

Age-Dependent Clinical Characteristics of Acute Lower Respiratory Infections in Young Hospitalized Children with Respiratory Syncytial Virus Infection

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Introduction: Human respiratory syncytial virus (HRSV) is the most common cause of acute lower respiratory infection (LRTI) in children. The main clinical manifestations are fever, cough, wheezing, and intercostal retractions. Its age-dependent clinical characteristics remain to be defined.

Objective: We investigated whether HRSV caused any age-related differences in clinical manifestations of LRTI.

Methods: We enrolled 130 hospitalized children with LRTI caused by HRSV. These were stratified into four age groups. The main signs and symptoms and rates thereof were compared across the four age groups.

Results: The incidence of pneumonia was the same in all four age groups. Patients in the 1–6 months old group experienced fever and the highest body temperature $\geq 38.5^{\circ}\text{C}$ less frequently than patients in other age groups. The frequency of fever increased with age among the patients under 24 months old. Children over 12 months old experienced less wheezing, tachypnoea, hypoxia, and intercostal retractions than children in the 1–6 months old group.

Conclusion: HRSV caused age-related differences in clinical manifestations of LRTI. Reduced fever responses among patients 6 months old and younger during RSV infection does not implicate less severity, wheezing, tachypnoea, hypoxia, and intercostal retractions are the main clinical manifestations, Fever responses were enhanced with advancing age among children under 24 months old.

Keywords: human respiratory syncytial virus, lower respiratory infections, clinical manifestation, hospitalized children

Introduction

Human respiratory syncytial virus (HRSV) is the most common viral etiological agent of acute respiratory tract infection. It causes significant morbidity and necessitates hospitalization in young children.¹ The infection occurs in all age groups, but most children are infected at or before 2 years of age.² Patients with HRSV bronchiolitis usually present with two to four days of upper respiratory tract symptoms such as fever, rhinorrhea, and congestion, followed by lower respiratory tract symptoms such as increasing cough, wheezing, and increased respiratory effort.³ However, it is not clear whether lower respiratory tract infections (LRTI) caused by HRSV cause different clinical manifestations in children of different ages. In this study, we determined whether there were any age-related differences in clinic manifestations of LRTIs caused by HRSV.

Materials and Methods

Enrolment and Data Collection

Shenzhen is located in southern China, closed to north of Hong Kong, with a typical subtropical monsoon climate. RSV was detected primarily during the spring and summer. We conducted a retrospective study of children under 5 years of



age hospitalized in Shenzhen Children's Hospital with LRTI caused by HRSV from July to October 2020. Patients were stratified into four age groups: 1–6 months old (group 1), 7–12 months old (group 2), 13–24 months old (group 3) and older than 24–59 months old (group 4). Trained research physicians collected data on demographics and clinical symptoms and extracted data concerning clinical signs at admission from medical records using a standard form.

Exclusion criteria were as follows: 1) previous use of palivizumab, 2) co-infection with any other virus, 3) bacterial infection of the respiratory tract or any other areas, 4) use of specific medications within the preceding three months, such as immunosuppressants, radiation therapy, anti-rheumatoid drugs, corticosteroids, and gamma globulins. The study flow is shown in Figure 1.

Study Definitions

The LRTI were defined according to clinical symptoms such as severe cough, fever, tachypnoea, and wheezing, and signs of respiratory distress such as nasal flaring, intercostal retraction, cyanosis, and abnormal auscultatory findings (wheezing and crackling), or radiologic evidence indicative of an LRTI.⁴

Fever was defined as body temperature $\geq 37.4^{\circ}\text{C}$. Defervescence was defined as body temperature remaining $< 37.4^{\circ}\text{C}$ for at least 24 hours. Axillary body temperature was measured using a standard mercury thermometer four times a day. We recorded whether a patient developed fever, duration of fever, and highest body temperature during that period.

Tachypnoea was defined with the definition used by the Indian Integrated Management of Neonatal and Childhood Illness (IMNCI): ≥ 60 breaths/min in children aged 0–2 months, ≥ 50 breaths/min in children aged 2–12 months, and ≥ 40 breaths/min in children aged 12 months to 5 years.⁵

Key respiratory signs and symptoms were defined as coughing and physician exam findings of wheezing, tachypnoea, intercostal retractions, and crackling.

Specimen Collection and Laboratory Methods

A PCR test on nasopharyngeal swabs or induced sputum with Ct (cycle threshold) value ≤ 40 is considered diagnostic for viruses wellknown to cause pneumonia.⁶ Nasopharyngeal secretion specimens (NPSs) were collected by a specialized nurse within 24 h of admission to the hospital using polyester swabs. The swabs were placed immediately in viral transport media and transported on ice to the laboratory for processing in a single day. The total nucleic acids of each specimen were extracted using an EasyPure Viral DNA/RNA Kit (TransGen Biotech, Beijing, China) according to the manufacturer's instructions. Eleven common respiratory pathogens and subtypes, *Influenza A* (Flu A), *Influenza B* (Flu B), *Human parainfluenza virus* (HPIV), *Human respiratory syncytial virus* (HRSV), *Human adenoviruses* (HAdVs), *Human metapneumovirus* (HMPV), *Human rhinovirus* (HRV), *Human bocavirus* (HBoV), *Human coronavirus* (HCoV), *Chlamydia* (Ch), and *Mycoplasma pneumoniae* (Mp), were detected using a GeXP-based multiplex reverse transcription polymerase chain reaction (PCR) assay. Sputum cultures, gram staining analyses, serology assay of Ch and Mp were done in all patients, blood culture were conducted in the patients who developed fever.

Statistical Analysis

Continuous variables are presented as median (IQR) or mean \pm standard deviation according to data distribution and compared using post-hoc test or analysis of variance, respectively. Categorical data are expressed as frequencies (%) and analyzed using χ^2 test or Fisher's exact test. Significance was set at $P < 0.05$.

Ethical Issues

All aspects of the study were performed in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration. The study protocol was approved by the Ethical Committee of Shenzhen Children's Hospital (number 201601304). Written informed consent was obtained from all of the participants' guardians.

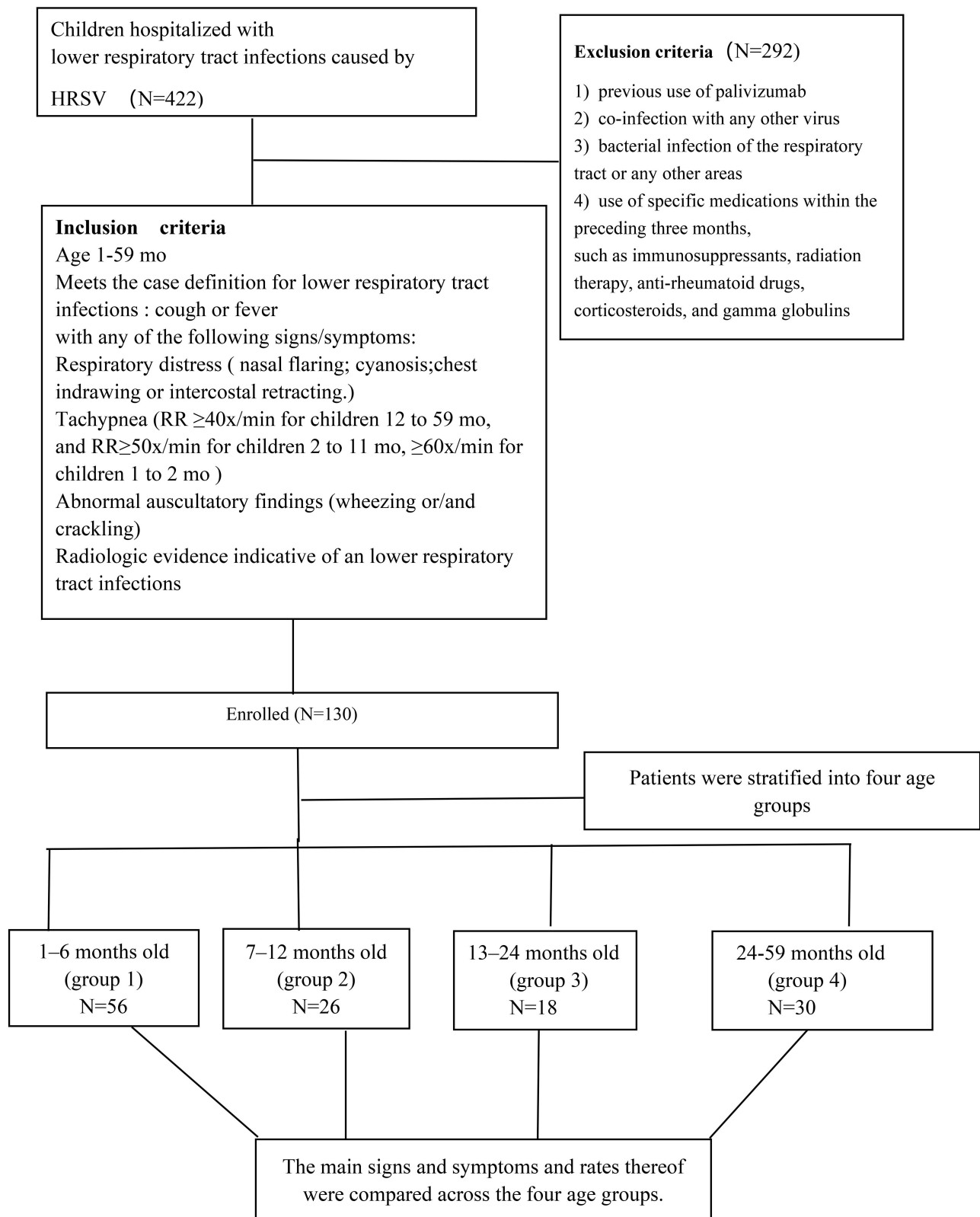


Figure 1 Subject screening, enrolment and research flow chart.

Results

Patient Characteristics and Clinical Symptoms

A total of 130 children were enrolled in this study. There were 56 patients in the group 1, 26 patients in the group 2, 18 patients in the group 3, and 30 patients in the group 4. The subjects included 80 boys (61.5%) and 50 girls (38.5%) (sex ratio, 1.6:1).

Of the 130 children, 17 (13%) had an underlying disease; 8 with respiratory disease (3 with Bronchiolitis obliterans, 3 with bronchopulmonary dysplasia, 2 with bronchial asthma), 2 with laryngomalacia, 2 with patent ductus arteriosus, 1 with bronchopulmonary dysplasia, pulmonary arterial hypertension, and atrial septal defect, 1 with hypothyroidism, 1 with epilepsy, and 1 with mitochondrial myopathy.

Sex, median age, and clinical symptoms in each age group are shown in Table 1. Coughing and wheezing were the major acute symptoms. Cough was present in all patients, wheezing in 72.3%, and pneumonia in 60%. There was no significant difference of the WBC count, CRP and length of hospital stay among the four groups.

Fever

The percentage of patients who experienced fever in each age group are shown in Figure 2A, The percentage of patients who experienced body temperatures of or over 38.5°C in each age group during the study period are shown in Figure 2B. About 38% of patients in 1–6 months old group had fevers and 19% had peak body temperatures of or over 38.5°C, significantly lower than in other age groups.

The median±SD (ranges) of fever duration were 4.50±2.24 (1–12) days in the 86 patients who developed fever. Broken down by age, median±SD duration of fever days were 3.19±1.990 (range 1–7) days in the group 1, 4.44±2.526 (range 1–11) days in the group 2, 4.89±1.605 (range 1–7) days in the group 3, and 4.86±2.356 (range 1–12) days in the group 4. There was no difference in the duration of fever among the four groups.

Table 1 Patient Characteristics and Clinical Signs and Symptoms

Age Group	Total n=130	1–6 mo(Group 1) n=56	7–12 mo(Group 2) n=26	13–24 mo(Group 3) n=18	Over24 mo(Group 4) n=30
Median month age (IQR)	9 (3–22.2)	3 (2–4)	9 (8–11)	20 (15–22)	38 (31.5–45)
Male sex. n (%)	80 (61.5)	33 (58.9)	16 (61.5)	13 (72.2)	18 (60)
Radiological evidence:	78 (60)	32 (57.1)	16 (61.5)	12 (66.6)	18 (60)
Pneumonia n (%)					
WBC count (10 ⁹ /L)	8.62±3.41	8.96±2.78	9.47±4.01	8.74±4.189	7.18±3.16
CRP(mg/L)	1.48 (0.5–5.02)	2.63 (0.5–5.36)	0.87 (0.5–4.3)	0.79 (0.5–3.84)	2.11 (0.58–7.38)
ICU admission	1 (0.7)	0	0	0	1(3.3)
HFNC	2 (1.4)	2 (3.6)	0	0	0
LOS	4.55± 1.92	4.05± 1.63	4.84± 2.27	5.06± 2.24	4.93± 1.74
Symptoms					
Fever n (%)	86 (66)	21 (38)	19 (73)	18 (100)	29 (97)
Cough n (%)	130 (100)	56 (100)	26 (100)	18 (100)	30 (100)
Wheezing n (%)	94 (72.3)	48 (85.7)	20 (76.9)	10 (55.5)	16 (53.3)
Signs					
Tachypnoea n (%)	46 (35.3)	28 (50)	11 (42.3)	1 (5.5)	6 (20)
Hypoxia n (%)	35 (26.9)	23 (41)	6 (23)	1 (5.5)	5 (16.6)
Intercostal retractions n (%)	30 (23)	19 (33.9)	6 (23)	1 (5.5)	4 (13.3)
Crackling n (%)	70 (53.8)	35 (62.5)	11 (42.3)	10 (55.5)	14 (46.6)

Notes: Categorical data are in n (%), continuous data are shown in mean ± SD, median [IQR].

Abbreviations: IQR, Interquartile range; WBC, White Blood Cells; CRP, C-reactive protein; mo, months; ICU, Intensive care unit; LOS, length of hospital stay; HFNC, high flow oxygen via nasal cannulae.

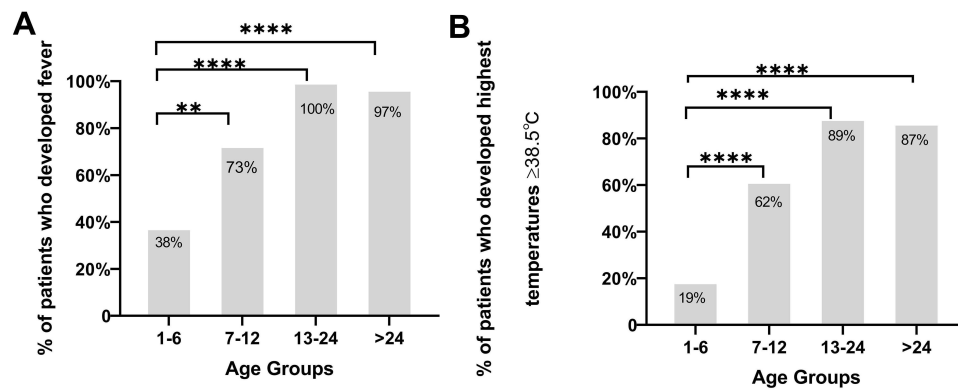


Figure 2 Proportions of patients who developed fever in each age group are shown in (A), and proportions of patients who developed the highest temperature of $\geq 38.5^{\circ}\text{C}$ in each age group are shown in (B). P-values by Fisher's exact between the age-group 1-6 months and other age groups are shown above the bars, patients of 1-6 months old less frequently experienced fever and the highest body temperature of $\geq 38.5^{\circ}\text{C}$ compared with other age groups. ** P < 0.01, **** P < 0.0001.

Wheezing

Proportions of patients developing wheezing in each age group are shown in Figure 3. The proportion of patients in 1-6 months old group with wheezing was about 85.7%, which was about the same as in the 7-12 months old group but significantly higher than in both groups of children over 12 months old.

Signs

Proportions of patients developing tachypnoea, hypoxia, and intercostal retractions in each age group are shown in Figure 4A-C. The proportions of patients in 1-6 months old group with tachypnoea, hypoxia, and intercostal retractions

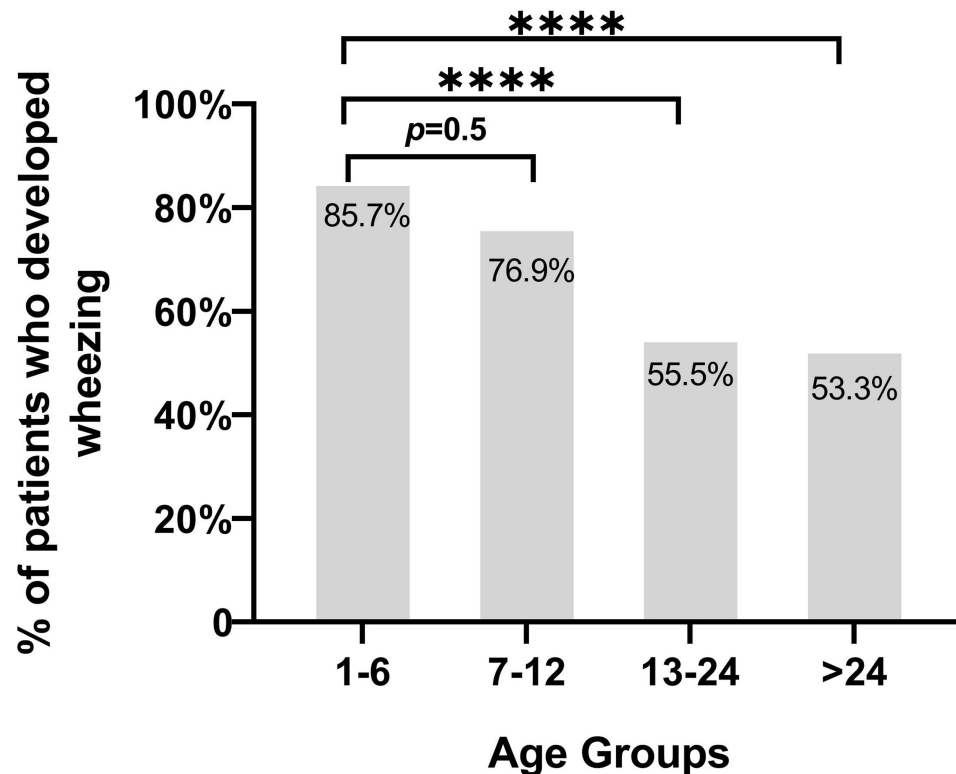


Figure 3 Proportions of patients who developed wheezing in each age group. P-values found using by Fisher's exact test indicating differences between children in 1-6 months old and other age groups are shown above the bars. Patients patients of 1-6 months old experienced wheezing more frequently than those over 12 months old. **** P < 0.0001.

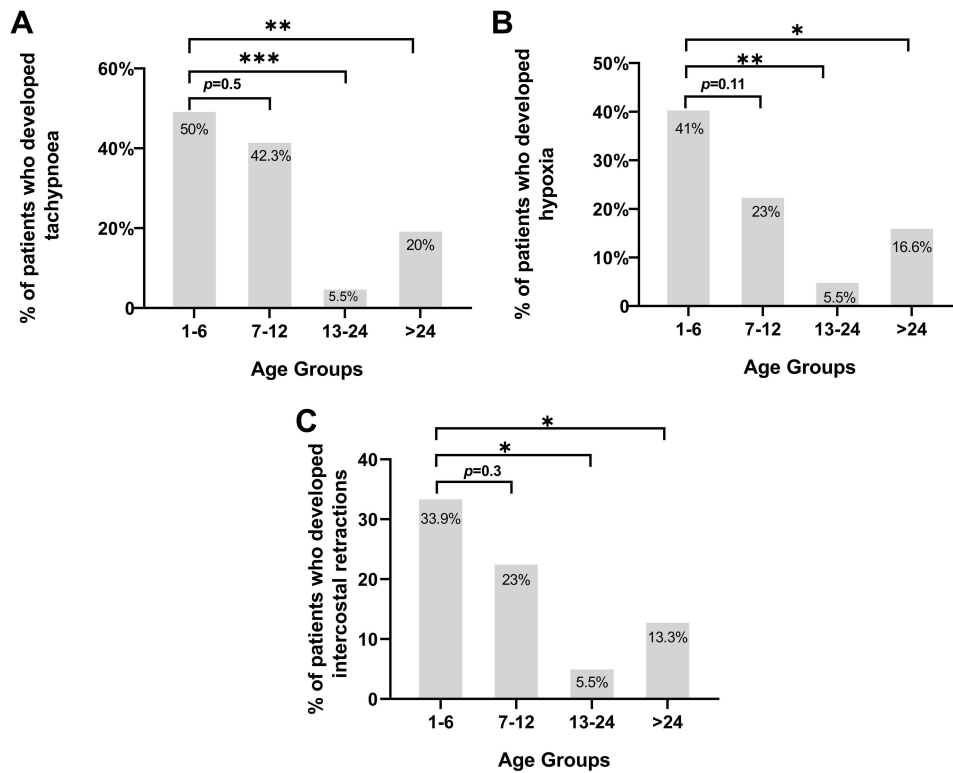


Figure 4 Proportions of patients who developed tachypnoea, hypoxia, and intercostal retractions in each age group are shown in 4A, 4B and 4C, respectively. P-values found using Fisher’s exact test indicating differences between children in 1–6 months old and other age groups are shown above the bars. Patients in 1–6 months old experienced tachypnoea, hypoxia, and intercostal retractions more frequently than children over 12 months old.* P <0.05, ** P <0.01, *** P < 0.001.

were about 50%, 41%, and 33.9%, respectively, which was significantly higher than in both groups of children over 12 months old.

Proportions of patients with crackling and radiological evidence of pneumonia showed no differences among the four groups.

Age-dependent clinical characteristics trend was shown in Figure 5

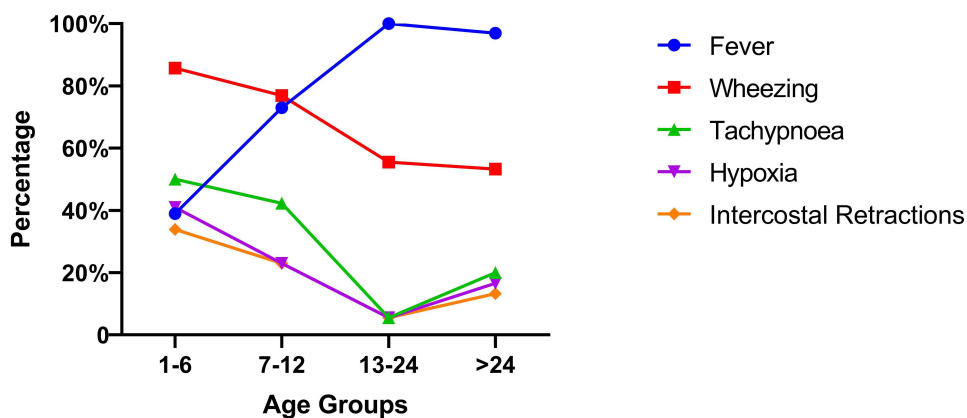


Figure 5 Age-dependent clinical characteristics trend was shown, fever responses were enhanced with advancing age among children under 24 months old, and wheezing, tachypnoea, hypoxia, intercostal retractions were reduced with advancing age among children under 24 months old.

Discussion

Human respiratory syncytial virus (HRSV) is the main viral etiological agent of lower respiratory tract infections (LRTI). It is the primary cause of hospitalization due to respiratory disease in infants.⁷ A total of 130 patients with LRTI caused by HRSV were involved in this study. A total of 60% had pneumonia. There was no difference in the proportion of patients who had pneumonia in the four age groups. Among these children, the association of HRSV infection with fever varied substantially with age; fever and temperatures of or over 38.5°C were less likely to co-occur in the 1–6 months old group but more likely to co-occur in children over 12 months old. The frequency of fever increased with age among the children under 24 months old. As defined by the World Health Organization, severe acute respiratory infection (SARI) is acute respiratory infection with history of fever or measured fever of or over 38°C and cough with onset within the previous 10 days. Our study showed that incorporating fever into the definition of SARI lowers the detection rate of HRSV cases among young children because 1–6 months old group with LRTI caused by HRSV may not have fever, which was consistent with findings reported by Brian Rha et al.⁸ Removing the fever requirement would have allowed clinicians to identify most missed cases.

The symptoms caused by HRSV, in fact, develop mainly as a result of host immune response. Once HRSV takes root in the airway epithelia, interaction with the host's innate immune system begins. In infants, where the adaptive immune system is immature, the innate immune system plays a central role in the defense against HRSV.⁹ The fever response is a hallmark of infection and inflammatory disease. The induction and maintenance of fever during infection involves the innate immune system. Innate immune cells are the first responders when viruses invade and trigger the production of fever-generating factors.¹⁰ Because infants during the early months have immature innate immunity, they cannot trigger the production of fever-generating factors and may not develop fever.¹¹ Some studies have shown that, due to the physiological immaturity of the immune system, infants under 6 months of age have deficient cytokine response to HRSV infection. The titer of neutralizing antibody produced in response to HRSV infection in children under 6 months old was significantly low, and children's antibody responses against HRSV mature over months and years.^{12,13} In our study, findings in children who are and under 6 months old tended to have less pronounced fever responses were consistent with this concept and with findings reported by Chiaki Kawakami.¹⁴

Some studies have shown that the combination of coughing, wheezing, and intercostal retractions is a good predictor of HRSV infection.^{15,16} In this study, we found that patients no more than 12 months old who had HRSV infection were more likely to develop wheezing, tachypnea, hypoxia, and intercostal retractions than patients over 12 months old. The frequency of these conditions decreased with age among children under 24 months old. Our findings suggest that wheezing, tachypnea, hypoxia, and intercostal retractions in patients no more than 12 months old predict HRSV infection well. However, for patients older than 12 months who have fever but no wheezing, tachypnea, hypoxia, or intercostal retractions, HRSV infection should still be considered. These findings provide further evidence that clinical presentations of HRSV can vary according to age. Infantile bronchioles, by virtue of their small size, are likely to become obstructed in response to peribronchiolar swelling, epithelial proliferation, and excessive mucus secretion during airway infection.¹⁷ Second, the cellular immune response to HRSV infection is balanced between Th-1 and Th-2 responses.¹⁸ The Th2 response is characterized by IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 production.¹⁹ Upon IL-13 induction, eosinophils and neutrophils are recruited to the lung and IL-5 secretion stimulates the production of mucus production by ciliated airway cells, which causes wheezing.²⁰ Infants under 3 months of age have higher Th-2 cytokines in nasal secretions than older children do.²¹ This might be why respiratory signs and symptoms were more common in patients under 12 months old.

The limitations of the present study were the relatively small number of child patients and the preselection bias given that all the patients were hospitalized. They may not be generally representative of all children with HRSV infection. However, we believe that our findings at least indicate that clinical presentations of HRSV can vary according to age. Also, although we excluded patients with co-infection involving more than two viruses and bacterial infections of the respiratory tract and other areas, we did not study the differences in treatment approaches, so the contribution of the efficacy to the improvement in symptoms is unclear.

In summary, there were age-related differences in the clinical manifestation of LRTI caused by HRSV. Reduced fever responses among patients 6 months old and younger during RSV infection does not implicate less severity, wheezing,

tachypnoea, hypoxia, and intercostal retractions are the main clinical manifestations, Fever responses were enhanced with advancing age among children under 24 months old.

Abbreviations

HRSV, Human respiratory syncytial virus; LRTI, Lower respiratory tract infections; SARI, Severe acute respiratory infection; PCR, Polymerase chain reaction, IQR: Interquartile range; ICU, Intensive care unit; LOS, Length of hospital stay; HFNC, High flow oxygen via nasal cannulae.

Data Sharing Statement

The key information and data generated and analyzed during this are given in this article.

Ethical Approval and Consent to Participate

Ethical approval for this study was obtained from the Ethical Committee of Shenzhen Children's Hospital (Shenzhen, Guangdong Province, China) under registration number 2016013. All of the experiments were performed under the relevant guidelines and regulations. Guardians of all of the children included in this study provided written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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