Characteristics of Viral Pneumonia in Immunocompromised and Immunocompetent Patients: A Retrospective Cohort Study

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Abstract

**Background:** Viral pneumonia has a high incidence and mortality and often presents with bacterial or fungal infections. However, only a few studies have examined viral infection in immunocompromised patients. In this study, we compared the clinical and etiologic characteristics of viral pneumonia in immunocompetent and immunocompromised patients.

**Methods:** We retrospectively recruited patients hospitalized with viral pneumonia from 6 academic hospitals in China between August 2016 and December 2019. We measured the prevalence of comorbidities, coinfections, nosocomial infections, and in-hospital mortalities.

**Results:** Of the 806 patients, 370 were immunocompromised and 436 were immunocompetent. Cytomegalovirus (CMV) was most common (58.1%) in immunocompromised patients, followed by influenza A virus (IFV-A, 21.4%), respiratory syncytial virus (RSV, 19.2%), and parainfluenza virus (PIV, 7.3%). IFV-A (46.1%) was the most common in immunocompetent patients, followed by RSV (20.6%), adenovirus (AdV, 10.6%), PIV (10.1%), and rhinovirus (HRV, 9.2%). Disease severity and in-hospital mortality of immunocompromised patients were higher than those of immunocompetent patients. Pneumocystis jirovecii pneumonia (PCP) (22.4%), Aspergillus (14.1%) and bacteria (13.8%) were most frequent coinfections in immunocompromised patients as to Aspergillus (10.8%), bacteria (7.1%) and mycoplasma (5.3%) in immunocompetent patients. Viral shedding was significantly longer in immunocompromised patients.

**Conclusions:** Immunocompromised patients have a high frequency of coinfections, and persistent viral shedding makes them contagious for prolonged periods. Most deaths were reported among those with CMV and two-or-more viruses, and we found the same disease severity and prognosis for IFV and non-IFV.

Background

Among transplant recipients and patients with hematological malignancy, viral pneumonia often leads to severe respiratory disease and death [1]. Viral lower respiratory tract infections in immunocompromised patients have generally been ascribed to herpes virus (HSV) and cytomegalovirus (CMV) [2]. In the recent years, influenza virus (IFV), parainfluenza virus (PIV), respiratory syncytial virus (RSV), and rhinovirus (HRV) have also been recognized as causes of serious infections, especially in patients undergoing treatment for hematologic malignancies and hematopoietic stem cell transplantation. There is a higher tendency to develop severe pneumonia and mortality rate as high as 25-70% [3-7]. These patients might experience prolonged viral shedding that potentially result in longer duration of infection, higher nosocomial transmission rate, and increase in mortality rate than immunocompetent hosts [8-9]. There are limited studies on viral pneumonia in immunocompromised hosts, and a lack of understanding of the severity of common respiratory viruses and CMV in this population.

The objective of this study was to examine the clinical and etiologic characteristics, and to identify the most common types of virus of viral pneumonia in immunocompromised patients and aimed to identify

Methods

**Study design and participants**

We retrospectively recruited patients admitted with community-acquired pneumonia (CAP) hospitalized between August 2016 and December 2019 at six secondary and tertiary academic hospitals in China. The diagnosis of CAP was based on the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) guidelines [10]. Immunocompromised patients were selected if they met any of the following inclusion criteria: (1) solid-organ, stem-cell, or bone-marrow transplant recipients; (2) undergoing chemotherapy for any hematological disease (including acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, myeloma, or lymphoma) or presence of a solid tumor within 6 months of admission or neutropenia (neutrophil count < 500 cells/mm$^3$); (3) chest radiation therapy within 3 months of admission; (4) autoimmune disease (including but not limited to systemic lupus erythematosus, rheumatoid arthritis, polymyalgia rheumatica, and interstitial lung disease) and receiving immunosuppressive therapy (including chronic glucocorticoid treatment: oral prednisone ≥ 10 mg/d or the equivalent for more than 3 weeks; methotrexate > 12.5 mg/week, cyclosporine, azathioprine, or biological modifiers such as etanercept or infliximab within 3 months of admission; and (5) splenectomy or cirrhosis [11-13]. Patients were excluded if (1) aged < 14 years, (2) experienced pneumonia onset ≥ 48 hours after admission, or (3) positive for human immunodeficiency virus.
Data collection

The following data were collected on patient and disease characteristics, initial oxygenation strategy, laboratory and microbiological data (blood, nasopharyngeal swabs, sputum, and/or bronchoalveolar lavage samples; bacterial or fungal cultures; viral nucleic acid detection; and antibiotic susceptibility patterns), associated organ dysfunction, and patient outcomes at hospital discharge.

Microbiological methods

Microbiological samplings were performed, bronchoalveolar lavage (BAL) samples were obtained according to clinical indication or judgement of the attending physician. Sputum, BAL samples or nasopharyngeal swabs were performed for atypical pathogen and viral PCR amplification tests. Respiratory viruses including CMV, RSV, IFV types A and B, PIV, HRV, human metapneumovirus (HMPV), or adenovirus (Adv) and Mycoplasma pneumoniae, Chlamydia pneumoniae, L. pneumophila, Pneumocystis jirovecii (PCP) were detected in nasopharyngeal swab, sputum, endotracheal aspirate (ETA), or BAL fluid using reverse-transcription real time polymerase chain reaction (RT-PCR) (Shanghai Zhijiang Biological Technology, China). Sputum, ETA, BAL samples were evaluated for bacteria cultures and fungal cultures; The Platelia Aspergillus test was used for galactomannan detection (Bio-Rad Laboratories, Marnes-la-Coquette, France).

Pathogen-specific diagnostic criteria

For diagnosing pneumonia caused by Aspergillus, one or more of the following criteria were required: (1) histopathologic or direct microscopic evidence of dichotomous septate hyphae with a positive culture for Aspergillus from tissue, (2) a positive Aspergillus culture from BAL fluid, (3) a galactomannan optical index in BAL fluid ≥ 1, (4) a galactomannan optical index in serum ≥ 0.5; (5) Aspergillus species identified by culture characteristics and microscopically [16,17].

The diagnosis of Pneumocystis jirovecii pneumonia (PCP) required one of the following: (1) high-resolution computed tomography imaging showing diffuse ground glass opacity with patchy distribution; (2) mycological criteria: microscopic examination of the respiratory sample revealing the presence of Pneumocystis cystic or trophic forms; or (3) a positive PCR test for Pneumocystis DNA [18].

Coinfection was considered if bacteria or fungi were isolated from lower respiratory tract specimens (qualified sputum, endotracheal aspirate, and BAL) and/or it was indicated by blood samples within 48 h of hospitalization. Nosocomial infection was diagnosed when patients showed clinical signs or symptoms of pneumonia or bacteremia and had a positive culture of a new pathogen obtained from lower respiratory tract specimens and/or blood samples taken ≥ 48 h after admission.

Statistical analysis

The demographics, clinical characteristics, and pathogen testing results were expressed as mean (± standard deviation), median (interquartile range), or numbers (percentage). Group comparisons were conducted using the Student’s t-test or Wilcoxon rank-sum test for continuous variables with and without normal distributions, respectively. Categorical variables of the two groups were compared using the c² test.

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

Patient and public involvement

No patient or the public were involved in the development of the research question, study design, recruitment, and the conduct of the study.

Results

A total of 860 adult patients with positive respiratory viral nucleic acid test were selected. After excluding patients with upper respiratory tract infection (N = 24) and those who failed to meet the diagnostic criteria for pneumonia (N = 30), 806 patients with viral pneumonia were included in the final analysis. These included 370 immunocompromised and 436 immunocompetent patients. Approximately 34.3%
of the immunocompromised patients were female with a median age of 60 years. The main presenting symptoms were fever (74.6%), cough (92.4%), and dyspnea (66.2%). The most common underlying immune-related diseases were connective tissue disease (36.2%), interstitial lung disease (44.6%), solid-organ transplantation (16.2%), and nephrotic syndrome or chronic glomerulonephritis (12.4%). D-dimer levels, Pneumonia severity index (PSI) scores, rates of noninvasive mechanical ventilation, septic shock, and in-hospital mortality were higher in the immunocompromised group (P < 0.05) (Table 1).
### Table 1
Clinical characteristics of viral pneumonia between immunocompetent and immunocompromised group

| Variables                              | Total, N = 806 | Immunocompromised group, n = 370 | Immunocompetent group, n = 436 |  Value |
|----------------------------------------|----------------|----------------------------------|---------------------------------|--------|
| Sex, female, n (%)                     | 290 (36.0)     | 127 (34.3)                       | 163 (37.4)                      | 0.367  |
| Age, median (IQR)                      | 62.0 (49.0–71.0)| 60.0 (49.0–68.0)                 | 63.0 (50.0–75.0)                 | 0.003  |
| Symptoms and signs, n (%)              |                |                                  |                                 |        |
| Fever                                  | 608 (75.4)     | 276 (74.6)                       | 332 (76.1)                      | 0.610  |
| Cough                                  | 764 (94.8)     | 342 (92.4)                       | 422 (96.8)                      | 0.006  |
| Expectoration                          | 732 (70.8)     | 322 (87.0)                       | 410 (94.0)                      | 0.001  |
| Dyspnea                                | 542 (67.2)     | 245 (66.2)                       | 297 (68.1)                      | 0.566  |
| White blood cell, ×10^9/L (IQR)        | 7.85 (5.62–11.34)| 8.20 (5.73–11.71)               | 7.55 (5.43–10.91)               | 0.086  |
| Neutrophils, ×10^9/L (IQR)             | 6.17 (3.82–9.22)| 6.73 (4.31–9.80)                | 5.52 (3.51–8.95)                | 0.014  |
| Lymphocyte, ×10^9/L (IQR)              | 0.95 (0.56–1.52)| 0.84 (0.45–1.40)                | 1.03 (0.61–1.58)                | 0.001  |
| Persistent lymphocytopenia             | 319 (42.7)     | 177 (47.8)                       | 142 (32.6)                      | <0.001 |
| Mean hemoglobin ± SD, g/L              | 117.8 ± 24.5   | 110.6 ± 23.6                     | 123.9 ± 23.6                    | <0.001 |
| Mean albumin ± SD, g/L                 | 34.4 ± 6.6     | 33.5 ± 6.6                       | 35.2 ± 6.5                      | <0.001 |
| Lactate dehydrogenase, U/L             | 302 (217–501)  | 357 (245–555)                    | 263 (199–454)                   | <0.001 |
| Blood urea nitrogen, mmol/L            | 5.95 (4.18–9.61)| 6.69 (4.61–11.62)               | 5.39 (3.90–7.89)                | <0.001 |
| D-Dimer, mmol/L                        | 1.61 (0.69–4.32)| 2.06 (0.84–9.42)                | 1.37 (0.58–3.10)                | <0.001 |
| Procalcitonin, ng/ml                   | 0.31 (0.17–0.82)| 0.32 (0.16–0.72)                | 0.31 (0.18–0.94)                | 0.372  |
| Oxygenation index                      | 203 (118–289)  | 186 (113–289)                    | 209 (126–292)                   | 0.401  |
| Severe pneumonia index score           | 78 (59–103)    | 83 (62–107)                      | 75 (56–99)                      | 0.001  |
| CURB65 score > 1                       | 261 (32.4)     | 117 (31.6)                       | 144 (33.0)                      | 0.671  |
| Underlying Diseases, n (%)             |                |                                  |                                 |        |
| Without underlying disease             | 106 (13.2)     | 0 (0)                            | 106 (24.3)                      | <0.001 |
| Diabetes mellitus                      | 194 (24.1)     | 103 (27.8)                       | 91 (20.9)                       | 0.021  |
| Tumor                                  | 62 (7.7)       | 41 (11.1)                        | 21 (4.8)                        | 0.001  |
| Connective tissue disease*             | 140 (17.4)     | 134 (36.2)                       | 6 (1.4)                         | <0.001 |

*Connective tissue disorders: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjogren's syndrome, etc.
| Variables | Total, N = 806 | Immunocompromised group, n = 370 | Immunocompetent group, n = 436 | p-Value |
|-----------|---------------|----------------------------------|---------------------------------|---------|
| Interstitial lung disease | 210 (26.1) | 165 (44.6) | 45 (10.3) | < 0.001 |
| Bronchiectasis | 28 (3.5) | 6 (1.6) | 22 (5.0) | 0.008 |
| Bronchial asthma | 17 (2.1) | 6 (1.6) | 11 (2.5) | 0.375 |
| Chronic obstructive pulmonary disease | 85 (10.5) | 24 (6.5) | 61 (14.0) | 0.001 |
| Cirrhosis | 5 (0.6) | 5 (1.4) | 0 (0) | 0.015 |
| Leukemia | 7 (0.9) | 79 (1.9) | 0 (0) | 0.004 |
| Lymphoma | 17 (2.1) | 16 (4.3) | 1 (0.2) | < 0.001 |
| Nephrotic syndrome or chronic glomerulonephritis | 50 (6.2) | 46 (12.4) | 4 (0.9) | < 0.001 |
| Chronic renal failure | 45 (5.6) | 29 (7.8) | 16 (3.7) | 0.003 |
| After bone marrow or hematopoietic stem cell transplantation | 5 (0.6) | 5 (1.4) | 0 (0) | 0.015 |
| Solid organ transplant | 60 (7.4) | 60 (16.2) | 0 (0) | < 0.001 |
| Current smoker or ex-smoker | 287 (35.6) | 128 (34.6) | 159 (36.5) | 0.599 |
| Bronchoalveolar lavage, n (%) | 609 (75.6) | 271 (73.2) | 338 (77.5) | 0.159 |
| Treatment, before admission, n (%) | | | | |
| Antibiotics | 665 (82.5) | 280 (75.7) | 385 (88.3) | < 0.001 |
| Antiviral drugs | 164 (20.3) | 83 (22.4) | 81 (18.6) | 0.176 |
| Treatment, during hospitalization, n (%) | | | | |
| Anti-Pseudomonas aeruginosa drugs | 627 (77.8) | 295 (79.7) | 332 (76.1) | 0.223 |
| Voriconazole or caspofungin | 288 (35.7) | 181 (48.9) | 107 (24.5) | < 0.001 |
| Ganciclovir | 254 (31.5) | 221 (59.7) | 33 (7.6) | < 0.001 |
| Trimethoprim | 270 (33.5) | 193 (52.2) | 14 (3.2) | < 0.001 |
| Complications, n (%) | | | | |
| Noninvasive ventilation | 146 (18.1) | 90 (24.3) | 56 (12.8) | < 0.001 |
| Invasive mechanical ventilation | 234 (29.0) | 98 (26.5) | 136 (31.2) | 0.183 |
| Mechanical ventilation | 310 (38.5) | 141 (38.1) | 169 (38.8) | 0.982 |
| Respiratory failure during admission | 397 (49.3) | 186 (50.3) | 211 (48.4) | 0.379 |
| ICU admission | 349 (43.3) | 156 (42.2) | 193 (44.3) | 0.532 |
| Septic shock during hospitalization | 170 (21.1) | 91 (24.6) | 79 (18.1) | 0.025 |
| Extracorporeal membrane oxygenation | 58 (7.2) | 24 (6.5) | 34 (7.8) | 0.922 |

*Connective tissue disorders: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjogren's syndrome, etc.*
CMV was most common (58.1%) in the immunocompromised group, followed by IFV-A (21.4%), RSV (19.2%), and PIV (7.3%). IFV-A (46.1%) was most common in the immunocompetent group, followed by RSV (20.6%), AdV (10.6%), PIV (10.1%), and HRV (9.2%). More cases of IFV-A, HRV, and AdV were identified in the immunocompetent group ($P<0.05$). For IFV-B and RSV, there were no differences between the two groups ($P>0.05$). Regarding coinfections in immunocompromised patients, PCP (22.4%), Aspergillus (14.1%) and bacteria (13.8%) were most frequent, while *Klebsiella pneumoniae* (4.1%), *Pseudomonas aeruginosa* (3.0%), and *Staphylococcus aureus* (3.0%) were the most common bacteria. As for the immunocompetent group, Aspergillus (10.8%), bacteria (7.1%), and mycoplasma (5.3%) were the main pathogens, while *S. aureus* (2.5%), *K. pneumoniae* (2.1%), and *S. pneumoniae* (1.1%) were the main bacteria. Among secondary nosocomial bacterial infections, *Acinetobacter baumannii*, *P. aeruginosa*, and *K. pneumoniae* were most common (Table 2). The CMV infection group had more patients with nephrotic syndrome, higher rate of PCP infection and ground glass shadows on computed tomography (CT) scans ($P<0.05$). In non-IFV and IFV groups, there were fewer patients required noninvasive ventilator use and ICU treatment, lower in-hospital mortality than CMV and more than two virus group. (Table 3).
Table 2

| Variables, n (%) | Immunocompromised group, n = 370 | Immunocompetent group, n = 436 | P-Value |
|------------------|---------------------------------|---------------------------------|---------|
| One virus        | 305 (82.2)                      | 396 (90.8)                      | < 0.001 |
| Two or more viruses | 65 (17.6)                      | 40 (9.2)                        | < 0.001 |
| Cytomegalovirus  | 215 (58.1)                      | 22 (5.0)                        | < 0.001 |
| Influenza A virus | 79 (21.4)                       | 201 (46.1)                      | 0.031   |
| Influenza B virus | 23 (6.2)                        | 30 (6.9)                        | 0.704   |
| Rhinovirus       | 8 (2.2)                         | 40 (9.2)                        | < 0.001 |
| Respiratory syncytial virus | 71 (19.2) | 90 (20.6) | 0.607   |
| Adenovirus       | 14 (3.8)                        | 46 (10.6)                       | < 0.001 |
| Parainfluenza virus | 27 (7.3)                       | 44 (10.1)                       | 0.163   |
| Human metapneumovirus | 1 (0.3)                       | 3 (0.7)                         | 0.400   |
| HSV-1            | 3 (0.8)                         | 0 (0)                           | 0.060   |
| Pathogenic types of coinfections | 204 (55.1) | 101 (23.2) | < 0.001 |
| Bacteria         | 51 (13.8)                       | 31 (7.1)                        | 0.002   |
| Streptococcus pneumoniae | 1 (0.3)                       | 5 (1.1)                         | 0.149   |
| Streptococcus constellatus | 1 (0.3)                       | 0 (0)                           | 0.277   |
| Haemophilus influenzae | 1 (0.3)                       | 0 (0)                           | 0.277   |
| Staphylococcus aureus | 11 (3.0)                       | 11 (2.5)                        | 0.696   |
| Escherichia coli | 3 (0.8)                         | 1 (0.2)                         | 0.242   |
| Enterobacter aerogenes | 0 (0)                         | 1 (0.2)                         | 0.357   |
| Enterobacter cloacae | 2 (0.5)                        | 0 (0)                           | 0.470   |
| Klebsiella pneumoniae | 15 (4.1)                      | 9 (2.1)                         | 0.098   |
| Pseudomonas      | 11 (3.0)                        | 4 (0.9)                         | 0.031   |
| Proteus mirabilis | 2 (0.5)                        | 0 (0)                           | 0.470   |
| Acinetobacter    | 2 (0.5)                         | 0 (0)                           | 0.470   |
| Nocardia         | 2 (0.5)                         | 0 (0)                           | 0.470   |
| Atypical         | 11 (3.0)                        | 23 (5.3)                        | 0.105   |
| Mycoplasma pneumoniae | 6 (1.6)                       | 23 (5.3)                        | 0.006   |
| Legionella       | 5 (1.4)                         | 0 (0)                           | 0.015   |
| Pneumocystis     | 83 (22.4)                       | 0 (0)                           | < 0.001 |
| Aspergillus      | 52 (14.1)                       | 47 (10.8)                       | 0.158   |
| Mycobacterium tuberculosis | 6 (1.6)                       | 0 (0)                           | 0.008   |
| Non-tuberculosis mycobacteria | 1 (0.3)                       | 0 (0)                           | 0.277   |
| Pathogens in nosocomial infection | 134 (36.2) | 168 (36.7) | 0.498   |

HSV-1: herpes simplex virus type 1;
| Variables, n (%)                        | Immunocompromised group, n = 370 | Immunocompetent group, n = 436 | P-Value |
|----------------------------------------|----------------------------------|-------------------------------|---------|
| *Acinetobacter*                        | 31(8.4)                          | 52(11.9)                      | 0.099   |
| *Pseudomonas*                          | 32(8.6)                          | 41(9.4)                       | 0.710   |
| *Klebsiella pneumoniae*                | 14(3.8)                          | 17(3.9)                       | 0.932   |
| *Burkholderia*                         | 11(3.0)                          | 17(3.9)                       | 0.474   |
| *Enterococcus*                         | 6(1.6)                           | 2(0.5)                        | 0.097   |
| *Enterobacter cloacae*                 | 3(0.8)                           | 0(0)                          | 0.060   |
| *Escherichia coli*                     | 4(1.1)                           | 1(0.2)                        | 0.125   |
| *Proteus mirabilis*                    | 0(0)                             | 2(0.5)                        | 0.192   |
| *Stenotrophomonas maltophilia*         | 4(1.1)                           | 11(2.5)                       | 0.131   |
| *Corynebacterium striatum*             | 6(1.6)                           | 11(2.5)                       | 0.375   |
| *Staphylococcus aureus*                | 4(1.1)                           | 0(0)                          | 0.030   |
| *Rolstonia mannitolytica*              | 1(0.3)                           | 5(1.1)                        | 0.149   |
| *Other bacteria*                       | 5(1.4)                           | 3(0.7)                        | 0.344   |
| *Aspergillus*                          | 12(3.2)                          | 6(1.4)                        | 0.074   |
| *Trichosporon asahii*                  | 1(0.3)                           | 0(0)                          | 0.277   |
| Only one virus                         | 123(33.2)                        | 259(59.4)                     | <0.001  |
| >one organism                          | 247(66.8)                        | 177(40.6)                     | <0.001  |

HSV-1: herpes simplex virus type 1;
### Table 3
Comparative analysis of different viral pneumonia in immunocompromised patients

| Variables                             | CMV N = 162 | IFV N = 65 | Non-IFV N = 79 | ≥two viruses N = 64 | P-Value |
|---------------------------------------|-------------|------------|----------------|---------------------|---------|
| Female, n (%)                         | 59 (49.6)   | 18 (44.3)  | 30 (33.3)      | 20 (31.3)           | 0.509   |
| Age, median (IQR), years              | 60.0 (47.0, 68.3) | 63.0 (54.0, 69.0) | 59.0 (47.0, 68.0) | 60.0 (50.3, 67.0)   | 0.616   |
| Symptoms and signs, n (%)             |             |            |                |                     |         |
| Fever                                 | 138 (85.2)  | 48 (73.9)  | 48 (60.8)      | 42 (65.6)           | < 0.001 |
| Cough                                 | 138 (85.2)  | 63 (96.9)  | 79 (100.0)     | 62 (96.9)           | < 0.001 |
| Expectoration                         | 122 (75.3)  | 63 (96.9)  | 77 (97.5)      | 60 (93.8)           | < 0.001 |
| Dyspnea                               | 108 (66.7)  | 43 (66.2)  | 51 (64.6)      | 43 (93.8)           | 0.987   |
| Underlying Diseases, n (%)            |             |            |                |                     |         |
| Connective tissue disease             | 69 (42.6)   | 19 (29.2)  | 21 (26.6)      | 25 (39.1)           | 0.054   |
| Interstitial lung disease             | 61 (37.7)   | 31 (47.7)  | 43 (54.4)      | 30 (46.9)           | 0.084   |
| Diabetes mellitus                     | 43 (26.5)   | 18 (27.7)  | 22 (27.9)      | 20 (31.3)           | 0.917   |
| Tumor                                 | 19 (11.7)   | 7 (10.8)   | 11 (13.9)      | 4 (6.3)             | 0.524   |
| Bronchial asthma                      | 6 (3.7)     | 0 (0)      | 0 (0)          | 0 (0)               | 0.050   |
| COPD                                  | 13 (8.0)    | 6 (9.2)    | 3 (3.8)        | 2 (3.1)             | 0.311   |
| Leukemia                              | 2 (1.2)     | 0 (0)      | 4 (5.1)        | 1 (1.6)             | 0.114   |
| Lymphoma                              | 5 (3.1)     | 2 (3.1)    | 5 (6.3)        | 4 (6.3)             | 0.535   |
| After bone marrow or HSCT             | 2 (1.2)     | 0 (0)      | 1 (1.3)        | 2 (3.1)             | 0.490   |
| Nephrotic syndrome or chronic glomerulonephritis | 36 (22.2) | 2 (3.1)    | 4 (5.1)        | 4 (6.3)             | < 0.001 |
| Solid organ transplant                | 7 (4.3)     | 17 (26.2)  | 23 (29.1)      | 13 (20.3)           | < 0.001 |
| Cirrhosis                             | 0 (0)       | 3 (4.6)    | 1 (1.3)        | 1 (1.6)             | 0.059   |
| Laboratory examination                |             |            |                |                     |         |
| White blood cell, ×10⁹/L (IQR)        | 8.50 (5.70, 12.52) | 7.95 (5.08, 11.07) | 7.57 (5.69, 11.47) | 8.50 (6.35, 11.45) | 0.587   |
| Neutrophils, ×10⁹/L (IQR)             | 7.08 (4.52, 10.94) | 6.80 (3.80, 9.24) | 5.69 (3.51, 8.81) | 6.90 (4.86, 9.77) | 0.081   |
| Lymphocyte, ×10⁹/L (IQR)              | 0.73 (0.41, 1.40) | 0.81 (0.41, 1.31) | 1.11 (0.60, 1.83) | 0.80 (0.45, 1.32) | 0.048   |
| Persistent lymphocytopenia            | 84 (51.9)   | 32 (49.2)  | 28 (35.4)      | 33 (51.6)           | 0.097   |
| D-Dimer, mg/L                         | 1.78 (0.78, 3.08) | 1.52 (0.58, 3.09) | 1.12 (0.55, 2.68) | 1.34 (0.60, 2.57) | 0.288   |

IFV: influenza A virus, influenza B virus; Non-IFV virus: respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human rhinovirus (HRV), adenovirus (ADV), and herpes simplex virus type 1 (HSV-1); HSCT: hematopoietic stem cell transplantation. COPD: Chronic obstructive pulmonary disease. *: The in-hospital mortality between non-IFV/non-CMV and IFV patients was not statistically different (P = 0.324), but lower than that of CMV group and ≥ two virus groups.
| Variables                              | CMV N = 162 | IFV N = 65 | Non-IFV N = 79 | ≥ two viruses N = 64 | P-Value |
|----------------------------------------|-------------|------------|----------------|----------------------|---------|
| Lactate dehydrogenase, U/L             | 395.5(255.8, 590.0) | 325.0(228.0, 482.0) | 300.0(206.0, 430.0) | 386.0(276.0, 553.9) | 0.007   |
| Oxygenation index                      | 184.2(113.5, 286.0) | 285.7(154.1,375.9) | 244.1(96.3, 277.1) | 122.4(92.5, 272.8) | 0.067   |
| Severe pneumonia index score           | 75.0(58.0, 107.0)  | 79.0(60.0,99.0)   | 79.0(61.0, 104.0)  | 80.5(57.8, 105.3)   | 0.508   |
| CURB65 score > 1                       | 55(34.0)     | 25(38.5)    | 19(24.1)        | 18(28.1)            | 0.234   |

Imaging features, n (%), 24 missing

|                          |            |
|--------------------------|------------|
| Consolidation or mass    | 71(43.8)   |
|                          | 24(36.9)   |
|                          | 39(49.4)   |
|                          | 34(53.1)   |
| Ground-glass opacity     | 99(61.1)   |
|                          | 30(46.2)   |
|                          | 42(53.2)   |
|                          | 35(54.7)   |
| Viral-PCP co-infection   | 64(39.5)   |
|                          | 4(6.2)     |
|                          | 3(3.8)     |
|                          | 7(10.9)    |
| Viral-aspergillus co-infection | 16(9.9) |
|                          | 9(13.8)    |
|                          | 12(15.2)   |
|                          | 15(23.4)   |
| Viral-bacteria co-infection | 22(13.6) |
|                          | 7(10.8)    |
|                          | 10(12.7)   |
|                          | 9(14.1)    |
| Viral-atypical co-infection | 6(3.7) |
|                          | 1(1.5)     |
|                          | 3(3.80)    |
|                          | 1(1.6)     |
| Nosocomial bacterial infection | 36(22.2) |
|                          | 17(26.2)   |
|                          | 17(21.5)   |
|                          | 22(34.4)   |

Complications, n (%)

|                          |            |
|--------------------------|------------|
| Noninvasive ventilation  | 54(33.3)   |
|                          | 10(15.4)   |
|                          | 9(11.4)    |
|                          | 17(26.6)   |
| Invasive mechanical ventilation | 45(27.8) |
|                          | 20(30.8)   |
|                          | 16(20.3)   |
|                          | 19(29.7)   |
| Respiratory failure      | 91(56.2)   |
|                          | 33(50.8)   |
|                          | 26(32.9)   |
|                          | 36(56.3)   |
| ICU care                 | 89(54.9)   |
|                          | 22(33.8)   |
|                          | 19(24.1)   |
|                          | 26(40.6)   |
| Septic shock             | 40(24.7)   |
|                          | 17(26.2)   |
|                          | 14(17.7)   |
|                          | 20(31.3)   |
| Extracorporeal membrane oxygenation | 4(2.5) |
|                          | 7(10.8)    |
|                          | 7(8.9)     |
|                          | 6(9.4)     |
| In-hospital mortality    | 50(30.9)   |
|                          | 14(21.5)   |
|                          | 12(15.2)   |
|                          | 22(34.4)   |

P-values are for comparisons between CMV and IFV groups, except for CMV vs. Non-IFV and ≥ two virus groups.

IFV: influenza A virus, influenza B virus; Non-IFV virus: respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human rhinovirus (HRV), adenovirus (ADV), and herpes simplex virus type 1 (HSV-1); HSCT: hematopoietic stem cell transplantation. COPD: Chronic obstructive pulmonary disease. *: The in-hospital mortality between non-IFV/non-CMV and IFV patients was not statistically different (P = 0.324), but lower than that of CMV group and ≥ two virus groups.

Patients with nephrotic syndrome and chronic glomerulonephritis had a lower oxygenation index and lymphocyte count, higher PCP infection rate, more noninvasive ventilator use and need for ICU treatment, and the highest in-hospital mortality rate. The in-hospital mortality rate of patients with connective tissue disease was the second highest (30%), while that of solid-organ transplantation patients was the lowest (10%) (Table 4). Viral shedding was significantly longer in immunocompromised hosts than in immunocompetent hosts (Table 5).
Table 4
Clinical characteristics of pneumonia with immunocompromised patients in different underlying disease

| Variables                                    | Connective tissue disease, N = 134 | Solid organ transplant, N = 60 | Nephrotic syndrome or chronic glomerulonephritis, N = 46 | Hematopoiesis diseases* N = 22 | Idiopathic interstitial pneumonia, N = 51 | Radiotherapy and chemotherapy of malignant solid tumor, N = 17 | P value |
|----------------------------------------------|-----------------------------------|-------------------------------|--------------------------------------------------------|--------------------------------|------------------------------------------|-------------------------------------------------------------|---------|
| Sex, female, n (%)                           | 64(47.8)                          | 11(18.3)                      | 11(23.9)                                               | 7(31.8)                       | 16(31.4)                                 | 3(17.6)                                                   | < 0.001 |
| Age, median (IGR)                            | 62.0(45.0, 70.3)                  | 58.0(47.0, 63.0)              | 58.0(47.8, 65.3)                                       | 55.0(32.8, 69.5)              | 59.0(53.0, 69.0)                          | 64.0(57.0, 67.0)                                          | 0.043   |
| Laboratory examination                       |                                   |                               |                                                        |                                |                                          |                                                             |         |
| White blood cell, x10^9/L (IQR)              | 8.59 (6.30, 11.72)                | 6.79 (4.47, 9.81)             | 8.83 (6.44, 11.97)                                     | 5.58 (3.21, 9.85)             | 7.85 (5.73, 11.48)                         | 8.01 (4.21, 10.77)                                        | 0.005   |
| Neutrophils, x10^9/L (IQR)                   | 6.99 (5.05, 9.80)                 | 4.63 (3.11, 7.70)             | 8.20 (5.2, 10.9)                                       | 4.19 (1.89, 7.51)             | 6.45 (4.60, 9.58)                         | 6.73 (2.91, 8.30)                                         | 0.001   |
| Lymphocyte, x10^9/L (IQR)                    | 0.81 (0.44, 1.45)                 | 0.95 (0.36, 1.62)             | 0.62 (0.33, 0.96)                                      | 0.70 (0.22, 1.34)             | 1.09 (0.70, 1.83)                         | 0.80 (0.46, 1.21)                                         | 0.039   |
| Persistent lymphocytopenia                   | 64(47.8)                          | 25(43.3)                      | 28(60.9)                                               | 11(50.0)                      | 24(47.1)                                 | 9(52.9)                                                    | 0.528   |
| Oxygenation index                            | 212.4 (116.8, 291.8)              | 244.1 (142.4, 331.1)          | 122.0 (78.6, 206.2)                                    | 225.8 (116.1, 368.2)          | 209.2 (111.3, 328.5)                     | 327.4 (296.2, 413.6)                                      | 0.026   |
| Severe pneumonia index score                 | 76.0 (50.8, 103.0)                | 83.0 (64.3, 100.0)            | 89.5 (66.8, 119.0)                                     | 87.5 (59.3, 119.0)            | 79.0 (63.0, 91.0)                         | 107.0 (80.0, 125.0)                                       | 0.018   |
| CURB65 score > 1                             | 37 (27.6)                         | 17 (28.3)                     | 19 (41.3)                                              | 4 (18.2)                      | 15 (29.4)                                | 6 (35.3)                                                   | 0.421   |
| Imaging features, n (%)                      | 126(94.0)                         | 59 (98.3)                     | 37 (80.4)                                              | 18 (81.8)                     | 51 (100.0)                               | 15 (88.2)                                                  | -       |
| Consolidation or mass                        | 86 (64.2)                         | 26 (43.3)                     | 27 (58.7)                                              | 5 (22.7)                      | 38 (74.5)                                | 8 (47.1)                                                   | < 0.001 |
| Ground-glass opacity                         | 65 (48.5)                         | 22 (36.7)                     | 21 (45.7)                                              | 11 (50.0)                     | 18 (35.3)                                | 10 (58.8)                                                  | 0.049   |
| Viral-PCP co-infection                       | 30 (22.4)                         | 3 (5.0)                       | 24 (52.2)                                              | 3 (13.6)                      | 9 (17.6)                                 | 4 (23.5)                                                   | < 0.001 |
| Viral-aspergillus co-infection               | 13 (9.7)                          | 17 (28.3)                     | 5 (10.9)                                               | 1 (4.5)                       | 6 (11.8)                                 | 2 (11.8)                                                   | 0.010   |
| Viral-bacteria co-infection                  | 16 (11.9)                         | 12 (20.0)                     | 6 (13.0)                                               | 1 (4.5)                       | 2 (3.9)                                  | 3 (17.6)                                                   | 0.134   |
| Viral-atypical co-infection                  | 4 (3.0)                           | 2 (3.3)                       | 3 (6.5)                                                | 1 (4.5)                       | 0 (0)                                    | 0 (0)                                                      | 0.518   |
| Nosocomial bacterial infection               | 26 (19.4)                         | 25 (41.7)                     | 12 (26.1)                                              | 5 (22.7)                      | 11 (21.6)                                | 2 (11.8)                                                   | 0.021   |
| Complications, n (%)                         |                                   |                               |                                                        |                                |                                          |                                                             |         |
| NIV                                          | 41 (13.1)                         | 8 (13.3)                      | 17 (37.0)                                              | 4 (18.2)                      | 15 (29.4)                                | 2 (11.8)                                                   | 0.035   |

NIV = Noninvasive ventilation, IMV = Invasive mechanical ventilation, ECMO = Extracorporeal membrane oxygenation

*Hematopoiesis diseases: Leukemia, lymphoma, bone marrow or hematopoietic stem cell transplantation.
### Variables

| Variables | Connective tissue disease, N = 134 | Solid organ transplant, N = 60 | Nephrotic syndrome or chronic glomerulonephritis, N = 46 | Hematopoiesis diseases* | Idiopathic interstitial pneumonia, N = 51 | Radiotherapy and chemotherapy of malignant solid tumor, N = 17 | P value |
|-----------|-----------------------------------|-------------------------------|------------------------------------------------------|--------------------------|------------------------------------------|---------------------------------------------------------------|---------|
| IMV       | 41(30.6)                          | 9(15.0)                       | 12(26.1)                                             | 3(13.6)                  | 17(33.3)                                 | 1(0)                                                          | 0.033   |
| Respiratory failure | 78 (58.2)                  | 21 (35.0)                      | 24 (52.2)                                            | 6 (27.3)                 | 28 (54.9)                                | 6 (37.5)                                                     | 0.004   |
| ICU care   | 66 (49.3)                          | 10 (16.7)                      | 28 (60.9)                                            | 8 (36.4)                 | 25 (49.0)                                | 2 (12.5)                                                     | < 0.001 |
| Septic shock | 31 (23.1)                    | 12 (20.0)                      | 17 (37.0)                                            | 3 (13.6)                 | 11 (21.6)                                | 5 (25.0)                                                     | 0.256   |
| ECMO       | 8 (6.0)                            | 4 (6.7)                        | 3 (6.5)                                              | 1 (4.5)                  | 7 (13.7)                                 | 0 (0)                                                        | 0.297   |
| In-hospital mortality | 40 (30.0)                  | 6 (10.0)                       | 18 (39.1)                                            | 3 (13.6)                 | 13 (25.5)                                | 4 (25.0)                                                     | 0.011   |

NIV = Noninvasive ventilation, IMV = Invasive mechanical ventilation, ECMO = Extracorporeal membrane oxygenation

*Hematopoiesis diseases: Leukemia, lymphoma, bone marrow or hematopoietic stem cell transplantation.

### Table 5

| Variables | Viral shedding in immunocompromised group(d) | Viral shedding in immunocompetent group(d) | P value |
|-----------|---------------------------------------------|-------------------------------------------|---------|
| IFV       | 12.0(6.5, 26.5)                             | 8.5(5.0, 13.0)                            | 0.022   |
| RSV       | 14.0(6.0, 30.0)                             | 6.5(3.0, 14.0)                            | 0.024   |

### Discussion

This study was a large-scale, multi-center, retrospective study of the etiology and clinical risk factors for CAP in immunocompromised patients. The main findings were as follows: (1) The disease severity and in-hospital mortality rate of immunocompromised patients were higher than those of immunocompetent patients; (2) CMV was more common in the immunocompromised group, and IFV-A, HRV, and AdV were more common in the immunocompetent group; (3) Among the coinfections of immunocompromised patients, PCP was the main pathogen, followed by Aspergillus and bacteria, and in the immunocompetent group, Aspergillus was the most common pathogen, followed by bacteria and mycoplasma; (4) The in-hospital mortality rates of the non-IFV infection groups were lower than those of the CMV group and the two-or-more viruses group; (5) The in-hospital mortality rate of patients with nephrotic syndrome or chronic glomerulonephritis was the highest, while that of solid-organ transplantation patients was the lowest; (6) Whether IFV (H1N1) or RSV, the period of viral shedding was significantly longer in immunocompromised hosts than in immunocompetent hosts.

In recent years, several studies have focused on respiratory virus infection in patients after hematopoietic cell transplantation (HCT) [19–24]. Sachiko studied HRV in the lower respiratory tract of patients with HCT and found that 55% of patients had coinfections and that the 90-day mortality rate was 41% [19], which was similar to lower respiratory tract infection caused by RSV, PIV, or IFV [20–22]. Among immunocompromised patients with IFV pneumonia, nearly 60% had an associated infection with at least one other organism, and the mortality rate among these patients was between 15–30% [23]. The mortality rate among hematologic malignancy patients with RSV...
was approximately 18%, and in HCT recipients who developed RSV lower respiratory tract infections, it can be as high as 83%. [24]. Similarly, our study showed that the disease severity and in-hospital mortality (26.5% vs 18.8%) of immunocompromised patients were higher than those of immunocompetent patients.

CMV, especially with PCP coinfection, has a high mortality rate in immunocompromised patients [25, 26]. However, at present, there are few comparative studies examining CMV and other respiratory viruses. Our findings indicate that non-CMV viral infections may also have PCP coinfection albeit less frequent. Comparably [27–28], we found no difference in the rate of virus-aspergillus coinfections irrespective of the type of viral infection.

The disease severity, complications, and outcomes in immunocompetent patients with CAP were similar between IFV and non-IFV related respiratory diseases [29–31]. We found that the in-hospital mortality was significantly higher in immunocompromised patients with CMV or two-or-more viruses infections. This suggests that when viral infection is suspected in an immunocompromised host, healthcare providers should look for the presence of CMV and other viral etiology, as early diagnosis and treatment are essential to improve outcome. We also found the highest mortality rate in patients with nephrotic syndrome or chronic glomerulonephritis, which there was a higher rate of CMV and PCP infection. This indicates that routinely screening for PCP and CMV infections should be considered in this group.

It has been suggested that viral respiratory infections in immunocompromised patients involves persistent viral shedding, making them contagious for prolonged periods [32–34]. Memoli reported the viral shedding period of immunocompromised patients was longer than that of immunocompetent patients with IFV pneumonia (19.04 vs. 6.38 days, respectively; P < 0.05) [33]. Virus detection for more than 30 days was reported in 29% of infected patients with hematological disorders [32]. In this study, we demonstrated that both H1N1 and RSV infections have longer viral shedding period in immunocompromised hosts, which made it necessary to extend the duration of antiviral therapy.

There were several limitations to this study. First, it had a retrospective design and might not capture all patients. Second, not every patient with pneumonia underwent a full array of pathogen testing. As such, the pathogen identification and diagnosis could have been incomplete. Third, many patients had been administered antibiotics before. Despite these limitations, our results were consistent with the literature and provided a detail insight into the clinical characteristics, pathogenic characteristics, and outcomes of different viral infections in immunocompromised hosts.

**Conclusions**

Immunocompromised patients have high frequencies of coinfections, nosocomial infections, and mortality rate. A longer viral shedding duration may lead to prolonged period of infectivity.

**Abbreviations**

CAP: Community-acquired pneumonia; CMV: cytomegalovirus; Flu A: Influenza A virus; Flu B: Influenza B virus; PIV: Parainfluenza virus; RSV: Respiratory syncytial virus; AdV: Adenovirus; HRV: Rhinovirus; HMPV: Human metapneumovirus; HSV: herpes virus; PCP: Pneumocystis jirovecii pneumonia. ETA: endotracheal aspirate. BAL: bronchoalveolar lavage. PSI: Pneumonia severity index. HCT: hematopoietic cell transplantation. RT-PCR: reverse-transcription real time polymerase chain reaction.

**Declarations**

**Authors’ contributions:**

Study design: LL, BC. Data collection: LL, WC, LB, SL, JS, YR, JW, XZ, JL. Statistical analysis: LL. Writing: LL, SH.H, BC. All authors take full responsibility for the study design, data analysis and interpretation, and preparation of the manuscript. All authors approved the final draft manuscript.

**Ethics approval and Consent to Participate:**

The Ethics Committee of China-Japan Friendship Hospital (no. 2015-86) granted approval for this retrospective study and orchestrated centralized collaboration and approval of all participating institutions.
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The authors declare that they have no competing interests.

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References
1. Camps Serra M, Cervera C, Pumarola T, et al. Virological diagnosis in community-acquired pneumonia in immunocompromised patients. Eur Respir J 2008; 31(3): 618-24.
2. Barton TD, Blumberg EA. Viral pneumonias other than cytomegalovirus in transplant recipients. Clin Chest Med 2005; 26: 707–20.
3. Marcolini JA, Malik S, Suki D, et al. Respiratory disease due to parainfluenza virus in adult leukemia patients. Eur J Clin Microbiol Infect Dis 2003; 22(2): 79-84.
4. Ebbert JO, Limper AH. Respiratory syncytial virus pneumonitis in immunocompromised adults: clinical features and outcome. Respiration 2005; 72(3): 263-9.
5. Ljungman P. Prevention and treatment of viral infections in stem cell transplant recipients. Br J Haematol. 2002; 118(1): 44-57.
6. Vakil E, Sheshadri A, Faiz SA, et al. Risk factors for mortality after respiratory syncytial virus lower respiratory tract infection in adults with hematologic malignancies. Transpl Infect Dis 2018; 20(6): e12994.
7. McCann S, Byrne JL, Rovira M, et al. Infectious Diseases Working Party of the EBMT. Outbreaks of infectious diseases in stem cell transplant units: a silent cause of death for patients and transplant programmes. Bone Marrow Transplant 2004;33: 519-29.
8. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. Am J Med 1997;102(3A): 2-9.
9. Vigil KJ, Adachi JA, Chemaly RF. Viral Pneumonias in Immunocompromised Adult Hosts. J Intensive Care Med 2010;25(6): 307-26.
10. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2015;171(40):388-416.
11. Sousa D, Justo I, Dominguez A, et al. Community-acquired pneumonia in immunocompromised older patients: incidence, causative organisms and outcome. Clin Microbiol Infect 2013;19(2):187-92.
12. Camps Serra M, Cervera C, Pumarola T, et al. Virological diagnosis in community acquired pneumonia in immunocompromised patients. Eur Respir J 2008;31(3): 618-624.
13. Denise Rossato Silva et al. Clinical characteristics and evolution of non-HIV-infected immunocompromised patients with an in-hospital diagnosis of tuberculosis. J Bras Pneumol 2010;36(4): 475-84.
14. Marti C, Garin N, Grosgeurin O, et al. Prediction of severe community-acquired pneumonia: a systematic review and meta-analysis. Crit Care 2012; 16(4): R141.
15. Kwok C S, Loke Y K, Woo K, et al. Risk prediction models for mortality in community-acquired pneumonia: a systematic review. Biomed Res Int 2013;2013(10): 504136.
16. Schauwvlieghe A F A D, Rijnders B J A, Nele P, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6(10): 782-792.
17. Patterson TF, Thompson GR 3rd, Denning DW. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 63(4): e1-e60.

18. Guo F, Chen Y, Yang S L, 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(7): e101943.

19. Seo S, Waghmare A, Scott EM, et al. Human rhinovirus detection in the lower respiratory tract of hematopoietic cell transplant recipients: association with mortality. Haematologica 2017;102(6):1120-30.

20. Martino R, Ramila E, Rabella N, et al. Respiratory virus infections in adults with hematologic malignancies: a prospective study. Clin Infect Dis 2003;36(1):1-8.

21. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004;39(9):1300-6.

22. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine (Baltimore) 2006;85(5):278-87.

23. Schnell D, Mayaux J, de Bazelaire C, et al. Risk factors for pneumonia in immunocompromised patients with influenza. Respir Med. 2010;104(7):1050-6.

24. Khawaja F, Chemaly RF. Respiratory syncytial virus in hematopoietic cell transplant recipients and patients with hematologic malignancies. Haematologica. 2019;104(7):1322-31.

25. Yu Q, Jia P, Su L, et al. Outcomes and prognostic factors of non-HIV patients with pneumocystis jirovecii pneumonia and pulmonary CMV co-Infection: A Retrospective Cohort Study. BMC Infect Dis 2017; 17(1):392.

26. Korkmaz Ekren P, Töreyin ZN, et al. The association between cytomegalovirus co-infection with pneumocystis pneumonia and mortality in immunocompromised non-HIV patients. Clin Respir J. 2018;12(11):2590-7.

27. Schauwvlieghe AFAD, Rijnders BJA, Philips N, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018; 6(10):782-92.

28. Ustun C, Slabý J, Shanley RM, et al. Human parainfluenza virus infection after hematopoietic stem cell transplantation: risk factors, management, mortality, and changes over time. Biol Blood Marrow Transplant 2012;18(10):1580-8.

29. Zhou F, Wang Y, Liu Y, 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(2):1802406.

30. Skowronski DM, De Serres G. 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.

31. Bjarnason A, Westin J, Lindh M, et al. Incidence, Etiology, and Outcomes of Community-Acquired Pneumonia: A Population-Based Study. Open Forum Infect Dis 2018;5(2): ofy010.

32. Lehners N, Tabatabai J, Priftet C, et al. Long-Term Shedding of Influenza Virus, Parainfluenza Virus, Respiratory Syncytial Virus and Nosocomial Epidemiology in Patients with Hematological Disorders. PLoS One 2016;11(2): e0148258.

33. Memoli MJ, Athota R, Reed S, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. Clin Infect Dis 2014;58(2):214-24.

34. de Lima CR, Mirandolli TB, Carneiro LC, et al. Prolonged respiratory viral shedding in transplant patients. Transpl Infect Dis 2014;16(1):165-9.