Brief report

Clinical characteristics and risk factors of severe respiratory syncytial virus-associated acute lower respiratory tract infections in hospitalized infants

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Background: **To investigate the clinical characteristics and analyze risk factors for severe respiratory syncytial virus (RSV) infection in hospitalized infants with acute lower respiratory tract infections (ALRIs).**

Methods: **A retrospective review of the medical records of infants with RSV-associated ALRIs between March 1st, 2011 and February 29th, 2012 was conducted. Subjects were followed up over the phone or by outpatient visit six and twelve months after discharge.**

Results: **Among 913 RSV-associated ALRIs infants, 288 (31.5%) had severe infections, which accounted for 4.2% of hospitalized children. The hospital RSV mortality rate was 1.0%. The proportions of cases with tachypnea, apnea, cyanosis, and fine rales were significantly higher in the severe ALRIs group (all *P*<0.001). Multivariate logistic regression showed that low-birth-weight [1.698 (1.028-2.805)], age less than 3 months old [3.385 (2.174-5.271)], congenital heart disease [1.667 (1.149-2.418)], bronchopulmonary dysplasia [8.505 (1.731-41.780)], and airway abnormalities [2.246 (1.008-5.005)] were independent risk factors for severe ALRIs. The incidence of bronchitis, pneumonia and readmission in the severe group was significantly higher than that of the non-severe group during the one-year follow-up (all *P*<0.001).**

Conclusions: **Younger age, low birth weight and underlying disease are associated with severe RSV-associated ALRIs. Furthermore, severe RSV infections may be associated with a higher frequency of subsequent bronchitis, pneumonia and re-hospitalization in the following year.**

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Introduction

Respiratory syncytial virus (RSV) is the leading viral cause of acute lower respiratory tract infections (ALRIs) globally. By the age of two years, almost all infants would have been exposed to RSV. A meta-analysis by Nair et al[1] revealed that in 2005, 66 000-199 000 children younger than 5 years of age died of RSV-associated severe ALRIs, with the vast majority (99%) in the developing countries. Currently, no RSV vaccines are available. Although RSV immunoglobin and palivizumab are effective for RSV infections,[2,3] they are expensive and not yet available in China. China has a large number of children with ALRIs, which has drawn greater attention of physicians to the clinical characteristics and risk factors of severe RSV infections.[4-7] However, most studies have focused on the demographic data and underlying diseases, and paid scant attention to the family status of the infants, which is considered to be an important risk factor for RSV infections.[8]

Though epidemiologic evidence suggests that RSV-associated ALRIs may be associated with subsequent development of recurrent wheezing and asthma in childhood,[9] it remains unelucidated whether subsequent respiratory illnesses vary with the severity of RSV infections. In the current study, we analyzed the clinical characteristics of hospitalized infants with RSV-associated ALRIs at a high volume children's hospital in China and determined the risk factors of severe RSV-associated ALRIs in infants.

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Methods

Subjects

We collected the demographic and clinical data of 1726 infants with ALRIs admitted to Children's Hospital of Fudan University, Shanghai, China, between March 1st, 2011 and February 29th, 2012. Children were eligible for enrollment if they were under 1 year of age, and had respiratory symptoms and radiologic evidence of ALRIs.[10,11] Patient information was collected by trained researchers using a standard case report form, which included demographic characteristics, family status, primary disease diagnosis and secondary diagnoses, clinical characteristics, and treatment.

The study was approved by the Ethics Committee of Children's Hospital of Fudan University. Written informed consents were obtained from the parents or legal surrogates of the study subjects.

Clinical samples

Sputum or endotracheal aspirates were collected within 48 hours of admission. RSV, influenza A and B, adenovirus, and parainfluenza virus type 1, 2, and 3 were identified by the Chemicon immunofluorescence assay. *Mycoplasma pneumoniae* and *Chlamydia trachomatis* were detected using real-time PCR with MP/CT fluorescent polymerase chain reaction diagnostic kit (Da-an gene Co. Guangzhou, China). Samples were stained and bacteria were identified by the Vitek Auto Microbic System (AMS)-60 (Biomerieux Company, France).

Follow-up

Follow-up interviews were conducted over the telephone or in the outpatient department at 6 and 12 months after discharge. The incidence of ALRIs, allergic diseases, and readmission were evaluated.

Clinical severity score

To avoid subjective assessment of disease severity, we used a severity index (SI) previously published.[12] A single point was assigned for apnea in the hospital, pH <7.35, PCO_2 >45, arterial SO_2 <87%, and length of stay (LOS) >5 days, and 2 points were assigned if mechanical ventilation was required. Scores on the SI ranged from a minimum of 0 to a maximum of 7, with higher scores indicating more severe disease. A score of ≥3 was categorized as a severe disease and <3 as a non-severe disease.

Statistical analysis

All statistical analyses were performed using the SPSS software (version 16.0). Means/medians and proportions were used to describe characteristics of the study population. Comparison between continuous variables was made using Student's *t* test or the Mann-Whitney *U* test. Proportions of patients were compared with the chi-squara test or Fisher's exact test. Logistic regression models were used to analyze risk factors for severe RSV infections in infants and odds ratio (OR) and 95% confidence interval (95% CI) was computed around the point estimation value. A *P* value <0.05 was considered statistically significant.

Results

Demographic data and household characteristics

During the study period, 6820 children less than one year old were admitted to our wards for internal medicine (including Neonatology department) and 1726 (25.3%) children were diagnosed with ALRIs and eligible for recruitment. Nine hundred thirteen infants had laboratory-confirmed RSV infections, including 288 (31.5%) severe cases and 625 (68.5%) non-severe cases. Infants with severe RSV-associated ALRIs accounted for 4.2% of hospitalized children. Their median age was 1.4 (0.5, 3.0) months and median gestational age 38.0 (36.0, 39.0) weeks and birth weight 3.05 (2.43, 3.50) kg. The male/female ratio among the severe cases was 2.0:1. More severe infants than non-severe infants infected with RSV were under the age of 3 months and preterm, and had low birth weights (*P*<0.001, severe *vs.* non-severe cases). There was a male preponderance in both groups, without significant difference (Table 1). In the severe cases, few patients lived in families with a monthly income more than 10 000 RMB (*P*<0.05 *vs.* non-severe cases). Moreover, 42.0% lived with 4 or more family members, 45.5% were exposed to cigarette smoke and 10.8% had a mother with allergic history (*P*>0.05 in all *vs.* non-severe cases).

Clinical characteristics of infants with ALRIs

The main clinical manifestations of infants with severe

Table 1. Demographic characteristics of infants with respiratory syncytial virus-associated acute lower respiratory tract infections

Variables	Non-severe	Severe	*P*
N	625	288	
Gender			
Male	409 (65.4)	191 (66.3)	0.822
Age, mon, *n* (%)			
<3	331 (53.0)*	216 (75.0)	
3-6	128 (20.5)*	42 (14.6)	<0.001
6-12	166 (26.6)*	30 (10.4)	
Gestational age, wk, *n* (%)			
<37	90 (14.4)	73 (25.3)	<0.001
≥37	535 (85.6)	215 (74.7)	
Body weight, g, *n* (%)			
<2500	80 (12.8)	74 (25.7)	<0.001
≥2500	545 (87.2)	214 (74.3)	

Severity index ≥3 was categorized as a severe disease and <3 as a non-severe disease. *: The data may not sum to total due to rounding.

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and non-severe RSV-associated ALRIs at admission are shown in Table 2. Cough (76.8%) and wheezing (35.3%) were the most common symptoms while Coarse (86.4%) and fine (33.2%) rales were the most common signs among all infants. There was no statistical difference in the proportions of infants with cough, fever, coarse rales and wheezing between infants with severe and non-severe ALRIs (P>0.05). By contrast, the proportions of infants with severe ALRIs who had tachypnea (for infants <2 months old, respiratory rate ≥60/min; for infants <12 months old, respiratory rate ≥50/min), apnea, cyanosis, and fine rales were significantly higher than infants with non-severe ALRIs (P<0.001 in all) (Table 2).

Underlying diseases

Five hundred forty-two (59.4%) infants with RSV-associated ALRIs had underlying diseases. There was a statistically significant difference in the proportion of patients with underlying disease between infants with severe (70.8%) and non-severe ALRIs (54.1%, P<0.001). Congenital heart disease (CHD) was the most common underlying disease in both groups (severe ALRIs, 41.7% *vs.* non-severe ALRIs, 23.7%; P<0.001). The proportions of bronchopulmonary dysplasia (BPD) and airway abnormalities were also statistically higher in infants with severe ALRIs (BPD: severe ALRIs, 3.8% *vs.* non-severe ALRIs, 0.3%, P<0.001; airway abnormalities: severe ALRIs, 5.2% *vs.* non-severe ALRIs, 2.2%, P<0.05).

Risk factors of severe ALRIs

Univariate logistic regression revealed that the following variables were statistically significant risk factors for severe RSV-associated ALRIs: premature birth, low birth weight, age younger than 6 months old, presence of underlying diseases (CHD, BPD, and airway abnormalities), and family income <5000 Yuan/month (Table 3). Multivariate logistic regression showed that low birth weight [1.698 (1.028-2.805)], age younger than 3 months old [3.385 (2.174-5.271)], CHD [1.667 (1.149-2.418)], BPD [8.505 (1.731-41.780)], and airway abnormalities [2.246 (1.008-5.005)] were independent risk factors for severe RSV-associated ALRIs. Family factors, which included family size and income, were not independently associated with the severity of ALRIs.

Follow-ups of RSV infections

At six months after discharge of infants with RSV-associated ALRIs, the incidences of bronchitis, pneumonia and readmission in infants with severe ALRIs were higher than those with non-severe ALRIs (all P<0.001). At 12 months of follow-up, the incidence of bronchitis remained significantly higher in infants with severe ALRIs (P<0.05). There was no significant difference in the incidence of atopic diseases between the two groups in both follow-ups (Table 4).

Table 2. Clinical manifestations of infants with respiratory syncytial virus-associated acute lower respiratory tract infections [*n* (%)]

Variables	Non-severe	Severe	Total	*P*
N	625	288	913	
Cough	491 (78.6)	210 (72.9)	701 (76.8)	0.061
Fever	72 (11.5)	38 (13.2)	110 (12.0)	0.470
Tachypnea	14 (2.2)	73 (25.3)	87 (9.5)	<0.001
Apnea	26 (4.2)	98 (34.0)	124 (13.6)	<0.001
Cyanosis	11 (1.8)	27 (9.4)	38 (4.2)	<0.001
Coarse rales	535 (85.6)	253 (87.8)	788 (86.4)	0.296
Fine rales	174 (27.8)	128 (44.4)	302 (33.2)	<0.001
Wheezing	230 (36.8)	92 (32.2)	322 (35.3)	0.175

Table 3. Univariate logistic regression analysis of risk factors of severe RSV-associated acute lower respiratory tract infections

Variables	OR	95% CI	*P*
Male	1.040	0.774-1.396	0.795
Gestational age <37 wk	2.018	1.427-2.855	<0.001
Body weight <2500 g	2.356	1.654-3.354	<0.001
Age, mon			
6-12	1.000		
3-6	1.816	1.077-3.061	0.025
<3	3.611	2.361-5.523	<0.001
Underlying diseases	2.062	1.529-2.780	<0.001
Congenital heart disease	2.302	1.709-3.102	<0.001
Bronchopulmonary dysplasia	12.370	2.724-56.179	0.001
Airway abnormalities	2.398	1.142-5.037	0.021
Immunodeficiency	0.359	0.043-3.000	0.345
Tobacco exposure	1.021	0.772-1.352	0.882
Mother atopic diseases	0.898	0.576-1.401	0.636
Family size ≥4	1.116	0.841-1.482	0.447
Family income, RMB/mon			
10 000-	1.000		
5000-	1.423	0.848-2.386	0.181
<5000	2.115	1.262-3.547	0.004

OR: odds ratio; CI: confidence interval; RSV: respiratory syncytial virus.

Table 4. One year follow-ups of infants with respiratory syncytial virus-associated acute lower respiratory tract infections

Variables	Non-severe	Severe	Total	*P*
Follow up at 6 mon	*n*=552	*n*=226	*n*=778	
Atopic dermatitis	136 (24.6)	48 (21.2)	184 (23.7)	0.311
Wheezing	77 (13.9)	39 (17.3)	116 (14.9)	0.240
Allergic rhinitis	32 (5.8)	19 (8.4)	51 (6.6)	0.182
Bronchitis	224 (40.6)	131 (58.0)	355 (45.6)	<0.001
Pneumonia	68 (12.3)	67 (29.6)	135 (17.4)	<0.001
Readmission	69 (12.5)	67 (29.6)	136 (17.5)	<0.001
Follow up at 12 mon	*n*=539	*n*=220	*n*=759	
Atopic dermatitis	110 (20.4)	41 (18.6)	151 (19.9)	0.579
Wheezing	100 (18.6)	46 (20.9)	146 (19.2)	0.455
Allergic rhinitis	39 (7.2)	18 (8.2)	57 (7.5)	0.654
Bronchitis	65 (12.1)	44 (20.0)	109 (14.4)	0.005
Pneumonia	10 (1.9)	7 (3.2)	17 (2.2)	0.395
Readmission	11 (2.0)	8 (3.6)	19 (2.5)	0.202

Values in each row were not mutually exclusive.

Discussion

We studied 913 infants with RSV-positive ALRIs in a one-year period, and approximately three out of ten patients developed severe ALRIs. The rate of RSV-associated severe ALRIs out of hospitalized infants was 4.2%. The results of studies from different countries have shown variable incidences of RSV-associated severe ALRIs, ranging from 10 per 1000 children per year in the Netherlands[13] to 166 per 1000 per year in a study in the USA.[14] The hospital RSV mortality rate in the current study (1.0%) is similar to that of other studies.[15] As analyzed by Nair et al.,[1] methodological factors affect estimates, especially case definition for non-severe and severe episodes. In this study, we used the severity criteria derived from 6 clinical findings in infants who were expected to have more severe illness.[12]

We found a high frequency of cough and coarse rales in RSV infected infants and a higher proportion of severe cases developed tachypnea, apnea or cyanosis in addition to fine rales. A similar finding was reported in Japan,[16] and recommended that medical staff should instruct parents to make an emergency visit if dyspnea in addition to cough and nasal discharge occur in their children, even in the absence of fever.

Furthermore, the presence of low birth weight, chronic lung disease, airway abnormalities, and CHD were associated with severe RSV-associated ALRIs in our study cohort. These risk factors were also reported in previous studies in Hong Kong, showing that prior sick contact is the only risk factor for RSV-associated mortality.[5,6] However, prematurity was not a risk factor for severe RSV infections in our study, which is in accordance with the study in Suzhou.[7] For household characteristics, although living in low income families was not an independent risk factor for severe RSV infections, infants with severe RSV-associated ALRIs were more likely to live in low income families. A lower socioeconomic status is often accompanied by crowded living conditions and less access to healthcare.[17]

RSV infections are associated with the development of abnormal pulmonary function, wheezing, and asthma in childhood.[18,19] We failed to find an association of atopic diseases and the severity of RSV infections, whereas the incidence of bronchitis, pneumonia and re-hospitalization was significantly higher in infants with severe ALRIs. The re-hospitalization rate within the first year after RSV hospitalization was reported as high as 20%.[20] In the present study, the re-hospitalization rate was 29.6% after 6 months and 3.6% after 12 months in infants with severe ALRIs. Some studies found that RSV re-hospitalization rate was associated with premature birth and BPD,[21,22] which were also risk factors for severe RSV infections.

In conclusion, we found that younger age, low birth weight, CHD, BPD and airway abnormalities were independently associated with severe RSV infections. Severe cases were more inclined to develop respiratory infections and to be re-hospitalized in the following year. Prevention strategies for RSV such as immunization when a suitable vaccine is available in the future should target high-risk infants to avoid severe RSV disease progression and decrease mortality.

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Ethical approval: The study was approved by the Ethics Committee of Children's Hospital of Fudan University. Written informed consents were obtained from the parents or legal surrogates of the study subjects.

Competing interest: None declared.

Contributors: Zhang XB proposed the project and wrote the paper. Liu LJ analyzed the data. Zhang XB and Liu LJ contributed equally to this paper. All authors contributed to the design and interpretation of the study and to further drafts. Wang LB is the guarantor.

References

1 Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375:1545-1555.
2 Morris SK, Dzolganovski B, Beyene J, Sung L. A meta-analysis of the effect of antibody therapy for the prevention of severe respiratory syncytial virus infection. BMC Infect Dis 2009;9:106.
3 Resch B. Respiratory syncytial virus infection in high-risk infants - an update on palivizumab prophylaxis. Open Microbiol J 2014;11:71-77.
4 Kong X, Liu C, Shou H, Shen K, Mai Y, Wang S, et al. Correlation between illness severity and risk factors for respiratory syncytial virus infection. Chin J Pediatr 2000;38:603-606.
5 Hon KL, Leung TF, Cheng WY, Ko NMW, Tang WK, Wong WW, et al. Respiratory syncytial virus morbidity, premorbid factors, seasonality, and implications for prophylaxis. J Crit Care 2012;27:464-468.
6 Leung T, Lam D, Miu T, Hon K, Chau C, Ku S, et al. Epidemiology and risk factors for severe respiratory syncytial virus infections requiring pediatric intensive care admission in Hong Kong children. Infection 2014;42:343-350.
7 Zhang T, Zhu Q, Zhang X, Ding Y, Steinhoff M, Black S, et al. Clinical characteristics and direct medical cost of respiratory syncytial virus infection in children hospitalized in Suzhou, China. Pediatr Infect Dis J 2014;33:337-341.
8 Oncel MY, Arayici S, Simsek GK, Calisici E, Erdeve O, Uras N, et al. Risk factors for hospitalization due to lower respiratory tract infection in preterm infants on palivizumab prophylaxis.

Iran J Pediatr 2013;23:693-700.
9 Piedimonte G. Respiratory syncytial virus and asthma: speed-dating or long-term relationship? Curr Opin Pediatr 2013;25:344-349.
10 Hu Y, Jiang Z. Practical Pediatric Textbook of Fu-tang Zhu, 7th ed. Beijing: People's Hygiene Publishing, 2005.
11 Subspecialty Group of Respiratory Diseases, Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics. Guidelines for management of childhood community acquired pneumonia (for trial implementation). Chin J Pediatr (Chin) 2007;45:83-90.
12 McConnochie KM, Hall CB, Walsh EE, Roghmann KJ. Variation in severity of respiratory syncytial virus infections with subtype. J Pediatr 1990;117:52-62.
13 Jansen AG, Sanders EA, Hoes AW, Van Loon A, Hak E. Influenza-and respiratory syncytial virus-associated mortality and hospitalisations. Eur Respir J 2007;30:1158-1166.
14 Singleton RJ, Bruden D, Bulkow LR. Respiratory syncytial virus season and hospitalizations in the Alaskan Yukon-Kuskokwim Delta. Pediatr Infect Dis J 2007;26:S46-S50.
15 Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. Arch Dis Child 2009;94:99-103.
16 Ito H, Osamura T, Nakajima F, Fujiwara D, Kuwabara Y, Yamamoto T, et al. Survey of severe respiratory syncytial virus infection in Kyoto Prefecture from 2003 to 2007. Pediatr Int 2010;52:273-278.
17 Grimwood K, Cohet C, Rich F, Cheng S, Wood C, Redshaw N, et al. Risk factors for respiratory syncytial virus bronchiolitis hospital admission in New Zealand. Epidemiol Infect 2008;136:1333-1341.
18 Castro-Rodríguez JA, Holberg CJ, Wright AL, Halonen M, Taussig LM, Morgan WJ, et al. Association of radiologically ascertained pneumonia before age 3 yr with asthmalike symptoms and pulmonary function during childhood: a prospective study. Am J Respir Crit Care Med 1999;159:1891-1897.
19 Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol 2007;119:1105-1110.
20 Eriksson M, Bennet R, Nilsson A. Wheezing following lower respiratory tract infections with respiratory syncytial virus and influenza A in infancy. Pediatr Allergy Immunol 2000;11:193-197.
21 Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med 2000;154:55-61.
22 Carbonell-Estrany X, Quero J, Bustos G, Cotero A, Domenech E, Figueras-Aloy J, et al. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. IRIS Study Group. Pediatr Infect Dis J 2000;19:592-597.

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