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ORIGINAL ARTICLE

Comparison of infections with respiratory syncytial virus between children and adults: a multicenter surveillance from 2015 to 2019 in Beijing, China

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Abstract

The objective of this study is to investigate the epidemiological and clinical characteristics of the acute respiratory tract infections (ARTI) caused by respiratory syncytial virus (RSV) among the population of all age categories in Beijing, China. Outpatients and inpatients with ARTI were enrolled from 35 sentinel hospitals in Beijing between March 2015 and February 2019. They were interviewed and their medical records were collected using a standardized form. Their respiratory specimens were collected and tested for the nucleic acid of RSV. The RSV-positive specimens were further genotyped into RSV-A and RSV-B groups. A total of 29,923 cases were included in this study. RSV was detected in 623 (2%, 623/29923) patients, with 391 (62.8%) genotypd as RSV-A, 126 (20.2%) as RSV-B, and 106 (17.0%) untyped. The RSV epidemic season usually occurred between October and March covering approximately 90% of annual RSV infections. The RSV-infected children aged < 5 years accounted for 52.2% of the total RSV infections with cough and fever as the most common manifestations. The RSV-infected elderly adults aged ≥ 60 years have the second largest proportion (25.2%) with dyspnea and lymphocytopenia as the most common manifestations and showed an elevated rate of hospitalization, an increased rate of ICU admission, an extended length of hospital stay, and an elevated mortality compared to the RSV-infected children. The RSV infections aged ≥ 60 years old, as the second largest population of the total annual RSV infections, usually developed worse outcomes than children and should be taken seriously.

Keywords Respiratory syncytial virus · Respiratory infection · Surveillance · Respiratory pathogen · Epidemiological characteristics · Clinical characteristics

Introduction

Respiratory syncytial virus (RSV) is one of the most important pathogens leading to severe lower respiratory tract infections in children. It causes 2.7–3.8 million hospitalizations and 94,600–149,400 deaths among children under 5 years of age each year [1]. It can also result in severe respiratory infections in high-risk adults or elderly healthy individuals [2]. There were annual 17,358 deaths attributed to RSV infection in the USA, and more than half of which were the elderly adults aged 65 years or older [3].

Generally, RSV infection has no distinguishable clinical presentations, which vary from asymptomatic carriage to acute respiratory distress. Unlike influenza, there is a considerable proportion of RSV-infected children who present no fever during their illness course [4], which made RSV surveillance become more challenging. RSV prevalence presented

Ming Luo, Cheng Gong, and Yan Zhang contributed equally.

Key points
- The RSV season in Beijing usually appears between October and March, which includes approximately 90% of annual RSV infections.
- The elderly adults aged ≥ 60 years, another high-morbidity population for RSV infection besides young children, usually develop more severe outcomes than the children aged < 5 years.

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a distinct seasonality, although regional variation occurred. In countries with temperate climate, RSV often circulated throughout the winter season and peaked between December and January, whereas in tropical countries, RSV usually breaks out during hot, humid, rainy days in the summer season. Its two genotypes (RSV-A and RSV-B) predominated alternatively or co-circulated in a single epidemic season [5].

RSV infection has raised widely public health concern and the related surveillance has been conducted in many countries. RSV was included into the National Respiratory and Enteric Virus Surveillance System in the USA since 1989 [6, 7] and included into the National Epidemiological Surveillance System for Infectious Diseases since 2003 [8]. The European Union has initiated RSV surveillance using the existing influenza surveillance network since 2003 [9, 10]. The USA also launched the Global Disease Detection project in 2004, which conducted a surveillance for influenza virus and RSV in multiple countries all over the world [11]. The World Health Organization started the RSV surveillance program using the global influenza network in 2017 [12]. The Beijing Respiratory Pathogen Surveillance System (RPSS), a regional surveillance program covering 11 respiratory viruses including RSV and 15 respiratory bacteria, was conducted since 2010. However, a nationwide RSV surveillance network has not been established in China so far.

There were several studies on RSV prevalence in China. Most of them focused on RSV infections among children and considered that the RSV infections accounted for 17–33% of patients with community-acquired pneumonia among Chinese children during the RSV epidemic season [13, 14]. RSV infection among elderly population has been confirmed to be associated with a higher risk of severe illness [2], whereas the reports on RSV prevalence among the adults in China, especially among the elderly people, are very limited. While China is the most populous country globally and the problem of population aging is becoming more prevalent, the proportion of the RSV-infected elderly adults will probably increase in the coming years. Moreover, there is no licensed RSV vaccine available. Palivizumab is the only prophylaxis biological product approved by the Food and Drug Administration in the USA for use in infants at high risk of severe RSV infection [15], while it has not been approved by the Chinese Food and Drug Administration. So, it is becoming more urgent to obtain the systemic and comprehensive insights into RSV infections among elderly adults applying long-term, representative RSV surveillance program in China.

Based on the Beijing Respiratory Pathogen Surveillance System, this study intended to cover a more complete illness profile of respiratory infections caused by RSV (including acute upper respiratory tract infection, non-severe pneumonia, and severe pneumonia), including patients of all age categories who presented at or were admitted to 35 sentinel hospitals in Beijing, and conduct a systematic and comprehensive exploration of the prevalence of RSV in Beijing between 2015 and 2019.

Population and methods

Ethics statement

This study was approved by the Ethics Committee at Beijing Center for Disease Prevention and Control. The written informed consent was obtained from each of enrollees (or their guardians if appropriate) after we declared the nature, purpose, procedures, and potential health impact regarding this study. Patients were required to provide consent by themselves if their age and health condition were appropriate.

Study population

The RPSS network included 35 public sentinel hospitals of different level, which were located in all of 16 districts in Beijing. The patients were enrolled if they visited any one of the sentinel hospitals for acute upper respiratory tract infection (AURTI) or community-acquired pneumonia (CAP) between March 1, 2015, and February 28. Each sentinel hospital was required to enroll more than 20 qualified patients per month as possible in line with the sample size determined by the study. AURTI patients were included if they presented with fever and/or respiratory symptoms, e.g., cough, sputum production, and sore throat. CAP patients were included if they had evidence of CAP according to the guidelines for the diagnosis and treatment of adult community-acquired pneumonia in China (2016 edition) and the guidelines for the management of community-acquired pneumonia in children (the revised edition of 2013) [16–18]. Namely, CAP was defined as a new or aggravated infiltrate in chest radiographs obtained within 72 h before or after presentation, which was accompanied by one of the following clinical characteristics: new cough or sputum production, aggravated underlying respiratory disease, fever (> 37.8 °C), hypothermia (< 35.6 °C), leukocytosis (> 10 × 109/L), leukopenia (< 4 × 109/L), or pulmonary consolidation or moist rale.

Patients were excluded if they had been hospitalized recently (< 28 days for immunocompetent patients and < 90 days for immunocompromised patients), had already been enrolled in the RPSS study within the previous 28 days, or had a clear alternative diagnosis of a respiratory disorder. We also excluded patients if they had lung cancer or tuberculosis, pneumoconiosis, noninfectious interstitial lung disease, pulmonary edema, pulmonary atelectasis, pulmonary thromboembolism, pulmonary infiltration with eosinophilia, or pulmonary vasculitis.

CAP patients were further classified as severe CAP (SCAP) and non-severe CAP (NSCAP) based on illness severity according to the criteria provided previously [19].

Specimen and data collection

All cases were investigated by their physicians after enrollment using a uniform questionnaire, including demographic data, epidemiological data, clinical manifestation, radiographical imaging data, and laboratory data. The comorbidity referred to 11 illness obtained before the acute respiratory infection as follows: asthma, bronchitis/bronchiolitis, chronic obstructive pneumonia disease, diabetes, hypertension, heart disease, chronic renal disease, chronic liver disease, malignancy, and stroke. All questionnaires were transferred to the Beijing Center for Disease Prevention and Control (BJCDC) for data cleaning and statistical analyses.

Respiratory specimens were collected as early as possible (upon presentation for outpatient or within 72 h of admission for inpatients), including at least one of the following specimen kinds: pharyngeal swabs, nasopharyngeal aspirates, sputum, pleural effusion, tracheal aspirates, or bronchoalveolar lavage fluid. All specimens were transferred to the laboratory in BJCDC under a frozen condition for etiological testing.

Laboratory examination

Total nucleic acids (RNA and DNA) were extracted from the respiratory specimens using an automated equipment in accordance with the manufacturer's instructions (Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processors, Thermo Fisher, MA, USA). A real-time PCR-based commercial diagnostic kit (Multiplex Combined Real-time PCR Detection Kit for Respiratory Viruses, Jiangsu Uninovo Biological Technology Co. Ltd., Jiangsu, China) was used for the test for RSV on the extracted nucleic acids. RSV-positive samples were further genotyped into RSV group A (RSV-A) or RSV group B (RSV-B) using a commercial kit (Duplex Real-Time PCR Kit for RSV, Beijing Kinghawk Pharmaceutical Co., Ltd., Beijing, China).

Statistical analysis

Continuous variables were presented as median (interquartile range, IQR) and compared between different groups with the Kruskal–Wallis test; categorical variables were presented as numbers (%), and comparisons between different groups were done by the χ^2 test or Fisher's exact test. A two-sided α of less than 0.05 was considered statistically significant. Cases with missing data of a variable were excluded out of the statistical analyses on this variable. All data were entered independently by two technicians using EpiData 3.1 (Odense, Denmark). All statistical analyses were done using SPSS statistical software version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics

Between March 1, 2015, and February 28, 2019, a total of 29,923 cases were finally included in this study, of which 8586 (29%) were with AURTI; 16,121 (54%) were with non-severe CAP (NSCAP); 4139 (14%) were with SCAP; and 1074 (4%) were with bronchitis (3 missing final diagnostic information). Male cases accounted for 56% (16,668) (93 missing gender information).

The youngest was 1 month old, and the oldest was 104 years old with a median age of 38 years old (IQR: 8–68, 120 patients missing age information).

RSV was detected in 623 (2%, 623/29923) enrolled patients, including 92 (15%, 92/623) patients with AURTI, 429 (69%, 429/623) with NSCAP, and 92 (15%, 92/623) with SCAP (10 missing diagnostic information). Among overall RSV-infected patients, 352 (57%) were male (4 missing gender information), the minimum age was 1 month old, and the maximum was 101 years old with a median age of 4 years old (IQR: 1–60 years old, three cases without age information).

Of the 623 RSV-positive cases, 391 (62.8%) were genotyped as RSV-A, 126 (20.2%) were genotyped as RSV-B, and 106 (17.0%) were not genotyped successfully.

Seasonality of RSV infections in Beijing

We observed an annual RSV epidemic around winter from March 2015 to February 2019. RSV-positive rate began to rise in October, peaked in December or January, and fell to background level in April, with about 90% of RSV infections occurring during the epidemic season (from October to March) (Fig. 1A). This epidemic season advanced or was postponed by about 1 month in different years. RSV-A and RSV-B co-circulated each year during the study period with RSV-A remaining a predominant proportion (62.8%) (Fig. 1B).

Comparison of RSV prevalence among different age-groups

The RSV-positive rate peaked to 6.07% in the 0–4-year group, then dramatically fell to 1.51% in the 5–17-year group, hovered at 0.76% in the 18–59-year group, and increased to1.57% again in the group with 60 years or older. RSV infections in the 0–4-year group accounted for 52% of the overall RSV infections, followed by those among the elderly adults aged 60 years or older (25%). Both of RSV-A and RSV-B were detected in the four age groups with RSV-A remaining a dominant percentage (Fig. 2A).

There were similar trends among four age groups that pneumonia patients (NSCAP and SCAP) exhibited a higher RSV-positive rate than AURTI patients (Fig. 3A). RSV-A

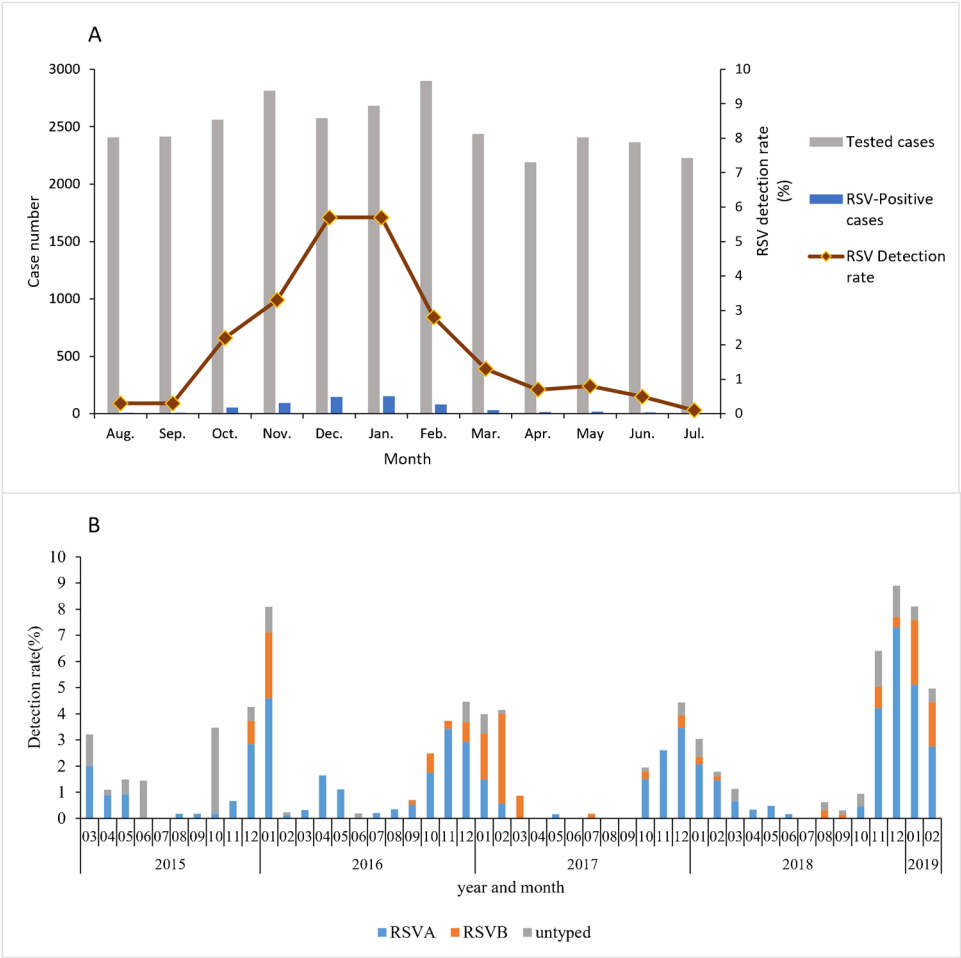

Fig. 1 RSV seasonality in Beijing. **A** The average percentage of RSV-positive cases per month among the tested cases in Beijing from March 2015 to February 2019. Gray bars denote the tested cases per month, blue bars denote the RSV-positive cases per month, and the brown line denotes the average percentage of RSV-positive cases per month among the tested cases. **B** RSV detection rate by month in Beijing from March 2015 to February 2019. The bars represent the RSV detection rate per month. Blue denotes RSV group A, orange denotes RSV group B, gray denotes untyped RSV. RSV, respiratory syncytial virus

and RSV-B were both detected in each illness category of patients per age group, with RSV-A remaining an approximate dominant proportion (Fig. 3B).

Comparison of clinical manifestations and laboratory findings of RSV-infected patients of different age groups

Among the 623 RSV-infected patients, the medical data were collected successfully from only 597. The proportion of cases with ≥ 1 comorbidity was 2.9% in the 0–4 years old group, 0% in 5–17 years old group, 22.4% in 18–44 years old group, and 57.2% in ≥ 60 years old group, approximately increasing as age ($p < 0.001$). Among the children with 0 to 4 years of age, the most common symptoms were cough (95.8%), fever (87.8%), sputum production (61.0%), rhinorrhea (42.9%), nasal congestion (33.5%), dyspnea (12.3%), and sore throat (11.6%), whereas among the adults with 60 years of age or older, the most common symptoms were cough (88.8%), sputum production (82.9%), fever (74.8%), dyspnea (52.6%), sore throat (18.4%), and rhinorrhea (17.1%). Notably, more than half of RSV-infected patients aged ≥ 60 years eventually developed dyspnea in their clinical course (52.6%; Table 1). The proportion was significantly higher than that of RSV-infected patients aged ≤ 4 years ($p < 0.001$).

There were many differences in blood analysis between the younger children and the elderly adults with RSV. The elderly patients frequently developed lymphopenia (5.1% for 0–4 years, 41.5% for ≥ 60 years, $p < 0.001$), neutrophilia (15.1% for 0–4 years, 71.2% for ≥ 60 years, $p < 0.001$), and an elevated C-reactive protein (CRP; 23.2% for 0–4 years, 73.6% for ≥ 60 years, $p < 0.001$). Whereas the younger children were more likely to develop elevated aspartate aminotransferase (AST; 34.9% for 0–4 years, 13% for ≥ 60 years, $p < 0.001$) and/or an elevated creatine kinase MB fraction (CKMB; 30.4% for 0–4 years, 2.5% for ≥ 60 years, $p < 0.001$) (Table 2).

Radiographic findings showed that the proportion of pneumonia among the overall RSV infections was associated with the age of the patient (23.2% for 0–4 years, 59.2% for ≥ 60 years, $p < 0.001$). Furthermore, about 50% of the abnormal radiographic findings involved bilateral lung (Table 2).

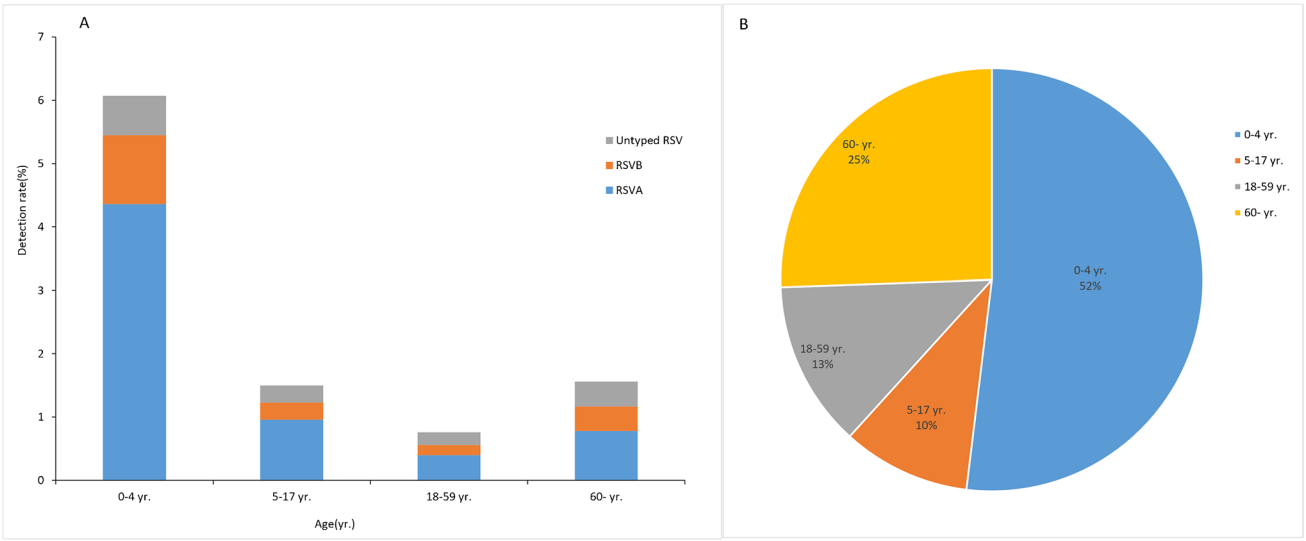

Fig. 2 Distribution of RSV infections by age group in Beijing from March 2015 to February 2019. **A** RSV detection rate by age group. The bar represents the RSV detection rate per age group. Blue denotes RSV group A, orange denotes RSV group B, and gray denotes untyped RSV. RSV, respiratory syncytial virus. **B** Proportion of RSV-positive cases by age group

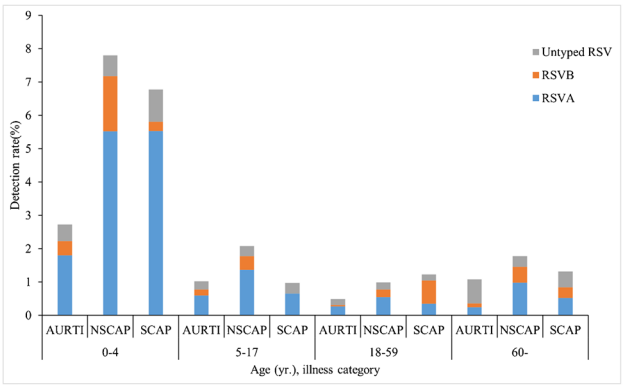

Fig. 3 The detection rates of RSV subgroups by age group and illness severity in Beijing from March 2015 to February 2019. The bar represents RSV detection rate per age group and illness severity. Blue denotes RSV group A, orange denotes RSV group B, and gray denotes untyped RSV. RSV, respiratory syncytial virus. AURTI, acute upper respiratory tract infection. NSCAP, non-severe community-acquired pneumonia. SCAP, severe community-acquired pneumonia

Comparisons of treatments and outcome measures of RSV-infected patients of different age groups

A total of 390 RSV infections (65%, 390/597) were inpatients in this study. The median time from illness onset to hospital admission of these inpatients was similar among four age groups (varied within 2.5–3.5 days, $p = 0.065$), whereas the hospitalization rates among the four age groups differed significantly as follows: 65.5% (0–4 years), 52.5% (5–17 years), 48.7% (18–44 years), and 78.3% (≥ 60 years) ($p < 0.001$). The hospitalization rate of the ≥ 60 years old group was significantly higher than those of other three groups (versus 0–4 years: $p = 0.005$; versus 5–17 years: $p < 0.001$; versus 18–59 years: $p < 0.001$). Moreover, the median length of hospital stay was also extended significantly when age increased as follows: 7 days (0–4 years: IQR 6–9 days), 8 days (5–17 years: IQR 5–11 days), 10 days (18–59 years: IQR 7–15 days), and 12 days (≥ 60 years: IQR 8.5–16 days) ($p < 0.001$). The rate of ICU admission among the four age groups differed obviously as follows: 0.6% (0–4 years), 0.0% (5–17 years), 10.5% (18–59 years), and 15.1% (≥ 60 years) ($p < 0.001$). So in terms of the rate of hospitalization, the length of hospital stay, and the rate of ICU admission, the patients with ≥ 60 years old all reached the highest among the four age groups (Table 3).

Compared with the children aged 0–4 years, the rates of antibiotic use (60.7%, 74.4%, $p < 0.001$), oxygen support therapy (12.6%, 62.5%, $p < 0.001$), and mechanical ventilation (8.4%, 12.5%, $p = 0.035$) among the elderly patients aged > 60 years were all significantly increased. However, the rates of vasoactive drug administration, corticosteroid use, and antiviral therapy among the four age groups were similar. A total of eight (8/597) RSV-infected patients were treated with extracorporeal membrane oxygenation (ECMO in this study), and only one case, a 63-year-old man, died in hospitalization (Table 3).

The most frequent complication among RSV-infected children was acute myocardial injury (9% in 0–4 years group, 6.8% in 5–17 years group), whereas that among RSV-infected adults was respiratory failure (11.8% in 18–59 years group, 15.8% in ≥ 60 years group). The RSV infections among adults with ≥ 60 years of age resulted

Table 1 Demographic and clinical characteristics of 597 patients infected with RSV

	0–4 yr n = 310	5–17 yr n = 59	18–59 yr n = 76	≥ 60 yr n = 152	p-value
Demographics and clinical characteristics					
Female	124 (40%)	26 (44.1%)	36 (47.4%)	70 (46.1%)	0.506
Inpatient	203 (65.5%)	31 (52.5%)	37 (48.7%)	119 (78.3%)	< 0.001
Time from illness onset to hospital admission, days	3.5 (2–5)	3 (1–6)	2.5 (1–6)	3 (1–6)	0.065
Comorbidity	9 (2.9%)	(0%)	17 (22.4%)	87 (57.2%)	< 0.001
Asthma	1 (0.3%)	0 (0%)	6 (7.9%)	7 (4.6%)	< 0.001
Bronchitis/bronchiolitis	1 (0.3%)	0 (0%)	1 (1.3%)	12 (7.9%)	< 0.001
Chronic obstructive pneumonia disease	0 (0%)	0 (0%)	3 (3.9%)	13 (8.6%)	< 0.001
Diabetes	1 (0.3%)	0 (0%)	5 (6.6%)	24 (15.8%)	< 0.001
Hypertension	2 (0.6%)	0 (0%)	9 (11.8%)	52 (34.2%)	< 0.001
Heart disease	4 (1.3%)	0 (0%)	1 (1.3%)	35 (23%)	< 0.001
Chronic renal disease	1 (0.3%)	0 (0%)	2 (2.6%)	2 (1.3%)	0.143
Chronic liver disease	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0.481
Malignancy	2 (0.6%)	0 (0%)	0 (0%)	6 (3.9%)	0.034
Stroke	0 (0%)	0 (0%)	1 (1.3%)	16 (10.5%)	< 0.001
Symptoms and signs					
Fever (temperature ≥ 37.3 °C)	267/304 (87.8%)	57/58 (98.3%)	67/75 (89.3%)	113/151 (74.8%)	< 0.001
Temperature, °C					
< 37.3	37/304 (12.2%)	1/58 (1.7%)	8/75 (10.7%)	38/151 (25.2%)	< 0.001
37.3–37.9	21/304 (6.9%)	3/58 (5.2%)	4/75 (5.3%)	21/151 (13.9%)	
38–38.9	129/304 (42.4%)	25/58 (43.1%)	41/75 (54.7%)	59/151 (39.1%)	
≥ 39	117/304 (38.5%)	29/58 (50%)	22/75 (29.3%)	33/151 (21.9%)	
Sore throat	36 (11.6%)	20 (33.9%)	27 (35.5%)	28 (18.4%)	< 0.001
Cough	297 (95.8%)	52 (88.1%)	66 (86.8%)	135 (88.8%)	0.003
Sputum production	189 (61%)	37 (62.7%)	55 (72.4%)	126 (82.9%)	< 0.001
Hemoptysis	2 (0.6%)	0 (0%)	2 (2.6%)	4 (2.6%)	0.138
Chest pain	1 (0.3%)	1 (1.7%)	5 (6.6%)	7 (4.6%)	0.001
Dyspnea	38 (12.3%)	0 (0%)	21 (27.6%)	80 (52.6%)	< 0.001
Nasal congestion	104 (33.5%)	18 (30.5%)	9 (11.8%)	12 (7.9%)	< 0.001
Rhinorrhea	133 (42.9%)	23 (39%)	22 (28.9%)	26 (17.1%)	< 0.001
Headache	1 (0.3%)	4 (6.8%)	8 (10.5%)	7 (4.6%)	< 0.001
Fatigue	2 (0.6%)	3 (5.1%)	11 (14.5%)	11 (7.2%)	< 0.001
Myalgia	0 (0%)	0 (0%)	3 (3.9%)	5 (3.3%)	0.002
Diarrhea	11 (3.5%)	0 (0%)	1 (1.3%)	4 (2.6%)	0.534
Abdominal pain	6 (1.9%)	0 (0%)	4 (5.3%)	2 (1.3%)	0.175
Nausea or vomiting	14 (4.5%)	1 (1.7%)	2 (2.6%)	4 (2.6%)	0.717
Oliguria	1 (0.3%)	0 (0%)	0 (0%)	1 (0.7%)	0.731
Disturbance of consciousness	0 (0%)	0 (0%)	3 (3.9%)	11 (7.2%)	< 0.001
Abnormal respiratory rate, beats/min	116/237 (48.9%)	5/46 (10.9%)	6/65 (9.2%)	10/137 (7.3%)	< 0.001

Data are median (IQR) or n (%). p-values were calculated by Kruskal–Wallis test, χ^2 test, or Fisher's exact test, as appropriate

in organ failures more frequently than the other three younger age groups, e.g., respiratory failure (15.8%), heart failure (13.2%), and renal failure (5.9%). A total of five RSV-infected adults (0.8%, 5/597) eventually developed acute respiratory distress syndrome (ARDS) in this study, two in the 18–59 age group and three in the ≥ 60 age group. (Table 3).

The median time from onset to discharge was 11 days (IQR 9–14 days) in 0–4 years old group, 13 days (IQR 10–17 days) in 5–17 years age group, 13 days (IQR 11–18 days) in 18–44 years old group, and 16 days (IQR 12–20 days) in ≥ 60 years old group and was extended significantly as age increased ($p < 0.001$). A total of 10 deaths in hospital (1.7%, 10/597) were observed in this study. Two

Table 2 Laboratory and radiographic findings of 597 patients infected with RSV

	0–4 yr n = 310	5–17 yr n = 59	18–59 yr n = 76	≥ 60 yr n = 152	p-value
Laboratory findings					
White blood cell count, × 109 per L	7.98 (6–10.8)	8.0 (6.4–10.4)	7.3 (5.5–10.0)	7.5 (5.9–10.7)	0.485
< 4	6/280 (2.1%)	/49 (0%)	7/71 (9.9%)	10/145 (6.9%)	0.037
4–10	189/280 (67.5%)	35/49 (71.4%)	47/71 (66.2%)	92/145 (63.4%)	
≥ 10	85/280 (30.4%)	14/49 (28.6%)	17/71 (23.9%)	43/145 (29.7%)	
Lymphocyte count, × 109 per L	3 (2–4.4)	2.05 (1.225–2.875)	1.4 (0.9–2.15)	1.1 (0.7–1.7)	< 0.001
< 1000	14/277 (5.1%)	8/48 (16.7%)	19/68 (27.9%)	54/130 (41.5%)	< 0.001
Neutrophil proportion, %	49 (32.0–62.5)	64.9 (58.1–74.0)	72.8 (57.3–83.3)	76.5 (67.6–84.3)	< 0.001
< 50	138/271 (50.9%)	7/49 (14.3%)	11/70 (15.7%)	5/139 (3.6%)	< 0.001
50–69%	92/271 (33.9%)	24/49 (49%)	19/70 (27.1%)	35/139 (25.2%)	
≥ 70%	41/271 (15.1%)	18/49 (36.7%)	40/70 (57.1%)	99/139 (71.2%)	
Platelet count, × 109 per L	294 (225–368.5)	292 (225–355.5)	200 (166.25–260)	197 (154–246)	< 0.001
< 100	1/285 (0.4%)	/51 (0%)	4/69 (5.8%)	10/154 (6.5%)	< 0.001
Creatinine, μmol/L	22 (18.6–26.9)	36.9 (29.7–39.8)	60 (51–78)	69.5 (56.5–87.6)	< 0.001
> 133	/98 (0%)	/16 (0%)	/25 (0%)	7/94 (7.4%)	0.02
Blood urea nitrogen, mmol/L	2.8 (2.1–3.625)	2.7 (2.3–4)	4.6 (2.95–6.025)	5.1 (3.9–7.55)	< 0.001
≥ 7.14	2/101 (2%)	1/15 (6.7%)	2/26 (7.7%)	27/90 (30%)	< 0.001
Alanine aminotransferase, U/L	20 (14–28)	13 (10–37.5)	22 (11.5–36.5)	16 (11–26)	0.174
Aspartate aminotransferase, U/L	34.5 (28.75–44)	27 (20–31.5)	24 (17–34)	21 (17–32.75)	< 0.001
> 40	37/106 (34.9%)	2/17 (11.8%)	4/26 (15.4%)	12/92 (13%)	0.001
Creatine kinase, U/L	77 (52.8–119.0)	81 (50.0–105.3)	78 (55.0–131.8)	77 (45.0–134.0)	0.951
Creatine kinase MB fraction, U/L	21 (15.5–29)	19.5 (14–21)	10.5 (2.8–17.3)	10 (5.3–14.0)	< 0.001
> 25	31/102 (30.4%)	3/17 (17.6%)	2/19 (10.5%)	2/79 (2.5%)	< 0.001
Sodium, mmol/L	137.5 (136–139)	139 (136–139.1)	138 (135.5–142)	138 (135–140)	0.619
Erythrocyte sedimentation rate, mm/hour	21 (15.5–29.3)	42 (14–59)	24.5 (15.8–48.8)	35 (25–60)	0.267
C-reactive protein, mg/L	8 (6–8)	9 (8–80)	18.55 (12.25–120.175)	26 (8.5–81.8)	< 0.001
≥ 10	13/56 (23.2%)	3/7 (42.9%)	14/16 (87.5%)	39/53 (73.6%)	< 0.001
Procalcitonin, ng/mL	0.15 (0.1–0.39)	0.39 (0.25–0.64)	0.055 (0.02–0.1675)	0.09 (0.05–0.31)	0.019
The arterial partial pressure of oxygen	97 (77.25–105.25)	96 (91–98)	82 (65–98)	92 (74–96)	0.099
Saturation of arterial blood oxygen, %	97 (92–99)	94.5 (89–97)	94 (88–99)	94 (88–98)	0.135
< 90	6/35 (17.1%)	2/8 (25%)	7/23 (30.4%)	33/105 (31.4%)	0.346
Radiographic findings					
Unilateral involvement of chest radiographs	40 (12.9%)	12 (20.3%)	16 (21.1%)	46 (30.3%)	< 0.001
Bilateral involvement of chest radiographs	32 (10.3%)	4 (6.8%)	19 (25%)	44 (28.9%)	

Data are median (IQR) or n (%). As appropriate, p-values were calculated by the Kruskal–Wallis test, χ^2 test, or Fisher's exact test

occurred in the 18–59 years age group (mortality 6.7%) and eight in the ≥ 60 years age group (mortality 7.8%). The median times from onset to death of the two age groups were 10.5 days (IQR 2–19 days) and 15.5 days (9.3–21.8 days), respectively (Table 3).

Discussion

This study explored the epidemic characteristics and clinical features of RSV infections in Beijing, China, between 2015 and 2019 using a multiple center based surveillance and reported three major findings: first, the RSV prevalence exhibited a typical seasonality in Beijing until 2019; second, the elderly aged ≥ 60 years, serving as another high-morbidity population besides young children, usually developed more severe outcomes than the children aged < 5 years; and third, the elderly RSV-infected patients more frequently developed dyspnea and lymphocytopenia, while the child RSV-infected patients under 5 years old more commonly presented tachypnea and neutropenia. These findings could promote a comprehensive insight into the illness and contribute to policy-making of RSV prevention and control.

Table 3 Treatments and outcomes of 597 patients infected with RSV

	0–4 yr n = 310	5–17 yr n = 59	18–59 yr n = 76	≥ 60 yr n = 152	p-value
Treatments					
Vasoactive drug	6 (1.9%)	1 (1.7%)	1 (1.3%)	6 (3.9%)	0.573
Antiviral treatment	19 (6.1%)	1 (1.7%)	7 (9.2%)	7 (4.6%)	0.288
Antibiotics	188 (60.6%)	30 (50.8%)	35 (46.1%)	113 (74.3%)	< 0.001
Corticosteroids	61 (19.7%)	11 (18.6%)	10 (13.2%)	24 (15.8%)	0.509
Oxygen therapy	39 (12.6%)	2 (3.4%)	27 (35.5%)	95 (62.5%)	< 0.001
Mechanical ventilation	26 (8.4%)	0 (0%)	6 (7.9%)	19 (12.5%)	0.035
Noninvasive	25 (8.1%)	0 (0%)	4 (5.3%)	7 (4.6%)	< 0.001
Invasive	1 (0.3%)	0 (0%)	2 (2.6%)	12 (7.9%)	
ECMO	1 (0.3%)	4 (6.8%)	1 (1.3%)	2 (1.3%)	0.006
Complications					
ARDS	0 (0%)	0 (0%)	2 (2.6%)	3 (2%)	0.03
Respiratory failure	24 (7.7%)	0 (0%)	9 (11.8%)	24 (15.8%)	0.002
Liver failure	2 (0.6%)	0 (0%)	3 (3.9%)	5 (3.3%)	0.042
Kidney failure	0 (0%)	0 (0%)	2 (2.6%)	9 (5.9%)	< 0.001
Dehydration	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0.481
Myocardial injury	28 (9%)	4 (6.8%)	1 (1.3%)	4 (2.6%)	0.01
Heart failure	0 (0%)	0 (0%)	2 (2.6%)	20 (13.2%)	< 0.001
Disseminated intravascular coagulation	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0.481
Complications in the nerve system	0 (0%)	0 (0%)	1 (1.3%)	3 (2%)	0.057
Disease severity status					
AURTI	42 (13.5%)	16 (27.1%)	22 (28.9%)	8 (5.3%)	< 0.001
NSCAP	213 (68.7%)	39 (66.1%)	46 (60.5%)	112 (73.7%)	
SCAP	49 (15.8%)	3 (5.1%)	7 (9.2%)	28 (18.4%)	
Other	6 (1.9%)	1 (1.7%)	1 (1.3%)	4 (2.6%)	
ICU admission	2 (0.6%)	0 (0%)	8 (10.5%)	23 (15.1%)	< 0.001
Discharge from hospital	182/182 (100%)	27/27 (100%)	28/30 (93.3%)	94/102 (92.2%)	0.001
Death in hospital	0/182 (0%)	0/27 (0%)	2/30 (6.7%)	8/102 (7.8%)	
Hospital length of stay (days)	7 (6–9)	8 (5–11)	10 (7–15)	12 (8.5–16)	< 0.001
Time from illness onset to discharge (days)	11 (9–14)	13 (10–17)	13 (11–18)	16 (12–20)	< 0.001
Time from illness onset to death (days)	(-)	(-)	10.5 (2–19)	15.5 (9.3–21.8)	0.694

Data are median (IQR) or n (%). As appropriate, p-values were calculated by the Kruskal–Wallis test, χ^2 test, or Fisher's exact test. *ECMO*, extracorporeal membrane oxygenation. *ARDS*, acute respiratory distress syndrome. *ICU*, intensive care unit. *AURTI*, acute upper respiratory tract infection. *NSCAP*, non-severe community-acquired pneumonia. *SCAP*, severe community-acquired pneumonia

As to the seasonality of RSV prevalence in Beijing, China. Yu et al. [20] has reported that RSV epidemic season started in October, ended in April in Beijing from 2007 to 2015, and peaked in January. The RSV season that they reported approximately ended later by 1 month than that we reported. However, given that the deviation by about 1 month of RSV epidemic season usually occurred among different years, the two independent studies could be considered to be consistent in this point. We also revealed that the seasonality of RSV epidemic has been remaining a stable pattern in Beijing during the past 13-year periods when integrating these findings together. Yu et al. [20] observed that RSV-A and RSV-B co-circulated and predominated alternatively in different years in Beijing from 2007 to 2015, while our sequential study showed that RSV-A has been remaining a dominant proportion since 2015, although RSV-B were also detected in each year. This distinct findings in this study meant that RSV-A prevalence increased since 2015. Another study [21] of ours also found that RSV epidemics in Beijing were significantly ameliorated when COVID-19 pandemic occurred. This meant that the RSV epidemic pattern was firstly profoundly influenced by the artificial measures against COVID-19.

This study showed that the RSV-positive rate was highest in children under 5 years of age (6.07%), followed by the elderly adults aged ≥ 60 years (1.57%). Ren et al. [22] reported that the RSV-positive rate among the individuals aged ≥ 66 years with acute respiratory tract infection (ARTI)

in Beijing reached 2% during 2005–2007. Feng et al. [13] reported that the average of RSV-positive rates was also 2% among patients with ARTI aged ≥ 65 years from 22 provinces in China from 2009 to 2013. These two estimates are slightly higher than ours, probably due to the inclusion of the population with 60–64 years of age in our study. In addition, we revealed that the ARTI patients with RSV aged ≥ 60 years accounted for 25.2% of the total RSV infections, only after the children under 5 years of age (52.0%), which showed that the elderly people aged ≥ 60 years were another key population that should be focused on. As there is the largest population in China worldwide, and its aging population is becoming more prevalent, the proportion of the RSV-positive patients aged ≥ 60 years will increase further as the body of the population with ≥ 60 years old enlarges continuously.

There was a significant difference in the clinical characteristics of RSV-infected patients among the populations of different age groups in Beijing. RSV-infected adults with ≥ 60 years of age developed dyspnea and lymphocytopenia more frequently and were more commonly complicated by respiratory failure, heart failure, and kidney failure compared to other age group. Whereas neutrophlia and elevated C-reactive protein were also commonly observed, which indicated that there was probably co-infecting respiratory bacteria that played a cooperative role in the pathogenesis of RSV infection among the elderly adults. In contrast, RSV-infected children under 5 years of age developed tachypnea and neutropenia more frequently and were more commonly complicated by acute myocardial injury compared to other age group. The similar findings had also been reported by Ling Gong et al. [23]. They observed that more than 60% of the hospitalized children with RSV infection exhibited elevated aspartate aminotransferase and creatine kinase-MB form with a rate of myocardial injury of 10%.

We also observed that multiple illness-severity–related indicators of the RSV infections among the elderly adult aged ≥ 60 years all became significantly worse than those among other younger age groups, including the rate of hospitalization, the rate of ICU admission, the rate of death in hospital, and the hospital length of stay. This worse outcome for the elderly RSV patients was probably attributed to the fact that more than half of RSV infections in elderly adults aged ≥ 60 years had underlying disease. Another study of ours had showed that underlying disease, abnormally elevated respiratory rate, and lymphocytopenia were the independent risk factors for the development of severe RSV pneumonia [24].

The length of hospital stay of RSV-infected patients with ≥ 60 years (12 days) in this study was shorter than that of the RSV-infected elderly adults in South Korea (20 days) [25]. The hospital mortality of RSV-infected patients aged ≥ 60 years (7.8%) was approximately consistent with that of RSV-infected patients aged ≥ 65 years in the USA (8%) [2], but lower than that of RSV-infected patients aged ≥ 65 years in South Korea [25], and also lower than what Ling Cheng et al. [26] reported (the 30-day mortality of 14% among the elderly adults [96% aged ≥ 50 years old] with RSV pneumonia). These differences were probably contributed to some confounding factors in different studies, such as local medical levels and baseline medical condition of the included patients. Notably, a total of eight RSV-infected patients with severe pneumonia were given ECMO therapy in this study, and finally seven cases recovered, and only one died, which indicated a benefit of the ECMO support for the critic RSV infection.

Although we took multiple measures to guarantee a better representativeness of this study, e.g., including 35 sentinel hospitals of different level with an overall catchment of more than 20 million of residents in Beijing; covering moderate, severe, and critical illness; and study period lasting for 4 consecutive RSV epidemic seasons, there were still some limitations in this study. First, the RPSS network was originally designed for pneumonia surveillance, which artificially increased the ratio of pneumonia cases among the total included ARTI cases and probably resulted in an overestimation of the mortality of RSV infection. Second, co-existing bacterium infections were not assessed, which occurred in the elderly adult more commonly. This co-infection probably confused us in understanding the outcomes of RSV infection. Third, although we collected samples before the initiation of therapeutic measures as possible as we can, there was still a slight proportion of patients who had received treatment at home before visiting the sentinel hospitals. This probably took an impact on the RSV detection rate.

In summary, the RSV epidemic season in Beijing usually occurred between October and March, covering 90% of annual RSV infections. The RSV infections in the elderly people aged ≥ 60 years old, as the second largest proportion of total RSV infections only after children under 5 years old, usually developed worse outcomes and should be taken seriously.

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Author contribution LM, GC, and ZY did data analysis and prepared the manuscript. HF and XWB conducted the study design and reviewed the manuscript. LM, GC, WX, LY, LQ, LAH, WYT, LMZ, and DM tested the specimens.

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Declarations

Ethics approval This study was approved by the Ethics Committee at Beijing Center for Disease Prevention and Control.

Consent to participate The written informed consent was obtained from each of enrollees (or their guardians if appropriate) after we declared the nature, purpose, procedures, and potential health impact regarding this study. Patients were required to provide consent by themselves if their age and medical condition were appropriate.

Conflict of interest The authors declare no competing interests.

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