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* , *Pneumocystisjirovecii* (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 *Pneumocystisjirovecii* 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 c^2 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%

(127/370) 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	*P*-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
Laboratory examination				
White blood cell, $\times 10^9$/L (IQR)	7.85 (5.62–11.34)	8.20 (5.73–11.71)	7.55 (5.43–10.91)	0.086
Neutrophils, $\times 10^9$/L (IQR)	6.17 (3.82–9.22)	6.73 (4.31–9.80)	5.52 (3.51–8.95)	0.014
Lymphocyte, $\times 10^9$/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.

Variables	Total, N = 806	Immunocompromised group, n = 370	Immunocompetent group, n = 436	*P*-Value
Hospital mortality	180 (22.3)	98 (26.5)	82 (18.8)	0.008

*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
The pathogen results of pneumonia between immunocompetent and immunocompromised group

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, $\times 10^9$/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, $\times 10^9$/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, $\times 10^9$/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 waw 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)	0.176
Ground-glass opacity	99(61.1)	30(46.2)	42(53.2)	35(54.7)	0.004
Viral-PCP co-infection	64(39.5)	4(6.2)	3(3.8)	7(10.9)	< 0.001
Viral-aspergillus co-infection	16(9.9)	9(13.8)	12(15.2)	15(23.4)	0.069
Viral-bacteria co-infection	22(13.6)	7(10.8)	10(12.7)	9(14.1)	0.939
Viral-atypical co-infection	6(3.7)	1(1.5)	3(3.80)	1(1.6)	0.708
Nosocomial bacterial infection	36(22.2)	17(26.2)	17(21.5)	22(34.4)	0.237
Complications, n (%)					
Noninvasive ventilation	54(33.3)	10(15.4)	9(11.4)	17(26.6)	0.001
Invasive mechanical ventilation	45(27.8)	20(30.8)	16(20.3)	19(29.7)	0.462
Respiratory failure	91(56.2)	33(50.8)	26(32.9)	36(56.3)	0.001
ICU care	89(54.9)	22(33.8)	19(24.1)	26(40.6)	< 0.001
Septic shock	40(24.7)	17(26.2)	14(17.7)	20(31.3)	0.305
Extracorporeal membrane oxygenation	4(2.5)	7(10.8)	7(8.9)	6(9.4)	0.268
In-hospital mortality	50(30.9)	14(21.5)	12(15.2)	22(34.4)	0.022*

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 waw 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, $\times 10^9$/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, $\times 10^9$/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, $\times 10^9$/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, 338.1)	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	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
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
viral shedding in of different groups

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 that 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 bothH1N1 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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