Comparison of Clinical Characteristics and Outcomes between Respiratory s yncytial Virus and Influenza-related Pneumonia in China from 2013 to 2019

Liang Chen (chenliang1995@sina.com)
Beijing jishuitan Hospital https://orcid.org/0000-0002-3147-5688
Xiudi Han
Qingdao Municipal Hospital Group
YanLi Li
Beijing Chao-Yang Hospital: Beijing Chaoyang Hospital
Chunxiao Zhang
Beijing Huimin Hospital
Xiqian Xing
The 2nd hospital of Yunnan province

Research

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Abstract

Background: Differences in the clinical features and outcomes between syncytial virus-related (RSV-p) and influenza-related pneumonia (Flu-p) are largely unknown. We aimed to compare clinical characteristics and severity between adults with the two conditions .

Methods: 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.

Results: 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.

Conclusions: The severity of RSV-p was less than that of FluA-p, but was comparable to FluB-p. Some clinical variables were useful for discriminating RSV-p from Flu-p.

Background

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 290–650 thousand 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 17000 annual cardiorespiratory deaths in China [9]. A study conducted in a Wisconsin community estimated the overall seasonal incidence of medically-attended RSV illness to be 154/10000 in individuals ≥ 50 years of age, and 199/10000 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 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

Hospitalized patients testing positive for influenza and RSV RNA at the Microbiology Labs of five teaching hospitals in China from Jan 1, 2013 through May 31, 2019 were screened for participation (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 branchoalveolar 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 hours 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, 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, 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 Kolmogorov–Smirnov tests. Variables evidencing normal distributions are presented as the mean ± SD. Those variables with non-normal distributions are expressed as the median. Categorical variables were analyzed using either the Chi-square 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 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) pmd09, 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. PO_2/FiO_2 < 250 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).

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)	**0.015**
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)	0.089
	194 (18.0)	155	39	38	**0.002**

Nosal congestion #		(22.4)	(10.1)	(29.9)	
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
PO_2/FiO_2 < 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: haemoglobin; ALB: albumin; BUN: blood urea nitrogen; PO_2/FiO_2: arterial pressure of oxygen/fraction of inspiration oxygen. #: variables cited in the table above were the candidates which 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.

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

All Flu-p patients were administrated antibiotics after admission and NAI during disease course, with early NAI administrated to 35.7% (385/1079) of patients. In total, 24.3% (262/1079) of Flu-p patients received 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 1).

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.

Coinfections were isolated in 30.7% (39/127) of RSV-p patients. The top three coinfected pathogens were *Klebsiella pneumoniae* (48.7%, 19/39), *Staphylococcus aureus* (20.5%, 8/39), and *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 1).

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)	**< 0.001**
Systemic corticosteroids use (n, %)	262 (24.3)	132 (19.0)	130 (33.7)	10 (7.9)	**< 0.001**
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)	**< 0.001**
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 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)	**< 0.001**
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.

Predictors of RSV-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 < 0.8×10^9/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 interva*l (*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), 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), respiratory rates ≥ 30 beats/min (*OR* 2.612, *95% CI* 1.105 - 6.173, p = 0.029), lymphocytes < 0.8×10^9/L (*OR* 0.145, *95% CI* 0.053 - 0.398, p < 0.001) and blood albumin < 35 g/L (*OR* 6.454, *95% CI* 2.842 - 14.661, p < 0.001) were all statistically significant, independent predictors of RSV-p (Fig. 3).

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 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 (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, 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 and 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. 3).

Table 3
Impact of viruses types on severe outcomes

Clinical outcomes	Viruses 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 (1.241-3.005)	0.004	2.313 (1.377-3.885)	0.002
	Influenza B	1.506 (0.944-2.403)	0.086	1.630 (0.958-2.741)	0.071
Invasive ventilation	Influenza A	2.384 (1.331-4.271)	0.003	2.680 (1.393-5.154)	0.003
	Influenza B	0.805 (0.418-1.550)	0.516	0.683 (0.333-1.400)	0.297
Admittance to ICU	Influenza A	2.748 (1.537-4.913)	0.001	2.067 (1.064-4.015)	0.032
	Influenza B	1.665 (0.900-3.080)	0.104	1.994 (0.993-4.005)	0.052
30-day mortality	Influenza A	1.479 (0.868-2.519)	0.150	2.503 (1.229-5.101)	0.012
	Influenza B	1.389 (0.793-2.432)	0.251	1.898 (0.937-3.846)	0.075

OR: odd ratio; CI: confidence interval; aOR: adjusted odd ratio. *: adjusted for age, sex, duration from illness onset to admisssion, comorbidities (cardiovascular disease, cerebrovascular disease, diabetes mellitus, chronic pulmonary disease, asthma, chronic kidney disease and solid malignant tumor), obesity, pregancy, smoking history, systemic corticosteroid use and coinfections.

Figure 4 shows that after adjusting for confounders, the 30-day mortality rate for FluA-p patients was significantly lower 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 .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, haemoglobin < 100 g/, blood urea nitrogen > 7 mmol/L, and PO_2/FiO_2 < 250 mmHg at admission, and the use of systemic corticosteroids during hospitalization, were higher in RSV-p patients with severe outcomes than in RSV-p patients without severe outcomes (Supplementary Material 5).

To explore the risk factors for severe outcomes in RSV-p patients, the following variables were entered into a logistic regression model: age, chronic pulmonary disease, smoking history, confusion, leukocytes > 10×10^9/L, lymphocytes < 0.8×10^9/L, haemoglobin < 100 g/, blood urea nitrogen > 7 mmol/L, PO_2/FiO_2 < 250 mmHg, and systemic corticosteroid use. Results indicated that age (OR 1.084, 95% CI 1.010 - 1.164, p = 0.026), chronic 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 < 0.8×10^9/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).

Table 4
Risk factor 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 < 0.8×10^9/L	6.011(1.376-26.249)	0.017
BUN > 7 mmol/L	3.588 (1.161-11.088)	0.026

Discussion

In our large cohort study examining hospitalized patients with Flu-p and RSV-p, we found two important results: ⍰) although Flu-p and RSV-p exhibited similar epidemiology and clinical characteristics, some variables were instrumental for making differential diagnoses; and ⍰) after adjusting for potential confounders, we found that RSV-p were comparable to FluB-p, but were 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 beats/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 [29] examined the characteristics of RSV relative to other viral infections in adults aged 50 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 < 0.8×10^9/L could effectively 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 50–100% [30–31], and was associated with reduced T lymphocytes in the peripheral blood [32]. Lymphopenia was also observed in RSV infection [33–34]. However, previous studies suggested that decreased lymphocytes occurred only in critically ill children with RSV infections [34]. 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 [35–36]. A study by Vakil [37] 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 + helper lymphocytes and CD8 + cytotoxic lymphocytes [38]. That virus-induced T lymphocyte depletion and compromised cellular immunity delayed the clearance of the viruses. Another possible explanation is that lymphocytes were sequestered or recruited at respiratory tracts from the circulating blood [39]. The aggregation of lymphocytes in the lungs caused severe inflammation and damage to tissues. Although statistically significant, the absolute values of the differences in these clinical indicators between patients with Flu-p and RSV-p were only 10% − 30%. We thick the clinical features are helpful for differential diagnosis, especially in in resouce-limited and primary hospitals, but not substitutes for etiological tests.

In our study, the 30-day mortality rate of RSV-p patients was 14.2%, consistent with previous reports of a 2–20% mortality rate in hospitalized adult patients with RSV infection [40–41]. Few studies have directly compared the clinical features and severity of Flu-p and RSV-p. Some studies only investigated the outcomes (e.g., hospitalizations and deaths), but did not control for potential confounders (e.g., study settings, population type, treatments, etc.) [17, 42–43]. In our study, after adjusting for confounders, we found that the severity of RSV-p and Flu-p were not the same. FluA-p was more severe than both RSV-p and FluB-p. Caini and colleagues [44] analyzed the severity of respiratory viral infections in Ecuador from 2009 to 2016 and found that after adjusting for age group, gender, year, type of surveillance scheme and region, the risk of death for patients infected with A (H1N1) pdm09 was 1.73 (1.38–2.17), which was higher than that for RSV (0.75, 0.57–0.98). Similarly, in a study by Minney-Smith et al [45], patients with influenza B and RSV experienced milder outcomes, including ICU admission [0.385 (0.151–0.984), 0.389 (0.162–0.936), respectively] and complications due to pneumonia [0.269 (0.130–0.557), 0.483 (0.246–0.951), respectively], relative to patients with influenza A (H1N1) pdm09, after controlling for age group, sex and comorbidities. However, these researchers didn't compare the severity of influenza B versus RSV. Our study did compare the outcomes of FluB-p and RSV-p, and found the severity of the two infections to

be similar. In both cases the severity of pneumonia was influenced by the combination of host, virus and environmental factors. Because we controlled for numerous potential confounders, our findings help to clarify the direct influence of virus type on clinical outcomes.

To our knowledge, this is the first cohort study that directly compared the clinical severity and outcomes of RSV-p to specific viral types of Flu-p. However, some limitations of our study should be noted. First, due to the retrospective nature of the study, potential selection bias could have impacted the results. Because attending physicians determined which 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 [46]. Finally, given that our study participants were immunocompetent adult hospitalized patients, our findings might not readily generalize to other populations such as immunocompromised patients, children, and outpatients.

Conclusion

In summary, the findings from this study indicate that some clinical characteristics would be helpful to discriminate RSV-p from Flu-p. Nevertheless, the differences in disease severity between RSV-p and Flu-p highlight the importance of virus type tests in the clinical management and control of both severe influenza and RSV infection.

Abbreviations

Flu-p: Influenza-related pneumonia; RSV-p: syncytial virus-related pneumonia; NAI: Neuraminidase inhibitor; OR: Odds ratio; HR: Hazard ratio; 95% IC: 95% Interval confidence; FluA-p: Influenza A-related pneumonia; RT-PCR: Reverse transcription-polymerase chain reaction; IQR: Interquartile range; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; Hb: Hemoglobin; ALB: Albumin; BUN: Blood urea nitrogen; pO_2/FiO_2: Arterial pressure of oxygen/fraction of inspiration oxygen; ICU: Intensive care unit.

Declarations

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Authors’ contributions

Study concept and design: LC, XdH. Acquisition of data: LC, XdH, YlL, CxZ, XqX. Statistical analysis of data: LC. Drafting of the manuscript: LC. Critical revision of the manuscript for important intellectual content: XdH, XqX. All authors agree with the article submission. All authors read and approved the final manuscript.

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Availability of data and materials

The data set supporting the conclusions in this article is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study design 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. This study used data collected from patient records while maintaining patient anonymity. No administrative permissions were required to access the raw data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

1. Department of Infectious Disease, Beijing Jishuitan Hospital, 4th Medical College of Peking University, Beijing, China. [2.] Department of Pulmonary and Critical Care Medicine, Qingdao Municipal Hospital, Qingdao City, Shandong Province, China. [3.] Department of Infectious Diseases and Clinical Microbiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China. [4.] Department of

Pulmonary and Critical Care Medicine, Beijing Huimin Hospital, Beijing, China. [5.] Department of Pulmonary and Critical Care Medicine, the 2nd People's Hospital of Yunnan Province, Kunming City, Yunnan Province, China.

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Figures

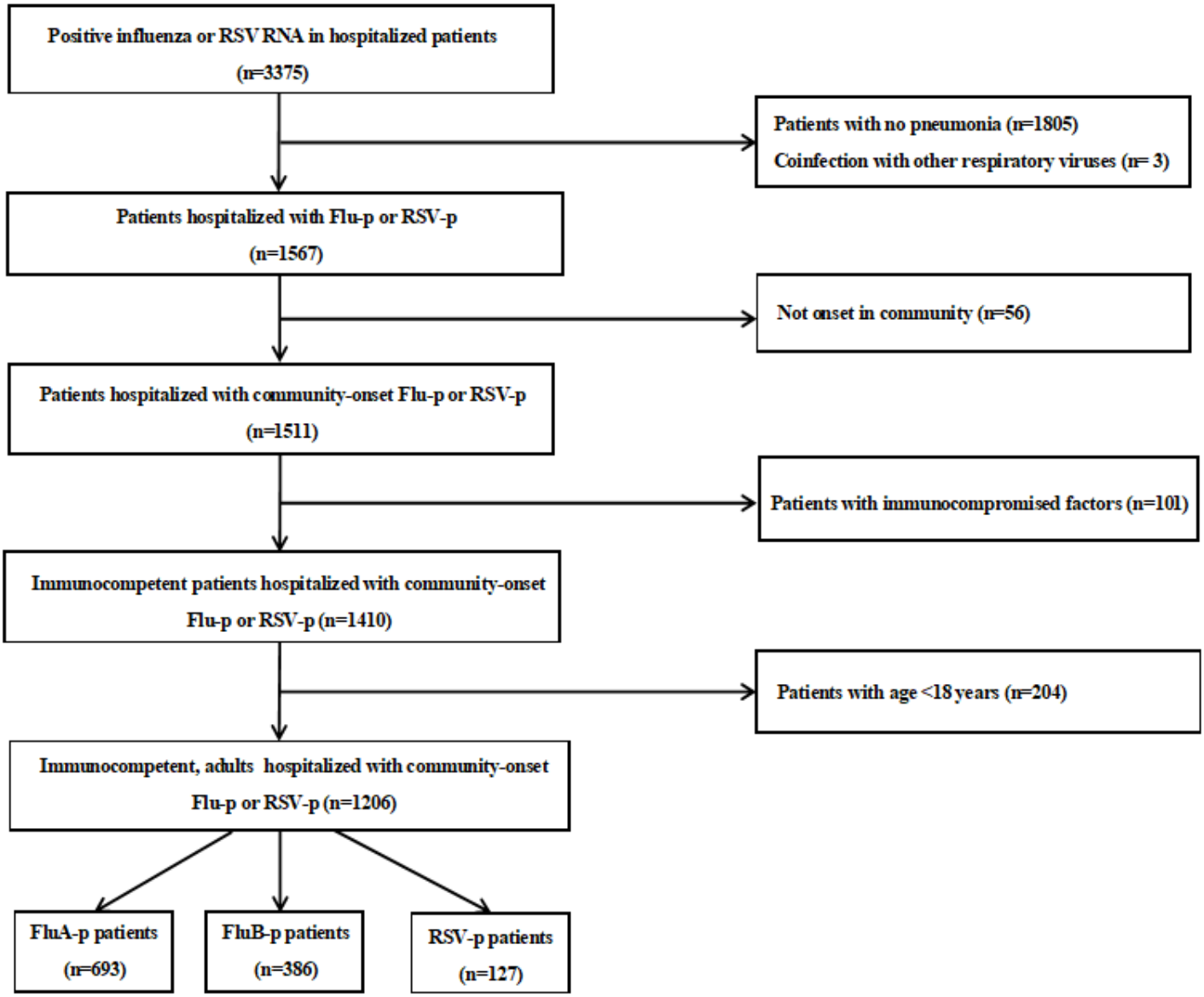

Figure 1

Screening algorithm of patients hospitalized with RSV-p and Flu-p. Figure legend 3375 patients with RSV or influenza RNA positive were sreened. 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.

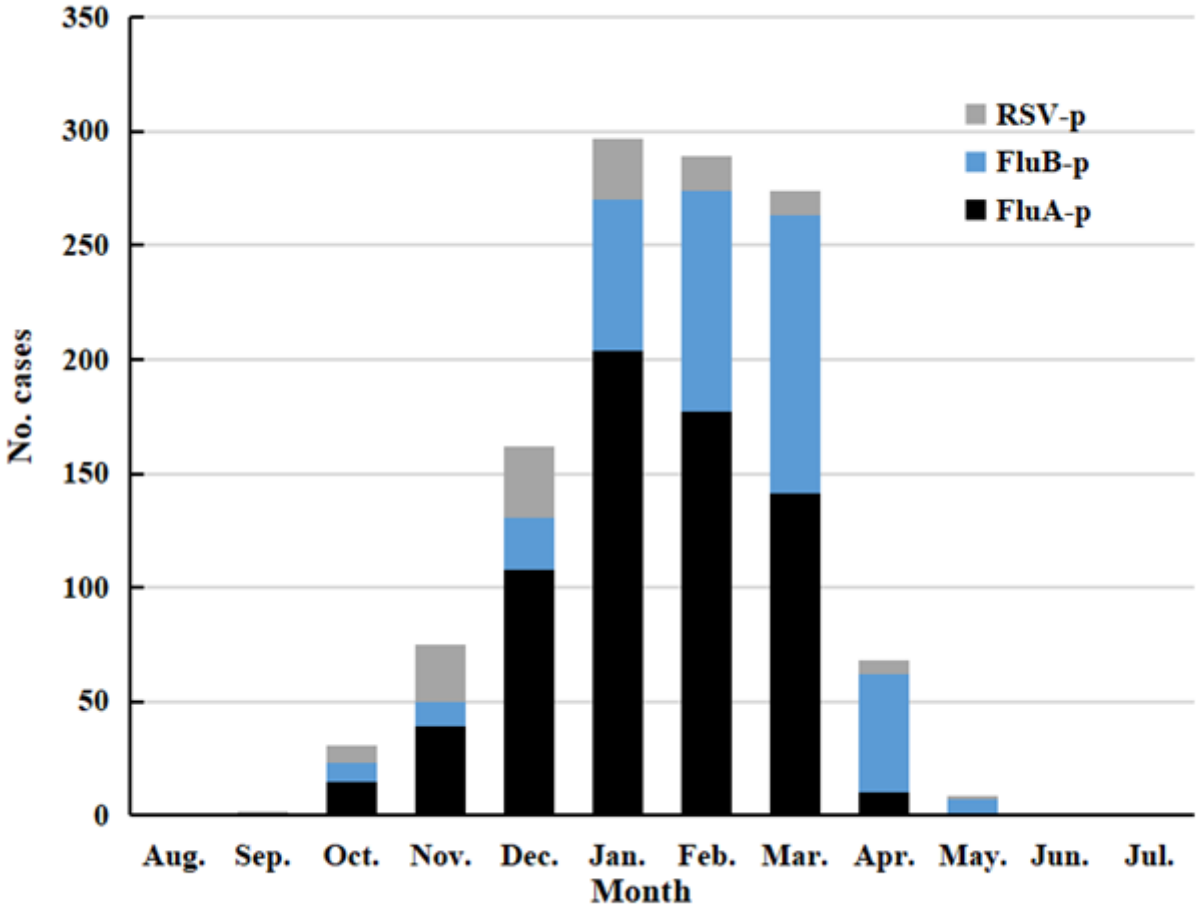

Figure 2

Distribution of patients with RSV-p and Flu-p by months. Figure legend RSV-p and Flu-p had the similar seasonality, both covered from October to May.

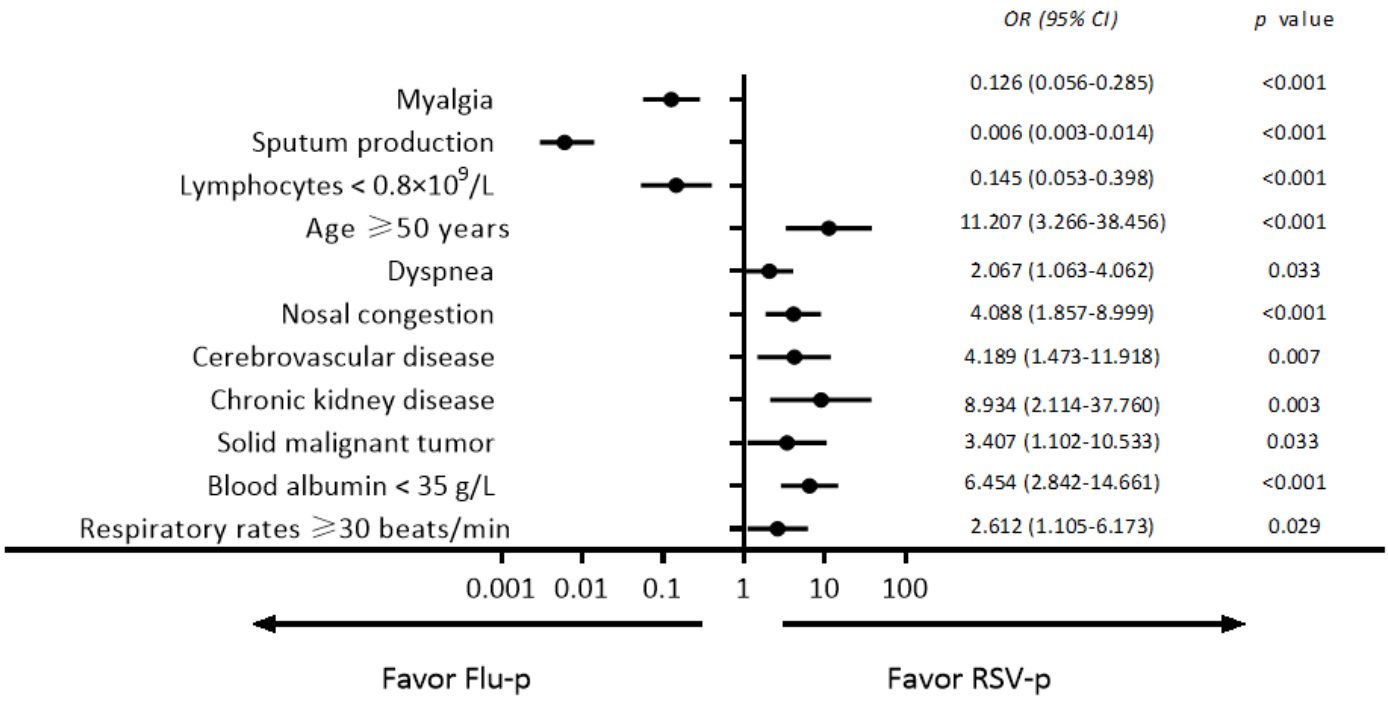

Figure 3

Forrest plot of predictors for RSV-p. Figure legend Age ≥ 50 years , cerebrovascular disease, chronic kidney disease, solid malignant tumor, nosal congestion, respiratory rates ≥ 30 beats/min and blood albumin < 35 g/L favored RSV-p; myalgia, sputum production and lymphocytes < 0.8×109/L favored Flu-p.

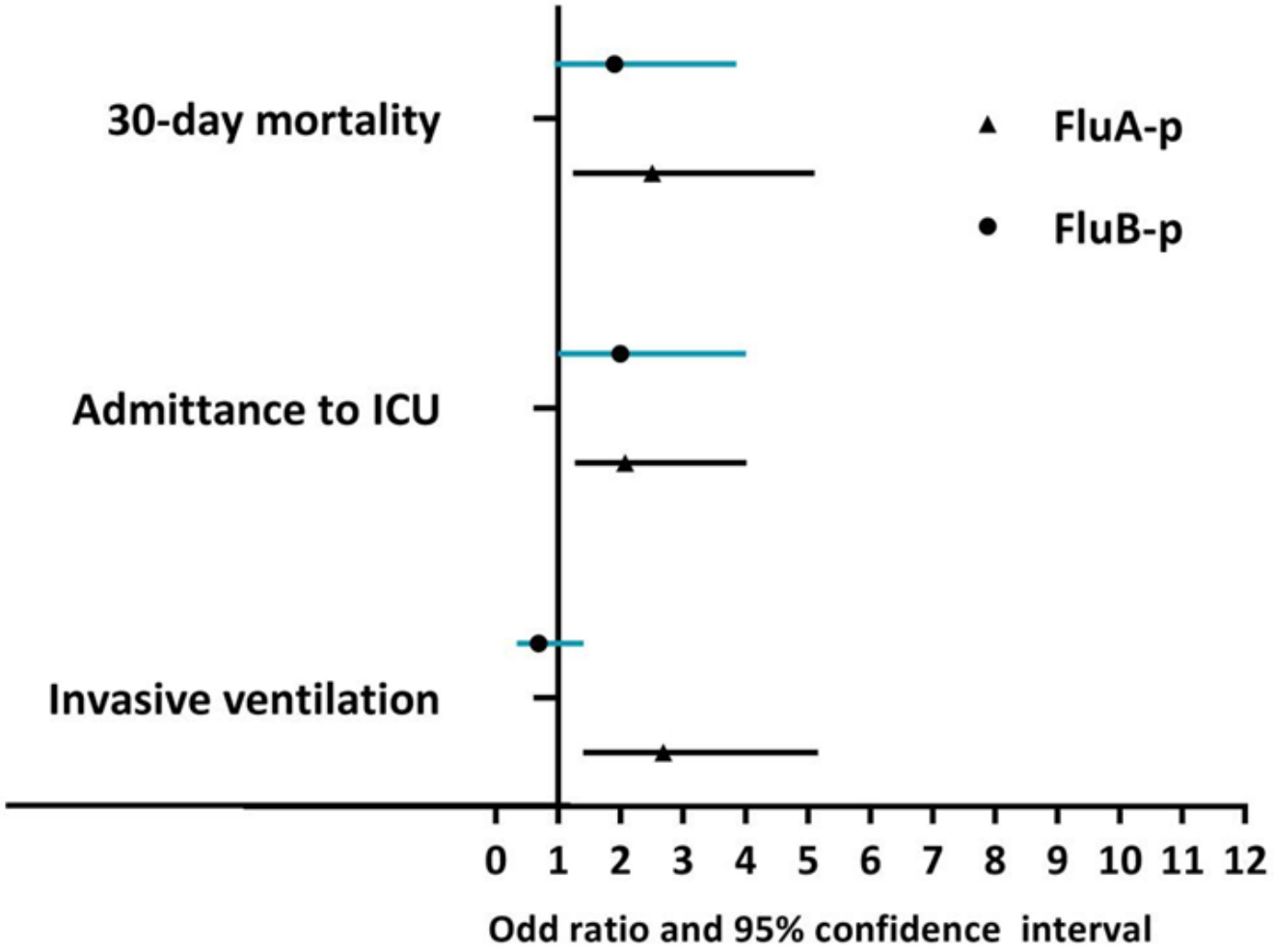

Figure 4

Comparison of severity and outcomes by viruses types (reference: RSV-p) Figure legend Compared to RSV-p, FluA-p was associated with increased risks for invasive ventilation, ICU admission and 30-day mortality; the risks for invasive ventilation, ICU admission and 30-day mortality of FluB-p were not significantly different with RSV-p.

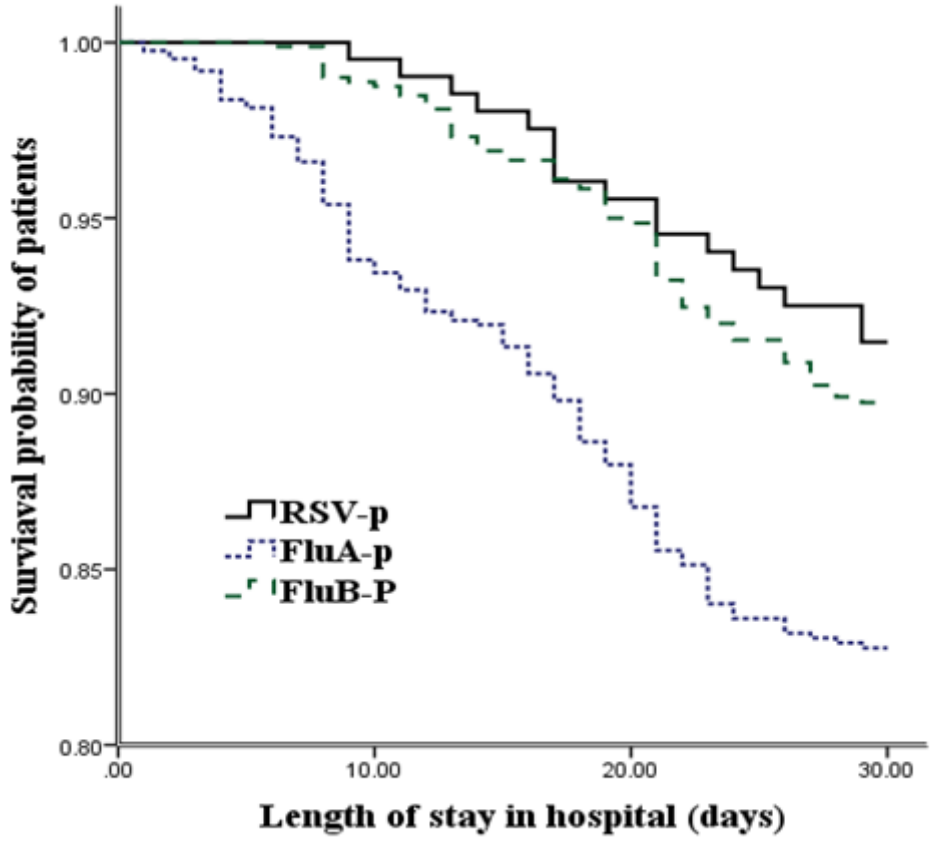

Figure 5

Survival rate of patients hospitalized with FluA-p, FluB-p and RSV-p (censored at 30d after admission) Figure legend After adjustment for confounders, the 30-day mortality FluA-p patients was significantly lower than that of RSV-p patients, while the 30-day mortality of patients with FluB-p and

Supplementary Files

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