Journal of Microbiology, Immunology and Infection 55 (2022) 820—828

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Original Article

Detection of influenza and non-influenza respiratory viruses in lower respiratory tract specimens among hospitalized adult patients and analysis of the clinical outcome

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Received 7 November 2020; received in revised form 23 November 2021; accepted 6 December 2021
Available online 14 December 2021

KEYWORDS
Non-influenza respiratory viruses;
Influenza;
Lower respiratory tract infection;
Respiratory virus;
Viral pneumonia

Abstract *Background:* Lower respiratory tract infection (LRTI) is one of the most fatal diseases for adults. Influenza is a well-recognized cause of severe pneumonia; however, the outcomes of LRTI caused by non-influenza respiratory viruses (NIRVs) have not been sufficiently investigated. This study aimed to describe the characteristics and outcomes of LRTI associated with respiratory viruses (RVs) in adults.
Materials/methods: A retrospective review was performed using medical records of adult patients whose lower respiratory tract (LRT) specimens (endotracheal aspirate and bronchoalveolar lavage fluid) tested positive for RVs using multiplex PCR. Underlying comorbidities, laboratory data, and clinical outcomes were analyzed.
Results: Among the 808 LRT specimens collected from 666 adult patients, RV was identified in 115 specimens (14%) from 106 patients (16%). The underlying comorbidities and laboratory data did not differ between patients with influenza- and NIRV-related LRTI. The 14-day and 30-day mortality

Abbreviations: LRTI, lower respiratory tract infection; RV, respiratory virus; NIRVs, non-influenza respiratory viruses; CAP, community-acquired pneumonia; ICUs, intensive care units; LRT, lower respiratory tract; BAL, bronchoalveolar lavage; TVGH, Taipei veterans general hospital; PIV, parainfluenza virus; RSV, respiratory syncytial virus; HMPV, human metapneumovirus; HCoV, human coronaviruses; HRV/ENT, human rhinovirus/enterovirus; HAP, hospital-acquired pneumonia; NHAP, nursing home-acquired pneumonia; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; KDIGO, kidney disease improving global outcomes.

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https://doi.org/10.1016/j.jmii.2021.12.001

rates were higher in the influenza group than in the NIRV group (24% versus 7%, p = 0.03 and 33% versus 13%, p = 0.02, respectively), whereas the 90-day mortality rate did not. In a multivariate Cox model to predict 90-day mortality, shock and acute kidney injury independently predicted a higher mortality rate (hazard ratio (HR): 4.28, 95% CI: 1.46–12.58, p = 0.01 and HR: 2.80, 95% CI: 1.28–6.15, p = 0.01, respectively), whereas the detection of influenza did not.
Conclusions: Influenza and NIRVs were associated with increased mortality due to LRTI in adults. Therefore, NIRVs are among key pathogens causing LRTI and should not be neglected by clinicians.

Introduction

Lower respiratory tract infection (LRTI) can be a severe disease and presents a large burden to public health systems worldwide. It is one of the most fatal infectious diseases in the world.[1] Although the mortality rate has decreased over the past decades, little is known about the etiology of LRTI, and the intended effects of specific antimicrobial therapies are typically not achieved because the causative pathogen is often uncertain.

The importance of respiratory virus (RV)-related LRTI has long been overlooked. This may be related to the low sensitivity and specificity of previous diagnostic techniques, such as virus culture and antigen detection tests. Recently, developments in molecular technologies have allowed simultaneous testing of multiple pathogens in individuals suspected to have respiratory infections. Influenza is the most well-known virus that causes severe pneumonia,[2] whereas most non-influenza respiratory viruses (NIRVs) are typically regarded as pathogens that cause upper respiratory tract infections. However, NIRVs can also cause severe LRTI; previous studies have reported that RVs were identified in a large portion of patients with community-acquired pneumonia (CAP) admitted to intensive care units (ICUs), and these patients had high mortality rates.[3,4]

The diagnosis of RV-related LRTI is also challenging. Previous studies have demonstrated that the sensitivity of nasal swabs for detecting RVs is poor.[5,6] Nasopharyngeal aspiration was reported to have higher specificity and negative predictive value for RV-related LRTI, but the poor sensitivity and low positive predictive value of this test make it unreliable to rule in the presence of specific RVs in LRTI.[7]

To better understand RV-related LRTI, we retrospectively reviewed the data of patients whose lower respiratory tract (LRT) specimens, collected from endotracheal aspirates or bronchoalveolar lavage (BAL) fluids, were positive for RVs (as determined by a molecular assay). Clinical characteristics and factors associated with the outcomes were delineated and compared between different RVs. This study aimed to describe the clinical characteristics and outcomes of RV-related LRTI in adult patients.

Methods

Patients, sampling procedures, and detection of respiratory viruses

This study was approved by the institutional review board of Taipei veterans general hospital (TVGH), a tertiary medical center located in northern Taiwan. We retrospectively reviewed the medical records of hospitalized adults who had acute LTR symptoms (cough, sputum production, chest pain, dyspnea, tachypnea, abnormal lung examination, or respiratory failure) accompanied by a deterioration noted on chest radiography or laboratory data and who had confirmed RV infection. Specimens from patients suspected to have RV infections were collected and analyzed in the virology laboratory of TVGH. Specimen types comprised nasopharyngeal swabs, endotracheal aspirates, and BAL fluids. Only patients with endotracheal aspirates and BAL fluids were included in the study. An endotracheal aspiration sample was obtained from patients who received mechanical ventilator support. The sample was collected using sterile suction catheters and mucus collectors. BAL was performed through bronchoscopy by chest physicians, who followed a standard operating procedure with 100–150 mL sterile saline solution instilled 2–3 times into the distal bronchial tree at the site of radiographic abnormality identified by chest X-ray or computed tomography. All retrieved specimens from endotracheal aspiration and BAL fluid were sent to a microbiology laboratory immediately after collection and underwent diagnostic tests, including cultures for bacteria, fungi, mycobacteria, antigen/PCR for cytomegalovirus, and RV PCR assay. The virological diagnosis of RVs was based on a positive result on an xTAG® Respiratory Virus Panel (Luminex Molecular Diagnostics, Toronto, Canada), a multiplex PCR assay that detected RVs including influenza, parainfluenza virus (PIV), adenovirus, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), human coronaviruses (HCoV), and human rhinovirus/enterovirus (HRV/ENT).

Data collection and definitions

Demographic information, comorbidities, length of hospital and ICU stay, requirement of intubation and duration of mechanical ventilation, laboratory findings at the time of LRT specimen collection, microbiology of coinfection and superinfection, anti-virus agents for RVs and other systematic non-RV infections, adverse events during hospitalization (including septic shock, hepatic dysfunction, acute kidney injury (AKI), pleural effusion), and new-onset renal replacement therapies were collected in this study.

The definition of types of pneumonia was based on Guidelines for the Diagnosis and Treatment of Pneumonia in Taiwan.[8] CAP refers to pneumonia acquired outside of the hospital or within 48 hours of hospitalization, hospital-acquired pneumonia (HAP) refers to pneumonia acquired

at least 48 hours after being admitted, and nursing home-acquired pneumonia (NHAP) refers to pneumonia acquired by a resident of a long-term care facility or nursing home.

Patients were classified according to the etiologies, outcome, and source of RV-related LRTI:

1. Mixed-infection group (more than one RV was detected in the specimen) and single-infection group (only one RV was detected from the specimen).
2. Influenza group and non-influenza group, depending on whether influenza was detected.
3. Survivor and non-survivor group, according to survival or mortality during hospitalization.
4. CAP group, HAP group, and NHAP group, depending on the type of pneumonia.

We determined the severity of illness using the acute physiology and chronic health evaluation (APACHE) II score[9] and sequential organ failure assessment (SOFA) score.[10] Shock was defined as systolic blood pressure less than 90 mmHg without inotropic agent administration; AKI was defined as an increase in serum creatinine to 1.5 times the baseline, according to the 2012 kidney disease improving global outcomes (KDIGO) guidelines[11]; and coinfection was defined as the isolation of bacteria, fungi, and non-RV virus concomitantly at the time of specimen collection, including pathogens identified from the testing of LRT specimens and those obtained from blood, urine, and other sterile sites. Superinfection was diagnosed if new microbiological evidence was identified 48 hours after LRT specimen collection. The use of corticosteroids during the disease course was defined as administration of more than 7.5 mg of prednisone per day or an equivalent dose of other types of corticosteroids lasting for at least a week. Mortality at 14, 30, and 90 days after admission was used to measure the outcomes. Other outcomes were the duration of mechanical ventilation, ICU stay, and hospital admission.

Statistical analysis

Categorical variables were compared using Pearson's chi-square test and Fisher's exact test; continuous variables were compared using ANOVA, the independent sample t-test, and the Mann—Whitney U test. Survival curves were analyzed using the Kaplan—Meier method and compared using the long-rank test. The associations between survival time and the predictor variables were analyzed by the Cox regression model. A P value < 0.05 was considered statistically significant.

Results

Epidemiology and distribution of respiratory viruses

From September 2016 to March 2019, 808 LRT specimens were collected from 666 patients. Among these, at least one virus was identified in 166 specimens (21%) collected from 152 patients. The origin of the specimen could not be ascertained for 51 specimens, which were thus were excluded. A total of 115 specimens (14%) had a confirmed sampling site of the LRT, 50 specimens (43%) were from BAL fluids, and 65 specimens (57%) were from endotracheal aspirations. After excluding the repetitive samples from eight patients, 106 patients (16%) were included in our final analysis.

The median time from symptom onset to BAL or intubation was two days (range: 0—31 days), and the median time from BAL or intubation to specimen collection was one day (when only patients who received BAL were analyzed, the median time was 0 days; range: 0—31 days).

The numbers of each identified RV among 106 patients are presented in Fig. 1A. Overall, HRV/ENT was the most common virus identified (n = 38, 36%), followed by PIV (n = 18, 18%) and influenza (n = 21, 17%). Ten patients were identified with two RVs; three had HRV/ENT and influenza, three had HRV/ENT and PIV, three had RSV and HCoV, and one had HRV/ENT and HMPV.

The seasonal distributions of the RVs identified in 106 patients are depicted in Fig. 1B. Both influenza and HRV/ENT were evenly distributed throughout the seasons. PIV was most frequently identified in spring and summer, whereas HCoV and RSV were most common in winter.

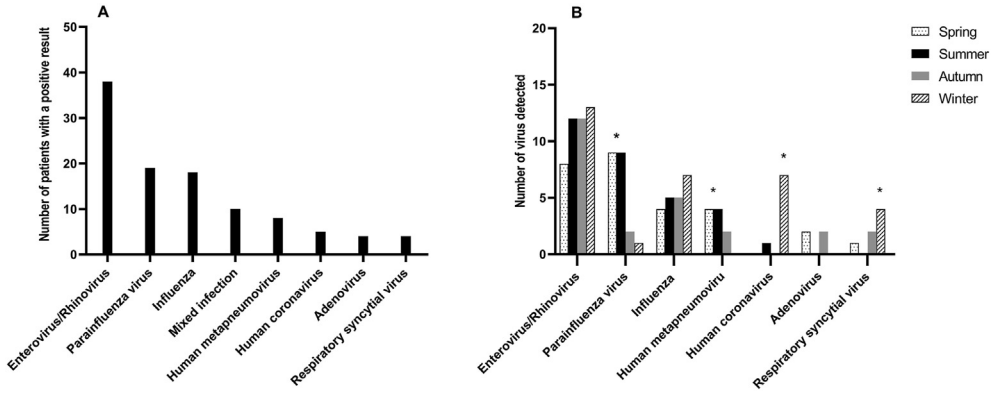

Figure 1. Number of patients with positive result in each respiratory virus during the study period (A) and seasonal distribution of each respiratory virus during the study period (B). *: virus with specific prevalent season, including parainfluenza virus: spring and summer; human coronavirus and respiratory syncytial virus: winter; human metapneumovirus: spring and early summer.

Of the 46 patients who received BAL, 28 (61%) were coinfected with bacteria; among the other 60 patients, whose samples were collected by endotracheal aspiration, 46 (77%) had bacterial coinfection. Among patients with LRT specimens who had bacterial coinfection, carbapenem-resistant *Acinetobacter baumannii* was the most commonly identified (n = 18, 24%) bacteria, followed by multidrug-resistant *Klebsiella pneumoniae* (n = 8, 11%) and *Stenotrophomonas maltophilia* (*n* = 7, 10%). Thirty patients (28%) had extra-respiratory coinfections during the same disease course as LRTI. Bacterial superinfections were identified in 47 patients (44%) and 19 patients (18%) had fungal superinfections. The CAP group had a lower coinfection rate than the HAP and NHAP groups ($p < 0.001$, Table S1).

Patient characteristics

Table 1 presents the demographic characteristics and underlying medical conditions between the mixed-infection group and the single-infection group. The cohort was predominantly male (n = 68, 64%), and the median age was 66 years old. No differences in gender, age, and underlying comorbidities between groups were observed. The platelet count was significantly higher in the mixed-infection group ($p = 0.002$). Other biochemical parameters did not differ between groups, including C-reactive protein, which averaged 10.8 mg/dL (Table 2). One patient received intravenous immunoglobulin injection for the treatment of parainfluenza virus; 51 patients (48%) received antiviral agents during the disease course (peramivir and oseltamivir for influenza, ganciclovir for cytomegalovirus, and acyclovir for varicella-zoster virus and herpes simplex virus).

Outcomes

Table 2 displays the clinical presentations and outcomes of the patients with respect to the virus type and whether influenza was detected. The average APACHE II and SOFA scores were 26.6 (range: 8–45) and 8.4 (range: 2–21), respectively. The median length of hospital stay, ICU stay, and mechanical ventilation were 36 (range: 3–352), 17 (range: 2–249), and 19 (range: 1–249) days, and these outcomes did not differ between the influenza and the NIRVs groups ($p = 0.99$, $p = 0.51$, and $p = 0.52$, respectively) or between the mixed and the single-infection groups ($p = 0.97$, $p = 0.52$, and $p = 0.85$, respectively). Table 3 compares the characteristics between the survivor group and the non-survivor group. Non-survivors were more likely to have diabetes mellitus than survivors ($p = 0.03$), and the presence of shock and AKI during the disease course was more frequently observed in the non-survivor group ($p < 0.001$). Coinfection with bacteria did not differ between the survivor group and the non-survivor group (65% and 78%, respectively, $p = 0.16$).

The 14-day, 30-day, and 90-day Kaplan–Meier curves comparing LRTI between each viral group are presented in Fig. 2. The survival analysis revealed that the 14-day, 30-day, and 90-day mortality rates did not differ between the mixed-infection and single-infection groups ($p = 0.96$, $p = 0.80$, and $p = 0.63$, respectively; Fig. 2A, B, and C). The 14-day and 30-day mortality rates differed significantly between the influenza and non-influenza groups, but only a marginally significant difference in the 90-day mortality rate was observed between the two groups ($p = 0.03$, $p = 0.02$, and $p = 0.06$, respectively; Fig. 2D, E, and F). The multivariate risk factors are shown in Table 4. The Cox proportional hazards model identified that occurrence of shock and AKI during the disease course independently predicted mortality (hazard ratio (HR): 4.28, 95% CI: 1.46–12.58, $p = 0.01$ and HR: 2.80, 95% CI: 1.28–6.15, $p = 0.01$, respectively). The detection of influenza was not associated with a higher risk of in-hospital mortality in the univariate and multivariate analysis ($p = 0.07$ and $p = 0.33$, respectively). In addition, coinfection with bacteria did not predict a higher mortality rate in the

Table 1 Demographic characteristics, underlying medical conditions of patients with single respiratory virus infections and mixed respiratory virus infection.

Characteristic	Overall patients, no. (%)		
	Single-infection n = 96 (91)	Mixed-infection n = 10 (9)	P
Male Sex	63 (66)	4 (40)	0.17
Age (years, mean ± SD)	66.4 ± 16.4	64.5 ± 17.9	0.99
Previous use of statins	14 (15)	1 (10)	1.00
Previous use of corticosteroids	20 (21)	3 (30)	0.45
Hypertension	48 (50)	4 (40)	1.00
Diabetes	50 (52)	3 (30)	0.32
Cancer	29 (30)	3 (30)	1.00
Solid organ transplantation	7 (7)	1 (10)	0.56
Chronic kidney diseases	23 (24)	2 (20)	1.00
Chronic heart diseases	26 (27)	3 (30)	1.00
Acute cardiac events	24 (25)	0 (0)	0.11
Chemotherapy or radiation therapy in recent one month	18 (19)	3 (30)	0.69
Autoimmune diseases	12 (13)	1 (10)	1.00
Lung diseases other than cancer and pneumonia	28 (29)	2 (20)	0.72

Data are presented as No (%) unless otherwise specified.

Table 2 Clinical presentations, lab data finding and outcome of patient with respiratory virus infection.

Characteristic	Overall patients, no (%)			Overall patients, no (%)		
	Influenza[a] n = 21 (20)	Non-influenza[a] n = 85 (80)	P[a]	Single-infection[b] n = 96 (91)	Mixed-infection[b] n = 10 (9)	P[b]
Medication in disease course						
Immunomodulators	1 (5)	10 (12)	0.31	10 (10)	1 (10)	1.00
Corticosteroids	15 (71)	65 (77)	0.41	71 (74)	9 (90)	0.45
Statins	3 (14)	12 (14)	0.61	14 (15)	1 (10)	1.00
Antiviral agents	15 (71)	36 (42)	0.02	47 (49)	4 (40)	0.74
Laboratory data						
WBC count, per 1000/μL (mean ± SD)	16.1 ± 13.1	11.0 ± 6.3	0.10	12.3 ± 8.5	8.8 ± 5.3	0.18
Platelet count, per 1000/μL (mean ± SD)	181.2 ± 134.5	203.3 ± 120.3	0.46	188.1 ± 120.2	305.5 ± 96.0	0.002
C-reactive protein, mg/dL (mean ± SD)	12.0 ± 11.7	10.3 ± 9.5	0.48	10.7 ± 9.5	8.6 ± 9.9	0.34
ALT IU/L (mean ± SD)	252 ± 735.7	159 ± 595.3	0.54	190.7 ± 656.3	57.0 ± 75.9	0.63
Coinfection						
From the testing respiratory specimen	15 (71)	56 (66)	0.80	63 (66)	8 (80)	0.49
From extra-respiratory origin	6 (69)	24 (68)	1.00	27 (28)	3 (30)	1.00
Superinfection						
Bacterial infection	8 (38)	39 (46)	0.63	41 (43)	6 (60)	0.33
Fungal infection	1 (5)	17 (20)	0.12	16 (17)	2 (20)	0.68
Severity of illness at ICU admission[c]						
APACHE II score (mean ± SD)	27 ± 7.3	26.0 ± 8.2	0.60	26.3 ± 7.9	26.6 ± 9.5	0.82
SOFA score (mean ± SD)	8.4 ± 2.7	8.4 ± 3.6	0.94	8.5 ± 3.5	7.7 ± 2.8	0.56
Length of ventilation, median day (range)	17.5 (3—249)	19 (1—217)	0.52	18 (1—249)	20 (6—51)	0.85
Length of ICU stay, median day (range)	17 (3—249)	17 (2—145)	0.51	16.5 (2—247)	20.5 (6—56)	0.52
Length of hospital stay, median day (range)	30.5 (3—249)	36 (3—352)	0.99	31 (3—352)	38.5 (6—107)	0.97
Mortality rate						
14-day deaths	5 (24)	6 (7)	0.04	10 (10)	1 (10)	0.59
30-day deaths	7 (33)	11 (13)	0.04	15 (16)	2 (20)	0.66
90-day deaths	10 (48)	25 (39)	0.13	31 (32)	4 (40)	0.73

[a] P value compared with people detected influenza (n = 21) with non-influenza detected (n = 85). Three patients of the influenza group had not only Influenza virus, but other respiratory virus detected, later classified into mixed infection group in the next comparison section.

[b] P value compared with patient with single respiratory virus infection and mixed respiratory virus infection group.

[c] Patient who were not admitted to ICU or using mechanical ventilation were excluded. Case numbers for each group: influenza detected, n = 20, non-influenza detected, n = 74; single infection, n = 86 mixed infection, n = 8.

WBC, white blood cell; ALT, alanine aminotransferase; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II.

univariate and multivariate analyses (p = 0.49 and p = 0.26, respectively). The use of corticosteroids and statins during the disease course did not provide a survival benefit for 14-day (p = 0.07 and p = 0.62, respectively), 30-day (p = 0.60 and p = 0.27, respectively), or 90-day mortality (p = 0.92 and p = 0.93, respectively, Fig. 3).

Discussion

Clinical awareness of NIRV-related LRTI in adults has long been narrowly focused on influenza. This limited awareness of NIRVs is largely related to the lack of availability of sensitive diagnostic tests, along with the impression that NIRVs play a minor role in LRTI in adult patients. For diagnosis of LRTI, both the sensitivity and specificity of LRT sampling have been reported to be higher than upper airway sampling.[13,14] Since only LRT-specific specimens were included for analysis in this study, the possibility of contamination with the oral flora was reduced.

Our results demonstrated that LRTI caused by either influenza or NIRVs may be associated with a high mortality rate. Although influenza-related LRTI was associated with a higher 14-day and 30-day mortality rate in our study, the 90-day mortality rates associated with NIRV-related and influenza-related LRTI were similar. NIRV-related LRTI was previously found to cause hospitalization in older adults more frequently than influenza.[15] Among NIRVs, RSV was reported to cause a higher proportion of respiratory failure and mortality than seasonal influenza in older adults and was less likely to be diagnosed.[16] HRV/ENT was once thought to cause only the common cold, but it was later found to cause LRTI in older adult patients.[17] Overall, the higher 14-day and 30-day mortality rates in this study indicate that influenza is likely to be more virulent than NIRVs.

The seasonality of individual RVs varied. HRV/ENT was the most commonly detected virus in our study, with year-round prevalence during the study period. In agreement with our results, a previous study reported that during the 2009—2010 influenza pandemic, HRV was detected

Table 3 Demographic characteristics, underlying medical conditions, clinical presentations difference between in hospital survive and non-survive group.

Characteristics	Overall patients, no. (%)		
	Survivor n = 69 (65)	Non-survivor n = 37 (35)	P
Male sex	48 (70)	19 (51)	0.06
Age (mean years ± SD)	64.7 ± 16.2	69.0 ± 16.7	0.20
Previous use of corticosteroids	14 (20)	9 (24)	0.63
Previous use of statins	11 (16)	4 (10)	0.47
Diabetes mellitus	29 (42)	24 (65)	0.03
Hypertension	33 (48)	19 (51)	0.73
Chronic heart diseases	15 (22)	14 (38)	0.44
Chronic kidney disease	17 (25)	8 (22)	0.73
Chemotherapy in recent one month	11 (16)	8 (22)	0.47
History of malignancy	19 (28)	13 (35)	0.47
Solid organ transplantation	6 (9)	2 (5)	0.54
Coronary artery diseases	15 (22)	9 (22)	0.76
Gastrointestinal and hepatobiliary diseases	21 (30)	10 (27)	0.71
Lung disease other than infection and malignancy	23 (33)	7 (19)	0.12
Central nervous system disease	12 (17)	5 (14)	0.60
Acute kidney injury in disease course	26 (38)	28 (76)	<0.001
Use of steroids in disease course	51 (74)	29 (78)	0.61
Use of statins in disease course	10 (15)	5 (14)	0.89
New hemodialysis in disease course	9 (13)	8 (22)	0.25
ECMO use in disease course	6 (8)	5 (14)	0.49
Acute gastrointestinal bleeding in disease course	14 (20)	4 (11)	0.22
Liver injury in disease course	25 (36)	16 (43)	0.48
Shock in disease course	33 (48)	33 (89)	<0.001
Acute decompensated heart in disease course	12 (17)	8 (22)	0.60
Coinfection with bacteria	45 (65)	29 (78)	0.16

ECMO, extracorporeal membrane oxygenation.

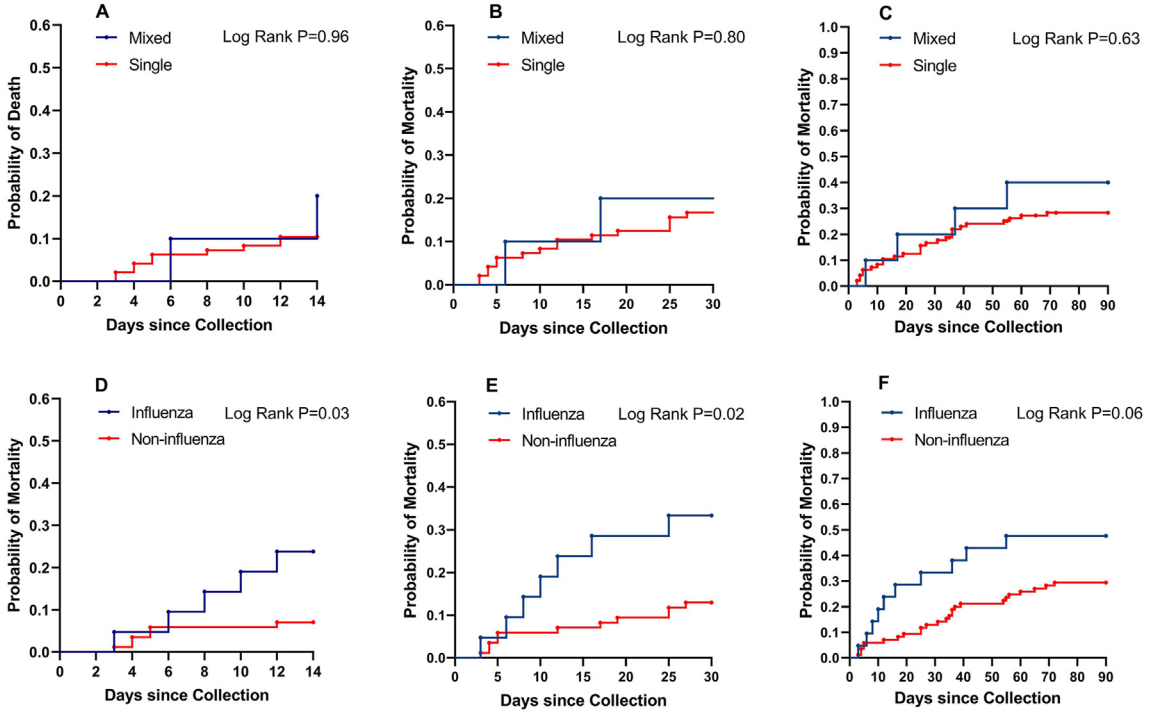

Figure 2. Kaplan–Meier Curves compared with 14-day, 30-day and 90-day mortality rate between 1. Mixed-infection versus single-infection group (Panel A, B, C) and 2. Influenza group versus non-influenza group (Panel D, E, F).

Table 4 Cox proportional-hazards models for prediction of 90-day mortality.

Variables	Univariate Cox model			Multivariate Cox model		
	HR	(95% CI)	P	HR	(95% CI)	P
Detection of influenza virus	1.98	(0.95–4.12)	0.07		N/A	0.33
Coinfection with bacteria	1.30	(0.61–2.78)	0.49		N/A	0.26
Diabetes mellitus	2.16	(1.07–4.33)	0.03		N/A	0.08
Shock episode in disease course	6.20	(2.19–17.58)	<0.001	4.28	(1.46–12.58)	0.01
Acute kidney injury in disease course	4.06	(1.84–8.94)	<0.001	2.80	(1.28–6.15)	0.01
Age more than 65-year-old	1.97	(0.96–4.02)	0.06		N/A	0.21
CRP>5 mg/dL	2.61	(1.19–5.76)	0.02		N/A	0.06

HR, hazard ratio; CRP, C-reactive protein; N/A, Not applicable.

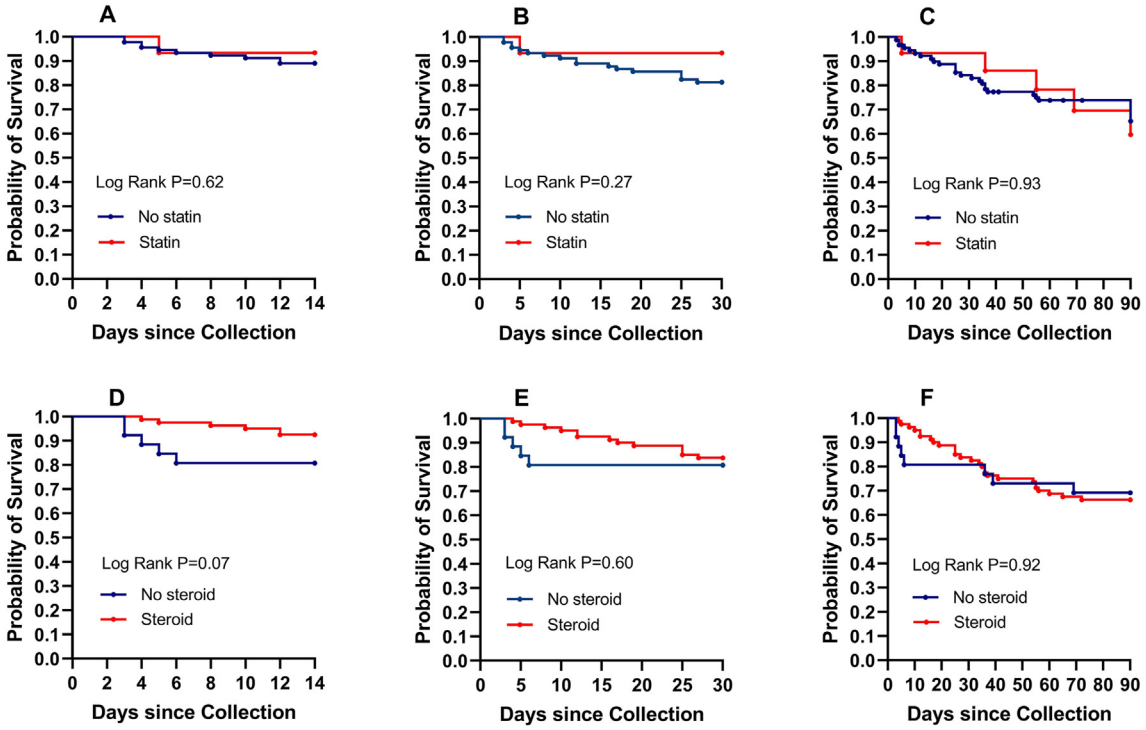

Figure 3. Kaplan–Meier Curves compared with 14-day, 30-day and 90-day survival rate between 1. Use statins in disease course or not (Panel A, B, C) and 2. Use corticosteroids in disease course or not (Panel D, E, F).

throughout the year in patients hospitalized with pneumonia.[18] The peak incidence of RSV and HCoV in our study was in the winter, which was consistent with a previous study.[19] Notably, the peak HMPV incidence spanned spring and early summer, whereas previous studies indicated that the peak of HMPV activity occurred in late winter and early spring.[20,21] Whether this difference in seasonal distribution is due to geographic variation remains unknown, and further long-term studies are necessary to confirm the seasonality patterns of each RV.

Previous studies were unable to elucidate whether mixed RV infection is associated with a poorer outcome.[22–24] In our analysis, neither concomitant detection of RVs nor superinfection with other microbes was associated with a poorer outcome. Counterintuitively, bacterial coinfection did not correlate with an increased mortality rate in this study, suggesting that the virus is virulent enough to cause the fatality of the host.

The administration of corticosteroids during the disease course was not associated with a favorable outcome. Corticosteroids modulate the production of proinflammatory cytokine transcription and can theoretically benefit lung injury caused by severe pneumonia, but whether routine corticosteroid therapy benefits these patients remains unclear.[25] For patients with influenza in critical condition, corticosteroid therapy has not been shown to improve outcomes.[26,27] Regarding NIRV infection, the administration of corticosteroids in patients with RSV pneumonia did not reduce the duration of ICU stay, hospital stay, or mechanical ventilation.[28] The results of our study do not support the routine use of corticosteroids in adult patients with RV-related LRTI. However,

corticosteroids may still benefit patients with RVs, especially those with acute exacerbation of chronic obstructive pulmonary disease.[29] Furthermore, our results also failed to reveal beneficial effects of statins in patients with RV-related LRTI, although statins were reported to benefit patients with sepsis because of their anti-inflammatory effects.[30]

Our study has several limitations. First, influenza may be underdiagnosed and its severity may be underestimated because some influenza cases were diagnosed by rapid antigen test and influenza RT-PCR; these severe influenza cases were not included in this study. Second, not all patients with LRTI who underwent BAL or LRT sampling received a PCR test for RVs, whereas at TVGH, a PCR test for RVs was regarded as routine clinical practice for patients with pneumonia. More studies are necessary to determine the true prevalence of various RVs in LRTI.

Conclusion

In non-immunocompromised patients diagnosed with pneumonia, influenza and NIRVs may be associated with significantly higher mortality. Additional prospective studies are necessary to delineate the association between disease severity and outcomes in patients with RV-related LRTI. Clinicians should be more vigilant of these infections and focus more on the early diagnosis of LRTI caused by various viruses.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.12.001.