Comparison of clinical characteristics and outcomes between respiratory syncytial virus and influenza-related pneumonia in China from 2013 to 2019

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Abstract
This study aims to compare clinical characteristics and severity between adults with respiratory syncytial virus (RSV-p) and influenza-related pneumonia (Flu-p). A total of 127 patients with RSV-p, 693 patients with influenza A-related pneumonia (FluA-p), and 386 patients with influenza B-related pneumonia (FluB-p) were retrospectively reviewed from 2013 through 2019 in five teaching hospitals in China. A multivariate logistic regression model indicated that age ≥ 50 years, cerebrovascular disease, chronic kidney disease, solid malignant tumor, nasal congestion, myalgia, sputum production, respiratory rates ≥ 30 beats/min, lymphocytes < 0.8×10^9/L, and blood albumin < 35 g/L were predictors that differentiated RSV-p from Flu-p. After adjusting for confounders, a multivariate logistic regression analysis confirmed that, relative to RSV-p, FluA-p (OR 2.313, 95% CI 1.377–3.885, p = 0.002) incurred an increased risk for severe outcomes, including invasive ventilation, ICU admission, and 30-day mortality; FluB-p (OR 1.630, 95% CI 0.958–2.741, p = 0.071) was not associated with increased risk. Some clinical variables were useful for discriminating RSV-p from Flu-p. The severity of RSV-p was less than that of FluA-p, but was comparable to FluB-p.

Keywords Respiratory syncytial virus · Influenza virus · Pneumonia · Clinical characteristic · Outcome

Introduction
Influenza is a common viral contagious disease, and epidemics or pandemics have occurred all over the world [1]. Despite economic and medical advances, influenza causes considerable morbidity and mortality [2, 3]. It is estimated that during an annual seasonal epidemic, 10–20% of the global population experienced symptomatic influenza, which included 3–5 million cases of severe illness and 290,000–650,000 deaths from influenza-related respiratory complications [4].

Human respiratory syncytial virus (RSV) is one of the most common viruses to infect children worldwide [5] and is increasingly recognized as an important cause of respiratory infections in adults, particularly the elderly and those with underlying chronic conditions [6, 7]. It has been estimated that each year RSV infects 3–7% of healthy elderly patients and 4–10% of high-risk adults [8]. From 1997 to 2009, RSV contributed to approximately 17,000 annual cardiorespiratory deaths in China [9]. A study conducted in a Wisconsin community estimated the overall seasonal incidences of medically attended RSV illness to be 154/10,000 in individuals aged ≥ 50 years and 199/10,000 among persons aged ≥ 70 years [10]. It is believed that both the incidence of hospitalization and the mortality rate of RSV infection are comparable to, and perhaps even higher than, non-pandemic influenza virus [11].
Both influenza virus and RSV are important causes of pneumonia, and these pathogens are implicated in 5–15% of community-acquired pneumonia cases in adults [12, 13]. Meanwhile, nearly 40–50% of severe influenza and RSV cases that result in hospitalizations and/or deaths present with pneumonia at some point, including primary viral pneumonia and secondary bacterial pneumonia [14, 15]. Unlike influenza, no licensed RSV vaccine is available, and the only approved specific therapy, palivizumab (anti-RSV antibody), is of limited use with infants [16]. Early differential diagnosis between the two respiratory viruses is critical for arranging prompt treatment and for making rational clinical decisions. One difficulty, however, is that influenza and RSV often present similar symptoms and they occur during the same season [17–19]. The overlapping seasonality of the two viruses makes them difficult to distinguish. Based on our review of the relevant research, it appears that no large-scale study has investigated the differences in the clinical characteristics of adults hospitalized with RSV-p versus Flu-p.

To address this omission from the literature, we conducted a multicenter cohort study with two principal aims: (i) to clinically differentiate RSV-p from Flu-p and (ii) to evaluate the impact of virus type on illness severity and pneumonia-related outcomes.

Methods

Study design and participants

The medical records of hospitalized patients testing positive for influenza and RSV RNA at the Microbiology Labs of five teaching hospitals in China from January 1, 2013 through May 31, 2019 were reviewed (details of the participating centers can be found in Supplementary Material 1). Patients with laboratory-confirmed Flu-p and RSV-p were included. Exclusion criteria were as follows: (i) being less than 18 years of age, (ii) not classified as community-onset pneumonia (i.e., pneumonia onset ≥48 h post-admission and hospitalized within the last 28 days [20]), (iii) coinfection with other respiratory viruses, and (iv) immunocompromised status. The last point is important because the clinical characteristics and outcomes of immunocompromised patients with influenza and RSV might be different from similarly infected immunocompetent hosts [21, 22].

Disease and treatment definitions

Patients with Flu-p or RSV-p were defined as patients positive for influenza virus or RSV by reverse transcription polymerase chain reaction (RT-PCR) performed on respiratory specimens (i.e., nasal/nasopharyngeal swabs, sputum, bronchial aspirates, or bronchoalveolar lavage fluid) and who presented with respiratory symptoms along with newly emerging pulmonary infiltrates on chest radiographs. Early neuraminidase inhibitor (NAI) therapy was defined as any NAI (oseltamivir, zanamivir, and peramivir) administered within 48 h of illness onset [23]. Treatment consisted of systemic corticosteroid use, defined as at least one dose of any systemic corticosteroid administered during hospitalization. Community-acquired respiratory coinfected pathogens were defined as any pathogen identified within the first 48 h after admission using standard microbiological procedures (the microbiological criteria for identifying coinfection are presented in Supplementary Material 2) [24]. Severe outcomes were defined as any of the following: invasive ventilation, intensive care unit (ICU) admission, or death within 30 days after admission.

Data collection

All data were retrospectively collected and included demographic information, chronic underlying conditions (see Supplementary Material 3 for definitions of conditions/comorbidities), clinical symptoms, vital signs, laboratory and radiological findings at admission, community-acquired respiratory coinfections, and clinical management and outcomes (e.g., administration of systemic corticosteroids and vasopressor agents, invasive and non-invasive mechanical ventilation, complications during hospitalization, admittance to the ICU, length of hospital stay, cost of hospitalization, and 30-day mortality). Those patients with hospital stays < 30 days were followed up via phone call to determine survival status.

Statistical analysis

Distributional normality assumptions were examined using Kolmogerov–Smirnov tests. Variables evidencing normal distributions are presented as the mean ± SD. Those variables with non-normal distributions are expressed as the median (interquartile range). Categorical variables were analyzed using either the chi-squared test or Fisher’s exact test. Continuous variables were analyzed using Student’s t-test or the Mann–Whitney U test. For all analyses, two-tailed probability values ≤0.05 were considered statistically significant.

We compared the demographic and baseline clinical features between patients diagnosed with RSV-p versus those infected with Flu-p. Variables with p-values < 0.1 in the univariate and bivariate analyses were then entered into a multivariate logistic regression model to identify the predictors of RSV-p.

In an effort to account for potential confounders, the multivariate logistic regression model was controlled for age, sex, duration from illness onset to admission, comorbidities, pregnancy, obesity, smoking history, early NAI therapy, systemic corticosteroid use, and coinfection with other pathogens. Because these factors have been shown to correlate with
clinical outcomes in patients with influenza and other respiratory virus infections [23], we adjusted for these variables when conducting our multivariate analysis.

Additional analyses compared the baseline characteristics of RSV-p patients with and without severe outcomes. Those variables with $p$-values < 0.1 were also entered into the multivariate logistic regression analysis. All statistical analyses were performed using SPSS Statistics version 22.0.

Results

Screening process

We screened 3375 patients who were RSV or influenza RNA positive. A total of 127 laboratory-confirmed RSV-p patients and 1079 Flu-p patients (including 693 FluA-p patients and 386 FluB-p patients) were included in the study (Fig. 1). Of the subset of FluA-p patients, 38.1% (264/693) were infected with A (H1N1) pdm09, 11.0% (76/693) were infected with A (H3N2), and 50.9% (353/693) were infected with an unclassified subtype.

Monthly distribution of patients with RSV-p and Flu-p

The monthly distribution of patients with RSV-p and Flu-p is presented in Fig. 2. Generally, the cases of RSV-p and Flu-p showed a similar seasonal pattern, with both infections occurring from October through May. The peak of RSV-p was from November through January. In contrast, the peaks of FluA-p and FluB-p were from December through February and January through March, respectively.

Overview of patients with Flu-p

In total, 74.4% (803/1079) of Flu-p patients were age 50 years and older, and males accounted for 54.1% (584/1079) of cases. In addition, 42.4% (457/1079) of Flu-p patients had at least one underlying disease, with the three most prevalent being cardiovascular disease (24.0%, 259/1079), diabetes mellitus (11.8%, 127/1079), and cerebrovascular disease (9.0%, 97/1079). Other findings were that 29.0% (313/1079) of Flu-p patients had a history of smoking, 98.2% (1060/1079) presented with cough, 79.1% (854/1079) had sputum production, and 75.4% (814/1079) had a fever. $\text{PO}_2/\text{FiO}_2 < 250 \text{ mmHg}$ and multilobar infiltrates on chest radiology were evident in 30.2% (310/1025) and 73.6% (794/1079) of Flu-p patients, respectively (Table 1). The chest radiology of pneumonia related to influenza and RSV could be seen in Supplementary Fig. 1.

Supplementary Material 4 shows that 34.0% (367/1079) of Flu-p patients were coinfected with other community-acquired pathogens. The most common coinfected pathogens were *Klebsiella pneumoniae* (31.6%, 116/367), *Streptococcus*
**pneumoniae** (29.7%, 109/367), and *Staphylococcus aureus* (19.3%, 71/367), respectively.

Although only 34.0% of Flu-p patients were coinfected with other community-acquired pathogens, all Flu-p patients were administrated with antibiotics after admission, and NAI during disease course, with early NAI, was administrated to 35.7% (385/1079) of patients. In total, 24.3% (262/1079) of Flu-p patients administered with systemic corticosteroids during hospitalization. Regarding adverse outcomes, 23.1% (249/1079) developed respiratory failure, 24.6% (265/1079) experienced heart failure, and 8.2% (89/1079) developed septic shock, respectively. In total, 17.9% (193/1079) of Flu-p patients received invasive ventilation and 22.4% (242/1079) were admitted to the ICU. The 30-day mortality rate for Flu-p patients was 19.3% (208/1079) (Table 2).

**Overview of patients with RSV-p**

In total, 59.1% (75/127) of RSV-p patients were male, and 96.9% (123/127) were age 50 years or older. Underlying medical conditions affected 65.4% (83/127) of RSV-p patients, and the top three conditions were cardiovascular disease (34.6%, 44/127), chronic pulmonary disease (23.6%, 30/127), and cerebrovascular disease (15.7%, 20/127). Cough (96.1%, 122/127) was the most common symptom, with sputum production (11.0%, 14/127) occurring significantly less often. Dyspnea and fever were present in 71.7% (91/127) and 55.9% (71/127) of RSV-p patients, respectively (Table 1).

Coinfections were isolated in 30.7% (39/127) of RSV-p patients. The top three coinfected pathogens were *K. pneumoniae* (48.7%, 19/39), *S. aureus* (20.5%, 8/39), and other *Streptococcus* spp. (7.7%, 3/39), respectively (see Supplementary Material 4).

All RSV-p patients received antibiotics, and 7.9% (10/127) were administered systemic corticosteroids during hospitalization. Noninvasive and invasive ventilation were performed in 25.2% (32/127) and 11.0% (14/127) of RSV-p patients, respectively. Heart failure (33.1%, 42/127) was the most frequent complication, followed by respiratory failure (29.1%, 37/127) and acute renal failure (6.3%, 8/127). In total, 11.0% (14/127) of RSV-p patients were admitted to the ICU, and the 30-day mortality rate was 14.2% (18/127) (Table 2).

**Predictors of RSV-p**

Compared with Flu-p, bivariate analyses indicated that RSV-p was associated with age ≥ 50 years, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, solid malignant tumor, fever, myalgia, sputum production, respiratory rates ≥ 30 beats/min, lymphocytes < 0.8×10⁹/L, and blood albumin < 35 g/L (Table 1).

A multivariate logistic regression model indicated that age ≥ 50 years (odds ratio (OR) 11.207, 95% confidence interval (CI) 3.266–38.456, p < 0.001), cerebrovascular disease (OR 4.189, 95% CI 1.473–11.918, p = 0.007), chronic kidney disease (OR 8.934, 95% CI 2.114–37.760, p = 0.003), solid malignant tumor (OR 3.407, 95% CI 1.102–10.533, p = 0.033), nasal congestion (OR 4.088, 95% CI 1.857–8.999, p < 0.001), respiratory rates ≥ 30 beats/min (OR 2.612, 95% CI 1.105–6.173, p = 0.029), and blood albumin < 35 g/L (OR 6.454, 95% CI 2.842–14.661, p < 0.001) were all positively associated with RSV-p, while myalgia (OR 0.126, 95% CI 0.056–0.285, p < 0.001), sputum production (OR 0.006, 95% CI 0.003–0.014, p < 0.001), and lymphocytes <
Impact of virus type on severity of outcomes

The effects of virus type on the severity of outcomes are presented in Table 3. Univariate logistic regression analyses indicated that, relative to RSV-p, FluA-p was associated with an increased risk for severe outcomes (OR 1.931, 95% CI 1.241–3.005, \( p = 0.004 \)), including invasive ventilation (OR 2.384, 95% CI 1.331–4.271, \( p = 0.003 \)) and ICU admission (OR 2.748, 95% CI 1.537–4.913, \( p = 0.001 \)). In contrast, the 30-day mortality rate was not significant for FluA-p (OR 1.479, 95% CI 0.868–2.519, \( p = 0.150 \)). Regarding FluB-p

\( 0.8 \times 10^9 / L \) (OR 0.145, 95% CI 0.053–0.398, \( p < 0.001 \)) were negatively related to RSV-p (Fig. 3).

### Table 1 Comparison of demographical and clinical features between patients with Flu-p and RSV-p

| Variable | Flu-p (\( n = 1079 \)) | FluA-p (\( n = 693 \)) | FluB-p (\( n = 386 \)) | RSV-p (\( n = 127 \)) | \( P \) value‡ |
|----------|-------------------------|-------------------------|-------------------------|-------------------------|----------------|
| Male (\( n, \% \)) | 584 (54.1) | 461 (66.5) | 123 (31.9) | 75 (59.1) | 0.291 |
| Age ≥ 50 years (\( n, \% \)) | 803 (74.4) | 463 (66.8) | 340 (88.1) | 123 (96.9) | < 0.001 |
| Duration from illness onset to admission (days, median, IQR) | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) | 3.0 (2.0–4.3) | 3.5 (2.0–5.0) | 0.628 |
| Chronic medical condition (\( n, \% \)) | 457 (42.4) | 262 (37.8) | 195 (50.5) | 83 (65.4) | < 0.001 |
| Cardiovascular disease\# | 259 (24.0) | 136 (19.6) | 123 (31.9) | 44 (34.6) | 0.009 |
| Cerebrovascular disease\# | 97 (9.0) | 72 (10.4) | 25 (6.5) | 20 (15.7) | < 0.001 |
| Diabetes mellitus | 127 (11.8) | 92 (13.3) | 35 (9.1) | 19 (15.0) | 0.297 |
| COPD\# | 91 (8.4) | 40 (5.8) | 51 (13.2) | 30 (23.6) | < 0.001 |
| Asthma | 33 (3.1) | 19 (2.7) | 14 (3.6) | 5 (3.9) | 0.789 |
| CKD\# | 30 (2.8) | 16 (2.3) | 14 (3.6) | 14 (11.0) | < 0.001 |
| Solid malignant tumor\# | 24 (2.2) | 16 (2.3) | 8 (2.1) | 16 (12.6) | < 0.001 |
| Obesity | 76 (7.0) | 48 (6.9) | 28 (7.3) | 8 (6.3) | 0.755 |
| Pregnancy | 8 (0.7) | 8 (1.2) | 0 (0.0) | 0 (0.0) | 1.000 |
| Smoking history | 313 (29.0) | 243 (35.1) | 70 (18.1) | 36 (28.3) | 0.876 |
| Baseline clinical features (\( n, \% \)) | | | | | |
| Fever ≥ 38°C\# | 814 (75.4) | 661 (95.4) | 153 (39.6) | 71 (55.9) | < 0.001 |
| Sore throat | 202 (18.7) | 163 (23.5) | 39 (10.1) | 23 (18.1) | 0.867 |
| Runny nose\# | 234 (21.7) | 155 (22.4) | 79 (20.5) | 36 (28.3) | < 0.001 |
| Nasal congestion\# | 194 (18.0) | 155 (22.4) | 39 (10.1) | 38 (29.9) | 0.002 |
| Myalgia\# | 376 (34.8) | 208 (30.0) | 168 (43.5) | 19 (15.0) | < 0.001 |
| Cough | 1060 (98.2) | 679 (98.0) | 381 (98.7) | 122 (96.1) | 0.185 |
| Sputum production\# | 854 (79.1) | 539 (77.8) | 315 (81.6) | 14 (11.0) | < 0.001 |
| Dyspnea\# | 690 (63.9) | 412 (59.5) | 278 (72.0) | 91 (71.7) | 0.086 |
| Thoracodynia | 182 (16.9) | 112 (16.2) | 70 (18.1) | 26 (20.5) | 0.309 |
| Confusion | 150 (13.9) | 32 (4.6) | 118 (30.6) | 16 (12.5) | 0.687 |
| Respiratory rates ≥ 30 beats/min\# | 146 (13.5) | 121 (17.5) | 25 (6.5) | 26 (20.5) | 0.034 |
| SBP < 90 mmHg | 15 (1.4) | 8 (1.2) | 7 (1.8) | 2 (1.6) | 1.000 |
| Leukocytes > 10×10^9/L | 283 (26.2) | 118 (17.0) | 165 (42.7) | 28 (22.0) | 0.308 |
| Lymphocytes < 0.8×10^9/L\# | 480/1063 (45.2) | 299/677 (44.2) | 181 (46.9) | 14 (11.0) | < 0.001 |
| HB < 100 g/L | 240 (22.2) | 69 (10.0) | 171 (44.3) | 28 (22.0) | 0.960 |
| ALB < 35 g/L# | 187/1025 (17.3) | 58/639 (9.1) | 129 (33.4) | 34 (26.8) | 0.021 |
| BUN > 7 mmol/L | 446/1071 (41.6) | 183/685 (26.7) | 263 (68.1) | 49 (38.6) | 0.508 |
| PaO2/FiO2 < 250 mmHg | 310/1025 (30.2) | 172/639 (26.9) | 138 (35.8) | 35 (27.6) | 0.533 |
| Multilobar infiltrate | 794 (73.6) | 546 (78.8) | 248 (64.2) | 87 (68.5) | 0.277 |
| Coinfections (\( n, \% \)) | 367 (34.0) | 265 (38.2) | 102 (26.4) | 39 (30.7) | 0.456 |

Flu-p influenza-related pneumonia, FluA-p influenza A-related pneumonia, FluB-p influenza B-related pneumonia, RSV-p respiratory syncytial virus-related pneumonia, IQR interquartile range, COPD chronic obstructive pulmonary disease, CKD chronic kidney disease, SBP systolic blood pressure, HB hemoglobin, ALB albumin, BUN blood urea nitrogen, PaO2/FiO2 arterial pressure of oxygen/fraction of inspiration oxygen. & Variables cited in the table above were the candidates that were entered into the multivariate logistic regression model. † Comparisons were made between patients with Flu-p and RSV-p. The bolded values are \( p \)-values < 0.05, which represented significant differences between patients with Flu-p and RSV-p.
and RSV-p, the risks were similar for all of the following: general risk for severe outcomes (OR 1.506, 95% CI 0.944–2.403, \( p = 0.086 \)), invasive ventilation (OR 0.805, 95% CI 0.418–1.550, \( p = 0.516 \)), ICU admission (OR 1.665, 95% CI 0.900–3.080, \( p = 0.104 \)), and 30-day mortality rate (OR 1.389, 95% CI 0.793–2.432, \( p = 0.251 \)).

A multivariate logistic regression analysis adjusting for age, sex, duration of illness onset to admission, comorbidities

### Table 2: Comparison of clinical management and outcomes between patients with Flu-p and RSV-p

| Variable                          | Flu-p (n=1079) | FluA-p (n=693) | FluB-p (n=386) | RSV-p (n=127) | \( P \)-value† |
|----------------------------------|---------------|---------------|---------------|--------------|--------------|
| Early NAI therapy                | 385 (35.7)    | 232 (33.5)    | 153 (39.6)    | 0 (0.0)      | <0.0-01      |
| Systemic corticosteroid use (n, %) | 262 (24.3)    | 132 (19.0)    | 130 (33.7)    | 10 (7.9)     | <0.0-01      |
| Noninvasive ventilation (n, %)   | 279 (25.9)    | 159 (22.9)    | 120 (31.1)    | 32 (25.2)    | 0.872        |
| Invasive ventilation (n, %)      | 193 (17.9)    | 158 (22.8)    | 35 (9.1)      | 14 (11.0)    | 0.052        |
| Vasopressor use (n, %)           | 40 (3.7)      | 27 (3.9)      | 13 (3.4)      | 6 (4.7)      | 0.748        |
| Complications (n, %)             |               |               |               |              |              |
| Respiratory failure              | 249 (23.1)    | 167 (24.1)    | 82 (21.2)     | 37 (29.1)    | 0.129        |
| Heart failure                    | 265 (24.6)    | 147 (21.2)    | 118 (30.6)    | 42 (33.1)    | <0.0-01      |
| Septic shock                     | 89 (8.2)      | 53 (4.9)      | 36 (5.2)      | 7 (5.5)      | 0.281        |
| Acute renal failure              | 66 (6.1)      | 39 (5.6)      | 27 (7.0)      | 8 (6.3)      | 0.935        |
| Gastrointestinal bleeding        | 48 (4.4)      | 40 (5.8)      | 8 (2.1)       | 3 (2.4)      | 0.269        |
| Admittance to the ICU (n, %)     | 242 (22.4)    | 176 (25.4)    | 66 (17.1)     | 14 (11.0)    | 0.003        |
| Length of stay in hospital (days, median, IQR) | 10.0 (8.0-14.0) | 12.0 (7.0-14.5) | 10.0 (8.0-17.0) | 14.0 (10.0-23.0) | <0.0-01 |
| Cost of hospitalization ($, median, IQR) | 3367.5 (1896.1, 10767.0) | 3405.6 (2704.8, 10360.9) | 2637.3 (1383.5, 10816.9) | 2919.1 (1172.1, 15627.4) | <0.0-01 |
| 30-day mortality (n, %)          | 208 (19.3)    | 136 (19.6)    | 72 (18.7)     | 18 (14.2)    | 0.163        |

NAI neuraminidase inhibitor, ICU intensive care unit. † Comparisons were made between patients with Flu-p and RSV-p. The bolded values are \( p \)-values < 0.05, which represented significant differences between patients with Flu-p and RSV-p.

Fig. 3 Forest plot of predictors for RSV-p. Age ≥ 50 years, cerebrovascular disease, chronic kidney disease, solid malignant tumor, nasal congestion, respiratory rates ≥ 30 beats/min, and blood albumin < 35 g/L favored RSV-p; myalgia, sputum production, and lymphocytes < \( 0.8 \times 10^9 \)/L favored Flu-p

OR (95% CI) \( p \)-value

- Myalgia: 0.126 (0.056-0.285) <0.001
- Sputum production: 0.006 (0.003-0.014) <0.001
- Lymphocytes < \( 0.8 \times 10^9 \)/L: 0.145 (0.053-0.398) <0.001
- Age ≥ 50 years: 33.207 (3.266-38.456) <0.001
- Dyspnea: 2.067 (1.063-4.062) 0.033
- Nasal congestion: 4.088 (1.857-8.999) <0.001
- Cerebrovascular disease: 4.189 (1.473-11.918) 0.007
- Chronic kidney disease: 8.934 (2.114-37.760) 0.003
- Solid malignant tumor: 3.407 (1.02-10.533) 0.033
- Blood albumin < 35 g/L: 6.454 (2.842-14.661) <0.001
- Respiratory rates ≥ 30 beats/min: 2.612 (1.105-6.173) 0.029

Favor Flu-p Favor RSV-p

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(cardiovascular disease, cerebrovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, asthma, chronic kidney disease, and solid malignant tumor), obesity, pregnancy, smoking history, administration of early NAI, systemic corticosteroid use during hospitalization, and coinfections indicated that, relative to RSV-p, FluA-p was associated with an increased risk for severe outcomes (adjusted OR (aOR) 2.313, 95% CI 1.377–3.885, \( p = 0.002 \)), including invasive ventilation (aOR 2.680, 95% CI 1.393–5.154, \( p = 0.003 \)), ICU admission (aOR 2.067, 95% CI 1.064–4.015, \( p = 0.032 \)), and 30-day mortality (aOR 2.503, 95% CI 1.229–5.101, \( p = 0.012 \)). Regarding FluB-p, compared with RSV-p, the risks were similar for all of the following: invasive ventilation (aOR 0.683, 95% CI 0.333–1.400, \( p = 0.297 \)), ICU admission (aOR 1.994, 95% CI 0.993–4.005, \( p = 0.052 \)), 30-day mortality (aOR 1.898, 95% CI 0.937–3.846, \( p = 0.075 \)), and total number of severe outcomes (aOR 1.630, 95% CI 0.958–2.741, \( p = 0.071 \)) (Table 3 and Fig. 4).

Figure 5 shows that after adjusting for confounders, the 30-day mortality rate for FluA-p patients was significantly higher than that of RSV-p patients (adjusted hazard ratio (aHR) 2.280, 95% CI 1.203–4.312, \( p = 0.011 \)). In contrast, the 30-day mortality rates for patients with FluB-p and RSV-p were similar (aHR 1.208, 95% CI 0.650–2.246, \( p = 0.549 \)).

### Risk factors for severe outcomes in RSV-p patients

Compared to RSV-p patients without severe outcomes, RSV-p patients with severe outcomes were older and were more likely to present with chronic pulmonary disease. The proportions of lymphocytes < 0.8×10^9/L, hemoglobin < 100 g/dL, blood urea nitrogen > 7 mmol/L, and PaO2/FiO2 < 250 mmHg at admission and the use of systemic corticosteroids during hospitalization were higher in RSV-p patients compared to FluA-p patients. To explore the risk factors for severe outcomes in RSV-p patients, the following variables were entered into a logistic regression model: age, chronic obstructive pulmonary disease, smoking history, confusion, leukocytes > 10×10^9/L, systemic corticosteroid use, and coinfections.

### Table 3 Impact of viruses types on severe outcomes

| Clinical outcomes | Virus types (reference: RSV) | Univariate logistic analysis | Multivariate logistic analysis |
|-------------------|-----------------------------|-----------------------------|-------------------------------|
|                   |                             | OR (95% CI) | P-value | aOR (95% CI) | P-value |
| Severe outcomes   | Influenza A                 | 1.931       | 0.004   | 2.313         | 0.002   |
|                   | (1.241–3.005)               |             |         | (1.377–3.885) |         |
|                   | Influenza B                 | 1.506       | 0.086   | 1.630         | 0.071   |
|                   | (0.944–2.403)               |             |         | (0.958–2.741) |         |
| Invasive ventilation | Influenza A               | 2.384       | 0.003   | 2.680         | 0.003   |
|                   | (1.331–4.271)               |             |         | (1.393–5.154) |         |
|                   | Influenza B                 | 0.805       | 0.516   | 0.683         | 0.297   |
|                   | (0.418–1.550)               |             |         | (0.333–1.400) |         |
| Admittance to the ICU | Influenza A             | 2.748       | 0.001   | 2.067         | 0.032   |
|                   | (1.537–4.913)               |             |         | (1.064–4.015) |         |
|                   | Influenza B                 | 1.665       | 0.144   | 1.994         | 0.052   |
|                   | (0.900–3.080)               |             |         | (0.993–4.005) |         |
| 30-day mortality  | Influenza A                 | 1.479       | 0.150   | 2.503         | 0.012   |
|                   | (0.868–2.519)               |             |         | (1.229–5.101) |         |
|                   | Influenza B                 | 1.389       | 0.251   | 1.898         | 0.075   |
|                   | (0.793–2.432)               |             |         | (0.937–3.846) |         |

OR odds ratio, CI confidence interval, aOR adjusted odds ratio. * Adjusted for age, sex, duration from illness onset to admission, comorbidities (cardiovascular disease, cerebrovascular disease, diabetes mellitus, chronic pulmonary disease, asthma, chronic kidney disease, and solid malignant tumor), obesity, pregnancy, smoking history, administration of early NAI, systemic corticosteroid use during hospitalization, and coinfections.
lymphocytes < 0.8×10⁹/L, hemoglobin < 100 g/dL, blood urea nitrogen > 7 mmol/L, PaO₂/FiO₂ < 250 mmHg, and systemic corticosteroid use. Results indicated that age (OR 1.084, 95% CI 1.010–1.164, p = 0.026), chronic obstructive pulmonary disease (OR 5.512, 95% CI 1.721–17.652, p = 0.004), confusion (OR 8.293, 95% CI 2.022–34.016, p = 0.003), lymphocytes < 0.8×10⁹/L (OR 6.011, 95% CI 1.376–26.249, p = 0.017), and blood urea nitrogen > 7 mmol/L (OR 3.588, 95% CI 1.161–11.088, p = 0.026) at admission were statistically significant independent risk factors for severe outcomes in RSV-p patients (Table 4).

### Discussion

In our large cohort study examining hospitalized patients with Flu-p and RSV-p, we found two important results: (i) although Flu-p and RSV-p exhibited similar epidemiology and clinical characteristics, some variables would be used potentially for making differential diagnoses in the future and (ii) after adjusting for potential confounders, we found that RSV-p was comparable to FluB-p, but was less severe than FluA-p.

In our study, compared to Flu-p patients, patients with RSV-p were older and experienced more frequent chronic medical conditions and hypoproteinemia. Although cough was a common symptom, sputum production was relatively rare. Nasal congestion, dyspnea, and respiratory rates ≥ 30 breaths/min were more common in RSV-p, whereas myalgia was more common in Flu-p patients. These findings are consistent with previous research. For example, Lee and colleagues [25] compared hospitalized patients with RSV and influenza and found that patients with RSV more often had systemic comorbidities, dry cough, wheezy breathing, and dyspnea. Data from a virological surveillance study of respiratory viruses in France showed that dyspnea was associated with an increased risk for RSV infection (OR 2.33, 95% CI 1.73–3.12) and a decreased risk for influenza virus infection (OR 0.56, 95% CI 0.46–0.70) [26]. The study by Casalegno and colleagues [27] suggested that myalgia and shortness of breath were useful for distinguishing influenza from other respiratory viruses. In Pedersen’s study [28], myalgia was found to be an independent predictor of influenza for patients with acute respiratory infection. A study by Sundaram [10] examined the characteristics of RSV relative to other viral infections in adults aged 50 years and older and found that RSV was associated with advanced age (OR 1.50, 95% CI 1.07–2.10), symptoms of nasal congestion (OR 2.15, 95% CI 1.32–3.52), and wheezing breath (OR 1.81, 95% CI 1.31–2.50).

In addition to the key findings discussed above, we found that lymphocytes < 0.8×10⁹/L could discriminate between RSV-p and Flu-p infections. This finding appears to be novel and has not been previously reported. Lymphopenia was very common in severe influenza with an incidence rate of 30–100% [29, 30] and was associated with reduced T lymphocytes in the peripheral blood [31]. Lymphopenia was also observed in RSV infection [32, 33]. However, previous studies suggested that decreased lymphocytes occurred only in critically ill children with RSV infections [33]. We suspect that lymphopenia is useful for differential diagnosis. Interestingly, we found that lymphopenia was associated with poor clinical outcomes. This finding is consistent with previous research on influenza or other viral pneumonias, in which lymphopenia was a predictor of increased mortality [34, 35]. A study by Vakil [36] likewise found that lymphopenia (OR 3.7, 95% CI 1.7–8.2, p = 0.001) was associated with 60-day mortality rate in hematologic malignancy patients with RSV infection. The mechanisms relating lymphopenia to RSV infection are not clear and require further investigation. A study with infants diagnosed with severe RSV bronchiolitis found that their plasma levels of soluble Fas ligand and caspase-1 were increased, which in turn caused the apoptosis of CD4+

### Table 4  Risk factors for severe outcomes in RSV-p patients

| Risk factors            | OR (95% CI)     | P-value |
|-------------------------|-----------------|---------|
| Age                     | 1.084 (1.010–1.164) | 0.026   |
| COPD                    | 5.512 (1.721–17.652) | 0.004   |
| Confusion               | 8.293 (2.022–34.016) | 0.003   |
| Lymphocytes < 0.8×10⁹/L | 6.011 (1.376–26.249) | 0.017   |
| BUN > 7 mmol/L          | 3.588 (1.161–11.088) | 0.026   |
patients received viral RNA tests, it is possible that more severe (or milder) patients were tested. Also, not all respiratory cases were eligible for swabbing, which is another factor that could induce some selection bias. Another limitation is that because of the retrospective design, the impact of vaccination on disease severity could not be evaluated. An additional limitation is that over 50% of the FluA-p patients and all of the RSV-p patients were not tested for viral subtypes. Further research is required to examine whether the clinical features vary across virus subtypes [45]. Finally, given that our study participants were immunocompetent adult hospitalized patients, our findings might not be readily generalizable to other populations such as immunocompromised patients, children, and outpatients.

In summary, our results indicate that some clinical characteristics identified in our study would be helpful to discriminate RSV-p from Flu-p. What is more, the differences in disease severity between them highlight the importance of virus type tests in the clinical management of both severe influenza and RSV infections.

### Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s10096-021-04217-2.

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### Data availability
All data generated or analyzed during this study are included in this published article/as supplementary information files.

### Declarations

#### Ethics approval
This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Jishuitan Hospital (No.201911-15). Given the retrospective nature of the study, the ethics committee determined that an informed consent was not necessary.

#### Informed consent
Not applicable to this study.

#### Conflict of interest
The authors declare no conflict of interest.

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