Clinical characteristics and outcomes of adult patients hospitalized with influenza, respiratory syncytial virus and human metapneumovirus infections: a prospective, cohort study

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Research

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Abstract

Background Respiratory syncytial virus (RSV), human metapneumovirus (hMPV), and influenza virus infections cause countless adult hospitalizations each year, yet the clinical characteristics and outcomes of RSV and hMPV infections in adults remain poorly understood. This study was thus designed to compare the clinical findings and severity between adult patients hospitalized with RSV/hMPV infections relative to those hospitalized with influenza.

Methods This study prospectively enrolled 594 patients that had been hospitalized with influenza-like illness and laboratory confirmed RSV, hMPV, or influenza viral infections over the course of three consecutive influenza seasons at a tertiary hospital in China. In order to identify clinical features associated with these three viral infections and with disease severity, univariate and multivariate logistic regression analyses were conducted.

Results Myalgia and lymphocyte counts < 0.8×109/L were positively correlated with the incidence of influenza infection, whereas age ≥ 65 years, nasal congestion, dyspnea, and the presence of solid malignant tumors were positively associated with RSV or hMPV infections. However, none of these variables exhibited good predictive performance as a means of discriminating among patients infected with these three different viruses (AUC < 0.70). After controlling for potential confounding variables, RSV infections in pneumonia patients were associated with a comparable 30-day mortality risk [odds ratio (OR) 1.016, 95% confidence interval (CI) 0.267-3.856, p = 0.982], whereas hMPV infection was associated with a reduced risk of mortality (OR 0.144, 95% CI 0.027-0.780, p = 0.025). In patients without pneumonia, however, 30-day mortality risk in patients infected with influenza virus was comparable to that in patients infected with RSV (OR 1.268, 95% CI 0.172-9.355, p = 0.816) or hMPV (OR 1.128, 95% CI 0.122-10.419, p = 0.916).

Conclusions Clinical features of influenza, RSV, and hMPV infections are helpful , but not sufficiently distinct to permit discrimination among these three different infection types, and specific pathogenic testing is thus necessary to understand the etiological basis for disease in patients with influenza-like illness. In addition, disease severity associated with these three types of viral infection was inconsistent when comparing patients with and without pneumonia.

Introduction

Viral respiratory tract infections (RTIs) are very common, yet result in millions of emergency medical visits and hospitalizations each year, resulting in significant morbidity and mortality globally [1–3]. Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are major pathogens responsible for of RTIs in young children [4–5], with most children experiencing a minimum of one RSV or hMPV infection before the age of two [6]. While classically studied in children, recent advances in molecular diagnostic techniques have led clinicians to recognize that RSV and hMPV can infect and cause significant disease in individuals of all ages [7–8]. In the United States, for example, RSV and hMPV were both associated

with hospitalization rates of 10–20 per 1000 persons over the age of 50 each year [9]. Notably, these rates are very similar to annual influenza-associated hospitalization rates in this same age group [10].

In regions with temperate climates, both RSV and hMPV exhibit defined seasonal patterns that overlap with influenza seasonality, with peak infection rates occurring between late fall and early April [11–12]. RSV and hMPV infections also typically present with symptoms similar to those characteristic of influenza infections, making clinical differentiation between these different infection types challenging. While influenza is typically the subject of significant research and testing, appropriate diagnostic tests for RSV and hMPV are often unavailable in many hospitals, and as such, little data is available regarding adult infections with these two pathogens [13–14].

The present prospective study was conducted in an effort to understand the clinical features and outcomes of patients with community-acquired RSV, hMPV, and influenza infections in order to identify reliable approaches to differentiating between these infections, and to evaluate the relationship between virus type and disease severity.

Patients And Methods

Study design and population

Hospitalized patients ≥ 18 years old with influenza-like illness (ILI) were prospectively enrolled in the present study during three consecutive influenza seasons (from November – March): 2016/2017, 2017/2018, and 2018/2019. This study was conducted at Beijing Jishuitan Hospital, a teaching hospital with 1500 beds, and all patients were evaluated for nine respiratory viruses: influenza virus A/B, human rhinovirus/enterovirus, RSV, hMPV, parainfluenza virus 1–4, human adenovirus, human coronavirus (HKU1, NL63, 229E and OC43). All patients found to have laboratory-confirmed cases of RSV, hMPV, or influenza were recruited to the present study. Patients were excluded from this analysis if they had been hospitalized within the last 28 days [15], or if they were coinfected with two or more respiratory viruses. Written informed consent were obtained from parents. Ethical approval was obtained from the Ethics Committee of Beijing Jishuitan Hospital (No. 202006-18).

Sample Collection

Blood samples, urine samples, and nasopharyngeal (NP) or oropharyngeal (OP) swabs were collected from all patients upon admission, and were transferred to the laboratory on ice for analysis. Sputum was additionally obtained from all patients with a productive cough. Endotracheal aspirates (ETA), bronchoalveolar fluid lavage (BALF), and pleural fluid samples obtained in the course of patient clinical evaluation and care were also assessed as appropriate. Samples were only tested for pathogens if they had been collected within 48 h of admission.

Pathogen Detection

Samples were considered positive for a specific virus if viral nucleic acids were detected via real-time polymerase chain reaction (PCR) (The FilmArray Pneumonia panel; BioFire Diagnostics, LLC, Salt Lake City, UT) [16] in analyzed samples.

Patients were considered to suffer from a community-acquired respiratory coinfection if they met the following criteria [17]:) patients were positive for *Legionella pneumophila* urinary antigen;) patients were positive for *Streptococcus pneumoniae* urinary antigen;) patients exhibited positive bacterial cultures from blood or pleural fluid samples, with the exception of coagulase negative *Staphylococcus spp.*;) patients exhibited bacteria in samples of purulent sputum (samples containing > 25 leukocytes and < 10 epithelial cells per 100 × field) with consistent Gram staining findings;) patients with *Mycoplasma pneumoniae* (MP), *Chlamydia pneumonia*, or *L pneumophila* in sputum/BALF/NP/OP swabs as detected via real-time PCR.

Disease And Treatment Definitions

ILI was defined as a combination of the following [18]: ( ) at least one of the following systemic symptoms: fever or feverishness, headache, myalgia or malaise, and (ii) at least one of the following respiratory symptoms: cough, sore throat or dyspnea. Pneumonia was defined based upon radiographic images indicating the presence of newly emergent consolidation or other infiltrates. Systemic corticosteroid use was defined by the use of a minimum of one dose of systemic corticosteroids during hospitalization. Complications associated with influenza, RSV or hMPV infections were defined as a new or exacerbated conditions that were confirmed by radiographic and laboratory testing. Lower respiratory tract (LRT) complications included pneumonia or the worsening of asthma/bronchitis/chronic obstructive pulmonary disease (COPD). Cardiovascular complications included the development or worsening of cardiac events such as acute myocardic infarction or decompensated heart failure.

Data Collection

A uniform case report form (CRF) was employed to assess the following information from all patients: demographic variables, underlying disease (see Supplementary material 1), clinical symptoms, vital signs, laboratory and radiological test results upon admission, community-acquired respiratory coinfections, management [the administration of neuraminidase inhibitors, antibiotics, systemic corticosteroids], and outcomes [LRT and cardiovascular complications on admission, invasive and non-invasive mechanical ventilation during hospitalization, intensive care unit (ICU) admission, duration of hospitalization and 30-day mortality]. For patients hospitalized for < 30 days, survival outcomes were assessed via telephone-based follow-up.

Statistical analysis

Kolmogorov-Smirnov tests were used to assess the normality of all data. Normally and non-normally distributed data are given as means ± standard deviations and medians, respectively. Continuous variables were analyzed using Student's t-tests and Mann-Whitney U-tests, as appropriate, whereas

categorical variables were analyzed via Chi-squared tests and Fisher's exact test, respectively. A two-tailed $P < 0.05$ was the significance threshold for this study. All statistical analyses were performed using IBM SPSS version 22.0 or MedCalc version 19.0.

Demographic and baseline clinical findings were compared between patients with influenza virus infections and patients with RSV/hMPV infections via a univariate analysis. Any variable that achieved a P-value < 0.05 in this initial analysis was retained for a subsequent multivariate logistic regression analysis that was used to identify predictors of RSV and hMPV infections. The performance of respective predictors was estimated by measuring the area under the receiver-operating characteristic (AUROC) curve, followed by the quantification of sensitivity and specificity measures.

After controlling for confounding variables, a multivariate logistic regression analysis was used to assess the relationship between viral infection type and patient outcomes (invasive ventilation, ICU admission, and 30-day mortality) in patients with and without pneumonia. Potential confounding variables included patient age, sex, obesity, smoking history, influenza vaccination status, systemic corticosteroid or antibiotic use during hospitalization, comorbidities, duration from illness onset to admission, coinfection with other community-acquired pathogens, and use of early neuraminidase inhibitor therapy in patients with influenza [19]. These risk factors have previously been found to be linked to clinical outcomes in patients with influenza and other respiratory viral infections [20–21].

Results

Study population

Over the course of the study period, 1491 patients with ILI were identified, of whom 594 were enrolled in the present study. These patients included 421 cases of influenza (303 cases with influenza A, and 118 cases with influenza B), 92 cases of RSV infection, and 81 cases of hMPV infection (Fig. 1).

The median age of this study cohort was 64.0 years old, with 48.3% (287/594) of patients being ≥ 65 years old. Of these patients, 53.5% (318/594) were male. The most prevalent comorbidities in these patients included COPD (52.7%, 313/594), cardiovascular disease (44.8%, 266/594), and cerebrovascular disease (16.3%, 97/594), while just 3.0% (18/594) of patients were immunocompromised. The most common symptoms at time of admission included cough (98.1%, 583/594), fever (71.9%, 427/594), sore throat (54.2%, 322/594), and dyspnea (38.6%, 229/594) (Table 1).

Table 1
Demographic and baseline clinical characteristics of patients with the three viruses infections

Variable	Total (*n* = 594)	Flu (*n* = 421)	RSV (*n* = 92)	P_1 value	hMPV (*n* = 81)	P_2 value
Male (*n*, %)	318 (53.5)	217 (51.5)	49 (53.3)	0.765	52 (64.2)	**0.037#**
Age (median, IQR, years)	64.0 (56.8–77.0)	60.0 (55.0–67.0)	70.0 (64.0–72.0)	**< 0.001**	69.0 (63.5–77.0)	**< 0.001**
≥ 65 years old (*n*, %)	287 (48.3)	163 (38.7)	68 (73.9)	**< 0.001#**	56 (69.1)	**< 0.001#**
Days from illness onset to admission (median, IQR)	3.0 (2.0–5.0)	2.5 (1.0–3.0)	4.0 (3.0–6.0)	**< 0.001**	3.0 (2.0–5.0)	**< 0.001**
Influenza vaccination in the past year (*n*, %)	64 (10.8)	34 (8.1)	16 (17.4)	**0.006**	14 (17.3)	**0.010**
Comorbidities (*n*, %)						
COPD	313 (52.7)	210 (49.9)	57 (62.0)	**0.036#**	46 (56.8)	0.255
Cardiovascular disease	266 (44.8)	196 (46.6)	39 (42.4)	0.468	31 (38.3)	0.170
Cerebrovascular disease	97 (16.3)	66 (15.7)	17 (18.5)	0.509	14 (17.3)	0.717
Diabetes mellitus	96 (16.2)	64 (15.2)	22 (23.9)	**0.043#**	10 (12.3)	0.507
Chronic kidney disease	36 (6.1)	20 (4.8)	11 (12.0)	**0.009#**	5 (6.2)	0.795
Solid malignant tumor	38 (6.4)	21 (5.0)	12 (13.0)	**0.004#**	5 (6.2)	0.867
Asthma	30 (5.1)	22 (5.2)	1 (1.1)	0.144	7 (8.6)	0.344
Immunocompromised status (*n*, %)	18 (3.0)	11 (2.6)	3 (3.3)	1.000	4 (4.9)	0.260
Obesity (*n*,%)	46 (7.7)	31 (7.4)	4 (4.3)	0.299	11 (13.6)	0.064

Flu: influenza; RSV: respiratory syncytial virus; hMPV: human metapneumovirus; IQR:; COPD: chronic obstructive pulmonary disease; #: The values were entered into the multivariate logistic regression model; p_1: patients with RSV infection versus patients with Flu; p_2: patients with hMPV infection versus patients with Flu; The bolded values are p-values < 0.05, which represented significant differences between two groups.

Variable	Total (n = 594)	Flu (n = 421)	RSV (n = 92)	P_1 value	hMPV (n = 81)	P_2 value
Smoking history (n, %)	256 (43.1)	172 (40.9)	42 (45.7)	0.398	42 (51.9)	0.067
Baseline clinical features (n, %)						
Fever ≥ 38°C	427 (71.9)	311 (73.9)	62 (67.4)	0.206	54 (66.7)	0.182
Nosal congestion	133 (22.4)	85 (20.2)	35 (38.0)	**< 0.001#**	17 (21.0)	0.870
Rhinorrhea	153 (25.8)	113 (26.8)	23 (25.0)	0.717	17 (21.0)	0.271
Sore throat	322 (54.2)	236 (56.1)	48 (52.2)	0.497	38 (46.9)	0.130
Myalgia	203 (34.2)	176 (41.8)	26 (28.3)	**0.016#**	16 (19.8)	**< 0.001#**
Cough	583 (98.1)	416 (98.8)	90 (97.8)	0.460	77 (95.1)	0.061
Sputum production	169 (28.5)	85 (20.2)	12 (13.0)	0.113	26 (32.1)	0.575
Chest pain	147 (24.7)	102 (24.2)	23 (25.0)	0.876	22 (27.2)	0.859
Dyspnea	229 (38.6)	133 (31.6)	62 (67.4)	**< 0.001**	34 (42.0)	0.069
Leukocytes > 10×10^9/L	76 (12.8)	54 (12.8)	11 (12.0)	0.820	11 (13.6)	0.853
Leukocytes < 4×10^9/L	44 (7.4)	28 (6.7)	7 (7.6)	0.741	9 (11.1)	0.159
Lymphocytes < 0.8×10^9/L	150 (25.3)	124 (29.5)	15 (16.3)	**0.010#**	11 (13.6)	**0.003#**
Coinfection (n, %)	162 (27.3)	107 (25.4)	18 (19.6)	0.236	22 (27.2)	0.742

Flu: influenza; RSV: respiratory syncytial virus; hMPV: human metapneumovirus; IQR:; COPD: chronic obstructive pulmonary disease; #: The values were entered into the multivariate logistic regression model; p_1: patients with RSV infection versus patients with Flu; p_2: patients with hMPV infection versus patients with Flu; The bolded values are p-values < 0.05, which represented significant differences between two groups.

Coinfection with other community-acquired respiratory pathogens was detected in 27.3% (162/594) of patients (Table 1). The most common coinfecting pathogen was *Klebsiella pneumoniae* (25.3%, 41/162), followed by *Streptococcus pneumoniae* (23.5%, 38/162) and *Staphylococcus aureus* (17.9%, 29/162) (Supplementary material 2).

A total of 97.8% (581/594) of patients suffered from LRT complications at time of admission, including pneumonia (47.1%, 280/594) and acute exacerbation of COPD (AECOPD) (40.4%, 240/594). Of these patients, 13.6% (81/594) had baseline cardiovascular complications. Antibiotics and systemic corticosteroids were administrated to 98.0% (98.0%, 582/594) and 48.0% (285/594) of patients, respectively. Overall, 12.0% (71/594) of patients underwent invasive ventilation, and 14.1% (84/594) of patients were admitted to ICU. The all-cause 30-day mortality rate in these patients was 8.4% (50/594). The most common cause of death was severe pneumonia 62.0% (31/50), followed by heart failure 28.0% (14/50), acute renal failure 4.0% (2/50), septic shock 4.0% (2/50), and acute myocardial infarction 1.0% (1/50) (Table 2).

Table 2
Clinical management and outcomes of patients with the three viruses infections

Variable	Total (n = 594)	Flu (n = 421)	RSV (n = 92)	P_1 value	hMPV (n = 81)	P_2 value
Baseline lower respiratory tract complications (n, %)	581 (97.8)	413 (98.1)	89 (96.7)	0.675	79 (97.5)	1.000
Pneumonia	280 (47.1)	184 (43.7)	49 (53.3)	0.095	47 (58.0)	**0.018**
AECOPD	240 (40.4)	187 (44.4)	30 (32.6)	**0.038**	23 (28.4)	**0.010**
bronchitis	40 (6.7)	23 (5.5)	9 (9.8)	0.121	8 (9.9)	0.131
Athma exacerbation	21 (3.5)	19 (4.5)	1 (1.1)	0.215	1 (1.2)	0.284
Baseline cardiovascular complications (n, %)	81 (13.6)	52 (12.4)	15 (16.3)	0.306	14 (17.3)	0.229
Decompensated heart failure	75 (12.6)	49 (11.6)	14 (15.2)	**0.009**	12 (14.8)	**0.002**
Acute myocardial infarction	6 (1.0)	3 (0.7)	1 (1.1)	0.548	2 (2.5)	0.185
Early NAI administration (n, %)	148 (24.9)	101 (24.0)	25 (27.2)	0.520	22 (27.2)	0.544
Antibiotics use (n, %)	582 (98.0)	411 (97.6)	92 (100.0)	0.282	79 (97.5)	1.000
Systemic corticosteroid use (n, %)	285 (48.0)	215 (51.1)	29 (31.5)	**0.001**	41 (50.6)	0.941
Noninvasive ventilation (n, %)	76 (12.8)	44 (10.5)	18 (19.6)	**0.015**	14 (17.3)	0.078
Invasive ventilation (n, %)	71 (12.0)	39 (9.3)	15 (16.3)	**0.046**	17 (21.0)	**0.002**
Admittance to ICU (n, %)	84 (14.1)	45 (10.7)	19 (20.7)	**0.009**	20 (24.7)	**0.001**
Length of stay in hospital (median, IQR, days)	10.0 (8.0–14.0)	9.0 (8.0–13.0)	14.0 (10.0–19.0)	**< 0.001**	10.0 (9.0–16.0)	**0.003**
30-day mortality (n, %)	50 (8.4)	26 (6.2)	10 (10.9)	0.110	14 (17.3)	**0.001**

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ICU: intensive care unit; AMI: Acute myocardial infarction. The bolded values are p-values < 0.05, which represented significant differences between two groups.

Variable	Total (n = 594)	Flu (n = 421)	RSV (n = 92)	P_1 value	hMPV (n = 81)	P_2 value
Direct cause of death				**< 0.001**		**< 0.001**
Severe pneumonia	32 (64.0)	21 (80.8)	6 (60.0)		5 (35.7)	
Heart failure	11 (22.0)	2 (7.7)	3 (30.0)		6 (42.9)	
Acute renal failure	2 (4.0)	0 (0.0)	0 (0.0)		2 (14.3)	
Septic shock	3 (6.0)	3 (11.5)	0 (0.0)		0 (0.0)	
AMI	2 (4.0)	0 (0.0)	1 (10.0)		1 (7.1)	

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ICU: intensive care unit; AMI: Acute myocardial infarction. The bolded values are p-values < 0.05, which represented significant differences between two groups.

Predictors Of Demographic And Clinical Features Of RSV Infection

Relative to patients infected with influenza, patients infected with RSV tended to be older (median: 70.0 vs. 60.0 years old), with significantly more of these patients being ≥ 65 years old (73.9% vs 38.7%). In addition, more patients with RSV had COPD (62.0% vs 49.9%), diabetes mellitus (23.9% vs 15.2%), chronic kidney disease (12.0% vs 4.8%), and solid malignant tumors (13.0% vs 5.0%) relative to patients with influenza. Nasal congestion (38.0% vs 20.2%) and dyspnea (67.4% vs 31.6%) were more common in RSV patients, whereas myalgia (28.3% vs 41.8%) and lymphocytes < 0.8×10^9/L (16.3% vs 29.5%) were more common in influenza patients relative to RSV patients (Table 1).

A multivariate logistic regression model revealed that relative to influenza, age ≥ 65 years old [*odds ratio* (*OR*) 3.972, *95% confidence interval* (*CI*) 2.330–6.769, $p < 0.001$; sensitivity 66.30%, specificity 61.28%, AUROC = 0.638], solid malignant tumors (*OR* 2.883, *95% CI* 1.203–6.907, $p = 0.018$; sensitivity 13.04%, specificity 95.10%, AUROC = 0.540), nasal congestion (*OR* 1.868, *95% CI* 1.064–3.279, $p = 0.030$; sensitivity 40.22%, specificity 79.81%, AUROC = 0.600), and dyspnea (*OR* 4.834, *95% CI* 2.671–8.750, $p < 0.001$; sensitivity 67.39%, specificity 64.80%, AUROC = 0.679) were positively associated with RSV infection, while myalgia (*OR* 0.494, *95% CI* 0.275–0.888, $p = 0.018$; sensitivity 73.91%, specificity 41.81%, AUROC = 0.579), and lymphocytes < 0.8×10^9/L (*OR* 0.411, *95% CI* 0.211-0.800, $p = 0.009$; sensitivity 83.70%, specificity 29.45%, AUROC = 0.566) were negatively associated with RSV infections to RSV infection (Fig. 2).

Predictors Of Demographic And Clinical Features Of HBPV Infection

Relative to patients with influenza, those infected with hMPV were more often male (64.2% vs 51.5%) and were older on average (median: 69.0 yrs vs 60.0 yrs), with an age ≥ 65 years old being more common in these hMPV patients (69.1% vs 38.7%). In contrast, myalgia (19.8% vs 41.8%) and lymphocytes < 0.8×10^9/L (13.6% vs 29.5%) were less commonly observed in patients with hMPV infections relative to patients with influenza (Table 1).

Multivariate logistic regression analysis indicated that relative to influenza, age ≥ 65 years old (*OR* 4.075, *95% CI* 2.394–6.938, $p < 0.001$; sensitivity 69.14%, specificity 61.28%, AUROC = 0.652) was positively correlated with hMPV infection, whereas myalgia (*OR* 0.280, *95% CI* 0.151–0.522, $p < 0.001$; sensitivity 80.25%, specificity 41.81%, AUROC = 0.610) and lymphocytes < 0.8×10^9/L (*OR* 0.339, *95% CI* 0.166–0.692, $p = 0.003$; sensitivity 86.42%, specificity 29.45%, AUROC = 0.579) were all negatively correlated with hMPV infections (Fig. 3).

The impact of RSV, hMPV, and influenza on clinical outcomes in patients with pneumonia

In patients with pneumonia, univariate analyses indicated that relative to influenza, RSV infections were associated with similar risks of invasive ventilation (*OR* 0.929, *95% CI* 0.379–2.274, $p = 0.871$), ICU admission (*OR* 1.429, *95% CI* 0.659–3.099, $p = 0.366$), and 30-day mortality (*OR* 1.367, *95% CI* 0.542–3.447, $p = 0.508$). In addition, these analyses revealed that relative to influenza, hMPV infections in pneumonia patients were associated with similar risks of invasive ventilation (*OR* 1.506, *95% CI* 0.672–3.372, $p = 0.320$) and ICU admission (*OR* 1.887, *95% CI* 0.894–3.982, $p = 0.096$), but were associated with an increased risk of 30-day mortality (*OR* 2.811, *95% CI* 1.259–6.278, $p = 0.012$) (Table 3).

Table 3
Impact of specific virus type on the clinical outcomes among patients with pneumonia

Clinical outcome	Virus type	Cases (*n*, %)	Univariate logistic analysis		Multivariate logistic analysis	
			OR (95% CI)	P **value**	*aOR (95% CI)	P **value**
Invasive ventilation	Flu	28/184 (15.2)	ref		ref	
	RSV	7/49 (14.3)	0.929 (0.379–2.274)	0.871	0.783 (0.231–2.656)	0.695
	hMPV	10/47 (21.3)	1.506 (0.672–3.372)	0.320	0.206 (0.044–0.959)	0.044
ICU admission	Flu	31/189 (16.4)	ref		ref	
	RSV	11/49 (22.4)	1.429 (0.659–3.099)	0.366	1.368 (0.470–3.978)	0.565
	hMPV	13/47 (27.7)	1.887 (0.894–3.982)	0.096	0.311 (0.075–1.298)	0.109
30-day mortality	Flu	20/184 (10.9)	ref		ref	
	RSV	7/49 (14.3)	1.367 (0.542–3.447)	0.508	1.016 (0.267–3.856)	0.982
	hMPV	12/47 (25.5)	2.811 (1.259–6.278)	0.012	0.144 (0.027–0.780)	0.025

*: adjusted for age, sex, comorbidities, obesity, smoking history, influenza vaccination and early neuraminidase inhibitor therapy in patients with Flu, antibiotics and systemic corticosteroids use in hospitalzation and coinfections. *OR*: odd ratio; *CI*: confidence interval.

After adjusting for confounding variables, multivariate logistic regression analyses suggested that RSV and influenza infections were associated with similar risks of invasive ventilation (*OR* 0.783, *95% CI* 0.231–2.656, $p = 0.695$), ICU admission (*OR* 1.368, *95% CI* 0.470–3.978, $p = 0.565$), and 30-day mortality (*OR* 1.016, *95% CI* 0.267–3.856, $p = 0.982$), whereas hMPV infections were associated with a similar risk of ICU admission (*OR* 0.311, *95% CI 0.075–1.298*, *p = 0.109*), but with decreased risk of invasive ventilation (*OR* 0.206, *95% CI* 0.044–0.959, $p = 0.044$) and 30-day mortality (*OR* 0.144, *95% CI* 0.027–0.780, $p = 0.025$) relative to influenza (Table 3).

Among patients with pneumonia, 30-day mortality rates were comparable in patients infected with RSV and influenza, and rates in both of these patient groups were significantly higher than those in patients with hMPV infections after adjusting for confounders (Fig. 4).

The impact of RSV, hMPV, and influenza on clinical outcomes in patients without pneumonia

In patients without pneumonia, univariate analyses revealed that RSV infection was associated with increased risks of invasive ventilation (*OR* 4.696, *95% CI* 1.766–12.485, $p = 0.002$) and ICU admission (*OR* 3.641, *95% CI* 1.424–9.310, $p = 0.007$), but with a similar risk for 30-day mortality (*OR* 2.887, *95% CI* 0.694–12.017, $p = 0.145$) relative to influenza infection. Similarly, hMPV infection was associated with an increased risk of invasive ventilation (*OR* 5.327, *95% CI* 1.905–14.894, $p < 0.001$) and ICU admission (*OR* 4.130, *95% CI* 1.532–11.128, $p = 0.005$), but with a similar risk of 30 day mortality (*OR* 2.406, *95% CI* 0.466–12.435, $p = 0.295$) relative to influenza infection (Table 4).

Table 4
Impact of specific virus type on the clinical outcomes among patients without pneumonia

Clinical outcome	Virus type	Cases (*n*, %)	Univariate logistic analysis		Multivariate logistic analysis	
			OR (95% CI)	P **value**	*aOR (95% CI)	P **value**
Invasive ventilation	Flu	11/237 (4.6)	ref		ref	
	RSV	8/43 (18.6)	4.696 (1.766–12.485)	0.002	2.904 (0.795–10.606)	0.107
	hMPV	7/34 (20.6)	5.327 (1.905–14.894)	< 0.001	2.878 (0.798–10.375)	0.106
ICU admission	Flu	14/237 (5.9)	ref		ref	
	RSV	8/43 (18.6)	3.641 (1.424–9.310)	0.007	2.533 (0.747–8.595)	0.136
	hMPV	7/34 (20.6)	4.130 (1.532–11.128)	0.005	2.329 (0.680–7.977)	0.178
30-day mortality	Flu	6/237 (2.5)	ref		ref	
	RSV	3/43 (7.0)	2.887 (0.694–12.017)	0.145	1.268 (0.172–9.355)	0.816
	hMPV	2/34 (5.9)	2.406 (0.466–12.435)	0.295	1.128 (0.122–10.419)	0.916

*: adjusted for age, sex, comorbidities, obesity, smoking history, influenza vaccination and early neuraminidase inhibitor therapy in patients with Flu, antibiotics and systemic corticosteroids use in hospitalzation and coinfections.

After adjusting for confounding variables, multivariate logistic regression analyses suggested that RSV and influenza infections were associated with similar risks of invasive ventilation (*OR* 2.904, *95% CI* 0.795–10.606, $p = 0.107$), ICU admission (*OR* 2.533, *95% CI* 0.747–8.595, $p = 0.136$), and 30-day mortality

(*OR* 1.268, *95% CI* 0.172–9.355, *p* = 0.816) in patients without pneumonia. Similarly, hMPV and influenza infections were associated with comparable risks for invasive ventilation (*OR* 2.878, *95% CI* 0.798–10.375, *p* = 0.106), ICU admission (*OR* 2.329, *95% CI* 0.680–7.977, *p* = 0.178), and 30-day mortality (*OR* 1.128, *95% CI 0*.122–10.419, *p* = 0.916) in patients without pneumonia (Table 4).

Rates of 30-day mortality were similar in all patients without pneumonia infected with influenza, RSV, and hMPV infections after adjusting for confounders (Fig. 5).

The impact of RSV, hMPV, and influenza on clinical outcomes in all patients

Relative to influenza infection, univariate analyses revealed that RSV infection was associated with an increased risk of invasive ventilation (*OR* 1.908, *95% CI* 1.002–3.633, *p* = 0.049) and ICU admission (*OR* 2.175, *95% CI* 1.203–3.931, *p* = 0.010), but with a similar risk of 30-day mortality (*OR* 1.853, *95% CI* 0.806–3.990, *p* = 0.115) in the overall patient population. In contrast, hMPV infection was associated with an increased risk of invasive ventilation (*OR* 2.602, *95% CI* 1.905–14.894, *p* = 0.003), ICU admission (*OR* 2.740, *95% CI* 1.515–4.953, *p* = 0.001), and 30-day mortality (*OR* 3.175, *95% CI* 1.577–6.389, *p* = 0.001) relative to influenza infection in the overall patient population (Supplementary material 3).

Relative to influenza infection, risks of invasive ventilation (*OR* 1.553, *95% CI* 0.702–3.436, *p* = 0.277; *OR* 1.616, *95% CI* 0.733–3.564, *p* = 0.234; respectively), ICU admission (*OR* 1.951, *95% CI* 0.949–4.013, *p* = 0.069; *OR* 1.983, *95% CI* 0.953–4.129, *p* = 0.067; respectively), and 30-day mortality (*OR* 1.658, *95% CI* 0.665–4.132, *p* = 0.278; *OR* 2.193, *95% CI* 0.914–5.262, *p* = 0.079; respectively) associated with RSV and hMPV infections were similar in the overall patient population after adjusting for potential confounding variables (Supplementary material 3).

Rates of 30-day mortality were similar in all patients without pneumonia infected with influenza, RSV, and hMPV infections after adjusting for confounders (Supplementary Fig. 1).

Discussion

In the present study, we conducted a comprehensive analysis of clinical characteristics and outcomes among adult patients hospitalized with RSV, hMPV, and influenza virus infections. While we found that certain clinical features were of some value as a means of differentiating among these three viral infections, none were sufficiently reliable predictors of infection. Additionally, we found that levels of disease severity associated with these three viruses differed in patients with and without pneumonia, such that influenza and RSV infections were more severe than hMPV infections in patients with pneumonia, whereas severity levels were similar for all three viruses in patients without pneumonia.

Prior analyses have shown that influenza is the most common cause of ILI during influenza season, accounting for 50–70% of such cases [22–23], whereas RSV and hMPV infections account for 3–6% of cases in previously healthy individuals [24–25]. In contrast, RSV and hMPV infections can be detected in 16–25% of hospitalized adults ≥ 65 years old with chronic medical conditions [26–27]. In our study cohort, the median age was 64.0 years and nearly a half of the patients suffered from cardiopulmonary

disease, likely explaining why RSV and hMPV infections were detected in 16% and 14% of the overall study population, respectively. In addition to these population-specific differences, frequencies of viral detection can vary based on the pathogen testing approach employed. Antibody-based tests often underestimate rates of RSV and hMPV infection owing to their low sensitivity [28–29]. In the present study, we utilized nucleic acid-based diagnostic approaches and detected a relatively high frequency of RSV/hMPV-associated hospitalizations in analyzed adults.

We found that clinical features associated with RSV, hMPV, and influenza virus infections were largely similar to one another, although certain features did differ between these three infection types. Consistent with prior study results, we found that patients with RSV and hMPV infections were more likely to be older and to suffer from underlying systemic diseases such as cancer [30–31]. The presence of myalgia was more often associated with influenza [32–33], whereas nasal congestion and dyspnea were more closely linked to RSV infection [34–35]. Indeed, wheezing and dyspnea are more characteristic of RSV infections in both infants and adults [34, 36–37], likely owing to the fact that RSV exhibits a specific tropism for small airway epithelial cells, thus resulting in lower respiratory tract involvement. The inflammation and edema associated with such involvement can cause consequent airflow obstruction [38]. Nasal or lower airway replication of RSV can also induce Th2-type immune responses that are associated with RSV-specific IgE and leukotriene production, leading to bronchospasm. In addition to these demographic and symptomatic findings, we also determined that a lymphocyte count $< 0.8 \times 10^9$/L was of value as a means of differentiating between RSV/hMPV infections and influenza, which was not reflected in prior reports. Lymphopenia occurs in 50–100% of patients with severe influenza, and is primarily associated with a reduction in T lymphocyte counts in the peripheral blood. Prior studies have also found that lymphocyte counts decline significantly in critically ill patients suffering from RSV and hMPV infections [39–40]. As such lymphopenia was less commonly associated with RSV/hMPV infections relative to influenza infections, it may be valuable for differential diagnosis. While we and others have identified certain clinical features that differentiate RSV/hMPV and influenza virus infections from one another, it remains challenging to reliably discriminate among patients with these three types of viral infections. None of these symptoms or demographic variables offered sufficient sensitivity or specificity as a means of differentiating among individuals infected with these three viruses. This was consistent with the findings of a prior study conducted by Walshey et al [41]. As such, while we believe that certain clinical indications may be of value for patient differential diagnosis, especially in resouce-limited and primary hospitals. However, they are not sufficient to serve as an alternative to molecular pathogen identification.

In our study, 6.2%, 10.9%, and 17.3% of patients hospitalized with influenza, RSV, and hMPV died within 30 days following admission, respectively. These mortality rates were consistent with those in prior studies of older adults hospitalized with these three viral infections [18, 26–27]. Many studies to date have assessed disease severity associated with these three types of viral infections, but the results of these studies have been inconsistent. These discrepancies may be attributable to the fact that clinical outcomes of various infectious diseases are associated with many factors, including hosts, pathogens, and the surrounding environment [42]. Controlling for these condounders is thus essential in order to

obtain reliable study results. For example, the studies conducted by Bjarnason A et al. [43] and Zhang et al. [44] directly compared patient outcomes associated with respiratory virus infections without controlling for any confounders. Similarly, Zhou et al. [45] only controlled for a limited number of confounding variables in their multivariate regression model, and they detected no differences in severe outcomes. Study population heterogeneity may also contribute to these inconsistent findings. For example, Lee et al. [34] retrospectively reviewed 607 patients with RSV infections and 547 patients with seasonal influenza infections in three hospitals in Hong Kong, and found that 42.3% and 36.7% of these patients, respectively, exhibited signs of pneumonia. The overall survival rates in this study did not differ significantly between patients infected with these two viruses, but the authors did not separate patients according to pneumonia status in their analyses. Herein, we found that disease severity for these three types of viral infections was inconsistent when comparing patients with and without pneumonia. In pneumonia patients, influenza and RSV disease severity was similar and more severe than that associated with hMPV infections. In contrast, disease severity was comparable for all three virus types in patients without pneumonia. Similarly, Howard et al. [46] conducted a population-based surveillance study in which they evaluated outcomes among adults with community-acquired pneumonia and found that RSV was associated with increased disease severity relative to hMPV (*OR* 1.82, *95% CI* 1.32–2.50). This may be linked to differences in the pathogenicity or tissue tropisms of these viruses. Other complications beyond pneumonia can also contribute to patient death. Loubet et al. [18] found that hMPV infection was independently associated with acute cardiac failure. The results were in line with our findings. We found that rates of decompensated heart failure was comparable or elevated in patients suffering from hMPV infections relative to patients infected by RSV or influenza virus. Accordingly, patients with RSV and influenza more often died due to severe pneumonia, whereas patients with hMPV infections were more likely to succumb to cardiovascular complications. As such, the mortality rates associated with these three viruses were similar in the overall study population.

There are multiple limitations to the present study. For one, while this study did have a prospective design, it was still a single-center study with a limited sample size. In addition, admission criteria for the patients in the present study were based upon the subjective judgements of attending physicians, potentially introducing selection bias associated with the enrollment of more severely ill patients. Caution should be taken, therefore, when applying these conclusions to outpatient populations. Furthermore, some studies have suggested that there are differences in clinical features and outcomes associated with particular respiratory virus subtypes [47–48]. As such subtyping was not performed in the present study, future research will be necessary in order to fully explore the relationship between viral subtypes, clinical findings, and disease severity.

Conclusions

In summary, our data suggest that while some clinical features may aid in the differentiation between patients with RSV/hMPV infections and patients suffering from influenza, the predictive performance of these features is limited. Molecular analyses thus remain essential to accurate patient diagnosis and management. We observed inconsistencies with respect to the relative severity of RSV, hMPV, and

influenza infections when comparing patients with and without pneumonia, but observed similar mortality rates associated with these three viruses in our overall patient population. These findings thus underscore the growing unmet medical and public health need to develop vaccines and therapeutics directed against RSV and hMPV.

Abbreviations

Flu: influenza; RSV: respiratory syncitial virus; hMPV: human metapneumovirus; ILI: influenza-like illness;Flu-p: influenza-related pneumonia ; RSV-p: respiratory syncitial virus-re;ated pneumonia; hMPV-p: human metapneumovirus-related pneumonia; OR: odd ratio; 95% CI: 95% confidence interval; AUROC: under the receiver-operating characteristic curve; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Jishuitan Hospital (No. 202006-18). Informed consent was obtained from all patients or guardians of patients for being included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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

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Figures

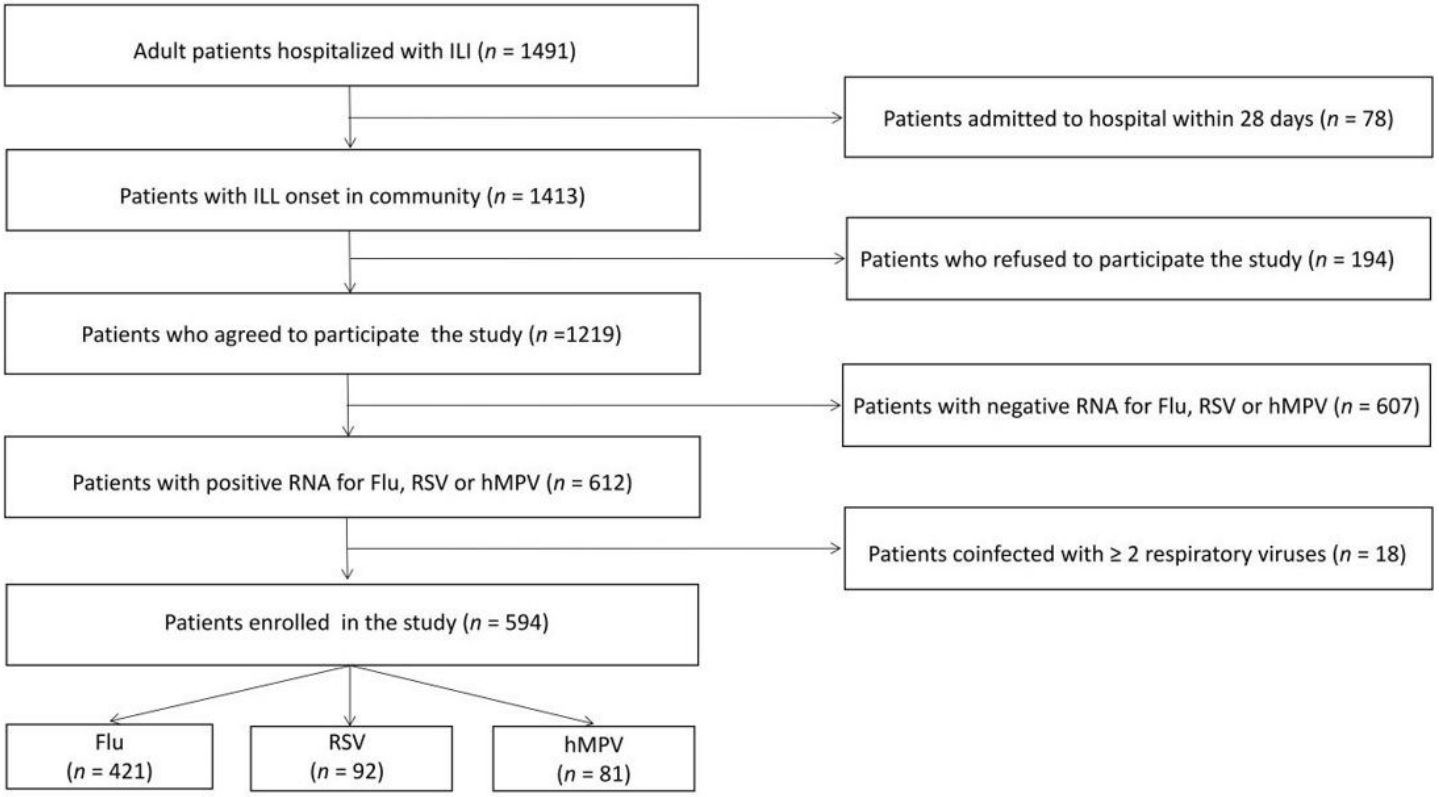

Figure 1

Flow chart of participant enrollment.1491 patients with ILI were identified, of whom 594 were enrolled in the present study.

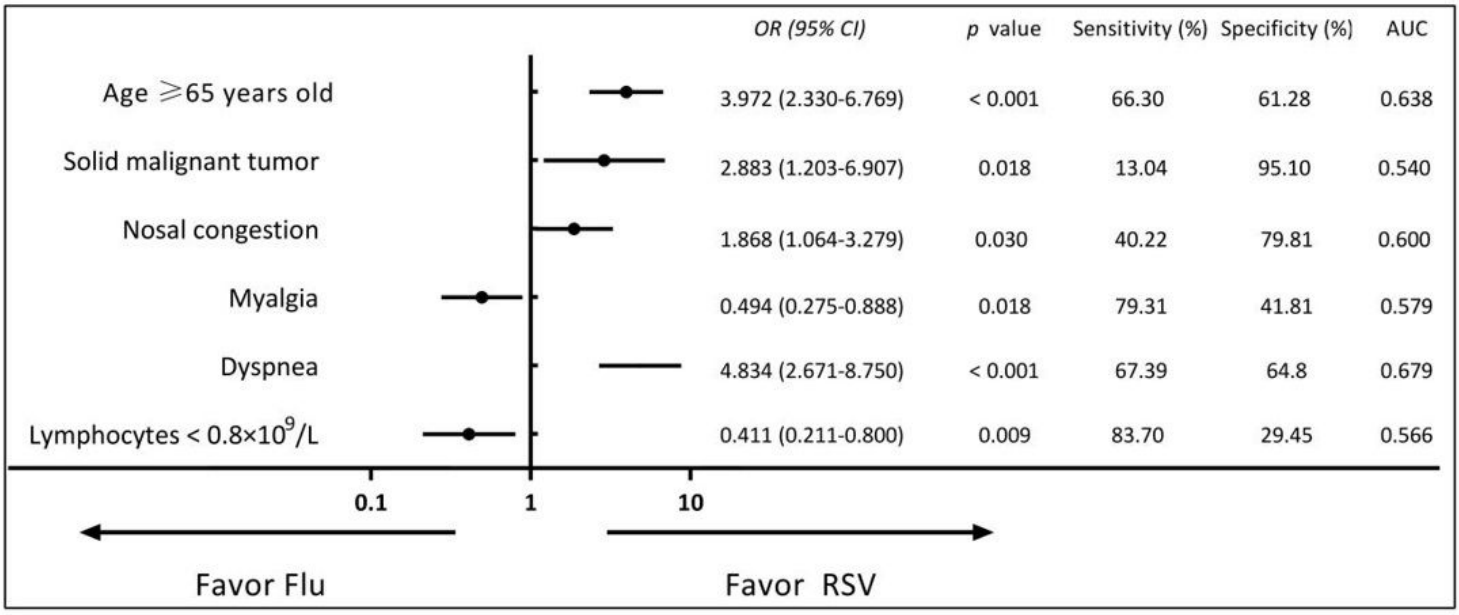

Figure 2

Predictors for Flu and RSV infection. Age ≥ 65 years old, solid malignant tumors, nasal congestion, and dyspnea were positively associated with RSV infection, while myalgia and lymphocytes < 0.8×109/LNwere negatively associated with RSV infections to RSV infection. None of these variables exhibited good predictive performance as a means of discriminating (area under the receiver-operating characteristic curve < 0.70).

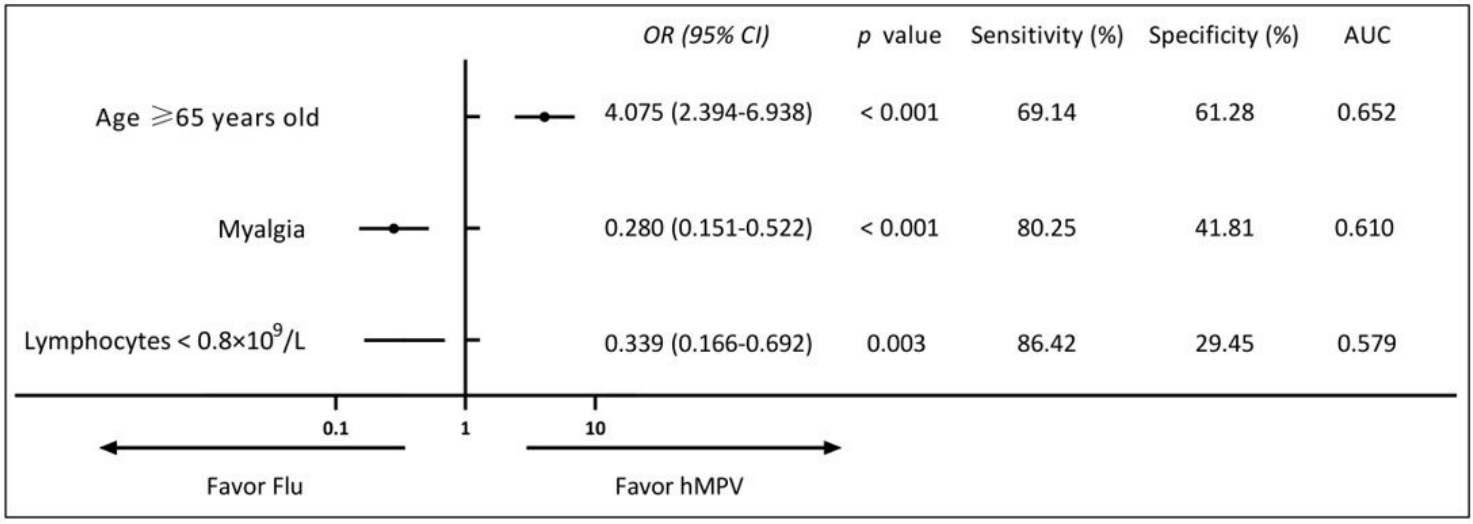

Figure 3

Predictors for Flu and hMPV infection. Age ≥ 65 years old was positively correlated with hMPV infection, whereas myalgia and lymphocytes < 0.8×109/L were all negatively correlated with hMPV infections. None of these variables exhibited good predictive performance as a means of discriminating (area under the receiver-operating characteristic curve < 0.70).

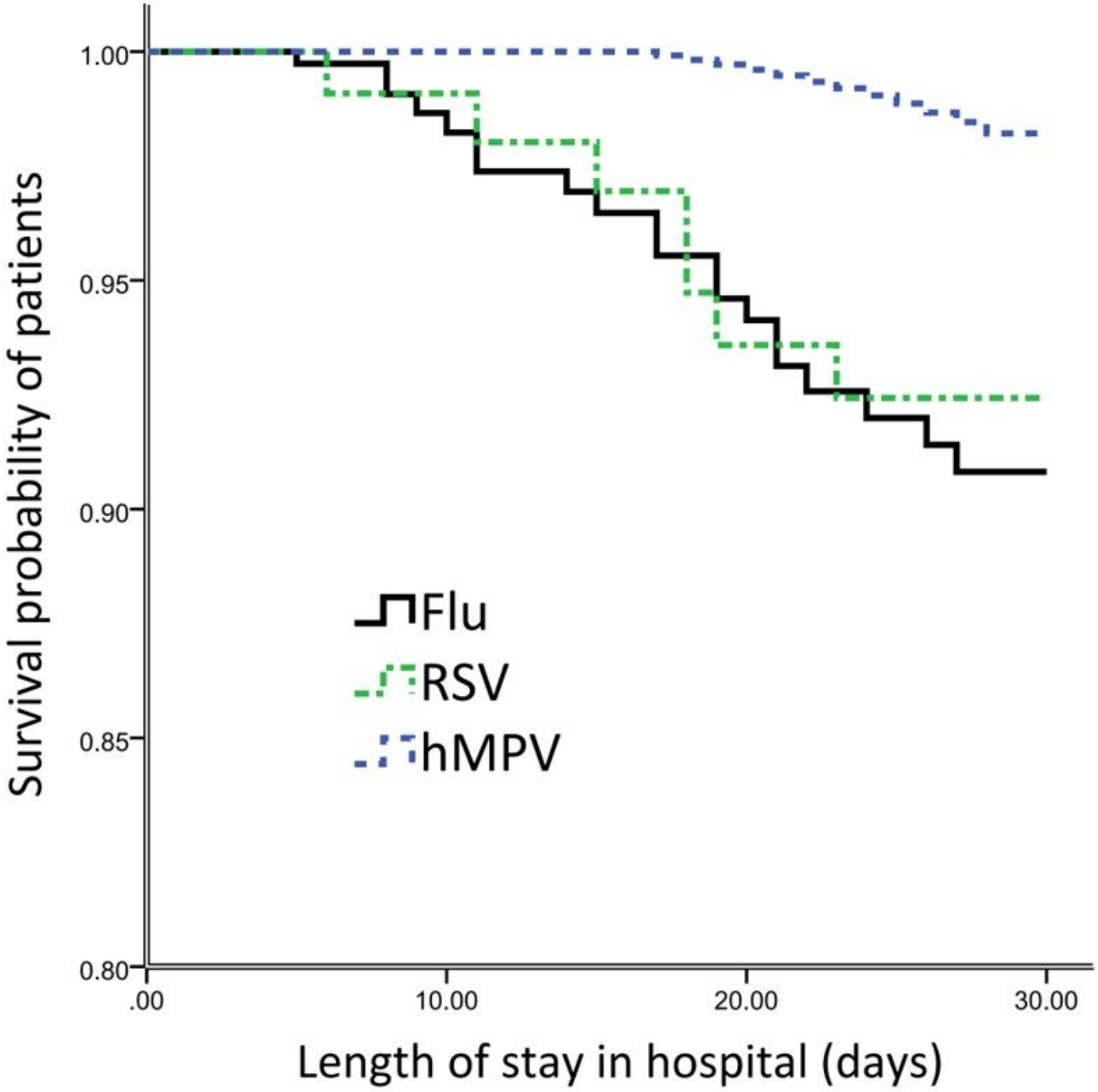

Figure 4

Survival curve of patients with pneumonia related to the three viruses (censored at 30d after admission). Among patients with pneumonia, 30-day mortality rates were comparable in patients infected with RSV and influenza, and rates in both of these patient groups were significantly higher than those in patients with hMPV infections after adjusting for confounders.

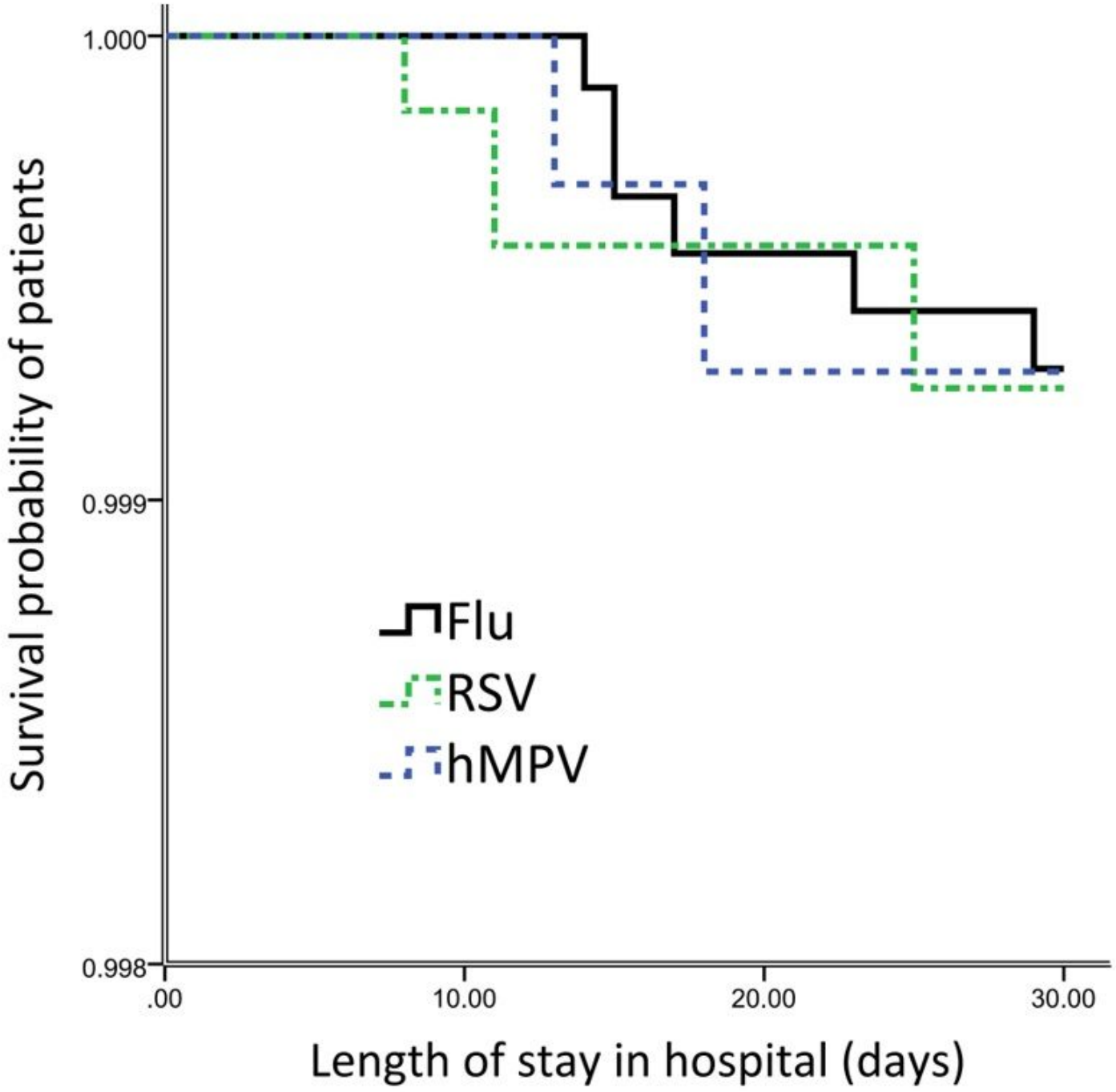

Figure 5

Survival curve of patients with the three viruses infection and without pneumonia (censored at 30d after admission). Rates of 30-day mortality were similar in all patients without pneumonia infected with influenza, RSV, and hMPV infections after adjusting for confounders

Supplementary Files

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- Supplementarymaterials.docx