Clinical characteristics and prognostic risk factors of mortality in patients with interstitial lung diseases and viral infection: a retrospective cohort study

Lijuan Li1, Chulei Wang1, Lingxiao Sun1, Xiaoqi Zhang2 and Guoru Yang1,*

Abstract

Introduction. Patients with interstitial lung disease (ILD) who subsequently develop a viral infection have high rates of morbidity and mortality.

Hypothesis/Gap Statement. Few large-scale epidemiological studies have investigated potential prognostic factors for morbidity and mortality in this patient group.

Aim. To evaluate the risk factors for morbidity and mortality in hospitalized patients with ILD and viral infection, as well as the clinical characteristics.

Methodology. This retrospective cohort study included patients with ILD who were hospitalized for a viral infection in two tertiary academic hospitals in China, between 1 January 2013 and 31 December 2019. We analysed the prevalence of comorbidities, clinical characteristics, 30 day mortality rates, and prognostic risk factors.

Results. A total of 282 patients were included; 195 and 87 were immunocompromised and immunocompetent, respectively. The most common underlying interstitial diseases were idiopathic pulmonary fibrosis (42.9%) and connective tissue disease (36.9%). The 30 day mortality rate was 20.6%. During the influenza season, an increase in influenza virus (IFV) (25.7%), respiratory syncytial virus (14.9%) and cytomegalovirus (CMV) (11.3%) cases was observed in the immunocompromised group. The most frequently detected virus in the immunocompetent group was IFV (44.8%), followed by respiratory syncytial virus (11.5%), and human rhinovirus (9.2%). During the non-influenza season, CMV (34.4%) was the main virus detected in the immunocompromised group. The 30 day mortality rates of non-IFV patients were higher than those of IFV patients. Older age (>60 years), respiratory failure, persistent lymphocytopenia, invasive mechanical ventilation and non-IFV virus infection were significantly associated with increased 30 day mortality.

Conclusion. Patients with ILD who develop viral infection have high rates of morbidity and mortality, which are associated with increased age (>60 years), respiratory failure, mechanical ventilation, persistent lymphocytopenia and non-IFV virus infection. These risk factors should be carefully considered when determining treatment strategies for this patient population.

INTRODUCTION

Few studies have evaluated the impact of viral infections on the acute exacerbation of idiopathic pulmonary fibrosis (IPF) and/or non-IPF interstitial lung disease (ILD). Saraya et al. documented respiratory virus infections in 19.2% of patients with acute exacerbation of interstitial pneumonia; no difference was observed between patients with IPF and non-IPF ILD [1]. In another study in which bronchoalveolar
| Variables                          | Total, N=282 | Immunocompromised group, n=195 | Immunocompetent group, n=87 | P-value |
|-----------------------------------|--------------|--------------------------------|-----------------------------|---------|
| Sex, female, n (%)                | 112 (39.7)   | 78 (40.0)                      | 27 (31.0)                   | 0.680   |
| Age, median (IQR)                 | 65.0 (56.0–72.0) | 62.0 (53.5–69.0) | 69.0 (63.0–76.0) | <0.001  |
| Symptoms and signs, n (%)         |              |                                |                             |         |
| Fever                             | 181 (64.2)   | 128 (65.6)                     | 53 (60.9)                   | 0.445   |
| Cough                             | 270 (95.7)   | 183 (93.8)                     | 87 (100.0)                  | 0.018   |
| Expectoration                     | 256 (90.8)   | 175 (89.7)                     | 81 (93.1)                   | 0.368   |
| Dyspnoea                          | 218 (77.3)   | 151 (77.4)                     | 67 (77.0)                   | 0.937   |
| Laboratory examination            |              |                                |                             |         |
| White blood cell,×10^9 l⁻¹ (IQR)  | 7.81 (5.73–11.04) | 8.47 (5.92–9.67) | 7.31 (5.38–9.17) | 0.007   |
| Neutrophils,×10^9 l⁻¹ (IQR)       | 6.17 (3.95–8.88) | 6.74 (4.57–9.67) | 5.09 (3.31–6.90) | <0.001  |
| Lymphocyte,×10^9 l⁻¹ (IQR)        | 1.10 (0.69–1.64) | 1.00 (0.60–1.51) | 1.37 (0.94–1.82) | 0.001   |
| Persistent lymphocytopenia         | 101 (35.8)   | 81 (41.5)                      | 20 (23.0)                   | 0.003   |
| Mean hemoglobin ±sd, g l⁻¹        | 120.5±23.8   | 116.0±24.6                     | 128.7±20.0                  | <0.001  |
| Mean albumin ±sd, g l⁻¹           | 35.2±5.3     | 34.7±5.2                       | 35.9±5.5                    | 0.078   |
| Lactate dehydrogenase, U l⁻¹      | 303 (224–433) | 328 (254–472) | 254 (200–333) | <0.001  |
| Blood urea nitrogen, mmol l⁻¹      | 5.61 (4.10–8.15) | 6.03 (4.30–10.42) | 4.80 (3.94–6.23) | <0.001  |
| d-dimer, mmol l⁻¹                  | 1.03 (0.40–2.89) | 1.10 (0.42–2.22) | 0.46 (0.16–1.37) | <0.001  |
| Procalcitonin, ng ml⁻¹             | 0.24 (0.09–0.39) | 0.27 (0.11–0.43) | 0.14 (0.07–0.30) | 0.002   |
| Oxygenation index                  | 274.0 (167.6–358.0) | 267.3 (142.1–357.0) | 282.0 (212.3–358.0) | 0.110   |
| Severe pneumonia index score       | 75 (63–98)   | 82 (62–106)                    | 69 (63–84)                  | 0.055   |
| CURB65 score >1                    | 75 (26.6)    | 55 (28.2)                      | 20 (23.0)                   | 0.360   |
| Underlying diseases, n (%)         |              |                                |                             |         |
| Diabetes mellitus                  | 80 (28.4)    | 64 (32.8)                      | 16 (18.4)                   | 0.013   |
| Connective tissue disease*         | 104 (36.9)   | 92 (47.2)                      | 12 (13.8)                   | <0.001  |
| Idiopathic pulmonary fibrosis      | 121 (42.9)   | 63 (32.3)                      | 58 (66.7)                   | <0.001  |
| Chronic obstructive pulmonary disease | 25 (8.9)   | 12 (6.2)                       | 13 (14.9)                   | 0.016   |
| Radiotherapy and chemotherapy of malignant solid tumour | 4 (1.4) | 4 (2.1) | 0 (0) | 0.178 |
| Unilateral lung transplantation†   | 30 (10.6)    | 30 (15.4)                      | 0 (0)                       | <0.001  |
| Current smoker or ex-smoker        | 109 (38.7)   | 66 (33.8)                      | 43 (49.4)                   | 0.013   |
| Bronchoalveolar lavage, n (%)      | 157 (55.7)   | 117 (60.0)                     | 40 (46.0)                   | 0.029   |
| Treatment, before admission, n (%) |              |                                |                             |         |
The acute exacerbation of IPF is a dangerous condition and has a mortality rate of over 50% [3]. Some reports have documented 1 year mortality rates of almost 100% in patients with an acute exacerbation of IPF [4, 5]. Weng found that 60% of samples collected from patients with an acute exacerbation of IPF were virus positive [6]. Drake et al. concluded that patients with ILD, particularly those with poor lung function and obesity, are at an increased risk of death from coronavirus disease [7]. However, there is a current lack of large-scale epidemiological studies that have investigated viral infections and prognosis in patients with ILD. Therefore, the purpose of this study was to evaluate potential risk factors for mortality in hospitalised patients with ILD and viral infections, as well as clinical characteristics.

**METHODS**  
**Study design and participants**

We retrospectively recruited patients with an acute exacerbation of ILD and viral infection, who were hospitalized between 1 January 2016 and 31 December 2019, at two secondary and tertiary academic hospitals in China. IPF was defined by the 2007 American Thoracic Society/European Respiratory Society criteria [8]; the definition was broadened to include patients with previously known or established fibrotic disease at admission [9]. We enrolled patients who had usual interstitial pneumonia patterns on their radiological examination, meaning those with an acute exacerbation of connective tissue disease (CTD)-associated interstitial pneumonia and unilateral lung transplantation for ILD. The inclusion criteria were as follows: (1) previous

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**Table 1.** Continued

| Variables                          | Total, N=282 | Immunocompromised group, n=195 | Immunocompetent group, n=87 | P-value |
|------------------------------------|--------------|--------------------------------|-----------------------------|---------|
| Antibiotics                        | 194 (68.8)   | 132 (67.7)                      | 62 (71.3)                   | 0.550   |
| Antiviral drugs                    | 52 (18.4)    | 38 (19.5)                       | 14 (16.1)                   | 0.497   |
| Treatment, during hospitalization, n (%) |             |                                |                             |         |
| Anti - Pseudomonas aeruginosa drugs | 198 (70.2)   | 145 (74.4)                      | 53 (60.9)                   | <0.001  |
| Voriconazole or caspofungin        | 100 (35.5)   | 91 (46.7)                       | 9 (10.3)                    | <0.001  |
| Ganciclovir                        | 120 (42.6)   | 113 (57.9)                      | 7 (8.0)                     | <0.001  |
| Trimethoprim                       | 103 (36.5)   | 101 (51.8)                      | 2 (2.3)                     | <0.001  |
| Complications, n (%)               |              |                                |                             |         |
| Noninvasive ventilation            | 67 (23.8)    | 54 (27.7)                       | 13 (14.9)                   | 0.020   |
| Invasive mechanical ventilation    | 70 (24.8)    | 57 (29.2)                       | 13 (14.9)                   | 0.010   |
| Mechanical ventilation             | 99 (35.1)    | 77 (39.5)                       | 22 (25.3)                   | 0.021   |
| Respiratory failure                | 137 (48.6)   | 108 (55.4)                      | 29 (33.3)                   | 0.001   |
| ICU admission                      | 95 (33.7)    | 80 (41.0)                       | 15 (17.2)                   | <0.001  |
| Septic shock during hospitalization| 47 (16.7)    | 43 (22.1)                       | 4 (4.6)                     | <0.001  |
| Extracorporeal membrane oxygenation| 19 (6.7)     | 17 (8.7)                        | 2 (2.3)                     | 0.047   |
| 30 day mortality                  | 58 (20.6)    | 46 (23.6)                       | 12 (13.8)                   | 0.060   |

*Connective tissue disorders: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjogren’s syndrome, etc.
†The reason of unilateral lung transplantation was interstitial lung disease.
‡Other interstitial pneumonia includes non-specific interstitial pneumonia, organizing pneumonia, allergic pneumonia, radiation pneumonia, drug-induced interstitial pneumonia, etc.

lavage was performed in 18 patients presenting with an acute decline in fibrotic lung disease, five had culture or PCR evidence of viral infection [one parainfluenza virus [PIV] case, two herpes simplex virus cases and two cytomegalovirus (CMV) cases] [2].

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Table 2. Pathogen results of pneumonia between the immunocompetent and immunocompromised group

| Variables, n (%) | Immunocompromised group, n=195 | Immunocompetent group, n=87 | P-Value |
|------------------|---------------------------------|-----------------------------|---------|
| One virus        | 161 (82.6)                      | 80 (92.0)                   | 0.039   |
| Two or more viruses | 34 (17.4)                      | 7 (8.0)                    | 0.039   |
| Influenza season |                                 |                             |         |
| Cytomegalovirus  | 22 (11.3)                       | 3 (3.4)                     | 0.022   |
| Influenza A virus| 36 (18.5)                       | 32 (36.8)                   | 0.088   |
| Influenza B virus| 14 (7.2)                        | 7 (8.0)                     | 0.527   |
| Rhinovirus       | 4 (2.1)                         | 8 (9.2)                     | 0.046   |
| Respiratory syncytial virus | 29 (14.9) | 10 (11.5) | 0.038   |
| Adenovirus       | 3 (1.5)                         | 0 (0)                       | 0.157   |
| Parainfluenza virus | 4 (2.1)                      | 3 (3.4)                     | 0.857   |
| Non-Influenza season |                                 |                             |         |
| Cytomegalovirus  | 67 (34.4)                       | 1 (1.1)                     | <0.001  |
| Influenza A virus| 13 (6.7)                        | 11 (12.6)                   | 0.001   |
| Influenza B virus| 3 (1.5)                         | 2 (2.3)                     | 0.289   |
| Rhinovirus       | 4 (2.1)                         | 4 (4.6)                     | 0.038   |
| Respiratory syncytial virus | 19 (9.7) | 3 (3.4) | 0.350   |
| Adenovirus       | 4 (2.1)                         | 5 (5.7)                     | 0.009   |
| Parainfluenza virus | 10 (5.1)                     | 2 (2.3)                     | 0.696   |
| Pathogenic types of coinfections | 82 (42.1) | 11 (12.6) | <0.001  |
| Bacteria         | 27 (13.8)                       | 3 (3.4)                     | 0.009   |
| Streptococcus pneumoniae | 1 (0.5)                      | 2 (2.3)                     | 0.177   |
| Staphylococcus aureus | 7 (3.6)                      | 0 (0)                       | 0.074   |
| Escherichia coli | 3 (1.5)                         | 0 (0)                       | 0.245   |
| Enterobacter cloacae | 1 (0.5)                      | 0 (0)                       | 0.503   |
| Klebsiella pneumoniae | 6 (3.1)                      | 1 (1.1)                     | 0.337   |
| Pseudomonas      | 6 (3.1)                         | 0 (0)                       | 0.098   |
| Proteus mirabilis| 1 (0.5)                         | 0 (0)                       | 0.503   |
| Acinetobacter    | 1 (0.5)                         | 0 (0)                       | 0.503   |
| Nocardia         | 1 (0.5)                         | 0 (0)                       | 0.503   |
| Atypical         | 5 (2.6)                         | 2 (2.3)                     | 0.895   |
| Mycoplasma pneumoniae | 3 (1.5)                      | 2 (2.3)                     | 0.655   |
| Legionella       | 2 (1.0)                         | 0 (0)                       | 0.404   |
| Pneumocystis     | 25 (12.8)                       | 0 (0)                       | <0.001  |
| Aspergillus      | 23 (11.8)                       | 6 (6.9)                     | 0.211   |
| Mycobacterium tuberculosis | 1 (0.5)                     | 0 (0)                       | 0.503   |
| Non-tuberculosis mycobacteria | 1 (0.5)                     | 0 (0)                       | 0.503   |
| Drug-resistant bacteria* | 5/14                      | 0/1                         | 0.464   |

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ILD; (2) acute respiratory infection symptoms, including fever, cough, expectoration or dyspnoea; (3) presence of new bilateral pulmonary ground-glass abnormalities, with consolidation superimposed on a background of a reticular and/or honeycomb pattern on chest computed tomography; and (4) positive viral nucleic acid obtained from nasopharyngeal swabs, sputum or bronchoalveolar lavage fluid (BALF). Patients without evidence of viral infection or a prior history of ILD were excluded.

**Study quality control**

Key investigators, including clinicians, statisticians, microbiologists and radiologists, worked together to draft the protocol and create a single formatted case report form (CRF) used by all centres. Before study initiation, all investigators from the six centres received training related to the study protocol, including the screening process, definitions of underlying diseases, and the formatted CRF. After the data were collected, CRFs were reviewed by a trained researcher to ensure completeness and data quality. The study was approved by the Ethics Committee of China–Japan Friendship Hospital. There was a centralized collaboration between all participating hospitals, which included anonymized data submission and collection.

**Data collection**

The following data were collected from the medical records of patients during their hospitalisation: (1) demographics; (2) clinical symptoms; (3) initial vital signs and lung examination findings; (4) severity of disease (indicated by intensive care unit [ICU] admission, use of invasive or non-invasive mechanical ventilation, pneumonia severity index (PSI) score and/or confusion-urea-respiratory rate-blood pressure-65 (CURB-65) score [10, 11]; (5) laboratory and microbiological data (blood, sputum and/or BALF samples, bacterial or fungal cultures, viral nucleic acid detection and antibiotic susceptibility patterns); (6) treatment information, including use of vasoactive agents, antimicrobials, glucocorticoids and/or other immunosuppressants; and (7) survival status 30 days after admission. High-dose steroid use within 30 days of admission was defined as a prednisolone or glucocorticoid dose of at least 30 mg/day. Persistent lymphopenia was defined as a peripheral blood lymphocyte count of <1×10^9 l⁻¹ for more than 7 days.

**Diagnostic procedures**

A viral aetiology was confirmed based on the following criteria: reverse transcription real-time (RT)-PCR (Shanghai Zhijiang Biological Technology, China) detection of

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### Table 2. Continued

| Variables, n (%)                  | Immunocompromised group, n=195 | Immunocompetent group, n=87 | P-Value |
|-----------------------------------|--------------------------------|-----------------------------|---------|
| Pathogens types of nosocomial infection | 69 (35.4)                    | 9 (10.3)                    | <0.001  |
| Bacteria                          | 61 (31.3)                     | 9 (10.3)                    | <0.001  |
| Acinetobacter                     | 19 (9.7)                      | 3 (3.4)                     | 0.069   |
| *Pseudomonas*                     | 10 (5.1)                      | 3 (3.4)                     | 0.534   |
| *Klebsiella pneumoniae*           | 9 (4.6)                       | 1 (1.1)                     | 0.146   |
| *Burkholderia*                    | 4 (2.1)                       | 0 (0)                       | 0.178   |
| *Enterococcus*                    | 4 (2.1)                       | 0 (0)                       | 0.178   |
| *Enterobacter cloacae*            | 2 (1.0)                       | 0 (0)                       | 0.343   |
| *Escherichia coli*                | 2 (1.0)                       | 0 (0)                       | 0.343   |
| *Enterobacter aerogenes*          | 0 (0)                         | 1 (1.1)                     | 0.134   |
| Stenotrophomonas maltophilia      | 2 (1.0)                       | 0 (0)                       | 0.343   |
| Corynebacterium striatum          | 3 (1.5)                       | 0 (0)                       | 0.245   |
| Staphylococcus aureus             | 2 (1.0)                       | 0 (0)                       | 0.343   |
| Rolstonia mannitoltytica          | 0 (0)                         | 1 (1.1)                     | 0.134   |
| Other bacteria                    | 4 (2.1)                       | 0 (0)                       | 0.178   |
| Aspergillus                       | 8 (4.1)                       | 0 (0)                       | 0.055   |
| Drug-resistant bacteria*          | 19/22                         | 4/5                         | 0.718   |

*Not all bacterial strains had drug-sensitivity results.
### Table 3. Comparative analysis of different viral pneumonia in patients with interstitial lung disease

| Variables                              | CMV N=64 | IFV-A N=75 | RSV N=47 | IFV-B N=21 | HPIV N=11 | ADV N=10 | HRV N=13 | ≥Two viruses N=41 | P-Value |
|----------------------------------------|----------|------------|----------|------------|-----------|----------|----------|------------------|---------|
| Female, n (%)                          | 26 (40.6)| 22 (29.3)  | 19 (40.4)| 9 (42.9)   | 3 (27.3)  | 2 (20.0) | 6 (46.2) | 18 (43.9)        | 0.567   |
| Age, median (IQR), years               | 62.0 (49.5, 69.0) | 68.0 (60.0, 74.0) | 61.0 (53.0, 67.0) | 66.0 (61.5, 71.5) | 75.0 (68.0, 81.0) | 64.0 (36.0, 70.8) | 69.0 (64.0, 76.5) | 65.0 (55.5, 69.5) | 0.001   |
| Symptoms and signs, n (%)              |          |            |          |            |           |          |          |                  |         |
| Fever                                  | 53 (82.8)| 47 (62.7)  | 25 (53.2)| 14 (66.7)  | 6 (54.5)  | 6 (60.0) | 4 (30.8) | 26 (63.4)        | 0.008   |
| Cough                                  | 57 (89.1)| 74 (98.7)  | 47 (100.0)| 18 (85.7)  | 11 (100.0)| 10 (100.0)| 13 (100.0)| 40 (97.6)        | 0.013   |
| Expectoration                          | 54 (84.4)| 71 (94.7)  | 46 (97.9)| 16 (76.2)  | 11 (100.0)| 10 (100.0)| 11 (84.6)| 37 (90.2)        | 0.031   |
| Dyspnoea                               | 53 (82.8)| 53 (70.7)  | 37 (78.7)| 13 (61.9)  | 9 (81.8)  | 10 (100.0)| 9 (69.2) | 34 (82.9)        | 0.179   |
| Underlying diseases, n (%)             | 37 (57.8)| 16 (21.3)  | 14 (29.8)| 5 (23.8)   | 4 (36.4)  | 1 (10.0) | 8 (61.5) | 19 (46.3)        | <0.001  |
| Connective tissue disease              | 21 (32.8)| 40 (53.3)  | 17 (36.2)| 14 (66.7)  | 4 (36.4)  | 4 (40.0) | 10 (76.9)| 11 (26.8)        | 0.002   |
| Idiopathic interstitial pneumonia      | 2 (3.1)  | 1 (1.3)    | 0 (0)    | 1 (4.8)    | 0 (0)     | 0 (0)    | 0 (0)    | 0 (0)            | 0.688   |
| Radiotherapy and chemotherapy of malignant solid | 0 (0)   | 8 (10.7)   | 12 (25.5)| 0 (0)      | 2 (18.2)  | 1 (10.0) | 0 (0)    | 7 (17.1)         | 0.001   |
| Laboratory examination                 | 9.10 (6.04, 13.65) | 7.69 (5.36, 10.77) | 8.20 (5.88, 11.13) | 5.83 (4.76, 7.91) | 7.94 (4.70, 11.2) | 7.19 (4.88, 12.27) | 7.66 (6.17, 10.15) | 8.30 (6.55, 11.15) | 0.079   |
| White blood cell,×10^9 l^{-1} (IQR)    | 7.12 (5.29, 11.50) | 5.92 (3.73, 8.23) | 5.70 (3.41, 8.91) | 3.96 (2.77, 5.78) | 5.53 (3.03, 7.68) | 5.10 (2.83, 8.81) | 5.88 (4.83, 6.93) | 6.48 (4.97, 9.24) | 0.004   |
| Neutrophils,×10^9 l^{-1} (IQR)         | 0.90 (0.60, 1.40) | 1.28 (0.72, 1.70) | 1.16 (0.82, 2.11) | 1.45 (0.90, 1.63) | 1.00 (0.79, 1.37) | 1.04 (0.86, 1.42) | 1.44 (1.15, 2.03) | 0.77 (0.33, 1.32) | 0.002   |
| Lymphocyte,×10^9 l^{-1} (IQR)          | 33 (51.6) | 23 (30.7)  | 13 (27.7)| 4 (19.0)   | 3 (27.3)  | 3 (30.0) | 4 (30.8) | 18 (43.9)        | 0.061   |
| Persistent lymphocytopenia             | 1.73 (0.73, 3.19) | 0.55 (0.29, 1.82) | 1.07 (0.52, 2.34) | 0.40 (0.14, 0.79) | 1.67 (0.80, 8.49) | 0.87 (0.24, 1.53) | 0.11 (0.03, 0.17) | 1.10 (0.60, 1.84) | <0.001  |
| Persistent lymphocytopenia             |          |            |          |            |           |          |          |                  |         |
| d-dimer, mg l^{-1}                     |          |            |          |            |           |          |          |                  |         |
| d-dimer, mg l^{-1}                     | 1.73 (0.73, 3.19) | 0.55 (0.29, 1.82) | 1.07 (0.52, 2.34) | 0.40 (0.14, 0.79) | 1.67 (0.80, 8.49) | 0.87 (0.24, 1.53) | 0.11 (0.03, 0.17) | 1.10 (0.60, 1.84) | <0.001  |

Continued
| Variables                        | CMV N=64 | IFV-A N=75 | RSV N=47 | IFV-B N=21 | HPIV N=11 | ADV N=10 | HRV N=13 | ≥Two viruses N=41 | P-Value |
|---------------------------------|----------|------------|----------|------------|-----------|----------|----------|------------------|---------|
| Lactate dehydrogenase, U l⁻¹    | 373.0    | 268.1      | 301.0    | 254.4      | 247.0     | 281.0    | 250.1    | 368.0 (274.0, 499.0) | 0.003   |
| Oxygenation index               | 204.3    | 281.0      | 314.3    | 323.8      | 306.7     | 281.0    | 220.5    | 249.7            | <0.001  |
| Severe pneumonia index score    | 87.0 (70.0, 121.3) | 77.0 (64.0, 92.0) | 80.0 (57.0, 82.0) | 88.0 (74.0, 102.0) | 69.0 (34.8, 93.5) | 68.0 (59.5, 71.5) | 85.0 (64.5, 108.5) | <0.001  |
| CURB65 score >1                 | 24 (37.5) | 19 (25.3)  | 6 (12.8) | 5 (23.8)   | 3 (27.3)  | 3 (30.0) | 1 (7.7)  | 14 (34.1)         | 0.092   |
| Imaging features, n (%)        | 1 (1.6)  | 1 (1.3)    | 0 (0)    | 0 (0)      | 0 (0)     | 0 (0)    | 1 (7.7)  | 3 (7.3)           |         |
| Consolidation                   | 31 (49.2) | 17 (23.0)  | 11 (23.4) | 3 (14.3)   | 5 (45.5)  | 2 (20.0) | 0 (0)    | 17 (41.5)         | <0.001  |
| Ground-glass opacity            | 49 (77.8) | 42 (56.8)  | 33 (70.2) | 12 (57.1)  | 5 (45.5)  | 5 (50.0) | 10 (76.9) | 25 (61.0)         | 0.084   |
| Honeycomb or reticular pattern  | 44 (69.8) | 56 (75.7)  | 35 (74.5) | 6 (28.6)   | 10 (90.9) | 4 (40.0) | 8 (61.5) | 27 (65.9)         | 0.002   |
| Pleural effusion                | 12 (19.0) | 9 (12.2)   | 6 (12.8) | 0 (0)      | 1 (9.1)   | 2 (20.0) | 0 (0)    | 4 (9.8)           | 0.358   |
| Viral-PCP co-infection          | 21 (32.8) | 0 (0)      | 0 (0)    | 1 (4.8)    | 0 (0)     | 0 (0)    | 0 (0)    | 3 (7.3)           | <0.001  |
| Viral-aspergillus co-infection  | 6 (9.4)   | 9 (12.0)   | 4 (8.5)  | 0 (0)      | 3 (27.3)  | 0 (0)    | 1 (7.7)  | 6 (14.6)          | 0.300   |
| Viral-bacteria co-infection     | 10 (15.6) | 5 (6.7)    | 5 (10.6) | 0 (0)      | 0 (0)     | 1 (10.0) | 1 (7.7)  | 5 (12.2)          | 0.401   |
| Viral-atypical co-infection     | 2 (3.1)   | 2 (2.7)    | 0 (0)    | 0 (0)      | 0 (0)     | 3 (30.0) | 0 (0)    | 0 (0)             | <0.001  |
| Nosocomial bacterial infection  | 9 (14.1)  | 13 (17.3)  | 9 (19.1) | 1 (4.8)    | 1 (9.1)   | 4 (40.0) | 0 (0)    | 12 (29.3)         | 0.055   |
| Complications, n (%)            | 31 (48.4) | 9 (12.0)   | 7 (14.9) | 3 (14.3)   | 3 (27.3)  | 1 (10.0) | 3 (23.1) | 10 (24.4)         | <0.001  |
| Non-invasive ventilation        | 22 (34.4) | 16 (21.3)  | 10 (21.3) | 1 (4.8)    | 3 (27.3)  | 1 (10.0) | 2 (15.4) | 15 (36.6)         | 0.064   |
| Invasive mechanical ventilation | 49 (76.6) | 33 (44.0)  | 16 (34.0) | 3 (14.3)   | 3 (27.3)  | 4 (40.0) | 5 (38.5) | 24 (58.5)         | <0.001  |
| Respiratory failure             | 42 (65.6) | 17 (22.7)  | 11 (23.4) | 1 (4.8)    | 3 (27.3)  | 1 (10.0) | 3 (23.1) | 17 (41.5)         | <0.001  |

Continued
respiratory viruses, including CMV, respiratory syncytial virus (RSV), influenza virus (IFV) types A and B, PIV, human rhinovirus (HRV), human metapneumovirus, adenovirus and *Pneumocystis jirovecii* in sputum, endotracheal aspirate; from the BALF or nasopharyngeal swabs. Bacteria or atypical pathogens were confirmed if one of the following criteria were met: (1) positive bacterial culture; (2) positive urinary antigen for *Legionella pneumophila* (Binax Now; Trinity Biotech, Bray, Ireland) or *Streptococcus pneumoniae* (Binax Now; Emergo Europe, Amsterdam, The Netherlands); and (3) detection of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *L. pneumophila* in sputum, BALF, endotracheal aspirate or nasopharyngeal swabs using RT-PCR. The Platelia *Aspergillus* test was used for galactomannan detection (Bio-Rad Laboratories, Marnes-la-Coquette, France).

**Pathogen-specific diagnostic information**

A diagnosis of pneumonia caused by *Aspergillus* required one or more of the following criteria: (1) histopathologic or direct microscopic evidence of dichotomous septate hyphae with a tissue culture positive for *Aspergillus*; (2) a positive *Aspergillus* culture from BALF; (3) a galactomannan optical index in BALF of ≥1; (4) a galactomannan optical index in serum of ≥0.5; and (5) *Aspergillus* species identified by culture and microscopic characteristics [12, 13].

The diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) was based on one of the following criteria: (1) high-resolution computed tomography imaging showing diffuse ground-glass opacity with a patchy distribution; (2) mycological criteria (microscopic examination of the respiratory sample revealing the presence of *Pneumocystis* cystic or trophic forms); and (3) a positive PCR test for *Pneumocystis* deoxyribonucleic acid [14].

Co-infection was documented if bacteria or fungi were isolated from lower respiratory tract specimens (qualified sputum, endotracheal aspirate and BALF) and/or blood samples within 48 h of hospitalization. Nosocomial infection was diagnosed based on clinical signs or symptoms of nosocomial pneumonia, bacteremia, and a positive culture of a new pathogen obtained from lower respiratory tract specimens and/or blood samples obtained ≥48 h after admission.

**Statistical analysis**

Patient demographics, clinical characteristics and pathogen testing results are expressed as mean (±standard deviation), median (interquartile range) or number (percentage). Group comparisons were conducted using Student’s *t*-test or the Wilcoxon rank-sum test for continuous variables with and without normal distributions, respectively. Categorical variables of the two groups were compared using the χ² test. Cox regression analysis was used to examine independent predictors of mortality, and its results were reported as hazard ratio (HR) and 95% CI. Kaplan–Meier survival curves were used to compare the 30 day survival rate for patients by the log-rank test.
| Variables                                      | Survivors, n=224 | Non-survivors, n=58 | P-value |
|-----------------------------------------------|------------------|---------------------|---------|
| Sex, female, n (%)                            | 89 (39.7)        | 16 (27.6)           | 0.088   |
| Age >60 years, n (%)                          | 138 (61.6)       | 45 (77.6)           | 0.023   |
| Symptoms and signs, n (%)                     |                  |                     |         |
| Fever                                         | 134 (59.8)       | 47 (81.0)           | 0.003   |
| Cough                                         | 213 (95.1)       | 57 (98.3)           | 0.284   |
| Expectoration                                 | 204 (91.1)       | 52 (89.7)           | 0.740   |
| Dyspnoea                                      | 165 (73.7)       | 53 (91.4)           | 0.004   |
| Laboratory examination                        |                  |                     |         |
| White blood cell,×10^9 l⁻¹ (IQR)              | 7.54 (5.61–10.63) | 9.27 (6.78–12.27)   | 0.004   |
| Neutrophils,×10^9 l⁻¹ (IQR)                   | 5.70 (3.51–8.25) | 7.05 (5.66–10.41)   | <0.001  |
| Lymphocyte,×10^9 l⁻¹ (IQR)                    | 1.16 (0.73–1.70) | 0.79 (0.59–1.23)    | 0.003   |
| Persistent lymphocytopenia                    | 66 (29.5)        | 35 (60.3)           | <0.001  |
| Mean hemoglobin ±sd, g l⁻¹                    | 122.3±23.0       | 113.5±25.5          | 0.012   |
| Mean albumin ±sd, g l⁻¹                       | 35.9±5.0         | 32.1±5.7            | <0.001  |
| Lactate dehydrogenase, U l⁻¹                  | 293 (213–397)    | 373 (256–502)       | 0.009   |
| Blood urea nitrogen, mmol l⁻¹                 | 5.25 (4.10–7.69) | 6.55 (5.26–11.14)   | 0.008   |
| d-dimer, mmol l⁻¹                             | 0.78 (0.32–1.84) | 1.35 (0.44–4.99)    | 0.014   |
| Procalcitonin, ng ml⁻¹                        | 0.24 (0.09–0.38) | 0.24 (0.10–0.47)    | 0.730   |
| Oxygenation index                             | 288.9 (211.6–375.9) | 145.0 (106.3–247.7) | <0.001  |
| Severe pneumonia index score                  | 72 (62–90)       | 91 (73–126)         | <0.001  |
| CURB65 score >1                               | 51 (22.8)        | 24 (41.4)           | 0.004   |
| Underlying diseases, n (%)                    |                  |                     |         |
| Diabetes mellitus                             | 62 (27.7)        | 18 (31.0)           | 0.613   |
| Connective tissue disease*                    | 76 (33.9)        | 28 (48.3)           | 0.044   |
| Idiopathic pulmonary fibrosis                 | 95 (42.4)        | 26 (44.8)           | 0.740   |
| Chronic obstructive pulmonary disease         | 23 (10.3)        | 2 (3.4)             | 0.103   |
| Radiotherapy and chemotherapy of malignant solid tumour | 2 (0.9)     | 2 (3.4)             | 0.142   |
| Unilateral lung transplantation&              | 27 (12.1)        | 3 (5.2)             | 0.130   |
| Current smoker or ex-smoker                   | 86 (38.4)        | 23 (39.7)           | 0.860   |
| Bronchoalveolar lavage, n (%)                 | 130 (58.0)       | 27 (46.6)           | 0.117   |
| Imaging features, n (%), 6 missing            | 220 (98.2)       | 56 (96.6)           |         |
| Consolidation                                 | 59 (26.8)        | 27 (48.2)           | 0.002   |
| Ground-glass opacity                          | 142 (64.3)       | 39 (69.4)           | 0.473   |
| Honeycomb or Reticular pattern                | 146 (66.3)       | 44 (78.6)           | 0.085   |
| Pleural effusion                              | 26 (11.8)        | 8 (14.3)            | 0.591   |
| Two or more viruses                           | 13 (5.8)         | 28 (48.3)           | 0.056   |
| Cytomegalovirus                               | 63 (28.1)        | 30 (51.7)           | 0.001   |
| Non-influenza virus                           | 124 (55.4)       | 43 (74.1)           | 0.009   |

Continued
Statistical analyses were performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). All tests were two-sided, and P-values < 0.05 were considered statistically significant.

**Patient and public involvement**
Neither patients nor the public were involved in the development of the research question, study design, patient recruitment or the conduct of the study.

**RESULTS**
A total of 282 patients with ILD who developed viral infection between 1 January 2013 and 31 December 2019 were identified. Approximately 36% of the patients were women, with a median age of 65.0. The main symptoms included fever (75.4%), cough (94.8%), expectoration (70.8%) and dyspnoea (67.2%). The most common underlying interstitial-related diseases were IPF (42.9%), CTD (36.9%), chronic obstructive pulmonary disease (8.9%) and ILD requiring unilateral lung transplantation (10.6%). Ninety-five (43.3%) patients were admitted to the ICU for treatment, with 23.8% and 24.8% having received non-invasive and invasive ventilation, respectively. The 30 day mortality rates were 20.6%, respectively. A total of 195 patients were immunocompromised, and 87 patients were immunocompetent. The following parameters were significantly higher in the immunocompromised group than in the immunocompetent group: proportion of patients with persistent lymphocytopenia, diabetes and IPF; use of anti-*Pseudomonas* drugs, anti-*Aspergillus* drugs, ganciclovir and sulfonamides; requirement for ICU admission, non-invasive ventilation, invasive mechanical ventilation and/or extracorporeal membrane oxygenation; adverse outcomes including respiratory failure and septic shock; peripheral blood leucocyte, neutrophil and lymphocyte counts; and lactate dehydrogenase, urea nitrogen, d-dimer and procalcitonin levels (P<0.05). Age, haemoglobin levels and the proportion of patients with cough symptoms and IPF were significantly lower in the immunocompromised group than in the immunocompetent group (Table 1).

During the influenza season (November, December, January, February), an increase in IFV (25.7%), RSV (14.9%) and CMV (11.3%) cases was found in the immunocompromised group. The most frequently detected virus in the immunocompetent group was IFV (44.8%), followed by RSV (11.5%) and HRV (9.2%). During the non-influenza season, CMV (34.4%) was the main virus detected in the immunocompromised group. No dominant virus type was observed in the immunocompetent group; the most frequently detected virus was IFV (15.9%), followed by adenovirus (5.7%), HRV (4.6%), RSV (3.4%) and PIV (2.3%) (Table 2). In immunocompromised patients, bacteria (13.8%), *Pneumocystis jirovecii* (12.8%) and *Aspergillus* (11.8%) were the most frequently detected pathogens; the most isolated bacteria were *Staphylococcus aureus* (3.6%), *Klebsiella pneumoniae* (3.1%) and *Pseudomonas aeruginosa* (3.1%). In the immunocompetent group, *Aspergillus* (6.9%), bacteria (3.4%) and *Mycoplasma* (2.3%) were the dominant pathogens. Secondary nosocomial bacterial infections were most frequently attributed to *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Table 2).

Patients with PIV had the highest average age (75 years) and the lowest incidence of fever (30.8%). Patients with CMV and two or more virus groups had higher neutrophil and lactate dehydrogenase levels and lower lymphocyte counts than other viruses. Patients with CMV had a lower oxygenation index (P<0.05). Patients with CMV, HRV, PIV or two or more virus groups had more frequently required non-invasive mechanical ventilation, invasive mechanical ventilation and ICU care, and had higher rates of respiratory failure, septic shock and 30 day mortality (Table 3).

| Table 4. | Continued |
|----------|------------|------------|-------------|
| Variables | Survivors, n=224 | Non-survivors, n=58 | P-value |
| Viral-PCP co-infection | 16 (7.1) | 9 (15.5) | 0.046 |
| Viral-aspergillus co-infection | 21 (9.4) | 8 (13.8) | 0.324 |
| Viral-bacteria co-infection | 23 (10.3) | 4 (6.9) | 0.437 |
| Viral-atypical co-infection | 6 (2.7) | 1 (1.7) | 0.677 |
| Nosocomial bacterial infection | 33 (14.7) | 16 (27.6) | 0.021 |
| Complications, n (%) | | | |
| Non-invasive ventilation | 33 (14.7) | 34 (58.6) | <0.001 |
| Invasive mechanical ventilation | 34 (15.2) | 36 (62.1) | <0.001 |
| Mechanical ventilation | 57 (25.4) | 42 (72.4) | <0.001 |
| Respiratory failure | 84 (37.5) | 53 (91.4) | <0.001 |
| ICU admission | 52 (23.2) | 43 (74.1) | <0.001 |
| Extracorporeal membrane oxygenation | 13 (5.8) | 6 (10.3) | 0.219 |
The following parameters were significantly higher in the non-survivors' group than in the survivors' group: age, underlying connective tissue disease, proportion of fever and dyspnoea, peripheral blood leukocytes, neutrophils, lactate dehydrogenase, urea nitrogen, d-dimer on the first day of admission, patients with persistent lymphocytopenia, consolidation on CT image, PSI score and CURB-65 score >1, CMV infection, PCP infection, non-IFV infection, nosocomial bacterial infection, requirement for ICU admission, non-invasive ventilation, invasive mechanical ventilation and/or extracorporeal membrane oxygenation; respiratory failure; (P<0.05). Lymphocytes, haemoglobin, and albumin were significantly lower in the non-survivors' group than in the survivors' group (Table 4).

Multivariate Cox regression analysis indicated that the following factors were independent predictors of 30 day mortality in patients with ILD: age >60 years, respiratory failure, persistent lymphocytopenia, invasive mechanical ventilation and non-IFV type A infection (Table 5, Fig. 1).

**DISCUSSION**

This study was a large-scale retrospective investigation of the clinical characteristics and prognostic risk factors of mortality in hospitalized patients with ILD who developed viral infection. The main findings are summarized as follows: (1) patients with ILD who developed viral infection had a higher mortality, with the 30 day rates being 20.6%, respectively; (2) the distribution of virus types in immunocompromised patients differed between influenza and non-influenza seasons; (3) the disease severity and mortality in non-IFV patients were higher than those of IFV patients; and (4) independent risk factors for mortality included age >60 years, respiratory failure, persistent lymphocytopenia, invasive mechanical ventilation and non-IFV infection.

Previous studies have shown that viruses, especially respiratory viruses, may be co-factors for the development or exacerbation of lung fibrosis [15]. One such study, which conducted...
autopsies in 42 patients with IPF, reported that 15% had a fungal, bacterial and/or viral infection [16]. Another study found that 28.8% of patients with an acute exacerbation of IPF, had bronchopneumonia (fungal, 13.5%; CMV, 11.5%; and bacterial, 9.6%) [17]. Wootton et al. reported that only 4 of 43 patients with an acute exacerbation of IPF had evidence of common respiratory viral infections (PIV \(n=1\), HRV \(n=2\), coronavirus \(n=1\)) [18]. Similarly, in a study conducted among 40 patients with IPF, Keyvani et al. documented infections in nine patients (22.5%); RSV, PIV, HRV and coronaviruses were found in 2.5%(1/40), 7.5% (3/40), 10%(4/40) and 2.5%(1/40) of the patients, respectively [19]. Our large-scale epidemiological study of patients with ILD and viral infection found that IFV and RSV were the main pathogens during the influenza season, followed by CMV. During the non-influenza season, CMV was the main pathogen in immunocompromised patients, followed by IFV, RSV, PIV and HRV. Therefore, in the case of patients with suspected interstitial disease complicated with virus infection, we suggest that the viral nucleic acid test should be performed as early as possible to confirm the etiological diagnosis.

The disease severity, complications, and outcomes of immunocompetent patients with community-acquired pneumonia were similar between IFV and non-IFV-related respiratory diseases [20–22]. For elderly hospitalized patients with respiratory symptoms, RSV, human metapneumovirus and PIV have been associated with higher mortality [23–26] and more complications [25] than influenza. Our study showed that disease severity and mortality in non-IFV patients were higher than those in IFV patients. This result can be attributed to the following reasons: (1) the early use of oseltamivir in patients with influenza; (2) the lack of a specific drug for HRV and PIV; and (3) CMV was closely related to immunocompromised patients and had high mortality [27, 28]. Thus, when patients with ILD develop symptoms of a viral infection, an increased vigilance is warranted for the detection of non-IFV infections.

Factors identified by previous studies as being associated with a poor prognosis in patients with ILD include a lower baseline forced vital capacity and carbon monoxide diffusing capacity; more extensive abnormalities on computed tomography at the time of acute exacerbation; and poor oxygenation and BALF neutrophil and lymphocyte percentages [29, 30]. Viral infections, mostly CMV and human herpesvirus 7, have been identified in patients with acute exacerbation of IPF and non-IPF ILDs; however, virus infection was not found to be an independent predictor of 60 day survival in a simple logistic regression analysis [5]. Moua et al. suggested that the following factors were predictive of increased in-hospital mortality: male sex, acute exacerbation, longer duration of hospitalization, ICU admission, mechanical ventilation, use of bronchoscopy in an ICU setting and the intravenous
administration of high-dose steroids [1]. In our study, we did not find a close relationship between high-dose hormone administration and poor prognosis, but we found that lymphopenia was directly related to poor prognosis, similar to the finding of other viral infection studies [31]. We also found that non-IFV virus infection was closely related to poor prognosis. Therefore, we must pay attention to the higher mortality rates due to viral infections such as CMV, HRV, PIV and mixed virus infections.

This study had several limitations. First, it utilized a retrospective observational design. Second, lung-function tests were not performed, as many of the patients could not undergo these tests. Third, we did not re-evaluate patient prognosis at a 1-year follow-up; therefore, it was impossible to suggest that viral infection was associated with poor long-term prognosis of ILD.

CONCLUSIONS

Patients with ILD who subsequently developed viral infection had high rates of morbidity and mortality, which were associated with increased age (>60 years), respiratory failure, mechanical ventilation, persistent lymphocytopenia and non-IFV virus infection. These risk factors should be carefully considered when determining treatment strategies for this patient population.

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Author contributions
Study design: L.L. and G.Y. Data collection: L.L., C.W., L.S. and X.Z. Statistical analysis: L.L. Writing: L.L. and G.Y. All authors take full responsibility for the study design, data analysis and interpretation, and preparation of the manuscript. All authors approved the final draft of the manuscript.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
The Ethics Committee of China-Japan Friendship Hospital (no. 2015-86) approved this retrospective study. Consent for procedures was obtained from all patients. The need for written informed consent for participation in this study was waived by the Ethics Committee of China-Japan Friendship Hospital. There was a centralized collaboration between all participating hospitals, which included anonymized data submission and collection.

References
1. Saraya T, Kimura H, Kurai D, Tamura M, Ogawa Y, et al. Clinical significance of respiratory virus detection in patients with acute exacerbation of interstitial lung diseases. Respir Med 2018;136:88–92.
2. Huie TJ, Olson AL, Cosgrove GP, Janssen WJ, Lara AR, et al. A detailed evaluation of acute respiratory decline in patients with fibrotic lung disease: aetiology and outcomes. Respirology 2010;15:909–917.
3. Ryerson CJ, Collard HR. Acute exacerbations complicating interstitial lung disease. Curr Opin Pulm Med 2014;20:436–441.
4. Agarwal R, Jindal SK. Acute exacerbation of idiopathic pulmonary fibrosis: a systematic review. Eur J Intern Med 2008;19:227–235.
5. Moua T, Westerly BD, Dulohery MM, Daniels CE, Ryu JH, et al. Patients with fibrotic interstitial lung disease hospitalized for acute respiratory worsening: a large cohort analysis. Chest 2016;149:1205–1214.
6. Weng D, Chen XQ, Qiu H, Zhang Y, Li QH, et al. The role of infection in acute exacerbation of idiopathic pulmonary fibrosis. Mediators Inflamm 2019;2019:5160694.
7. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, et al. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. Am J Multicenter Study. Am J Respir Crit Care Med 2020;202:1656–1665.
8. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176:636–643.
9. Prasad JD, Mahar A, Bleasel J, Ellis SJ, Chambers DC, et al. The interstitial lung disease multidisciplinary meeting: a position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia. Respirology 2017;22:1459–1472.
10. Marti C, Garin N, Grosseur O, Poncet A, Combescure C, et al. Prediction of severe community-acquired pneumonia: a systematic review and meta-analysis. Crit Care 2012;16:R141.
11. Kwok CS, Loke YK, Woo K, Myint PK. Risk prediction models for mortality in community-acquired pneumonia: a systematic review. BioMed Res Int 2013;2013:304136.
12. Schauwvlieghe A, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6:782–792.
13. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63:e1–e60.
14. Guo F, Chen Y, Yang SL, Xia H, Li XW, et al. Pneumocystis pneumonia in HIV-infected and immunocompromised non-HIV-infected patients: A retrospective study of two centers in China. PLOS ONE 2014;9:e101943.
15. Vannella KM, Moore BB. Viruses as co-factors for the initiation or exacerbation of lung fibrosis. Fibrogenesis Tissue Repair 2008;1:2.
16. Daniels CE, Yi ES, Ryu JH. Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. Eur Respir J 2008;32:170–174.
17. Oda K, Ishimoto H, Yamada S, Kushima H, Ishii H, et al. Autopsy analyses in acute exacerbation of idiopathic pulmonary fibrosis. Respir Res 2014;15:109.
18. Wootton SC, Kim DS, Kondoh Y, Chen E, Lee JS, et al. Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183:1698–1702.
19. Keyvani H, Moghhoefei M, Bokharaei-Salim F, Mostafaei S, Javad Mousavi SA, et al. Prevalence of respiratory viruses in Iranian patients with idiopathic pulmonary fibrosis. J Med Microbiol 2017;66:1602–1606.
20. Zhou F, Wang Y, Liu Y, Liu X, Gu L, et al. Disease severity and clinical outcomes of community acquired pneumonia caused by non-influenza respiratory viruses in adults: a multicenter prospective registry study from CAP-China Network. Eur Respir J 2019;54:1802406.
21. Gilca R, Amini R, Douville-Fradet M, Charest H, Dubouge J, et al. Other respiratory viruses are important contributors to adult respiratory hospitalizations and mortality even during peak weeks of the influenza season. Open Forum Infect Dis 2014;1:ofu086.
22. Bjarnason A, Westin J, Lindh M, Andersson LM, Kristinsson KG, et al. Incidence, etiology, and outcomes of community-acquired pneumonia: a population-based study. Open Forum Infect Dis 2018;5:ofi010.
23. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, et al. Rates of hospitalizations for respiratory syncytial virus, human Metapneumovirus, and influenza virus in older adults. J Infect Dis 2012;206:56–62.
24. Widmer K, Griffin MR, Zhu Y, Williams JV, Talbot HK. Respiratory syncytial virus- and human metapneumovirus-associated emergency department and hospital burden in adults. *Influenza Other Respir Viruses* 2014;8:347–352.

25. Ackerson B, Tseng HF, LS S, Solano Z, Slezak J, et al. Severe morbidity and mortality associated with respiratory syncytial virus versus influenza infection in hospitalized older adults. *Clin Infect Dis* 2019;69:197–203.

26. van Asten L, van den Wijngaard C, van Pelt W, van de Kassteele J, Meijer A, et al. Mortality attributable to 9 common infections: significant effect of influenza A, respiratory syncytial virus, influenza B, Norovirus, and parainfluenza in elderly persons. *J Infect Dis* 2012;206:628–639.

27. Ngai JJ, Chong KL, Oli Mohamed S. Cytomegalovirus retinitis in primary immune deficiency disease. *Case Rep Ophthalmol Med* 2018;2018:8125806.

28. Dioverti MV, Razonable RR. Cytomegalovirus. *Microbiol Spectr* 2016;4.

29. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016;194:265–275.

30. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011;37:356–363.

31. Guo L, Wei D, Zhang X, Wu Y, Li Q, et al. Clinical features predicting mortality risk in patients with viral pneumonia: The MuLBSTA Score. *Front Microbiol* 2019;10:2752.

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