**RESEARCH ARTICLE**                                                                     **Open Access**

# Comparison of clinical features of acute lower respiratory tract infections in infants with RSV/HRV infection, and incidences of subsequent wheezing or asthma in childhood

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## Abstract

**Background:** To compare the clinical characteristics of acute lower respiratory tract infections (ALRTIs) caused by respiratory syncytial virus (RSV) and human rhinovirus (HRV) and to explore the relationship between the development of recurrent wheezing/asthma and RSV/ HRV infections in infancy.

**Methods:** Retrospective study was conducted to compare the clinical characteristics of acute lower respiratory tract infections (ALRTIs). Hospitalized patients with ALRTIs from March 2007 to December 2016 were screened. Single RSV cases (s-RSV), single HRV cases (s-HRV), and cases who had co-infection with the two viruses were enrolled. Follow-up was performed to determine whether either specific respiratory virus infection was related to subsequent development of recurrent wheezing/asthma.

**Results:** The s-RSV children were the youngest ($P = 0.021$), they experienced the most serious condition ($P < 0.001$) and respiratory failure ($P < 0.001$), they also required highest demand of oxygen therapy ($P < 0.001$). And in s-RSV group, the incidence of development of recurrent wheezing was significantly higher in subgroup with the family history of wheezing than that without ($P < 0.001$).

**Conclusion:** The s-RSV cases suffered from the worst severity of illness, respiratory failure and required highest demand of oxygen therapy. Recurrent wheezing was more common in s-RSV group with family history of wheezing than those without.

**Keywords:** Respiratory syncytial virus, Human rhinovirus, Acute lower respiratory tract infection, Recurrent wheezing, Asthma

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# Background

Respiratory syncytial virus (RSV) and human rhinovirus (HRV) are the most common viral pathogens causing respiratory tract infection in infants and young children. RSV is a member of the *Pneumovirus* genus in the *Paramyxoviridae* family. Nearly all children experience at least one RSV infection by the age of 2 years, and in the globle, more than 60% of acute lower respiratory tract infections (ALRTIs) in young children and 80% in infants less than 1 year old are caused by RSV [1]. HRV is a virus belonging to the *Enterovirus* genus in the *Picornaviridae* family. HRV is also a commonly detected virus in nasal/throat swabs from young children who have been hospitalized for wheezing and from infants hospitalized for pneumonia [2, 3]. Although some studies have described the clinical features of RSV and HRV [4, 5], there are few studies about comparison of clinical features of ALRTIs in infants with RSV and HRV infection. The co-infection rate of RSV and HRV is very high in ALRTIs in infants [6], and whether the co-infection is related to the severity of disease also has not been well documented.

The relationship between RSV or HRV ALRTIs in infants with the subsequent development of wheezing/asthma in childhood is still controversial. Some studies found that RSV infection in childhood increased the risk of persistent wheezing and asthma [7, 8]. A rencent Australian study also reported that hospitalization for severe RSV disease in the first 2 years of life was associated with the subsequent hospitalization for the first episode of asthma hospitalisation [9]. Other studies found that wheezing caused by HRV in infants and young children increased the risk of childhood asthma [10] and diagnosis of childhood asthma as well as acute asthma attacks were also related to HRV infection [11, 12]. A research from Finland reported that current asthma was present in 64% of the cases with HRV-induced wheezing [13]. Kumar also found that about 50–85% of acute asthma exacerbations were caused by viral infections, of which 2/3 were caused by HRV [14].

As mentioned above, the co-infection rate of RSV and HRV was very high in ALRTIs in infants [6]. Whether the co-infection of RSV and HRV ALRTIs in infants has an impact on the subsequent development of wheezing/asthma in childhood was not clear. So, in this study, we compared the clinical characteristics of ALRTIs caused by single RSV infection (s-RSV), single HRV infection (s-HRV) and co-infection with these two viruses (co-infection) in infants, and explored whether the incidences of subsequent wheezing/asthma in childhood after ALRTIs with s-RSV, s-HRV and co-infection in infancy were different.

# Methods

## Patients

From March 2007 to December 2016, children who were diagnosed with ALRTIs and hospitalized at Beijing Children's Hospital were screened for this study. ALRTIs were defined by the presence of signs and symptoms of respiratory tract infection (i.e., fever, coughing, tachypnea, dyspnea, wheezing or rales on auscultation) [15]. The inclusion criteria of patients are as followes: (1) less than 3 years of age; (2) the infectious agent was single RSV, single HRV, or co-infection with both. Patients with any of the following conditions were excluded: (1) immune deficiency; (2) congenital heart disease; (3) congenital airway and lung malformations or dysplasia; (4) foreign bodies in the airway; (5) co-infection with other pathogens; (6) sepsis, tumor, or leukemia; and (7) trauma.

## Collection of specimens and clinical information

Nasopharyngeal aspirates or throat swab specimens were collected from each patient within 24 h of hospitalization. All samples were stored at – 80 °C until testing.

Age, gender, symptoms, signs, exam results, diagnoses, complications, the need for oxygen and family history of wheezing were examined (Table 1), and all cases were scored according to their clinical characteristics (Supplement 1) [16] The diagnostic criteria for respiratory failure are as follows [17]: $PaO_2 <$ (arterial blood) with or without $PaCO_2 > 45$ mmHg. Heart failure would be diagnosed if meeting 4 of the following 6 criteria: (1) respiratory rate accelerated suddenly (> 60 beats/min); (2) heart rate elevated suddenly (> 180 beats/min); (3) dysphoria and cyanosis; (4) gallop rhythm, jugular venous distention and muffled heart sounds; (5) liver enlargement; (6) oliguria or anuria, and edema. Increase of creatine kinase isoenzyme (CK-MB) > 25 U/L or/and changing of ST-T in electrocardiogram (ECG) indicate myocardial damage. Aspartate aminotransferase (AST) > 40 U/L or/and alanine aminotransferase (ALT) > 40 U/L reflect liver dysfunction.

## Preparation of nucleic acids

Total nucleic acids (DNA and RNA) were extracted from 200 μl nasopharyngeal aspirates or throat swab specimens using the Nucli Senseasy MAG™ automated extraction system (bioMérieux, Marcyl' Etoile, France) according to the manufacturer's instructions and eluted with 60 μl elution buffer.

## Detection of respiratory viruses

The presence of common respiratory viral agents, including RSV, parainfluenza virus (PIV) type 1–4, 2009 H1N1 influenza virus (2009H1N1), H3 subtype influenza virus(H3), seasonal H1 subtype influenza virus(H1), influenza B virus (Flu B), human rhinovirus/enterovirus (HRV/HEV), human coronavirus (HCoV 229E, NL63,

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**Table 1** Clinical features of ALRTIs with different viruses

| | s-RSV (n = 199) | s-HRV (n = 47) | Co-infection (n = 73) | P |
|---|---|---|---|---|
| Age (yr)($\overline{X} \pm S$) | 0.46 ± 0.56[d] | 0.80 ± 0.78[d] | 0.53 ± 0.47 | 0.021[*] |
| Gender | | | | |
|   M n(%) | 137 (68.84) | 38 (80.85) | 56 (76.71) | 0.164 |
|   F n(%) | 62 (31.16) | 9 (19.15) | 17 (23.29) | |
| Temperature (℃)($\overline{X} \pm S$) | 37.94 ± 0.75 | 38.10 ± 0.85 | 37.55 ± 4.52 | 0.349 |
| Wheezing n(%) | 112 (56.28) | 28 (59.57) | 47 (64.38) | 0.480 |
| Lung infiltrates n(%) | 134 (67.34) | 35 (74.47) | 47 (64.38) | 0.506 |
| WBC(*10⁹) ($\overline{X} \pm S$) | 9.59 ± 5.04 | 9.89 ± 5.11 | 9.44 ± 4.60 | 0.889 |
| PMN(*10⁹) ($\overline{X} \pm S$) | 35.73 ± 15.38 | 38.50 ± 17.96 | 35.16 ± 18.54 | 0.526 |
| EOS(*10⁹) ($\overline{X} \pm S$) | 0.26 ± 0.30 | 0.25 ± 0.20 | 0.30 ± 0.46 | 0.561 |
| CRP[b] | 31/195[c] | 5/47 | 4/71[c] | 0.076 |
| Complications | | | | |
|   Liver damage n(%) | 38 (19.10) | 5 (10.64) | 11 (15.07) | 0.338 |
|   Myocardial damage n(%) | 69 (34.67) | 11 (23.40) | 29 (39.73) | 0.179 |
|   Respiratory failure n(%) | 50 (25.13) | 5 (10.64) | 5 (6.85) | < 0.001[*] |
|   Heart failure n(%) | 25 (12.63) | 1 (2.13) | 8 (10.96) | 0.111 |
| Oxygen therapy[a] n(%) | 148 (74.37) | 22 (46.81) | 50 (68.49) | 0.001[*] |
| NCPAP n(%) | 50 (25.13) | 5 (10.64) | 6 (8.22) | 0.002[*] |
| Clinical score[e] ($\overline{X} \pm S$) | 4.10 ± 2.32[d] | 3.13 ± 1.65[d] | 3.25 ± 1.47[d] | < 0.001[*] |
| Bronchiolitis n(%) | 39 (19.60) | 4 (8.51) | 18 (24.66) | 0.086 |
| Pneumonia n(%) | 155 (77.89) | 40 (85.11) | 53 (72.60) | 0.274 |
| Bronchitis n(%) | 5 (2.51) | 3 (6.38) | 2 (2.74) | 0.365 |

[a]Oxygen therapy includes nasal catheter oxygen inhalation and nasal continuous positive airway pressure (NCPAP);
[b]CRP (C-Reactive Protein): Only when the value of CRP was greater than/ equal to 8, the specific value would be displayed;
[c]In s-RSV group, CRP values were collected from 195 patients, and there were 31 patients with CRP greater than 8; all the 47 cases in s-HRV group were tested for CRP, and 5 cases with CRP greater than 8; in co-infection group, CRP values were collected from 71 patients, and only 4 patients with CRP greater than 8;
[d]Games-Howell test; [e] The clinical score system was showed in supplement 1
[*]P value of < 0.05 was considered statistically significant

HKU1, and OC43), human metapneumovirus (HMPV), human bocavirus (HBoV), and human adenovirus (HAdV), were determined using multiplex RT-PCR, single RT-PCR, or PCR assays as described previously [18, 19]. Blank virus transport media served as a negative control for nucleic acid extraction and PCR analysis.

### Follow up
Telephone follow-up was conducted to assess the subsequent development of wheezing episode and asthma in childhood at June, 2017. The questionnaire of follow-up is shown in the supplementary materials (Supplement 2).

### Statistical analysis
Continuous variables are expressed as means ± standard deviations (SD) or medians. For categorical variables, the relative numbers of patients in each category were calculated. Differences between groups were assessed using Pearson's Chi square test or Fisher's exact test for categorical variables and one-way analysis of variance (ANOVA) and independent-samples test for continuous variables. Games-Howell test was used for the data that do not meet the hypothesis of variance homogeneity. All analyses were performed using SPSS software, version 20.0 (IBM Corporation, Armonk, NY, USA). All calculations were made in a two-tailed manner, and P value < 0.05 was considered statistically significant.

## Results
### Patients enrolled
From March 2007 to December 2016, a total of 4348 children were screened for this study, and 319 children were finally enrolled, including 199 s-RSV, 47 s-HRV and 73 co-infection cases through the selection process (Fig. 1). January was the peak month for these three groups. March and December were the peak months for s-RSV and co-infection. (Fig. 2). The mean age was 0.46 ± 0.56 years, 0.80 ± 0.78 years and 0.53 ± 0.47 years in s-RSV group, s-HRV group and co-infection group respectively, and most of them were less than 1 year
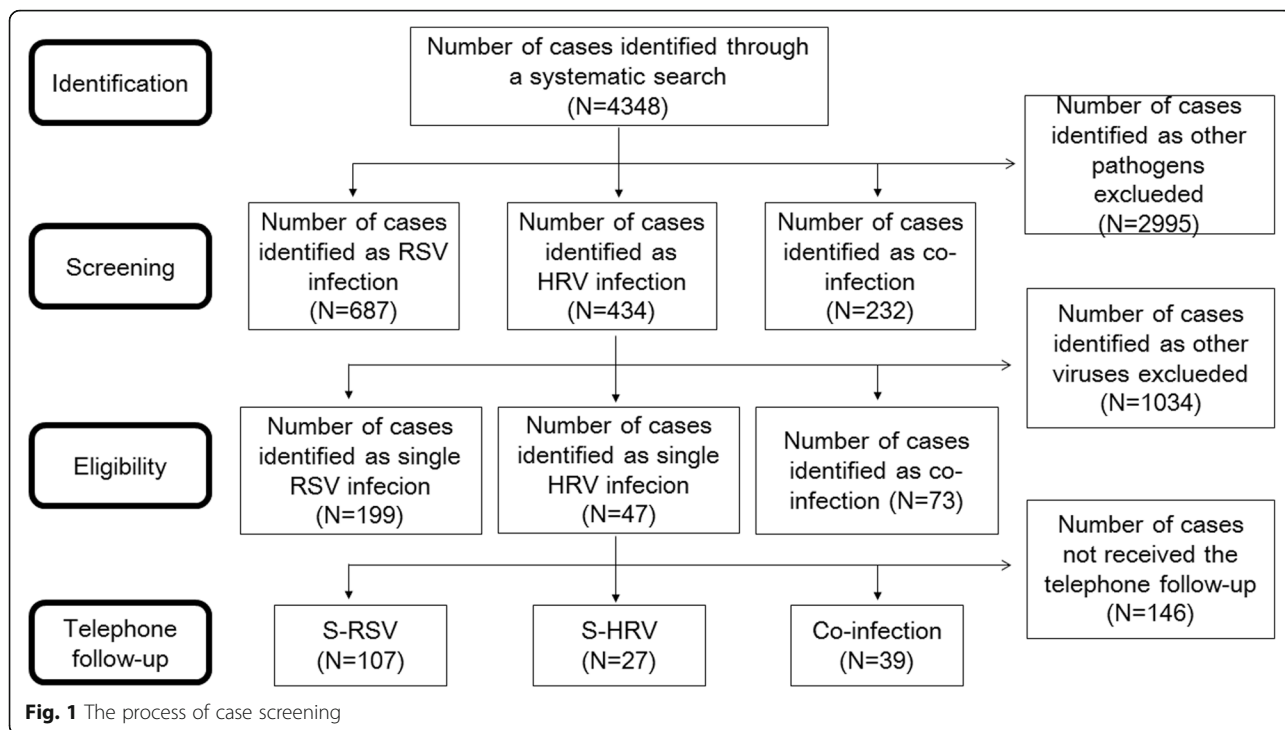
**Fig. 1** The process of case screening

(Fig. 3). The male-to-female ratio of was 2.21:1, 4.22:1 and 3.29:1 in s-RSV group, s-HRV group and co-infection group respectively.

**Clinical features and main diagnoses of the enrolled cases**

The mean age of s-RSV group was younger than that of s-HRV group ($P = 0.021$, Table 1). There were significant differences in disease scores among the three groups ($P < 0.001$, Table 1), with the average disease scores showing the following trend: s-RSV group> co-infection group > s-HRV group. This result indicated that s-RSV group had more severe disease than s-HRV or co-infection groups.

The s-RSV group was most likely to experience respiratory failure ($P < 0.001$, Table 1). And both the oxygen therapy (nasal catheter oxygen inhalation and nasal continuous positive airway pressure, NCPAP) ($P = 0.001$, Table 1) and NCPAP ($P = 0.001$, Table 1) were highest in s-RSV group.

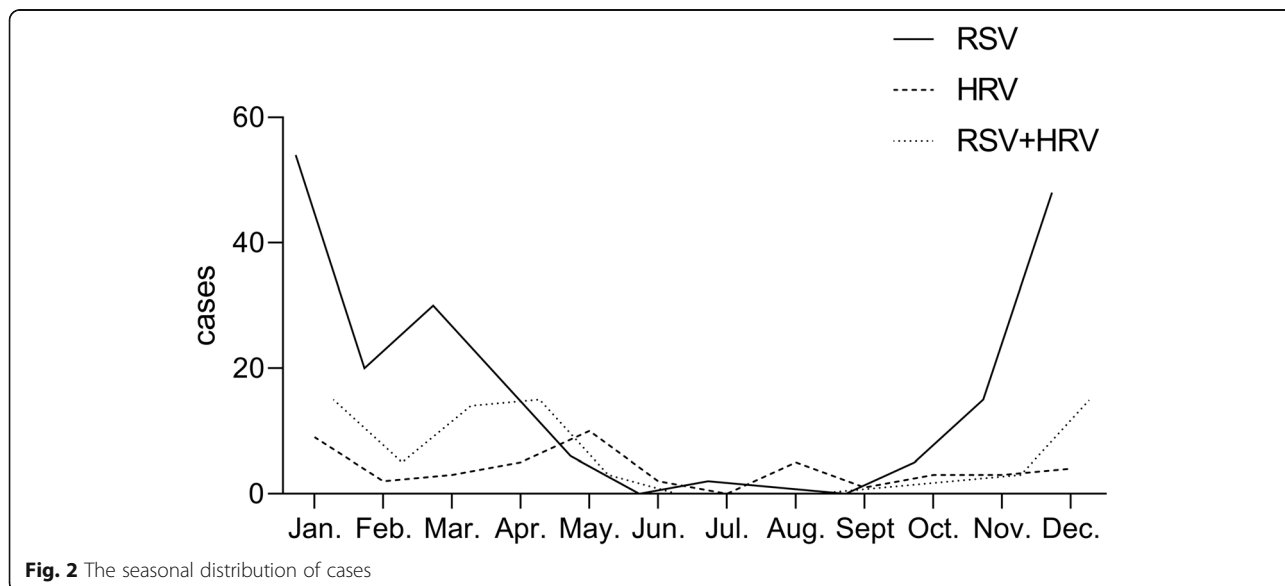There were no statistically significant differences among the three groups in terms of gender, temperature,



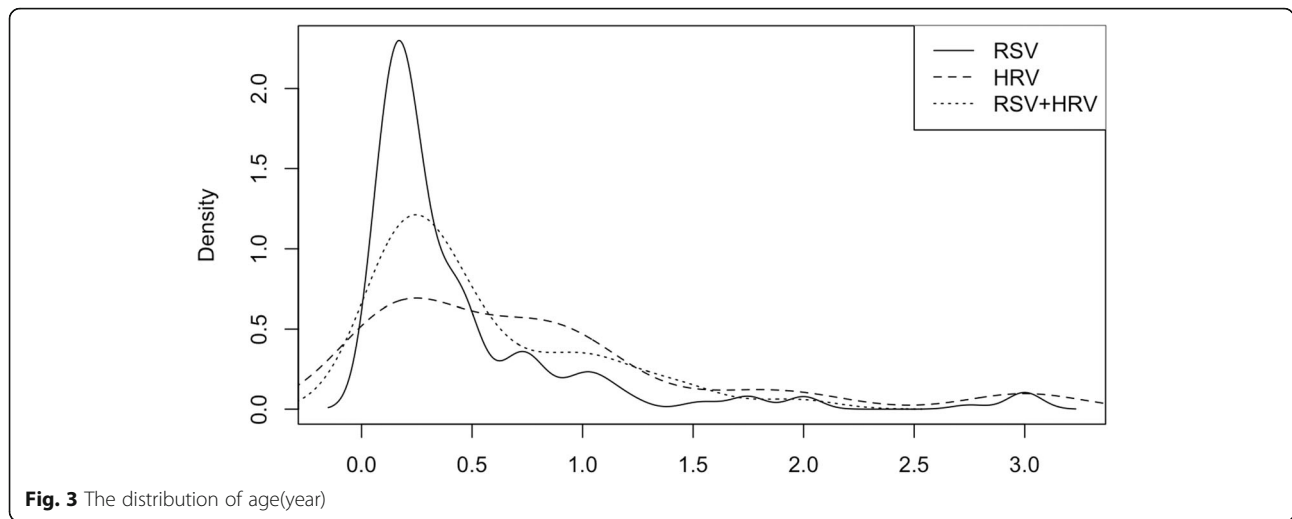**Fig. 2** The seasonal distribution of cases

**Fig. 3** The distribution of age(year)

wheezing, lung infiltrates, the count of WBC, PMN, eo-sinophil, CRP, liver damage, myocardial damage, or heart failure during hospitalization.

Upon discharge there were no significant differences in clinical diagnoses of bronchiolitis, pneumonia, and bronchitis among the three groups (Table 1). More-over, when stratified by family history, there were no statistically significant differences in the major clinical diagnosis (Table 2).

### Results of follow-up

A total of 173 cases, including 107 s-RSV cases, 27 s-HRV cases and 39 co-infection cases, received a telephone follow-up 6 months to 10.3 years after dis-charge. The rate of recurrent wheezing of the three group was 41.1% (s-RSV), 22.2% (s-HRV) and 41% (co-infection), while the rate of asthma was 7.5% (s-RSV), 11.1% (s-HRV) and 12.8% (co-infection). But whether the family history was positive or not, there was no sig-nificant difference in recurrent wheezing/asthma among the three groups (Table 3).

Each group was further classified into two subgroups by family history of wheezing. Only in s-RSV group, the incidence of recurrent wheezing was significantly higher in the subgroup with family history of wheezing than the subgroup without family history of wheezing ($P < 0.001$,

**Table 2** The main clinical diagnosis in groups with/without family history of wheezing(%)

|  |  | Bronchiolitis n(%) | Pneumonia n(%) | Bronchitis n(%) |
|---|---|---|---|---|
| P (n = 72) | s-RSV (n = 42) | 12 (28.57) | 29 (69.05) | 1 (2.38) |
|  | s-HRV (n = 11) | 1 (9.09) | 9 (81.82) | 1 (9.09) |
|  | Co-infection (n = 19) | 5 (26.32) | 13 (68.42) | 1 (5.26) |
|  | χ2 | 1.624 | 0.761 | 1.794□ |
|  | P | 0.512 | 0.684 | 0.374 |
| N (n = 101) | s-RSV (n = 65) | 9 (13.85) | 54 (83.08) | 2 (3.08) |
|  | s-HRV (n = 16) | 1 (6.25) | 14 (87.50) | 1 (6.25) |
|  | Co-infection (n = 20) | 1 (5.00) | 18 (90.00) | 1 (5.00) |
|  | χ2 | 1.148□ | 0.492□ | 1.163□ |
|  | P | 0.576 | 0.918 | 0.449 |
| Total (n = 173) | s-RSV (n = 107) | 21 (19.63) | 83 (77.57) | 3 (2.80) |
|  | s-HRV (n = 27) | 2 (7.41) | 23 (85.19) | 2 (7.41) |
|  | Co-infection (n = 39) | 6 (15.38) | 31 (79.49) | 2 (5.13) |
|  | χ2 | 2.375 | 0.761 | 1.858□ |
|  | P | 0.305 | 0.683 | 0.465 |

□Fisher's exact test
P: positive family history of wheezing. N: negative family history of wheezing

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**Table 3** Incidence of recurrent wheezing/asthma in groups with/without family history of wheezing(%)

| Family history | Groups | Recurrent wheezing N (%) | Asthma N (%) |
|---|---|---|---|
| P (n = 72) | s-RSV(n = 42) | 28 (66.67) | 3 (7.14) |
| | s-HRV(n = 11) | 3 (27.27) | 3 (27.27) |
| | co-infection(n = 19) | 11 (57.89) | 4 (21.05) |
| | P | 0.062 | 0.120□ |
| N (n = 101) | s-RSV(n = 65) | 16 (24.62) | 5 (7.69) |
| | s-HRV(n = 16) | 3 (18.75) | 0 (0.00) |
| | co-infection(n = 20) | 5 (25.00) | 1 (5.00) |
| | P | 0.889□ | 0.829□ |

□Fisher's exact test

P: positive family history of wheezing. N: negative family history of wheezing

Table 4), but the incidence of asthma was not significantly different between these two subgroups ($P = 1.000$, Table 4). In the other two groups, no significant differences in recurrent wheezing/asthma were found between subgroups ($P > 0.05$, Table 4). This result indicated that patients with family history of wheezing were more likely to develop recurrent wheezing after ALRTIs caused by RSV in infancy than those without.

## Discussion

### Differences in clinical manifestations of ALRTIs with s-RSV, s-HRV, and co-infection

In infants and young children, ALRTIs are most frequently caused by respiratory viruses, such as RSV and HRV, both of which play a significant role in pediatric respiratory tract infections [20, 21]. Co-infection is common in ALRTIs, while RSV and HRV are the most common viruses in co-infections, with a rate higher than 50% [22]. Our findings provide details on the characteristics of s-RSV, s-HRV and co-infection of the two viruses among children under 3 years of age in Beijing Children's Hospital. Our study showed that the peak months for s-HRV

and s-HRV infection were January. And the mean age of children in s-HRV group was older than those in the other groups, but most cases in every group were less than 1 year. The s-RSV cases were more likely to experience the respiratory failure and had the highest demand of nasal catheter oxygen inhalation and NCPAP. These results were consistent with the disease score and indicated that s-RSV cases was more severe than co-infection groups. Another study also suggested that RSV infection was more likely to cause coughing, wheezing, and shortness of breath than HRV infection [23].

It's controversial about the role of co-infection of viruses in the severity of disease. Martin et al. found that comparing with children infected with a single virus, children with mixed viruses infection were less frequently admitted to the inpatient ward or to the intensive care unit and less likely to require supplemental oxygen or hospital stays longer than 3 days [24]. Nascimento et al. found that co-infections were not associated with poorer outcomes [25]. A prospective analysis including 322 hospitalized infant patients with acute respiratory disease (ARD) revealed that co-infections were significantly more common in mild respiratory diseases [26]. Brand et al. also found that the severity of illness in children with bronchiolitis is not associated with multiple viruses infection [27]. These results are coincident with that of our study, and demonstrated that co-infection in ALRTIs could not cause more severe condition. A most recent Italian research showed that infants with co-infection seemed to mount a lower inflammatory response [28], the antagonism caused by non-specific innate immune responses stimulated by co-infection virus maybe a possible reason.

However, other studies had different results. Calvo et al. reported that patients with mixed viruses infection had more frequent fever, longer hospital stays, and more antibiotic treatment than patients infected with RSV alone [29]. Aberle et al. also reported that co-infection

**Table 4** Incidence of recurrent wheezing/asthma in subgroups with/without family history of wheezing

| Groups | Family history of wheezing | Recurrent wheezing N(%) | Asthma N(%) |
|---|---|---|---|
| s-RSV(n = 107) | P(n = 42) | 28 (66.67) | 3 (7.14) |
| | N(n = 65) | 16 (24.62) | 5 (7.69) |
| | P | < 0.001 | 1.000□ |
| s-HRV(n = 27) | P(n = 11) | 3 (27.27) | 3 (27.27) |
| | N(n = 16) | 3 (18.75) | 0 (0.00) |
| | P | 0.662 | 0.056□ |
| Co-infection(n = 39) | P (n = 19) | 11 (57.89) | 4 (21.05) |
| | N(n = 20) | 5 (25.00) | 1 (5.00) |
| | P | 0.054□ | 0.182□ |

□Fisher's exact test

P: positive family history of wheezing. N: negative family history of wheezing

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(HRV and HAdV) with RSV was associated with the severity of illness, hypoxemia, and fever [30]. Richard et al. found that dual viral infection was a relevant risk factor for admission to PICU [31]. The different results of co-infection of viruses on the severity of disease may be associated with several reasons, such as study population, research design, and standard of evaluation and so on. Multicenter studies are needed.

### Incidences of subsequent wheezing/asthma in childhood

A large number of studies have identified a link between RSV/HRV infection and an increased likelihood to develop either recurrent wheezing or asthma. Previous studies showed that with RSV infection, the risk of developing recurrent wheezing was from 28.1 to 30% [32, 33], and for asthma, the rate was from 30 to 38.4% [32, 34]. For HRV-infected children, the risk for developing asthma at 6 years of age being more than four-fold higher compared with HRV-negative cases [35]. In the large, prospective Childhood Origins of Asthma (COAST) study performed in children at increased risk of developing allergies and asthma, HRV infections represented a significantly increased risk (OR = 10) for developing asthma by 6 years of age [10]. From our study, the rate of recurrent wheezing of the three group was 41.1% (s-RSV), 22.2% (s-HRV) and 41% (co-infection), while the rate of asthma was 7.5% (s-RSV), 11.1% (s-HRV) and 12.8% (co-infection). Taking the number of enrolled cases into account, especially s-HRV and co-infection cases were small in our study and this may also a potential bias of the result. So, further studies are needed to explore the mechanism of different immune response to RSV and HRV infection in infants.

We found that there were no significant differences in the development of asthma among subgroups of the three groups with or without family history of wheezing. And only s-RSV group with positive family history had a tend to have recurrent wheezing than those without. This result is consistent with that of the following studies. A Japanese study found no connection between RSV-based ALRTIs in infants and childhood asthma [36]. Kusel, et al. reported that RSV and HRV infections in the first year after birth were associated with wheezing and asthma at the age of 5 years, with no difference between the two groups [37]. Uppala R.et al. reported that the specific pathogens (RSV/HRV) did not account for a statistically significant difference in subsequent wheezing or asthma development [38].

However, some studies supported that RSV or HRV infection in early childhood was associated with chronic airway diseases, especially in the subsequent development of wheezing and asthma. From some population-based birth cohort studies, RSV bronchiolitis was found to be associated with subsequent wheezing and asthma, especially in children with family histories of atopy and asthma [32, 39]. Another high-risk birth cohort study showed that among outpatients viral wheezing illnesses in infancy and early childhood, those associated with HRV infections were the most significant risk factors of subsequent development of asthma at the age of 6 years [10]. We found the different immune response induced by RSV and HRV may be the cause of this result. For instance, IL-8 level in the nasal aspirate is higher in ALRTIs associated with RSV in children than those associated with HRV, and higher respiratory tract IL-8 level was associated with hypoxia and need for ventilation in infants [40, 41]. Another previous research reported that RSV bronchiolitis, with higher nasal levels of IFN-λ than HRV infection, and higher nasal IFN-λ levels were associated with increased disease severity [42, 43], and severe bronchiolitis was the risk factor for recurrent wheezing [44]. Other studies suggested that IL-5 was significantly elevated in the HRV group compared with the RSV group in both serum and nasal secretions [45], and as we all know, IL-5 has the effect of inducing eosinophil accumulation in airways.

## Conclusions

The severity of disease in s-RSV cases was higher than that of s-HRV or Co-infection groups, with a higher demand for nasal catheter oxygen inhalation and NCPAP and higher risk for respiratory failure. No matter with or without family history of wheezing, there are no significant differences in the incidence of subsequent development of recurrent wheezing and asthma among s-RSV, s-HRV and co-infection groups. But patients with family history of wheezing are subject to have recurrent wheezing after ALRTIs caused by RSV in infancy than those without the family history.

## Supplementary information

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**Additional file 1: Supplement 1.** Clinical Scoring System. **Supplement 2.** Follow-up questionnaire for recurrent wheezing and asthma.

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#### Authors' contributions
QD reviewed the medical records, analyzed and interpreted the data, and drafted the manuscript. LLX and YZ interpreted the data and drafted the manuscript. BPX, YLD and XPC analyzed and interpreted the data. ZDX and KLS designed and oversaw the study, interpreted the data, and revised the

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