonia, respiratory syncytial virus (RSV) stands out as a leading cause (Nair *et al*., 2010; Scheltman *et al*., 2017). RSV is estimated to cause 33.8 million new episodes of acute lower respiratory infections (ALRI) in children under 5 years of age each year. Of these, 3.4 million episodes are severe enough to require hospitalization. RSV is a major cause of pneumonia in children under 5 years of age in India (Chakrabarti *et al*., 2019; Noble *et al*., 2022). An estimated 1.5 million children under 5 years of age are hospitalized with RSV-induced pneumonia each year in India. Of these, an estimated 30,000 to 60,000 children die (Broor *et al*., 2018). RSV-induced pneumonia is a highly contagious viral infection transmitted through contact with contaminated respiratory secretions. The clinical presentation of RSV pneumonia typically includes fever, cough, wheezing, tachypnea, hypoxemia, altered levels of reactive C protein (CRP), and pulmonary abnormalities such as increased texture or mottled

shadows (Kaler *et al*., 2023). Infants with congenital heart disease (CHD) are particularly susceptible to severe outcomes associated with RSV pneumonia (Checchia *et al*., 2017; Daurach *et al*., 2019). Hospitalizations resulting from RSV infection in this patient population carry a high risk of severe or even fatal illness. In fact, RSV pneumonia exacerbations can further complicate underlying comorbid conditions, including chronic obstructive pulmonary disease and congestive heart failure (Fixler *et al*., 1996; Altman *et al*., 2000; Jung *et al*., 2011; Paes *et al*., 2016). While community outbreaks contribute to the spread of RSV, sporadic outbreaks can occur outside the typical RSV season (Thorburn *et al*., 2004; Broberg *et al*., 2018; Eden *et al*., 2022; Garg *et al*., 2022). The economic burden of RSV-induced pneumonia is significant. In the United States, the annual cost of RSV-related hospitalizations is estimated to be over $1 billion (Bhuiyan *et al*., 2010; Baral *et al*., 2020; Yoon *et al*., 2020). RSV-induced pneumonia is also a leading cause of death in infants and young children in developing countries (Rodriguez *et al*., 2014). Therefore, controlling RSV transmission and preventing pneumonia primarily revolve around measures aimed at minimizing close contact with infected individuals and reducing exposure to infectious respiratory secretions. It is crucial to recognize that mortality rates associated with RSV-induced pneumonia are generally low among healthy infants but significantly increase among children with CHD. Infants with CHD and preterm newborns with low birth weight exhibit a higher likelihood of hospitalization, including admission to intensive care units, ventilator support, and other medical procedures, further escalating the risk of additional infections (Figueras-Aloy *et al*., 2016; Checchia *et al*., 2017). The aim of the present study is to determine the impact of RSV infection on mortality and morbidity rates in CHD patients and to provide a better understanding of the relationship between RSV and CHD where the improved health outcomes and quality of life for infants with CHD by providing a better understanding of the factors that contribute to their risk of severe respiratory illness.

MATERIALS AND METHODS

Sample collection and inclusion criteria

We prospectively studied all infants under the age group of one year, who were admitted in a tertiary care centre, at Hyderabad. A total of 100 infants with congenital anomalies were diagnosed. Inclusion criteria: All the infants with CHD were included in this study. **Exclusion criteria**: Infants other than CHD were excluded in this study. For analysis infants with CHD were subsequently grouped into those with Pneumonia and without Pneumonia. All the infants with CHD were initially evaluated and assessed for the type of lesions based on 2D echo Cardiogram findings. Patient evaluation included the demographic details regarding gender, date of birth, gestational age, birth weight, clinical abnormalities, Cardio diagnosis and daily review of the treatment given documented in the medical charts. Infants with abnormalities other than CHD were excluded. Nasopharyngeal swab samples were collected from all the patients and stored at -20 ºC until processed.

Nucleic acid extraction and RT-PCR analysis

RNA extraction was done using Qline RNA extraction kit (Q-Line Biotech Pvt., Ltd., India) and then the samples were subjected for detection of Respiratory 20 Panel (Genepath D, India), which included RSV A and B antigen. The assay consists of enzyme (Reverse Transcriptase and Taq DNA polymerase), PCR buffer, dNTPs, target specific primers and Probes (PR Mix 1, 2, 3, 4, 5, 6, 7), dH2O and RNAse inhibitors. The PCR master mix includes target specific probe-primer mixes (Parainfluenza1, Parainfluenza2, Parainfluenza4, Enterovirus, Metapneumovirus, Influenza A, RSV A/B, Parainfluenza 3, Bocavirus, Rhinovirus, Coronavirus229E Coronavirus OC43, Coronavirus NL63, Corona virus HKU1, *H. influenza* type B, Influenza B, *M. Pneumoniae*, Pandemic H1N1, Parechovirus, Adenovirus) for the direct detection of the specific amplicon in FAM, Texas Red, Cy5 and HEX channel. In addition, it contains an internal control amplification system to identify possible PCR inhibition and RNA purification efficiency. External positive control is supplied by the manufacturer and used as qualitative determination.

RESULTS AND DISCUSSION

A total of 100 infants with Congenital Anomalies were diagnosed and only total of 64 werecongenital heart disease (CHD) were included in this study, with 32 infants presenting with pneumonia and 32 without Pneumonia. All infants were within the age range of 0-12 months, and the sample consisted of 37 males and 27 females. A comparison between

patients with CHD who have been diagnosed with pneumonia and those without pneumonia (Table 1). Of the infants with pneumonia, one male and one female were co-infected with both RSV A and B and ultimately died from Congestive Heart Failure during treatment. Comparison of the characteristics and disease course between the two groups revealed a significant difference in the severity of RSV infection. Infants with CHD and pneumonia were more likely to require ICU care, and the occurrence of catastrophic outcomes was found to be 6.4% among infants with pneumonia compared to those without (Figure 1).

Table 1. The characteristic of the study participants.

S. No.	Characteristics	Patients with CHD	
		With Pneumonia	Without Pneumonia
1	No. of infants	32	32
2	Male: Female ratio	13:19	14:18
3	Mean age	0.5	0.46
4	Mean birth weight	2.26	2.64
5	Mean Hospitalisation for RSV (Days)	32	30
6	Mortality rate	6.4	Zero
7	No. of deaths	2	Zero

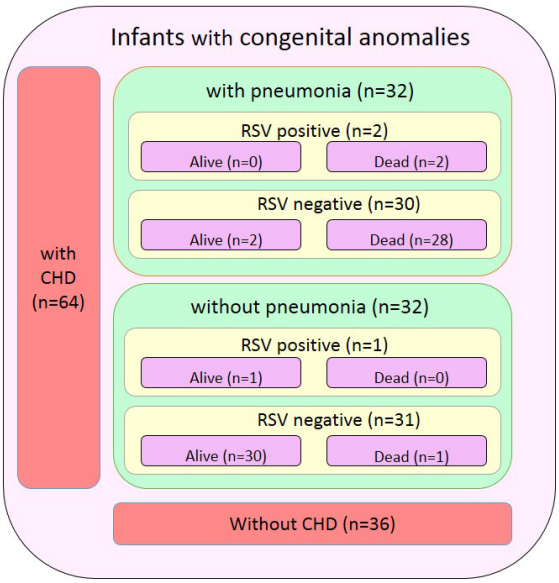

Fig. 1. Relationship diagram of infants having congenital anomalies and pneumonia with and without RSV infection.

These findings suggest that the presence of pneumonia in infants with CHD is associated with a more severe disease course and higher risk of adverse outcomes, particularly in the case of RSV co-infection. Further research is needed to identify effective interventions to prevent and manage pneumonia in this vulnerable population. The distribution of congenital heart defect (CHD) cases along with associated complications, highlighting fatal and non-fatal outcomes were represented in Table 2. The dataset includes two fatal cases and sixteen non-fatal cases. Various types of CHD are presented, each associated with specific additional defects.

Table 2. Comparison of CHD infants with and without pneumonia

Diagnosis	Fatal case (n=2)	Non-fatal case (n=16)
ASD with PDA	1	-
Large 2.3 mm PDA, Small VSD	1	-
CHD with PFO	-	1
CHD with ASD, PDA	-	2
CHD with PDA.PFO	-	5
CHD with MUSCULAR VSD	-	1
CHD with PDA	-	3
CHD with ASD, PDA	-	2
CHD with ASD, VSD	-	1
CHD with ASD	-	1

*CHD- Congenital Heart Disease; ASD- Artial Septal Defect; VSD- Ventricular Septal Defect; PDA- Patent Ductus Arteriosus; PFO- Patent Foramen Ovale.

Infants with Congenital Heart Disease (CHD) and pulmonary hypertension are particularly vulnerable to mortality. In this study, there was no mortality observed in infants without pneumonia, but infants with CHD and pneumonia were found to be at a higher risk of mortality. The mean age and birth weight did not differ significantly between the two groups, and they were similar in terms of age, type of cardiac lesions, and presence of pulmonary hypertension. Two infants with ASD with PDA and VSD with PDA, respectively, were infected with RSV and pneumonia, leading to Congestive Cardiac Failure. This highlights the unique nature of severe RSV disease in high-risk children, which can lead to serious respiratory compromise, including deterioration of pulmonary function, pneumonia, and even death (Eden *et al*., 2022). Previous studies have also found that RSV infection is linked to higher morbidity in infants with CHD, increasing their likelihood of developing a serious illness (Broberg *et al*., 2018).Infants with low birth weight were also found to be at higher risk of developing

infections, and comorbidities such as Broncho pulmonary dysplasia, malnutrition, chronic respiratory disease, and neurological disease were commonly observed in patients with CHD and RSV infection (Garg *et al*., 2022). Pulmonary hypertension was found to be a significant co-morbid condition in children with CHD and RSV lower respiratory tract infections (Thorburn *et al*., 2004; Bhuiyan *et al*., 2017). Improvements in inpatient management in the critical care unit and paediatric cardiac surgery have contributed significantly to the drop in mortality from RSV infection in infants with congenital heart disease over the years (Baral *et al*., 2020). Although mortality rates have decreased, morbidity rates are still associated with complex chronic conditions, emphasizing the need for continued efforts to prevent and manage RSV infections in vulnerable populations.

CONCLUSION

Despite the decline in hospitalization and mortality rates associated with respiratory syncytial virus (RSV) infections; viral respiratory infections continue to pose a significant risk for respiratory and cardiac failure in young infants with congenital heart disease. RSV is now being recognized as an opportunistic pathogen in this high-risk group of infants, highlighting the importance of increased attention to RSV prevention and management. Preoperative screening for RSV in new-borns with symptoms and strict adherence to infection control guidelines are essential for reducing postoperative morbidity and mortality. These measures can help to identify and manage RSV infections early, prevent its spread, and reduce the associated risks for vulnerable populations. The continued attention and effort towards preventing and managing RSV infections in infants with congenital heart disease are crucial to reduce the risk of respiratory and cardiac failure and improve overall health outcomes.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support from the Department of Health Research, Government of India and Indian Council of Medical Research, Government of India under the scheme "PM-ABHIM-VRDL".

Conflicts of Interest

The authors declare that they don't have any conflict of interest.

Authors Contribution

Study design: VSR, HS, PSR; Sample and data collection: PMMR; Sample analysis: WS; Data analysis and manuscript preparation: WS, MS; Manuscript review: SFM; Manuscript proof reading: VSR, HS, PSR.

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