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Etiology and prognostic risk factors of mortality among pneumonia patients receiving long-term glucocorticoids: a retrospective cohort study

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ABSTRACT

Objective: Long-term use of high dose glucocorticoids may result in severe immunosuppression, a high risk of treatment-resistant pneumonia, and high mortality. In this study, we investigated the etiology and prognostic risk factors of mortality in hospitalized patients with pneumonia and receiving long-term glucocorticoid therapy.

Design: Retrospective cohort study

Setting: Six secondary and tertiary academic hospitals in China

Participants: Patients undergoing treatment with long-term glucocorticoids who were hospitalized with pneumonia between 1st January 2013 and 31st December 2019.

Primary and Secondary Outcomes: Prevalence of comorbidities, microbiology and antibiotic susceptibility patterns,30-day and 90-day mortality. Prognostic risk factors were analyzed.

Results: A total of 614 patients were included in this study, pathogens were identified in 66.9% of patients. Patients experienced significant morbidity, with 44.8% developing respiratory failure, 41.5% requiring intensive care unit (ICU) transfer, 24.4% requiring invasive mechanical ventilation, 25.1% requiring noninvasive mechanical ventilation, and 4.2% requiring extracorporeal membrane oxygenation. The 90-day mortality was 26.7%. Diagnosis of pneumonia occurred within 6 months of glucocorticoid initiation for 69.7% of patients with *Cytomegalovirus* (CMV) pneumonia and 78.4% of patients with *Pneumocystis jirovecii* pneumonia (PCP). Pathogens (PCP, CMV, and multidrug resistant bacteria) were identified more frequently in patients with persistent lymphocytopenia and high-dose glucocorticoid use group. For non-CMV virus pneumonia, the 90-day mortality was similar as patients with PCP and CMV (29.2% vs 37.2% vs 26.4%, P>0.05). Cox regression analysis indicated that septic shock, respiratory failure, high-dose steroids, and persistent lymphocytopenia were independent negative predictors of 30-

day mortality, interstitial lung disease, mechanical ventilation, septic shock, respiratory failure, and persistent lymphocytopenia were independent negative predictors of 90-day mortality.

Conclusions: Patients receiving long-term glucocorticoid therapy with pneumonia experience higher rates of infection with opportunistic pathogens, significant morbidity, high mortality, and specific risk factors. This information should be carefully considered when determining treatment for this patient population.

KEYWORDS: Pneumonia; Immunocompromised; Glucocorticoids; Prognosis.

ARTICLE SUMMARY

Strengths and limitations of this study

The strengths of this study include the large sample size, multicenter (six hospitals in China), and all patients were examined for sputum or BAL etiology.

A limitation of this study is including it had a retrospective design.

A limitation of this study is including not all patients with pneumonia underwent full pathogen testing.

A limitation of this study is that some pathogens were not identified until at least 48 hours after admission, increasing the possibility of nosocomial infections.

INTRODUCTION

Long-term use of glucocorticoids at high doses may result in severe immunosuppression and serious infections in patients. [1] Pulmonary infections occur most commonly, and remain one of the leading causes of death in immunocompromised patients.[1-4] Infections caused by opportunistic pulmonary pathogens, including *Cytomegalovirus* (CMV), *Pneumocystis*, and *Aspergillus*, have been reported in immunocompromised patients receiving glucocorticoids.[2-4] High mortality have also been

demonstrated in these immunocompromised patients. Agustí et al. reported a mortality of 45% for patients with pulmonary infections secondary to rheumatic immune disease treated with long-term glucocorticoids.[1] For those requiring mechanical ventilation, the mortality increased to 93%. Unfortunately, there are limited studies of the prognostic risk factors for patients receiving long-term glucocorticoid therapy who develop pneumonia (LTGP). Without adequate research, pneumonia in these immunocompromised individuals may be mismanaged. Prevalence may be underestimated, with high rates of treatment failure. Alternatively, disease burden may be overestimated, leading to an excessive use of broad-spectrum antibiotics. Given the significant morbidity and mortality associated with glucocorticoid-induced immunosuppression, our study aims to identify the clinical characteristics, pathogenic etiologies, and prognostic risk factors of pneumonia in this population.

METHODS

Study design and participants

We retrospectively recruited patients with pneumonia hospitalized between 1st January 2013 and 31st December 2017 at the departments of Pulmonary and Critical Care Medicine or Rheumatology at six tertiary or secondary academic hospitals in China. Diagnosis of pneumonia was based on the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) guidelines.[5-6] Pneumonia was defined as the presence of a new pulmonary infiltrate on chest radiograph during hospitalization and was combined with 1 or more of the following criteria: (1) new or increased cough with/without sputum production and/or purulent respiratory secretions; (2) fever or hypothermia; and (3) evidence of systemic inflammation (i.e., abnormal white blood cell count or increased levels of C-reactive or procalcitonin proteins). Patients with connective tissue disease, nephrotic syndrome or chronic glomerulonephritis, idiopathic interstitial pneumonia, bronchial asthma or chronic obstructive pulmonary disease, or other immunocompromised hosts were selected. All selected patients were required to meet the following inclusion criteria: (1) long-term glucocorticoid treatment with greater than 10 mg/day of prednisolone or equivalent for ≥ 21 days; [7-9] (2) diagnosed pneumonia at admission or during hospitalization; (3) at least 16-year-old. The exclusion criteria were as follows: (1) non-infectious pulmonary diseases including lung cancer, interstitial lung disease without infection, pulmonary

embolism, heart failure; (2) less than 16 years old; (3) Glucocorticoid treatment < 21 days, or less than 10 mg of prednisolone or equivalent per day.

Quality control of the study

Key investigators, including clinicians, statisticians, microbiologists and radiologists, worked together to draft the protocol and created a single formatted case report form (CRF) that was used by all centres. Before study initiation, all investigators from the 6 centres received training on the protocol, screening process, definition of under- lying diseases and formatted CRF. After data were collected, the CRF was reviewed by a trained researcher to ensure its completeness and data quality.

Data collection

The following data were collected from the medical records of patients during hospitalization: (1) demographics; (2) clinical symptoms; (3) initial vital signs and lung examination; (4) severity of the pneumonia [evaluated by intensive care unit (ICU) admission, use of invasive or noninvasive mechanical ventilation, Pneumonia Severity Index (PSI) score, and/or CURB-65 score);[10-12] (5) laboratory and microbiological data (blood, sputum, and/or bronchoalveolar lavage samples; bacterial or fungal cultures; viral nucleic acid detection; antibiotic susceptibility patterns); (6) treatment information including vasoactive, antimicrobial drug, glucocorticoids and other immunosuppressants use; (7) survival status during 30 days and 90 days after admission. High-dose steroid use was defined as > 30mg/day prednisolone or equivalent for greater than 21 days. Persistent lymphocytopenia was defined as peripheral blood lymphocyte count lower than 1×10^9/L for greater than 7 days.

Diagnostic procedures

After identification of pulmonary infiltrates on chest radiograph, bronchoalveolar lavage (BAL) or sputum samples were obtained by treating physicians. Microorganisms were identified and tested for drug sensitivity. Bronchoalveolar examination was performed according to general guidelines. Lidocaine spray was applied for local anesthesia, followed by the instillation of 60–120 mL of sterile saline solution 2–4 times into the distal bronchial tree, either at the site of radiographic abnormalities or in the middle lung lobes of patients with more diffuse radiographic abnormalities. Bronchoalveolar lavage specimens were aliquoted and immediately transported to the laboratories. The bacterial cultures were incubated at 35℃ in 5–10% CO_2 for 48 hours. If

Nocardia was suspected, the incubation time was prolonged. Fungal cultures were incubated at 27℃ for 5 days under ambient conditions. The species were identified using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (Brooks Instrument, Germany) or the BACTEC 9102 culture instrument (BD Biosciences, USA). Respiratory viral and atypical pathogens were detected by polymerase chain reaction (PCR) (Shanghai Zhijiang Biological Technology, China). The Platelia Aspergillus test was used for galactomannan detection in some patients (Bio-Rad Laboratories, Marnes-la-Coquette, France).

Pathogen-specific diagnostic information

We defined multidrug resistance (MDR) in specific organisms using the European Centre for Disease Prevention and Control (ECDC) and Centers for Disease Control and Prevention (CDC) criteria. We included the following species in this category: methicillin-resistant *Staphylococcus aureus* (MRSA); vancomycin-resistant *Enterococcus* (VRE); *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBL). *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and other nonfermenting Gram-negative bacilli were considered to be MDR pathogens if not susceptible to at least one agent in three or more antimicrobial categories. [13 14]

For the diagnosis of pneumonia caused by atypical pathogens, the demonstration of *Legionella* spp, *Mycoplasma pneumoniae*, or *Mycobacterium* DNA by PCR was considered positive. Diagnosis of viral infections depended on nucleic acid positivity in BAL fluid or sputum by PCR. For the diagnosis of pneumonia caused by *Aspergillus*, one or more of the following criteria were required for a positive diagnosis: (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, (3) a galactomannan optical index on BAL of ≥ 1, (4) a galactomannan optical index on serum of ≥ 0.5. (5) *Aspergillus* species identified by culture characteristics and microscopic morphology. [15 16]

Diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) required the following criteria: (1) high-resolution computed tomography (HRCT) imaging showing diffuse ground glass opacity (GGO) with patchy distribution; (2) mycological criteria: microscopic examination revealing the presence of *Pneumocystis* cystic or trophic forms in the respiratory samples or the respiratory sample testing positive for *Pneumocystis* DNA using PCR.[17]

Statistical analysis

The demographic and clinical characteristics and pathogen testing results were expressed as mean ± standard deviation, median (interquartile range), or numbers (proportion). Group comparisons was conducted using the t-test or Wilcoxon rank-sum test for continuous variables with and without normal distributions, respectively. Comparisons between groups for categorical variables were made using the χ^2 test. Histogram chart was used to draw glucocorticoid application time (time chart). Distributions for the duration of glucocorticoid use among different respiratory pathogens were also compared with χ^2 test. Cox regression models were used to analyze the association of septic shock, interstitial lung disease, invasive and noninvasive mechanical ventilation, PO_2/FIO_2, and persistent lymphocytopenia with 30-day and 90-day mortality. In the cox logistic analysis, age, gender, noninvasive mechanical ventilation, invasive mechanical ventilation, respiratory failure, septic shock, ICU admission, high-dose steroids, persistent lymphocytopenia, combined with interstitial lung disease, severe pneumonia index score, CURB65 score, combined with PCP, combined with CMV, combined with non-CMV viral infection were adjusted.

Statistical analyses were performed using SPSS, version 19.0 (SPSS, Inc., Chicago, Illinois). All tests were 2 sided, and *P* value < 0.05 was considered to be statistically significant.

Patient and Public Involvement

Not required.

RESULTS

Between 1st January 2013 and 31st December 2017, 1397patients with pneumonia had connective tissue disease, nephrotic syndrome, chronic nephritis, idiopathic pulmonary fibrosis, or other diseases with immunocompromised. After excluding patients not receiving long-term glucocorticoids (N=700) and patients without sputum or BALF for pathogen testing (N=83), 614 were included in the final analysis (Figure 1). The positive rate of pathogen testing was 66.94% (411/614). Of patients with LTGP, 52.0% were diagnosed with connective tissue disease and 13.8% were diagnosed with nephrotic syndrome or chronic glomerulonephritis. The average time of taking glucocorticoids was 4 (2,19) months. The proportions of adding other immunosuppressants and admission to ICU were 56.7% and 41.5%, respectively. For mechanical ventilation, 24.4% patients required invasive and 25.1% patients required noninvasive ventilation, respectively (Table 1). The 30-day and 90-day mortality after admission were 23.0% (141/614)

and 26.7% (164/614). Patients died 90 days after admission received more intense treatment both before admission and during hospitalization and have more complications than patients who were survival. For example, the percentages of patients with ICU admission and septic shock were higher in patients who died (Table 1).

MDR bacteria and CMV were more commonly identified as causative pathogens for hospital-acquired pneumonia (HAP) than community-acquired pneumonia (CAP) (P<0.05) (Table 2). Pneumonia pathogens were detected more commonly in the persistent lymphocytopenia group than non-lymphocytopenia group (P<0.05). The positive rates of PCP, influenza A virus, CMV and MDR bacteria were lower among the non-lymphocytopenia group (P<0.05). Patients with high-dose steroid use developed pneumonias more frequently from infections of *Klebsiella pneumoniae,* MDR bacteria, PCP, CMV, Aspergillus, and Mycobacterium tuberculosis than those in the low-dose steroid group (P<0.05). Pneumonia pathogens were more commonly detected in the non-survivor group, and pneumonias were more commonly caused by PCP, mixed viral, bacterial, fungal infections. Aspergillus; *Acinetobacter, Burkholderia*, MDR bacteria, and influenza A virus were also more common among the non-survival group (P<0.05). For non-CMV viral pneumonias, respiratory syncytial virus (RSV,43 strains) was detected most frequently, followed by influenza A virus (38 strains), human parainfluenza virus (HPIV,20 strains), influenza B virus (14 strains), human rhinovirus (HRV,8 strains), herpes simplex virus type 1(HSV-1,4 strains).and adenovirus(ADV,3 strains) (Table2). Although patients with non-CMV viral pneumonias had higher oxygenation indexes and lower respiratory failure rates, the 30-day and 90-day mortality was similar as patients with PCP and CMV(P> 0.05) (Table 3, Figure 2-3).

Time analysis showed that 60.2% of the patients developed pneumonia within 6 months of starting glucocorticoid therapy and 72.3% of patients developed pneumonia within 1 year (Figure 2). Of confirmed *Pneumocystis* pneumonia cases, 78.4% of patients developed disease within 6 months of starting glucocorticoid therapy and 87.2% developed pneumonia within 1 year. Of confirmed CMV pneumonia cases, 69.7% of patients developed disease within 6 months of starting glucocorticoid therapy and 81.4% of patients developed pneumonia within 1 year (Figure 3). For non-CMV virus, *Aspergillus*, and bacterial pneumonias, most patients developed illness within 6 months of starting glucocorticoid therapy; however, the percentage was not as high as for patients with CMV and *Pneumocystis* pneumonias, and there was an additional incident peak 1

year later (Figure 4).

Cox regression analysis indicated that the following factors were independent predictors of 30-day mortality in LTGP: septic shock (OR = 6.306, 95% CI: 4.297-9.255; *P*< 0.001); respiratory failure(OR = 12.583, 95% CI:4.995-31.699;*P* = 0.001);high-dose steroids (OR = 1.402, 95% CI: 1.007-1.952; *P*=0.046); and persistent lymphocytopenia (OR = 1.606, 95% CI: 1.126-2.291*; P* = 0.009). Septic shock (OR =5.942, 95% CI: 4.126-8.556; *P*< 0.001), respiratory failure(OR = 9.053, 95% CI:3.639-22.524; *P*< 0.001), interstitial lung disease (OR = 1.483, 95% CI: 1.085-2.027*; P* =0.013),mechanical ventilation(OR=1.968, 95% CI: 1.215-3.188*; P* =0.006)and persistent lymphocytopenia (OR = 1.478, 95% CI:1.068-2.045; *P*=0.018)were independent negative predictors of 90-day mortality (Table 4).

DISCUSSION

This study was the first large-scale retrospective investigation of the etiology and prognostic risk factors of pneumonia in patients with long-term glucocorticoid use. The main findings of the present study are summarized as follows: (1) More than 60% of the patients developed pneumonia within 6 months of glucocorticoid therapy initiation, especially patients with PCP and CMV pneumonias. (2) Persistent lymphocytopenia was associated with significantly higher rates of infection by opportunistic pathogens, mixed pathogen types, and MDR bacteria. (3) Patients using high dose glucocorticoids were significantly more likely to develop opportunistic pneumonias than patients using low dose glucocorticoids. (4) The 30-day and 90-day mortality of non-CMV viral pneumonias were similar as that of PCP. (5) Septic shock, invasive or noninvasive mechanical ventilation, interstitial lung disease, low oxygenation index, and lymphocytopenia for more than 7 days were independent predictors of 90-day mortality in LTGP.

The use of glucocorticoids and other immunosuppressive agents are risk factors for the development of CMV, *Pneumocystis*, *Aspergillus*, and other opportunistic infections. [18-23] .A review of 33 pneumonia patients with long-term glucocorticoid use showed that *Staphylococcus aureus* was the most common pathogen in pneumonia, with a wide range of other causative pathogens, including bacteria, fungi, viruses, *Pneumocystis*, *Mycobacterium*, etc. [1] Marta conducted an international multicenter study of immunocompromised patients, with chronic steroid users accounting for 45%.[24] That study showed that the main causative pathogens for

pneumonia were *Streptococcus pneumoniae, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus*, influenza viruses, and PCP. In our study, the most common isolated pathogen types were bacterial (252), CMV (193), non-CMV viruses (140), PCP (135), *Aspergillus* or *Cryptococcus* (64), atypicals (11), and *Mycobacterium tuberculosis* (10). For bacterial infections, the most commonly isolated pathogens were *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae*, *and Staphylococcus aureus* because most patients had received antibiotic therapy before admission. In some patients, the timing of the BAL or sputum samples taking was more than 48 hours after admission, so bacteria such as *Acinetobacter baumannii* were most likely acquired in the hospital.

Studies have reported associations between mixed pulmonary infections and treatment with glucocorticoids for nephrotic syndrome, lung transplantation, and other disorders requiring immunosuppression.[25-27] In our study, the incidence of mixed infections was more than 50% and the proportion of mixed infections caused by bacteria, fungi, and viruses was as high as 10%. Glucocorticoid use may also be a risk factor for MDR bacterial infection. We demonstrated that rates of MDR bacterial infection was significantly higher in the high dose steroid and the persistent lymphocytopenia subgroups. When treating pneumonia in patients with long-term and high dose steroids or with persistent lymphocytopenia, MDR pathogens must be considered when selecting antimicrobial agents. In previous studies, [30 31] a clear association between low $CD4^{+}T$ lymphocyte counts and PCP infection has been demonstrated. Low absolute lymphocyte count and prolonged high dose steroid therapy have also been found to be predictors of PCP and CMV infection. [32-39] Yang demonstrated that the average time until diagnosis of PCP was only 2.4 months after immunosuppressant initiation in glomerulonephritis patients. [40] Our results demonstrate the importance of considering PCP infection in patients for at least 6 months after glucocorticoid initiation, especially when receiving high doses. This study also indicates that high dose glucocorticoid use is associated with *Mycobacterium tuberculosis* and *Aspergillus* pneumonias. It has been shown that glucocorticoids have profound effects on the distributions and functions of immune cells, including decreasing macrophage antifungal activity through inhibiting reactive oxidant intermediates and directly stimulating the growth of *Aspergillus fumigatus*.[41]

Respiratory viruses have also been recognized as a potential cause of pneumonia and death in immunocompromised individuals with hematopoietic stem cell transplants or hematologic

malignancies. Jacobs studied 32 patients with hematologic malignancies with HRV lower respiratory tract infections, overall 30-day mortality was 25%.[42] A higher mortality (27%) was observed by Dimpy in patients with lower respiratory tract infections caused by parainfluenza virus in hematopoietic cell transplant recipients and hematologic malignancy patients.[43] Chatzis showed that 21.3% of an immunocompromised adult cohort with RSV infection presented with pneumonia requiring ICU transfer, resulting in mortality of almost 20%. [44] Crotty conducted an observational cohort study of 284 patients with viral pneumonia, in which the majority (51.8%) were immunocompromised and the overall in-hospital mortality was high (23.2%). [45] In our study, invasive mechanical ventilation was required for 32.1% of patients with non-CMV viral pneumonia, and the 90-day mortality of these patients was 29.2%, PCP and CMV showed similar results ($p > 0.05$). Therefore, it is extremely important to prevent infection with respiratory tract viruses in LTGP. If ground glass lesions were detected on CT imaging, PCP and viral infections should be considered, viral nucleic acid testing should be obtained, and antiviral treatment should be started as early as possible.

Mortality from pulmonary infections in patients receiving long-term glucocorticoid therapy can be as high as 45%, [1] with a similar rate in patients with other causes of immunosuppression. [21] Respiratory failure and the need for mechanical ventilation has been shown to be the strongest predictor of mortality in immunocompromised patients with or without pneumonia. [46 47] Lymphopenia is also significantly associated with increased mortality in non-HIV-infected patients with PCP or viral pneumonias. [32 48] Vial-Dupuy indicated high-dose steroids during ICU stay (OR=0.19; [95% CI, 0.04-0.99]) were independent determinants of in-hospital mortality with interstitial lung disease admitted to the intensive care unit[49]. Kotani's study indicated underlying disease of interstitial lung disease was a risk factor associated with the mortality of Pneumocystis jirovecii pneumonia (PCP) who required mechanical ventilation (MV).[50] Our research pointed out that patients with high-dose glucocorticoid, persistent lymphocytopenia, and interstitial lung disease should pay attention to the poor prognosis.

This study had some limitations. First, it had a retrospective design. Second, not all patients with pneumonia underwent full pathogen testing, so pathogen identification and diagnosis may be incomplete. Third, some pathogens were not identified until at least 48 hours after admission, increasing the possibility of nosocomial infections. Despite these limitations, our study results are

consistent with the existing literature and provide more detailed insights into the clinical characteristics, pathogenic etiologies, and prognostic factors that should be carefully considered when managing patients on long-term glucocorticoid therapy.

CONCLUSIONS

Patients receiving long-term glucocorticoid therapy with pneumonia experience higher rates of infection with opportunistic pathogens, significant morbidity, and high mortality, especially with specific risk factors. This information should be carefully considered when determining treatment strategies for this patient population.

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Figure legend/caption:

Figure1: Study flowchart

Figure2: 30-day mortality of pneumocystis infection group and viral infection group

Figure3: 90-day mortality of pneumocystis infection group and viral infection group

Figure4: Duration of glucocorticoid use among long-term glucocorticoid users with pneumonia

60.2% of the patients developed pneumonia within 6 months of starting glucocorticoid therapy and 72.3% of patients developed pneumonia within 1 year.

78.4% of PCP patients developed disease within 6 months of starting glucocorticoid therapy and 87.2% developed pneumonia within 1 year.

Of confirmed CMV pneumonia cases, 69.7% of patients developed disease within 6 months of starting glucocorticoid therapy and 81.4% of patients developed pneumonia within 1 year.

Table1 Clinical characteristics of long-term glucocorticoid users with pneumonia between survivors and those who died in 90-days after admission

Variables	Total, N=614	Survivors, N=450	Died, N=164	*P*-Value
Sex, female, n (%)	311(50.7)	236(52.4)	75(45.7)	0.141
Age, median (IQR)	60(58,103)	59.0(47.0,68.0)	62.0(52.0,70.0)	0.008
Symptoms and signs, n (%)				
Fever	471(76.7)	322(71.6)	149(90.9)	<0.001
Cough	526(85.7)	377(83.8)	149(90.9)	0.027
Expectoration	478(77.9)	348(77.3)	130(79.3)	0.523
Dyspnea	366(59.6)	232(51.6)	134(81.7)	<0.001
Disturbance of consciousness	38(6.2)	18(4.0)	20(12.2)	<0.001
Laboratory examination				
White blood cell, $\times10^9$/L (IQR)	7.93(5.78,11.60)	7.64 (5.71,10.98)	9.27 (6.17,13.00)	0.001
Neutrophils, $\times10^9$/L (IQR)	6.5(4.29,10.10)	6.16(4.02,9.03)	8.11 (5.37,11.40)	<0.001
Lymphocyte, $\times10^9$/L (IQR)	0.84(0.50,1.40)	0.96 (0.60,1.49)	0.60 (0.36,1.01)	<0.001
Persistent lymphocytopenia	262(42.7)	156(34.7)	106(64.6)	<0.001
Mean hemoglobin±SD, g/L	111.8±23.9	113.1±24.2	108.4±22.8	0.034
Mean albumin±SD, g/L	32.4±6.4	33.3±6.2	29.9±6.1	<0.001
Lactate dehydrogenase, U/L	329.5(224.3,506.0)	291.0 (204.0,417.0)	488.0 (338.0,622.0)	<0.001
Blood urea nitrogen, mmol/L	6.23(4.58,9.33)	5.81 (4.30,8.14)	8.11 (5.81,12.71)	<0.001
Serum creatinine, mmol/L	63.0(50.0,89.9)	62.7 (49.9,83.9)	68.3 (50.0,107.0)	0.077
Procalcitonin, ng/ml	0.28(0.13,0.83)	0.27 (0.13,0.67)	0.40(0.12,1.64)	0.039
Oxygenation index	231.0(126.3,342.9)	280.7(187.7,376.1)	126.3(80.0,198.4)	<0.001
Severe pneumonia index score	77.0(58.0,103.0)	72.0(55.0,92.0)	96.5(75.0,122.8)	<0.001
CURB65 score	1(0,2)	1.0(0,1.0)	1.5(1.0,2.0)	<0.001
Underlying immune defect, n (%)				
Diabetes mellitus	146(23.8)	99(22.0)	47(28.7)	0.086
Tumor	36(5.9)	23(5.1)	13(7.9)	0.189
Connective tissue disease	319(52.0)	230(51.1)	89(54.3)	0.488
Interstitial lung disease	257(41.9)	172(38.2)	85(51.8)	0.009
Nephrotic syndrome or chronic glomerulonephritis	85(13.8)	61(13.6)	24(14.6)	0.732
Idiopathic interstitial pneumonia	64(10.4)	47(10.4)	17(10.4)	0.978
Bronchial asthma or chronic obstructive pulmonary disease	28(4.6)	23(5.1)	5(3.0)	0.278
Lymphoma	16(2.6)	12(2.7)	4(2.4)	0.876
After bone marrow or hematopoietic stem cell transplantation	7(1.1)	5(1.1)	2(1.2)	0.911
Postoperative solid organ transplantation	30(4.9)	23(5.1)	7(4.3)	0.668
Radiation pneumonitis	7(1.1)	5(1.1)	2(1.2)	0.911
Other immunocompromised hosts	58(9.4)	44(9.8)	14(8.5)	0.642
Bronchoalveolar lavage, n (%)	366(59.6)	248(55.1)	118(72.0)	<0.001
Treatment, before admission, n (%)				
High-dose steroids(>1mg/kg/day)	216(35.2)	134(29.8)	82(50.0)	<0.001

Variables	Total, N=614	Survivors, N=450	Died, N=164	*P*-Value
Time of steroids use, median (IQR), month	4(2,19)	3.0(1.0,8.5)	5.0(2.0,24.0)	<0.001
Receiving other immunosuppressive therapy	348(56.7)	247(14.0)	101(61.6)	0.138
Antibiotics†	411(66.9)	287(63.8)	124(75.6)	0.006
Antiviral drugs	95(15.5)	54(12.0)	41(25.0)	<0.001
Treatment, during hospitalization, n (%)				
Anti - Pseudomonas aeruginosa drugs	461(75.1)	306(68.0)	155(94.5)	<0.001
Voriconazole or caspofungin	233(37.9)	129(28.7)	104(63.4)	<0.001
Ganciclovir	276(45.0)	172(38.2)	104(63.4)	<0.001
Trimethoprim	270(44.0)	172(38.2)	98(59.8)	<0.001
Complications, n (%)				
Noninvasive ventilation	154(25.1)	60(13.3)	94(57.3)	<0.001
Invasive mechanical ventilation	150(24.4)	47(10.4)	103(79.3)	<0.001
Mechanical ventilation	225(36.6)	87(19.3)	138(84.1)	<0.001
Respiratory failure during admission	275(44.8)	131(29.1)	144(87.8)	<0.001
ICU admission	255(41.5)	119(26.4)	136(82.9)	<0.001
Septic shock during hospitalization	132(21.5)	18(4.0)	114(69.5)	<0.001
CAP	542(88.3)	408(90.7)	134(81.7)	<0.001
Extracorporeal membrane oxygenation	26(4.2)	11(2.4)	15(9.1)	<0.001

*Connective tissue disorders: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjogren's syndrome, etc.@ Immunosuppressive drugs: glucocorticoid, tacrolimus, sirolimus, cyclosporine, methotrexate, etc.

*Other immunocompromised hosts: eczema, myelitis, autoimmune encephalitis, idiopathic thrombocytopenic purpura, etc.

† other immunosuppressants: methotrexate, cyclophosphamide, tacrolimus, azathioprine, etc.

Table 2 The pathogen testing result of long-term glucocorticoid users with pneumonia according to different subgroup

Variables, n (%)	CAP （N=542）	HAP (N=72)	*P*-Value	Patients discharged alive, N=450	Patients died during hospitalization, N=164	*P*-Value	Persistent lymphocytopenia group, N=262	Non-lymphocytopenia group, N=352	*P*-Value	Patients use high-dose steroids, N=216	Patients use low-dose steroids, N=398	*P*-Value
Total pathogenic positive rate	361(66.6)	53(73.6)	0.222	289(64.2)	125(76.2)	0.007	188(71.8)	226(64.2)	0.048	177(81.9)	237(59.5)	<0.001
One bacterium	36(6.6)	6(8.3)	0.593	36(8.0)	6(3.7)	0.059	16(6.1)	26(7.4)	0.534	12(5.6)	30(7.5)	0.353
Two or more bacteria	16(3.0)	4(5.6)	0.242	11(2.4)	9(5.5)	0.060	7(2.7)	13(3.7)	0.481	12(5.6)	8(2.0)	0.018
One virus	87(16.1)	9(12.5)	0.436	75(16.7)	21(12.8)	0.244	35(13.4)	61(17.3)	0.180	32(14.8)	64(16.1)	0.680
Two or more viruses	16(3.0)	0(0)	0.140	10(2.2)	6(3.7)	0.323	8(3.1)	8(2.3)	0.548	3(1.4)	13(3.3)	0.163
Pneumocystis	32(5.9)	3(4.2)	0.550	25(5.6)	10(6.1)	0.798	14(5.3)	21(6.0)	0.742	19(8.8)	16(4.0)	0.015

Aspergillus	9(1.7)	0(0)	0.271	6(1.3)	3(1.8)	0.651	4(2.5)	5(1.4)	0.914	6(2.8)	3(0.8)	0.046
Atypical pathogen	7(1.3)	0(0)	0.332	7(1.6)	0(0)	0.108	1(0.4)	6(1.7)	0.127	2(0.9)	5(1.3)	0.713
Virus and bacteria	34(6.3)	6(8.3)	0.506	23(5.1)	17(10.4)	0.020	20(7.6)	20(5.7)	0.332	16(7.4)	24(6.0)	0.509
Virus and aspergillus	12(2.2)	2(2.8)	0.763	9(2.0)	5(3.0)	0.441	6(2.3)	8(2.3)	0.989	7(3.2)	7(1.8)	0.240
Virus, bacteria and fungi	49(9.0)	10(13.9)	0.190	34(7.6)	25(15.2)	0.004	33(12.6)	26(7.4)	0.030	26(12.0)	33(8.3)	0.133
Bacteria and pneumocystis	8(1.5)	2(2.8)	0.412	4(0.9)	6(3.7)	0.016	7(2.7)	3(0.9)	0.078	6(2.8)	4(1.0)	0.097
Aspergillus and pneumocystis	3(0.6)	0(0)	0.527	3(0.7)	0(0)	0.295	2(0.8)	1(0.3)	0.400	1(0.5)	2(0.5)	0.946
Bacteria and Aspergillus	4(0.7)	1(1.4)	0.564	4(0.9)	1(0.6)	0.733	2(0.8)	3(0.9)	0.903	2(0.9)	3(0.8)	0.821
Pneumocystis and virus or atypical pathogen	39(7.2)	9(12.5)	0.115	34(7.6)	14(8.5)	0.689	27(10.3)	21(6.0)	0.048	26(12.0)	22(5.5)	0.004
Mycobacterium tuberculosis and another pathogen	9(1.7)	1(1.4)	0.864	8(1.8)	2(1.2)	0.629	6(2.3)	4(1.1)	0.264	7(3.2)	3(0.8)	0.020
Pathogenic types in different groups (Total)	674	109	-	512	271	-	378	405	-	345	438	
Pathogens covered by CAP therapy	130(24.0)	18(25.0)	0.850	109(24.2)	39(23.8)	0.910	60(22.9)	88(25.0)	0.547	69(31.9)	79(19.8)	0.001
Streptococcus pneumoniae	4(0.7)	0(0)	0.465	4(0.9)	0(0)	0.226	1(0.4)	3(0.9)	0.473	0(0)	4(1.0)	0.139
Haemophilus influenzae	2(0.4)	0(0)	0.606	2(0.4)	0(0)	0.392	1(0.4)	1(0.3)	0.834	2(0.9)	0(0)	0.055
Staphylococcus aureus	13(2.4)	3(4.2)	0.376	9(2.0)	7(4.3)	0.119	7(2.7)	9(2.6)	0.930	9(4.2)	7(1.8)	0.073
Escherichia coli	12(2.2)	3(4.2)	0.313	12(2.7)	3(1.8)	0.552	4(1.5)	11(3.1)	0.205	6(2.8)	9(2.3)	0.692
Enterobacter aerogenes	2(0.4)	0(0)	0.606	1(0.2)	1(0.6)	0.456	1(0.4)	1(0.3)	0.834	0(0)	2(0.5)	0.297
Enterobacter cloacae	5(0.9)	2(2.8)	0.164	5(1.1)	2(1.2)	0.911	2(0.8)	5(1.4)	0.448	4(1.9)	3(0.8)	0.221
Klebsiella pneumoniae	35(6.5)	3(4.2)	0.448	26(5.8)	12(7.3)	0.484	18(4.8)	20(5.7)	0.546	21(9.7)	17(4.3)	0.007
Pseudomonas	43(7.9)	7(9.7)	0.602	37(8.2)	13(7.9)	0.906	20(6.9)	30(8.5)	0.690	22(10.2)	28(7.0)	0.173
Proteus mirabilis	3(0.6)	0(0)	0.527	3(0.7)	0(0)	0.295	3(1.1)	0(0)	0.044	2(0.9)	1(0.3)	0.252
Mycoplasma pneumoniae	3(0.6)	0(0)	0.527	3(0.7)	0(0)	0.295	0(0)	3(0.9)	0.134	2(0.9)	1(0.3)	0.252
Legionella	8(1.5)	0(0)	0.299	7(1.6)	1(0.6)	0.361	3(1.1)	5(1.4)	0.766	1(0.5)	7(1.8)	0.176
Pathogens not covered by CAP therapy	81(14.9)	22(30.6)	0.001	50(11.1)	53(32.3)	<0.001	52(19.8)	51(14.5)	0.079	39(18.1)	64(16.1)	0.532
Acinetobacter	37(6.8)	13(18.1)	0.001	24(5.3)	26(15.9)	<0.001	29(11.1)	21(6.0)	0.022	15(6.9)	35(8.8)	0.340

Burkholderia	16(3.0)	2(2.8)	0.934	4(0.9)	14(8.5)	<0.001	7(2.7)	11(3.1)	0.742	9(4.2)	9(2.3)	0.181
Enterococcus	7(1.3)	2(2.8)	0.324	4(0.9)	5(3.0)	0.049	2(0.8)	7(2.0)	0.211	2(0.9)	7(1.8)	0.412
Stenotrophomonas maltophilia	11(2.0)	2(2.8)	0.679	8(1.7)	5(3.0)	0.333	9(3.4)	4(1.1)	0.050	6(2.8)	7(1.8)	0.402
Nocardia	7(1.3)	0(0)	0.332	6(1.3)	1(0.6)	0.455	3(1.1)	4(1.1)	0.992	4(1.9)	3(0.8)	0.221
Corynebacterium striatum	1(0.2)	1(1.4)	0.092	1(0.2)	1(0.6)	0.456	0(0)	2(0.6)	0.222	1(0.5)	1(0.2)	0.660
Comamonas acidovorans	1(0.2)	1(1.4)	0.092	1(0.2)	1(0.6)	0.456	2(0.8)	0(0)	0.101	1(0.5)	1(0.3)	0.660
Cupriavidus pauculus	1(0.2)	0(0)	-	1(0.2)	0(0)	-	0(0)	1(0.3)	-	0(0)	1(0.3)	-
Listeria monocytogenes	0(0)	1(1.4)	-	1(0.2)	0(0)	-	0(0)	1(0.3)	-	1(0.5)	0(0)	-
Multidrug resistance bacteria/ bacteria	72(13.3)	17(23.6)	0.019	44(9.8)	45(27.4)	<0.001	49(43.8)	40(28.8)	0.011	44(20.4)	45(11.3)	0.002
Fungus	170(31.4)	29(40.3)	0.129	124(27.5)	75(45.7)	<0.001	104(27.5)	95(23.5)	0.001	101(46.8)	98(24.6)	<0.001
Pneumocystis	114(21.0)	21(29.2)	0.117	86(19.1)	49(29.9)	0.004	77(20.4)	58(14.3)	<0.001	72(33.3)	63(15.8)	<0.001
Aspergillus	55(10.1)	8(11.1)	0.800	37(8.2)	26(15.9)	0.006	27(7.1)	36(8.9)	0.975	29(13.4)	34(8.5)	0.057
Cryptococcus	1(0.2)	0(0)	-	1(0.2)	0(0)	-	0(0)	1(0.2)	-	0(0)	1(0.3)	-
Virus	293(54.1)	40(55.6)	0.811	229(50.9)	104(63.4)	0.006	162(42.9)	171(42.2)	0.001	136(63.0)	197(49.5)	0.001
Cytomegalovirus	163(30.1)	30(41.7)	0.047	132(29.3)	61(37.2)	0.063	98(25.9)	95(23.5)	0.006	91(42.1)	102(25.6)	<0.001
Influenza A virus	36(6.6)	2(2.8)	0.201	22(4.9)	16(9.8)	0.027	22(5.8)	16(4.0)	0.050	10(4.6)	28(7.0)	0.237
Influenza B virus	13(2.4)	1(1.4)	0.590	10(2.2)	4(2.4)	0.642	8(2.1)	6(1.5)	0.268	8(2.2)	6(1.5)	0.082
Rhinovirus	8(1.5)	0(0)	0.299	5(1.1)	3(1.8)	0.487	5(1.3)	3(0.7)	0.254	2(0.9)	6(1.5)	0.544
Respiratory syncytial virus	38(7.0)	5(6.9)	0.983	35(7.8)	8(4.9)	0.213	12(3.2)	31(7.7)	0.042	11(5.1)	32(8.0)	0.172
Adenovirus	3(0.6)	0(0)	0.527	2(0.4)	1(0.6)	0.795	1(0.3)	2(0.5)	0.743	1(0.5)	2(0.4)	0.946
Parainfluenza virus	18(3.3)	2(2.8)	0.807	12(2.7)	8(4.9)	0.172	6(1.6)	14(3.5)	0.244	4(1.9)	16(3.7)	0.148
HSV-1	4(0.7)	0(0)	0.465	3(0.7)	1(0.6)	0.938	4(1.1)	0(0)	0.020	2(0.9)	2(0.5)	0.533
Mycobacterium tuberculosis	10(1.8)	0(0)	0.245	8(1.8)	2(1.2)	0.629	6(1.6)	4(1.0)	0.264	7(3.2)	3(0.8)	0.020

CAP, community-acquired pneumonia; HAP: hospital-acquired pneumonia; HSV-1: herpes simplex virus type 1.

Table 3 Comparative analysis of Pneumocystis infection group and viral infection group

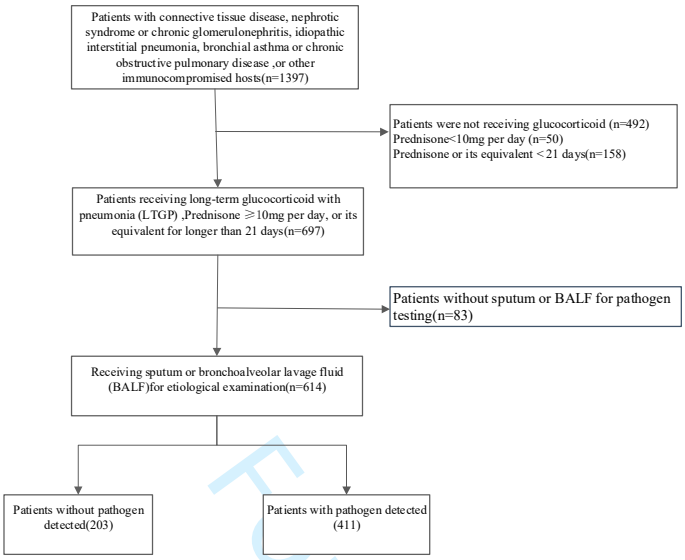
Variables	Pneumocystis infection group, N=121	Non-CMV viral infection group, N=106	CMV viral infection group，N=87	P-Value
Sex, female, n (%)	60(49.6)	47(44.3)	29(33.3)	0.063
Age, median (IGR)	56.0(43.5,65.0)	62.0(51.8,68.3)	63.0(52.0,70.0)	0.001
Nephrotic syndrome or chronic glomerulonephritis	34(28.1)	9(8.5)	2(2.3)	0.001
Postoperative solid organ transplantation	7(5.0)	10(9.4)	5(5.7)	0.485
Idiopathic interstitial pneumonia	11(9.1)	24(22.6)	12(13.8)	0.016
Laboratory examination				
White blood cell, $\times10^9$/L (IQR)	8.22 (5.59,11.48)	8.76 (5.99,11.76)	7.88(5.73,12.7)	0.608
Neutrophils, $\times10^9$/L (IQR)	7.10(4.72,10.18)	6.79 (4.64,9.79)	6.33(4.39,10.77)	0.723
Lymphocyte, $\times10^9$/L (IQR)	0.61 (0.40,1.00)	0.90 (0.60,1.54)	0.96(0.54,1.63)	<0.001
Persistent lymphocytopenia	67(55.4)	42(39.6)	35(40.2)	0.028
Oxygenation index	153.8(103.3,248.6)	285.7(154.1,375.9)	180.0(110.7,336.9)	<0.001
Severe pneumonia index score	75.0(58.0,107.0)	79.0(60.0,99.0)	89.0(69.0,117.0)	0.980
CURB65 score>1	34 (28.1)	33(31.1)	31(35.6)	0.512
Imaging features, n (%),24 missing				
Consolidation or mass	53(51.0)	47(44.3)	37(42.5)	0.761
Ground-glass opacity	92(88.5)	63(59.4)	45(51.7)	<0.001
Treatment, before admission, n (%)				
High-dose steroids(>30mg/day)	65(53.7)	28(26.4)	38(43.7)	<0.001
Time of steroids use (month)	3.0(2.0,5.0)	6.0(2.0,24.0)	4.0(2.0,12.0)	0.033
Receiving other immunosuppressants	52(43.0)	55(51.9)	42(48.3)	0.400
Antibiotics	89(73.6)	69(65.1)	68(78.2)	0.117
Antiviral drugs	25(20.7)	22(20.8)	15(17.2)	0.788
Complications, n (%)				
Noninvasive ventilation	46(38.0)	24(22.6)	27(31.0)	0.044
Invasive mechanical ventilation	36(29.8)	33(31.1)	23(26.4)	0.768
Respiratory failure	93(76.9)	48(45.3)	49(56.3)	<0.001
ICU care	75(62.0)	42(39.6)	44(50.6)	0.003
Septic shock	35(28.9)	28(26.4)	19(21.8)	0.516
Extracorporeal membrane oxygenation	4(3.3)	14(13.2)	4(4.6)	0.008
30-day mortality	39(32.2)	26(24.5)	20(23.0)	0.257

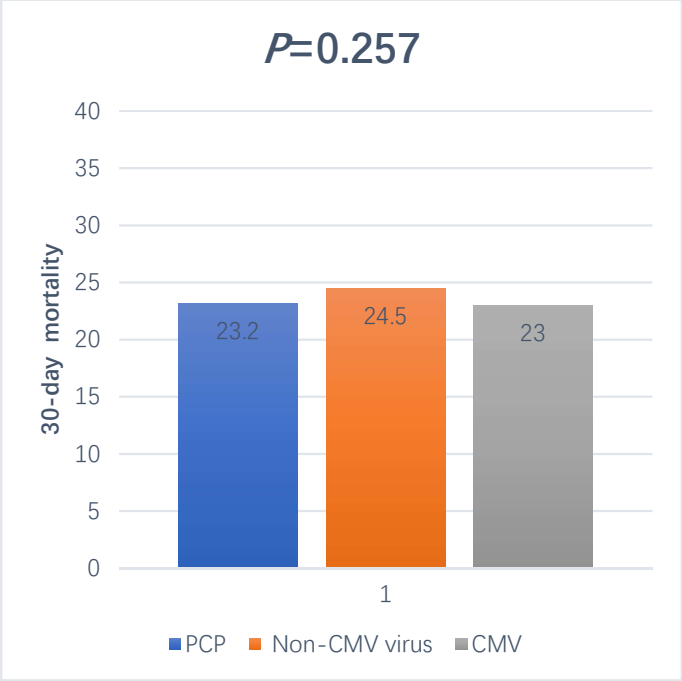
Variables	Pneumocystis infection group, N=121	Non-CMV viral infection group, N=106	CMV viral infection group，N=87	P-Value
90-day mortality	45(37.2)	31(29.2)	23(26.4)	0.213

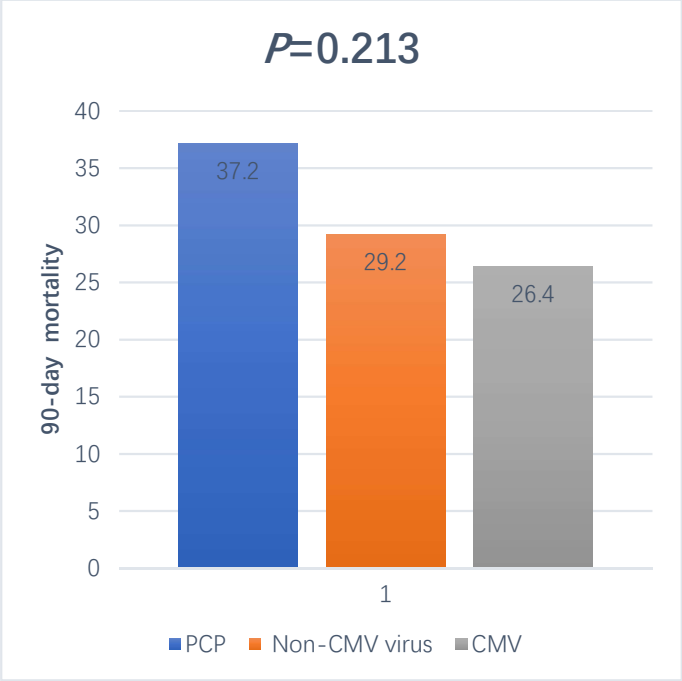
Non-CMV virus: respiratory syncytial virus (RSV), influenza A virus, influenza B virus, human parainfluenza virus (HPIV), human rhinovirus (HRV), and adenovirus.

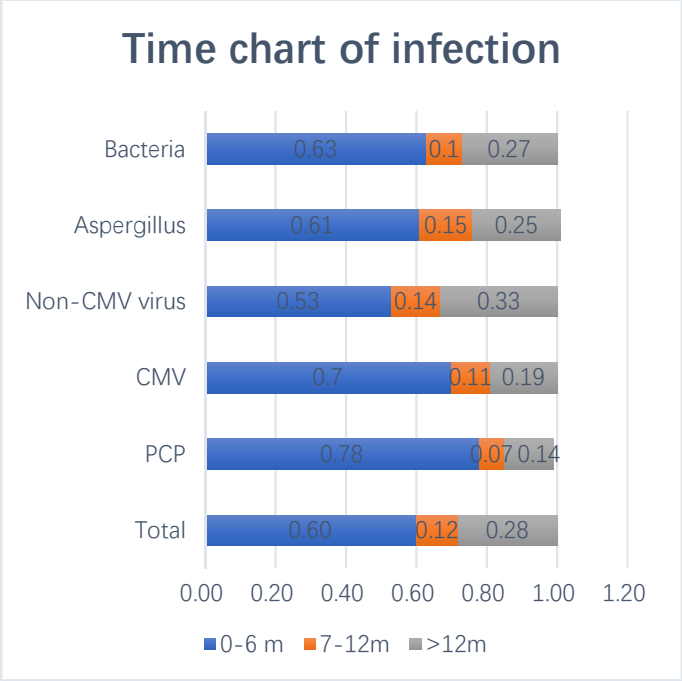
Table 4 Cox regression analysis of prognostic factors in long-term glucocorticoid users with pneumonia patients

Variables	30-day mortality			90-day mortality		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Septic shock	6.306	4.297-9.255	<0.001	5.942	4.126-8.556	<0.001
Interstitial lung disease	-	-	-	1.483	1.085-2.027	0.013
Respiratory failure	12.583	4.995-31.699	0.001	9.053	3.639-22.524	<0.001
Persistent lymphocytopenia	1.606	1.126-2.291	0.009	1.478	1.068-2.045	0.018
Mechanical ventilation	-	-		1.968	1.215-3.188	0.006
High-dose steroids	1.402	1.007-1.952	0.046	-	-	-









STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	2-3
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7 and Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8,Table3
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Etiology and prognostic risk factors of mortality among pneumonia patients receiving long-term glucocorticoids: a retrospective cohort study

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Etiology and prognostic risk factors of mortality among pneumonia patients receiving glucocorticoids: a retrospective cohort study

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ABSTRACT

Objective: Long-term use of high-dose glucocorticoids may result in severe immunosuppression, and leads to increase risk of treatment-resistant pneumonia and mortality. We investigated the etiology and prognostic risk factors of mortality in hospitalized patients with pneumonia and receiving glucocorticoid therapy.

Design: A retrospective cohort study.

Setting: Six secondary and tertiary academic hospitals in China.

Participants: Patients receiving glucocorticoids who were hospitalized with pneumonia between 1st January 2013 and 31st December 2019.

Main Outcomes: Prevalence of comorbidities, microbiology and antibiotic susceptibility patterns, 30-day and 90-day mortality, and prognostic risk factors were analysed.

Results: A total of 716 patients were included. Pathogens were identified in 69.8% of patients. Significant morbidities including respiratory failure (50.8%), intensive care unit (ICU) transfer (40.8%), and mechanical ventilation (36%). The 90-day mortality was 26.0%. Diagnosis of pneumonia occurred within 6 months of glucocorticoid initiation for 69.7% of patients with Cytomegalovirus (CMV) pneumonia and 79.0% of patients with Pneumocystis jirovecii pneumonia (PCP). Pathogens, including PCP, CMV, and multidrug-resistant bacteria, were identified more frequently in patients with persistent lymphocytopenia and high-dose glucocorticoid(≥ 30 mg/day of prednisolone or equivalent within 30 days before admission). For non-CMV viral pneumonia, the 90-day mortality was lower than those with PCP (P<0.05) but similar to CMV (24.2% vs 38.1% vs 27.4%). Cox regression analysis indicated septic shock, respiratory failure, persistent lymphocytopenia, interstitial lung disease, and high-dose glucocorticoid use were independent negative predictors for mortality.

Conclusions: Patients receiving glucocorticoid therapy with pneumonia experienced higher rates of opportunistic infections, and significantly increased risks of morbidity and mortality. This information should be carefully considered when determining treatment for this patient population.

KEYWORDS: Pneumonia; Immunocompromised; Glucocorticoids; Prognosis.

ARTICLE SUMMARY

Strengths and limitations of this study

This is the first large-scale investigation of the etiology and prognostic risk factors of pneumonia in patients with glucocorticoid use.

The study includes a large sample size, multicenter (six hospitals in China), and sputum or bronchoalveolar lavage examined in all patients.

The retrospective design poses a limitation. Not all pneumonia patients underwent a full array of pathogen testing, and some pathogens were not identified until at least 48 hours after admission, increasing the possibility of nosocomial infections.

INTRODUCTION

Long-term use of glucocorticoids at high-doses may result in severe immunosuppression and serious infections. [1] Pulmonary infections occur most commonly and remain one of the leading causes of death in immunocompromised patients.[1-4] Infections caused by opportunistic pathogens, including

Cytomegalovirus (CMV), *Pneumocystis*, and *Aspergillus*, have been reported in immunocompromised patients receiving glucocorticoids.[2-4] Mortality up to 45% was found in rheumatic patients on long-term glucocorticoids who developed pulmonary infections, and it increased to 93% for those requiring mechanical ventilation.[1] The paucity of studies regarding patients receiving glucocorticoid therapy who develop pneumonia may potentially lead to an underestimate of its prevalence and overestimate the disease burden. This may result in mismanagement with excessive use of broad-spectrum antibiotics and treatment failure in the absence of therapeutic guidance based on pathogenic data. Given the significant morbidity and mortality associated with glucocorticoid-induced immunosuppression, our study aims to identify the clinical characteristics, pathogenic etiologies, and prognostic risk factors of pneumonia in this population.

METHODS

Study design and participants

We retrospectively recruited patients with pneumonia hospitalized between 1st January 2013 and 31st December 2017 at 6 secondary and tertiary academic hospitals in China. Diagnosis of pneumonia was based on the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) guidelines.[5-6] Pneumonia was defined as the presence of a new pulmonary infiltrate on chest radiograph or CT scan showing infiltrate or interstitial changes and was combined with 1 or more of the following clinical manifestations: (1) recent cough, sputum or aggravation of respiratory symptoms, the emergence of purulent sputum, with or without chest pain; (2) fever (defined as axillary temperature $\geqslant$ 37.3°C) or hypothermia (axillary temperature < 36°C); (3) signs of pulmonary consolidation and (or) moist crackles; or (4) white cell count >10×10^9/L or <4×10^9/L, with or without neutrophil predominance. Patients with connective tissue disease, nephrotic syndrome or chronic glomerulonephritis, idiopathic interstitial pneumonia, bronchial asthma or chronic obstructive pulmonary disease, or other immunocompromised hosts were selected. All patients were selected based on the following inclusion criteria: (1) oral or intravenous glucocorticoid treatment[7-9] before admission; (2) diagnosed pneumonia on admission or during hospitalization; (3) at least 16-year-old. The exclusion criteria were as follows: (1) non-infectious pulmonary diseases including lung cancer,

interstitial lung disease without infection, pulmonary embolism, and heart failure; (2) less than 16 years old; (3) those who cannot provide consent for procedure.

Quality control of the study

Key investigators, including clinicians, statisticians, microbiologists, and radiologists, worked together to draft the protocol and created a single formatted case report form (CRF) that was used by all centers. Before the study initiation, all investigators from the 6 centers received training on the protocol, screening process, definition of underlying diseases, and formatted CRF. After data were collected, the CRF was reviewed by a trained researcher to ensure its completeness and data quality. The study was led and approved by the Ethics Committee at China-Japan Friendship Hospital with centralised collaboration with all participating hospitals, which included the anonymized data submission and collection.

Data collection

The following data were collected from the medical records of patients during hospitalization: (1) demographics; (2) clinical symptoms; (3) initial vital signs and lung examination; (4) severity of disease [evaluated by intensive care unit (ICU) admission, use of invasive or noninvasive mechanical ventilation, Pneumonia Severity Index (PSI) score, and/or CURB-65 score); [10-12] (5) laboratory and microbiological data (blood, sputum and/or bronchoalveolar lavage samples, bacterial or fungal cultures, viral nucleic acid detection, and antibiotic susceptibility patterns); (6) treatment information including vasoactive(s), antimicrobial(s), glucocorticoids, and other immunosuppressants use; (7) survival status during 30 days and 90 days after admission. High-dose steroid use was defined as equal to or greater than 30mg per day of prednisolone or equivalent within 30 days after admission. Persistent lymphocytopenia was defined as peripheral blood lymphocyte count lower than 1×10^9/L for greater than 7 days.

Diagnostic procedures

After the identification of pulmonary infiltrates on chest radiograph, bronchoalveolar lavage (BAL) or sputum samples were obtained by treating physicians. Microorganisms were identified and tested for drug sensitivity. Bronchoscopic examination was performed according to general guidelines. Lidocaine spray was applied for local anesthesia to upper airway and carina, and airways were thoroughly examined. The BAL was performed by instilling 60 to 120 mL of sterile

saline solution 2 to 4 times into the distal bronchial tree, either at the affected lobe or in the middle lung lobe with more radiographic abnormalities. BAL specimens were aliquoted and immediately transported to the laboratories. The bacterial cultures were incubated at 35℃ in 5–10% CO_2 for 48 hours. If *Nocardia* was suspected, the incubation time was prolonged. Fungal cultures were incubated at 27℃ for 5 days under ambient conditions. The species were identified using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (Brooks Instrument, Germany) or the BACTEC 9102 culture instrument (BD Biosciences, USA). Respiratory viral and atypical pathogens were detected by polymerase chain reaction (PCR) (Shanghai Zhijiang Biological Technology, China). The Platelia Aspergillus test was used for galactomannan detection (Bio-Rad Laboratories, Marnes-la-Coquette, France).

Pathogen-specific diagnostic information

We defined multidrug-resistance (MDR) in specific organisms using the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) criteria. We included the following species in this category: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBL). *Pseudomonas aeruginosa*, *Acinetobacter baumanii* and other nonfermenting Gram-negative bacilli were considered to be MDR pathogens if not susceptible to at least one agent in three or more antimicrobial categories. [13 14]

For the diagnosis of pneumonia caused by atypical pathogens, the demonstration of *Legionella* spp, *Mycoplasma pneumoniae*, or *Mycobacterium* DNA by PCR was considered positive. The diagnosis of viral infections was based on positive nucleic acid test. As for the pneumonia caused by *Aspergillus*, one or more of the following criteria were required for a positive diagnosis: (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, (3) a galactomannan optical index on BAL of ≥ 1, (4) a galactomannan optical index on serum of ≥ 0.5. (5) *Aspergillus* species identified by culture characteristics and microscopic morphology. [15 16]

The diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) required the following criteria: (1) high-resolution computed tomography (HRCT) imaging showing diffuse ground-glass opacity

(GGO) with patchy distribution; (2) mycological criteria: microscopic examination of the respiratory sample revealing the presence of *Pneumocystis* cystic or trophic forms or the PCR testing positive for *Pneumocystis* DNA using PCR.[17]

Statistical analysis

The demographics, clinical characteristics, and pathogen testing results were expressed as mean (± standard deviation), median (interquartile range), or numbers (percentage). The group comparisons were conducted using the t-test or Wilcoxon rank-sum test for continuous variables with and without normal distributions, respectively. Comparisons between groups for categorical variables were made using the χ^2 test. Histogram chart was used to depict the glucocorticoid application timeline. Distributions for the duration of glucocorticoid use among different respiratory pathogens were also compared using χ^2 test. Cox regression models were used to analyse the association of septic shock, interstitial lung disease, invasive and noninvasive mechanical ventilation, partial pressure of arterial oxygen and fraction of inspired oxygen ratio (PaO_2/FiO_2), and persistent lymphocytopenia with 30-day and 90-day mortality. In the Cox analysis, age, gender, noninvasive mechanical ventilation, invasive mechanical ventilation, respiratory failure, septic shock, ICU admission, high-dose corticosteroids, persistent lymphocytopenia, interstitial lung disease, severe pneumonia index score, CURB65 score, PCP, CMV, and non-CMV viral infection were adjusted.

Statistical analyses were performed using SPSS, version 19.0 (SPSS, Inc., Chicago, Illinois). All tests were 2 sided, and *P*-value < 0.05 was considered to be statistically significant.

Patient and Public Involvement

No patients nor the public were involved in the development of the research question or study design and will not be involved in recruitment or conduct of the study.

RESULTS

Between 1st January 2013 and 31st December 2017, 1397 immunocompromised patients with pneumonia were selected. The underlying diseases including connective tissue disease, nephrotic syndrome, chronic nephritis, idiopathic pulmonary fibrosis, or other diseases with immunocompromised state. After excluding patients not receiving oral or intravenous glucocorticoids (N=492) and those without sputum or BAL for pathogen testing (N=189), 716 pneumonia with receiving glucocorticoids (GP) were included in the final analysis (Figure 1).

About 48% of patients were female with a median age of 60. The main presenting symptoms were fever (74.6%), cough (87.7%), and dyspnea (60.2%). The most common underlying immune-related diseases were connective tissue disease (52.1%), interstitial lung disease (45.3%), diabetes (25%), and nephrotic syndrome or chronic glomerulonephritis (12.8%). The average time (months, IQR) of taking glucocorticoids was 4 (2,18) months. The positive rate of pathogen testing was 69.8% (500/716). Among the 292 (40.8%) patients who required ICU admission, 24.2% and 24% received noninvasive and invasive ventilation, respectively. The 30-day and 90-day mortality were 22.6% and 26.0%, respectively. The complication rates were similar between patients on glucocorticoid and immunosuppressant and those on glucocorticoid only (Table 1).

Table1 Clinical characteristics of pneumonia between glucocorticoid users and those glucocorticoids with immunosuppressants users

Variables	Total, N=716	Glucocorticoid users, N=297	Glucocorticoid with immunosuppressants* users, N=419	P-Value
Sex, female, n (%)	341(47.6)	123(41.4)	218(52.0)	0.005
Age, median (IQR)	60(49, 68)	62.0(52.0, 70.0)	59.0(46.0, 67.0)	<0.001
Symptoms and signs, n (%)				
Fever	534(74.6)	225(75.8)	309(73.7)	0.543
Cough	628(87.7)	267(89.9)	361(86.2)	0.133
Sputum production	580(81.0)	239(80.5)	341(81.4)	0.829
Dyspnea	431(60.2)	185(62.3)	246(58.7)	0.335
Disturbance of consciousness	40(6.2)	11(3.7)	29(6.9)	0.065
Laboratory examination				
White blood cell, $\times 10^9$/L (IQR)	7.94(5.79, 11.60)	9.27 (6.37, 12.63)	7.51 (5.37, 10.97)	<0.001
Neutrophils, $\times 10^9$/L (IQR)	6.49(4.28, 10.08)	7.35(4.89, 10.83)	6.05 (4.10, 9.35)	<0.001
Lymphocyte, $\times 10^9$/L (IQR)	0.85(0.50, 1.38)	0.95 (0.60, 1.46)	0.80 (0.45, 1.30)	0.004
Persistent lymphocytopenia	304(42.7)	113(38.0)	191(45.6)	0.044
Mean hemoglobin±SD, g/L	111.8±23.9	113.1±24.2	108.4±22.8	0.034
Mean albumin±SD, g/L	32.4±6.4	33.3±6.2	29.9±6.1	<0.001
Lactate dehydrogenase, U/L	328.5(227.8, 506.0)	338.0 (226.0, 528.0)	312.0 (228.5, 495.0)	0.525
Blood urea nitrogen, mmol/L	6.28(4.60, 9.80)	6.24 (4.60, 9.40)	6.50 (4.63, 10.24)	0.372
Serum creatinine, mmol/L	64.0(50.8, 90.2)	62.6 (50.0, 81.2)	65.9 (51.1, 99.1)	0.157
Procalcitonin, ng/ml	0.28(0.12, 0.77)	0.29 (0.14, 0.71)	0.27(0.11, 0.81)	0.613
Oxygenation index	241.4(126.6, 347.6)	228.0(128.1, 351.2)	243.1(122.4, 347.6)	<0.001
Severe pneumonia index score	76.5(59.3, 101.0)	77.0(60.0, 103.0)	76.0(57.0, 100.0)	0.845
CURB65 score>1	211(29.5)	88(29.6)	123(1.0, 2.0)	0.937

Variables	Total, N=716	Glucocorticoid users, N=297	Glucocorticoid with immunosuppressants* users, N=419	P-Value
Underlying immune defect, n (%)				
Diabetes mellitus	179(25.0)	63(21.2)	116(27.7)	0.049
Tumor	43(6.0)	20(6.7)	23(5.5)	0.490
Connective tissue disease**	368(51.4)	111(37.4)	257(61.3)	<0.001
Interstitial lung disease	324(45.3)	115(38.7)	209(49.9)	0.003
Nephrotic syndrome or chronic glomerulonephritis	90(12.6)	42(14.1)	48(11.5)	0.286
Idiopathic interstitial pneumonia	73(10.2)	56(18.9)	17(4.1)	<0.001
Bronchial asthma or chronic obstructive pulmonary disease	30(4.2)	30(10.1)	0(0)	<0.001
Lymphoma	17(2.4)	8(2.7)	9(2.1)	0.628
Bone marrow or hematopoietic stem cell transplant	7(1.0)	1(0.3)	6(1.4)	0.144
Solid organ transplant	63(8.8)	0(0)	63(15.0)	<0.001
Radiation pneumonitis	8(1.1)	7(2.4)	1(0.2)	0.008
Other immunocompromised hosts†	65(9.1)	46(15.5)	19(4.5)	<0.001
Bronchoalveolar lavage, n (%)	366(51.1)	248(83.5)	118(28.2)	<0.001
Total pathogenic positive rate	500(69.8)	218(73.4)	282(67.3)	0.080
Treatment, before admission, n (%)				
High-dose steroids(>1mg/kg/day)	216(30.2)	134(45.1)	82(19.6)	<0.001
Time of steroids use, median (IQR), month	4.0(2.0, 18.0)	3.0(1.6, 9.0)	6.0(2.0, 24.0)	<0.001
Accumulated dose of glucocorticoids, methylprednisolone, g (IQR)	38(1.9, 8.8)	3.0(1.5, 5.4)	4.8(2.2, 12.5)	<0.001
Antibiotics	502(70.1)	219(73.7)	283(67.5)	0.074
Antiviral drugs	113(15.8)	44(14.8)	69(16.5)	0.550
Treatment, during hospitalization, n (%)				
Anti - Pseudomonas aeruginosa drugs	547(76.4)	220(74.1)	327(78.0)	0.218
Voriconazole or caspofungin	282(39.4)	105(35.4)	177(42.2)	0.063
Ganciclovir	336(46.9)	120(40.4)	216(51.6)	0.003
Trimethoprim	333(46.5)	111(37.4)	222(53.0)	<0.001
Complications, n (%)				
Noninvasive ventilation	173(24.2)	63(21.2)	110(26.3)	0.121
Invasive mechanical ventilation	172(24.0)	70(23.6)	102(24.3)	0.811
Mechanical ventilation	258(36.0)	106(35.7)	152(36.3)	0.872
Respiratory failure	364(50.8)	155(52.2)	209(49.9)	0.543
ICU admission	292(40.8)	116(39.1)	176(42.0)	0.429
Septic shock during hospitalization	154(21.5)	64(21.5)	90(21.5)	0.982
CAP	635(88.7)	263(88.6)	372(88.8)	0.924
Extracorporeal membrane oxygenation	36(4.2)	15(5.1)	21(5.0)	0.981
30-day mortality	162(22.6)	66(22.2)	96(22.9)	0.828
90-day mortality	186(26.0)	76(25.6)	110(26.3)	0.842

* other immunosuppressants: methotrexate, cyclosporine, cyclophosphamide, tacrolimus, sirolimus, and azathioprine.

**Connective tissue disorders: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjogren's syndrome, etc.@ Immunosuppressive drugs: glucocorticoid, tacrolimus, sirolimus, cyclosporine, methotrexate, etc.

†Other immunocompromised hosts: eczema, myelitis, autoimmune encephalitis, idiopathic thrombocytopenic purpura, etc.

MDR bacteria and CMV were more common in hospital-acquired pneumonia (HAP) than community-acquired pneumonia (CAP) (P<0.05) (Table 2). More pathogens were detected in the persistent lymphocytopenia group than non-lymphocytopenia group in CAP (P<0.05), including PCP, influenza A virus, CMV and MDR bacteria. Patients on high-dose corticosteroid developed pneumonia than those in the low-dose corticosteroid group in CAP and HAP, and more frequently from *Klebsiella pneumoniae,* MDR bacteria, PCP, CMV, and Mycobacterium tuberculosis in the high-dose corticosteroid group than those in the low-dose corticosteroid group in CAP (P<0.05). In the non-survivor group, pathogen positive rate was higher, and MDR bacteria was also more common than those who survived in CAP and HAP(P<0.05)(Table2-3). For non-CMV viral pneumonia, respiratory syncytial virus (RSV, 64 strains) was detected most frequently, followed b*y* influenza A virus (62 strains), human parainfluenza virus (HPIV, 20 strains), influenza B virus (20 strains), human rhinovirus (HRV, 8 strains), herpes simplex virus type 1 (HSV-1,4 strains). and adenovirus(ADV, 9 strains) (Table2).

Table 2 The pathogen results of glucocorticoid users with community-acquired pneumonia according to different subgroup

Variables, n (%)	CAP, N=635	HAP, N=81	Simple glucocorticoid users, N=263	Glucocorticoid with immunosuppressants users, N=372	Patients discharged alive, N=479	Patients died during hospitalization, N=156	Persistent lymphocytopenia group, N=264	Non-lymphocytopenia group, N=371	Patients use high-dose steroids, N=219	Patients use low-dose steroids, N=416
Total pathogenic positive rate	438(69.0)	62(76.5)	190(72.2)	248(66.7)	321(67.0)	117(75.0)	190(72.0)	248(66.8)	181(82.6)	257(61.8) #
Pathogens covered by CAP therapy	167(26.3)	24(29.6)	79(30.3)	88(23.7)	126(26.3)	41(26.3)	77(29.2)	90(24.3)	70(32.0)	97(23.3) *
Streptococcus pneumoniae	6(0.9)	0(0)	2(0.8)	4(1.1)	6(1.3)	0(0)	2(0.8)	4(1.1)	1(0.5)	5(1.2)
Haemophilus influenzae	2(0.3)	0(0)	1(0.4)	1(0.3)	2(0.4)	0(0)	1(0.4)	1(0.3)	2(0.9)	0(0)
Staphylococcus aureus	18(2.8)	5(6.2)	10(3.8)	8(2.2)	13(2.7)	5(3.2)	10(3.8)	8(2.2)	7(3.2)	11(2.6)
Escherichia coli	16(2.5)	3(3.7)	6(2.3)	10(2.7)	12(2.5)	4(2.6)	7(2.7)	9(2.4)	6(2.7)	10(2.4)
Enterobacter aerogenes	2(0.3)	0(0)	0(0)	2(0.5)	1(0.2)	1(0.6)	1(0.4)	1(0.3)	0(0)	2(0.5)
Enterobacter cloacae	7(1.1)	3(3.7)	3(1.1)	4(1.1)	5(1.0)	2(1.3)	2(0.8)	5(1.3)	4(1.8)	3(0.7)
Klebsiella pneumoniae	43(6.8)	4(4.9)	25(9.5)	18(4.8)	29(6.1)	14(9.0)	20(7.6)	23(6.2)	21(9.6)	22(5.3) *
Pseudomonas	57(9.0)	9(11.1)	28(10.6)	29(7.8)	42(8.8)	15(9.6)	28(10.6)	29(7.8)	24(11.0)	33(7.9)
Proteus mirabilis	3(0.5)	0(0)	1(0.4)	2(0.5)	3(0.6)	0(0)	3(1.1)	0(0)	2(0.9)	1(0.2)
Mycoplasma pneumoniae	6(0.9)	0(0)	1(0.4)	5(1.3)	6(1.3)	0(0)	1(0.4)	5(1.3)	2(0.9)	4(1.0)
Legionella	7(1.1)	0(0)	2(0.8)	5(1.3)	7(1.5)	0(0.6)	2(0.8)	5(1.3)	1(0.5)	6(1.4)
Pathogens not covered by CAP therapy	98(15.4)	24(29.6) #	37(14.1)	61(16.4)	50(10.4)	48(30.8) #	47(17.8)	51(13.7)	35(16.0)	63(15.1)
Acinetobacter	45(7.1)	15(18.5) #	18(6.8)	27(7.3)	22(4.6)	23(14.7) #	27(10.2)	18(4.9)	14(6.4)	31(7.5)
Burkholderia	17(2.7)	2(2.5)	7(2.7)	10(2.7)	3(0.6)	14(9.0) #	6(2.3)	11(3.0)	9(4.1)	8(1.9)
Enterococcus	12(1.9)	2(2.5)	2(0.8)	10(2.7)	7(1.5)	5(3.2)	2(0.8)	10(2.7)	3(1.4)	9(2.2)
Stenotrophomonas maltophilia	13(2.0)	2(2.5)	5(1.9)	8(2.2)	10(2.1)	3(1.9)	7(1.5)	6(1.6)	4(1.8)	9(2.2)
Nocardia	8(1.3)	0(0)	4(1.5)	4(1.1)	6(1.3)	2(1.3)	4(1.5)	4(1.1)	4(1.8)	4(1.0)
Corynebacterium striatum	1(0.2)	2(2.5)	1(0.4)	0(0)	1(0.2)	0(0)	0(0)	1(0.6)	0(0)	1(0.2)
Comamonas acidovorans	1(0.2)	1(1.2)	0(0)	1(0.3)	0(0)	1(0.6)	1(0.4)	0(0)	1(0.5)	0(0)
Cupriavidus pauculus	1(0.2)	0(0)	0(0)	1(0.3)	1(0.2)	0(0)	0(0)	1(0.3)	0(0)	1(0.2)

Multidrug resistance bacteria/ bacteria	108(17.0)	40(49.4) #	68(13.3)	40(10.8)	57(11.9)	51(32.7) #	61(23.1)	47(12.7) #	51(23.3)	57(13.7) #
Fungus	212(33.3)	34(42.0)	80(30.4)	132(35.5)	141(29.4)	71(45.5) #	109(41.3)	103(27.8) #	105(47.9)	107(25.7) #
Pneumocystis	128(20.2)	21(25.9)	48(18.3)	80(21.5)	88(18.4)	40(25.6) *	70(26.5)	58(15.6) #	71(32.4)	57(13.7) #
Aspergillus	81(12.8)	13(16.0)	32(12.2)	49(13.2)	52(10.9)	29(18.6) *	38(14.4)	43(11.6)	33(15.1)	48(11.5)
Rhizopus/ Trichoderma	2(0.3)	0(0)	0(0)	2(0.5)	0(0)	2(1.3)	1(0.4)	1(0.3)	1(0.5)	1(0.2)
Cryptococcus	1(0.2)	0(0)	0(0)	1(0.3)	1(0.2)	0(0)	0(0)	1(0.3)	0(0)	1(0.2)
Virus	355(55.9)	51(63.0)	154(58.6)	201(54.0)	257(53.7)	98(62.8) *	167(63.3)	188(50.7) #	132(60.3)	223(53.6)
Cytomegalovirus	186(29.3)	33(40.7) *	79(30.0)	107(28.8)	133(27.8)	53(34.0)	93(35.2)	93(25.1) #	84(38.4)	102(24.5) #
Influenza A virus	55(8.7)	7(8.6)	29(11.0)	26(7.0)	36(7.5)	19(12.2)	30(11.4)	25(6.7) *	15(6.8)	40(9.6)
Influenza B virus	19(3.0)	1(1.2)	7(2.7)	12(3.2)	15(3.1)	4(2.6)	9(3.4)	10(2.7)	9(4.1)	10(2.4)
Rhinovirus	8(1.3)	0(0)	2(0.8)	6(1.6)	5(1.0)	3(1.9)	5(1.9)	3(0.8)	2(0.9)	6(1.4)
Respiratory syncytial virus	56(8.8)	8(9.9)	27(10.3)	29(7.8)	45(9.4)	11(7.1)	18(6.8)	38(10.2) *	14(6.4)	42(10.1)
Adenovirus	9(1.4)	0(0)	4(1.5)	5(1.3)	8(1.7)	1(0.6)	2(0.8)	7(1.9)	2(0.9)	7(1.7)
Parainfluenza virus	18(2.8)	2(2.5)	5(1.9)	13(3.5)	12(2.5)	6(3.8)	6(2.3)	12(3.2)	4(1.8)	14(3.4)
Herpes simplex virus type 1	4(0.6)	0(0)	1(0.4)	3(0.8)	3(0.6)	1(0.6)	4(1.5)	0(0)	2(0.9)	2(0.5)
Mycobacterium tuberculosis	12(1.9)	0(0)	3(1.1)	9(2.4)	10(2.1)	2(1.3)	5(1.9)	7(1.9)	8(3.7)	4(1.0) *
Nontuberculosis mycobacteria	3(0.5)	0(0)	3(1.1)	0(0)	1(0.2)	2(1.3)	3(1.1)	0(0)	1(0.5)	2(0.5)
Pathogenic types in different groups (Total)	847(133.4)	133(164.2)	356(135.4)	491(132.0)	585(122.1)	262(167.9)	408(154.5)	439(118.3)	351(160.3)	496(119.2)

#:P<0.01, *:P<0.05

Table 3 The pathogen testing result of glucocorticoid users with hospital acquired pneumonia in different subgroup

Variables, n (%)	Patients discharged alive, N=51	Patients died during hospitalization, N=30	Persistent lymphocytopenia group, N=40	Non-lymphocytopenia group, N=41	Patients use high-dose steroids, N=30	Patients use low-dose steroids, N=51
Total pathogenic positive rate	34(66.7)	28(93.3) #	33(82.5)	29(70.7)	27(90.0)	35(68.6) *
Bacteria	22(43.1)	26(86.7) #	23(57.5)	25(61.0)	21(70.0)	27(52.9)
Staphylococcus aureus	2(3.9)	3(10.0)	2(5.0)	3(7.3)	3(10.0)	2(3.9)
Escherichia coli	2(3.9)	1(3.3)	0(0)	3(7.3)	2(6.7)	1(2.0)
Enterobacter cloacae	0(0)	3(10.0) *	1(2.5)	2(4.9)	1(3.3)	2(3.9)
Klebsiella pneumoniae	1(2.0)	3(10.0)	2(5.0)	2(4.9)	2(6.7)	2(3.9)
Pseudomonas	3(5.9)	6(20.0)	5(12.5)	4(9.8)	3(10.0)	6(11.8)
Acinetobacter	8(15.7)	7(23.3)	8(20.0)	7(17.1)	5(16.7)	10(19.6)
Burkholderia	1(2.0)	1(3.3)	1(2.5)	1(2.4)	1(3.3)	1(2.0)
Enterococcus	2(3.9)	0(0)	2(5.0)	0(0)	1(3.3)	1(2.0)
Stenotrophomonas maltophilia	2(3.9)	0(0)	1(2.5)	1(2.4)	2(6.7)	0(0)
Others bacteria	1(2.0)	2(6.7)	1(2.5)	2(4.9)	1(3.3)	2(3.9)
Multidrug resistance bacteria/ bacteria	11(21.6)	13(43.3) *	13(32.5)	11(26.8)	8(26.7)	16(31.4)
Fungus	21(41.2)	13(43.3)	21(52.5)	13(31.7)	14(46.7)	20(39.2)
Pneumocystis	15(29.4)	6(20.0)	14(35.0)	7(17.1)	10(33.3)	11(21.6)
Aspergillus	6(11.8)	7(23.3)	7(17.5)	6(14.6)	4(13.3)	9(17.6)
Virus	20(39.2)	31(103.3) #	25(62.5)	26(63.4)	20(66.7)	31(60.8)
Cytomegalovirus	16(31.4)	17(56.7) *	18(45.0)	15(36.6)	17(56.7)	16(31.4) *
Influenza A virus	1(2.0)	6(20.0) #	5(12.5)	2(4.9)	2(6.7)	5(9.8)
Influenza B virus	0(0)	1(3.3)	1(2.5)	0(0)	0(0)	1(2.0)
Respiratory syncytial virus	1(2.0)	7(23.3) #	1(2.5)	7(17.1) *	1(3.3)	7(13.7)
Parainfluenza virus	2(3.9)	0(0)	0(0)	2(4.9)	0(0)	2(3.9)

Pathogenic types in different groups (Total)	63(123.5)	70(233.3)	69(172.5)	64(156.1)	55(183.3)	78(152.9)

#:P<0.01, *:P<0.05

Patients with non-CMV viral pneumonia had higher PaO_2/FiO_2 ratio and lower number of respiratory failure, and the 30-day and 90-day mortality were lower than those patients with PCP and CMV*(P*<0.05) (Table 4). There were more PCP and CMV in nephrotic syndrome and chronic glomerulonephritis group, and more Aspergillus and non-CMV virus in solid organ transplant group, however, there was no statistical difference in mortality between different underlying diseases(Table 5). Time analysis showed that 58.0% of the patients developed pneumonia within 6 months of starting glucocorticoid therapy and 74.0% of patients developed pneumonia within 1 year (Figure 2). Of the confirmed PCP cases, 79.0% developed the disease within 6 months of starting glucocorticoid therapy and 86.0% within 1 year. Of the confirmed CMV pneumonia cases, 71.0% developed the disease within 6 months of starting glucocorticoid therapy and 82.0% within 1 year (Figure 3). For non-CMV viruses, *Aspergillus*, and bacterial pneumonia, most patients developed the disease within 6 months of starting glucocorticoid therapy, although less than patients with CMV and *Pneumocystis* pneumonia (Figure 2). The trends in the incidence of these types of pneumonia were similar between glucocorticoid with immunosuppressant and glucocorticoid only groups(Figure3-4).

Table 4 Comparative analysis of pneumocystis infection group and viral infection group

Variables	Pneumocystis infection group, N=134	Non-CMV viral infection group, N=157	CMV viral infection group, N=95	P-Value
Sex, female, n (%)	65(48.5)	56(35.7)	32(33.7)	0.033
Age, median (IGR)	56.0(45.8,65.0)	60.0(52.0, 68.0)	64.0(53.0, 71.0)	<0.001
Nephrotic syndrome or chronic glomerulonephritis	38(28.4)	10(6.4)	13(13.7)	<0.001
Solid organ transplant	7(5.2)	43(27.4)	5(5.3)	<0.001
Connective tissue disease	58(44.0)	50(33.1)	43(46.3)	0.051
Interstitial lung disease	49(36.6)	95(60.5)	42(44.2)	<0.001
Idiopathic interstitial pneumonia	12(9.1)	28(17.8)	14(14.7)	0.091
Laboratory examination				
White blood cell, $\times10^9$/L (IQR)	8.22 (5.50, 11.46)	8.45 (5.94, 11.59)	7.96(5.77, 12.65)	0.888
Neutrophils, $\times10^9$/L (IQR)	7.12(4.66, 10.50)	6.56 (4.47, 9.51)	6.47(4.39, 10.77)	0.438
Lymphocyte, $\times10^9$/L (IQR)	0.60 (0.40, 1.00)	0.99 (0.60, 1.55)	0.91(0.49, 1.57)	<0.001
Persistent lymphocytopenia	74(55.2)	62(39.5)	39(41.1)	0.017
Oxygenation index	154.4(93.6, 251.4)	295.2(171.3, 403.3)	177.8(102.5, 321.0)	<0.001
Severe pneumonia index score	75.5(57.0,105.3)	79.0(61.0, 98.0)	89.0(68.0, 118.0)	0.017

Variables	Pneumocystis infection group, N=134	Non-CMV viral infection group, N=157	CMV viral infection group, N=95	P-Value
CURB65 score>1	39 (29.1)	46(29.3)	34(35.8)	0.512
Imaging features, n (%), 35missing				
Consolidation or mass	57(42.5)	66(42.0)	41(43.2)	0.547
Ground-glass opacity	102(76.1)	83(52.9)	51(53.7)	<0.001
Treatment, before admission, n (%)				
High-dose steroids(>30mg/day)	73(54.5)	39(24.8)	41(43.2)	<0.001
Accumulated dose of glucocorticoids, methylprednisolone, g (IQR)	3.3(2.2, 5.8)	2.9(1.2, 6.8)	4.0(2.1, 7.4)	0.186
Time of steroids use (month)	3.0(2.0, 5.0)	5.0(2.0, 16.0)	4.0(2.0, 12.0)	0.291
Receiving other immunosuppressants	58(43.3)	67(42.7)	45(47.4)	0.749
Complications, n (%)				
Noninvasive ventilation	51(38.1)	29(18.5)	29(30.5)	0.001
Invasive mechanical ventilation	41(30.6)	43(27.4)	27(28.4)	0.831
Respiratory failure	104(77.6)	69(43.9)	55(57.9)	<0.001
ICU care	84(62.7)	52(33.1)	49(51.6)	<0.001
Septic shock	38(28.4)	40(25.5)	22(23.2)	0.667
Extracorporeal membrane oxygenation	6(4.5)	17(10.8)	6(6.3)	0.108
30-day mortality	45(33.6)	32(20.4)	23(24.2)	0.034
90-day mortality	51(38.1)	38(24.2)	26(27.4)	0.030

Non-CMV virus: respiratory syncytial virus (RSV), influenza A virus, influenza B virus, human parainfluenza virus (HPIV), human rhinovirus (HRV), and adenovirus.

Table 5 Clinical characteristics of pneumonia with glucocorticoid users in different underlying disease

Variables	Connective tissue disease, N=368	Nephrotic syndrome or chronic glomerulonephritis, N=90	Solid organ transplant, N=63	Bone marrow or HSCT, N=7	Lymphoma, N=17	Bronchial asthma or COPD, N=30	Idiopathic interstitial pneumonia, N=73	Radiation pneumonitis, N=8	*P* value
Sex, female, n (%)	228(62.0)	28(31.1)	15(23.8)	1(14.3)	4(23.5)	9(30.0)	28(38.4)	0(0)	<0.001
Age, median (IGR)	60.0(47.3,69.8)	57.0(41.8, 66.0)	56.0(46.0, 63.0)	33.0(32.0, 53.0)	65.0(53.5, 75.0)	62.0(57.0, 73.3)	65.0(55.0,71.0)	62.5(52.0, 66.8)	<0.001
Laboratory examination									
White blood cell, $\times 10^9$/L (IQR)	7.79 (5.72, 11.19)	8.31 (6.47, 11.81)	6.92(4.45, 9.93)	5.27(3.80, 11.6)	5.16(2.85, 9.23)	9.42(6.59, 12.82)	9.58(7.15, 12.91)	6.95(5.52, 10.82)	0.001
Neutrophils, $\times 10^9$/L (IQR)	6.36(4.29, 9.80)	7.48 (5.30, 10.81)	4.80(3.2, 7.7)	3.85(0.90, 7.05)	3.52(1.89, 7.91)	6.94(4.45, 9.13)	8.13(4.87, 11.07)	6.16(5.20, 9.50)	<0.001
Lymphocyte, $\times 10^9$/L (IQR)	0.83 (0.50, 1.34)	0.77 (0.40, 1.22)	0.80(0.33, 1.31)	0.61(0.43, 2.07)	0.86(0.38, 1.42)	1.15(0.76, 1.73)	1.10(0.70, 1.61)	0.50(0.09, 0.94)	0.014
Persistent lymphocytopenia	160(43.5)	39(43.3)	29(46.0)	3(42.9)	8(47.1)	8(26.7)	29(39.7)	5	0.634
Oxygenation index	243.1(126.6, 343.8)	176.5(103.4, 279.0)	323.8(207.1, 424.5)	265.5(148.8, 304.7)	197.8(80.0,350.7)	264.6(181.6, 444.0)	242.9(128.0, 364.3)	307.4(244.1, 442.0)	0.001
Severe pneumonia index score	73.0(54.0,96.0)	88.0(67.8, 113.5)	83.0(64.0, 100.0)	64.0(42.0, 86.0)	96.0(73.5, 141.5)	74.5(60.8, 92.5)	75.0(63.0, 96.5)	91.5(85.0, 131.0)	<0.001
CURB65 score>1	105 (28.5)	34(37.8)	15(23.8)	1(14.3)	4(23.5)	6(20.0)	25(34.2)	2(25.0)	0.391
Imaging features, n (%)	316(85.9)	74(82.2)	61(96.8)	5(71.4)	13(76.5)	21(70.0)	67(91.8)	6(75.0)	
Consolidation or mass	163(51.6	41(55.4)	23(37.7)	3(60.0)	5(38.5)	7(23.3)	19(28.4)	5(83.3)	0.005
Ground-glass opacity	203(64.2)	50(67.6)	29(47.5)	2((40.0)	8(61.5)	16(53.3)	51(76.1)	4(66.7)	0.04
Total pathogenic positive rate									
Bacteria	104(28.3)	29(32.2)	31(49.2)	2(28.6)	2(11.8)	11(36.7)	18(24.7)	4(50.0)	0.015
PCP	63(17.1)	40(44.4)	10(15.9)	0(0)	4(23.5)	3(10.0)	12(16.4)	3(37.5)	<0.001
Aspergillus	33(9.0)	9(10.0)	26(41.3)	0(0)	1(5.9)	5(16.7)	10(13.7)	2(25.0)	<0.001
CMV	85(23.1)	41(45.6)	15(23.8)	3(42.9)	8(47.1)	4(13.3)	26(35.6)	5(62.5)	<0.001
Non-CMV virus	56(15.2)	12(13.3)	47(74.6)	2(28.6)	4(23.5)	3(10.0)	28(38.4)	1(12.5)	<0.001

Variables	Connective tissue disease, N=368	Nephrotic syndrome or chronic glomerulonephritis, N=90	Solid organ transplant, N=63	Bone marrow or HSCT, N=7	Lymphoma, N=17	Bronchial asthma or COPD, N=30	Idiopathic interstitial pneumonia, N=73	Radiation pneumonitis, N=8	*P* value
Treatment, before admission, n (%)									
High-dose steroids use	140(38.0)	32(35.6)	3(4.8)	1(14.3)	9(52.9)	7(23.3)	27(37.0)	3(37.5)	<0.001
Accumulated dose of glucocorticoids, methylprednisolone, g (IQR)	5.4(2.4, 13.7)	3.8(2.5, 6.6)	1.9(0.9, 3.3)	1.3(0.6, 7.3)	2.9(2.4, 36)	0.6(0.3, 2.4)	3.6(2.0, 6.5)	5.9(3.1, 6.7)	<0.001
Time of steroids use (month)	5.9(2.0, 29.8)	3.0(3.0, 11.0)	7.0(2.0, 15.0)	6.0(3.0, 18.0)	3.5(2.0, 5.0)	1.0(1.0,13.5)	3.5(2.0, 12.0)	3.0(2.0, 8.0)	0.024
Receiving other immunosuppressants	257(69.8)	48(53.3)	63(100.0)	6	9(52.9)	0(0)	17(23.3)	1(12.5)	<0.001
Complications, n (%)									
Noninvasive ventilation	98(26.6)	25(27.8)	8(12.7)	1(14.3)	4(23.5)	3(10.0)	19(26.0)	2(25.0)	0.183
Invasive mechanical ventilation	89(24.2)	25(27.8)	10(15.9)	1(14.3)	4(23.5)	6(20.0)	24(32.9)	0(0)	0.237
Respiratory failure	179(48.6)	58(64.4)	24(38.1)	3(42.9)	6(35.3)	14(46.7)	41(56.2)	3(37.5)	0.040
ICU care	152(41.3)	49(54.4)	14(22.2)	3(42.9)	6(35.3)	6(20.0)	35(47.9)	1(12.5)	0.001
Septic shock	68(18.5)	25(27.8)	15(23.8)	2(28.6)	4(23.5)	5(16.7)	20(27.4)	2(25.0)	0.481
Extracorporeal membrane oxygenation	15(4.1)	4(4.4)	4(6.3)	0(0)	1(5.9)	0(0)	10(13.7)	0(0)	0.044
30-day mortality	88(23.9)	23(25.6)	8(12.7)	2(28.6)	3(17.6)	4(13.3)	17(23.3)	2(25.0)	0.509
90-day mortality	103(28.0)	25(27.8)	9(14.3)	2(28.6)	4(23.5)	6(20.0)	20(27.4)	2(25.0)	0.528

HSCT: hematopoietic stem cell transplant; COPD: chronic obstructive pulmonary disease

Cox regression analysis indicated that the following factors were independent predictors of 30-day and 90-day mortality in both glucocorticoid with immunosuppressant and glucocorticoid only groups with CAP: septic shock, respiratory failure, and persistent lymphocytopenia. In the glucocorticoid-only group, high-dose corticosteroid and invasive mechanical ventilation were independent negative predictors of 90-day mortality (Table 6). Interstitial lung disease and mechanical ventilation were independent negative predictors of 90-day mortality in the glucocorticoid and immunosuppressants group (Table 7).

Table 6 Cox regression analysis of prognostic factors in glucocorticoid users with community acquired pneumonia patients

Variables	30-day mortality			90-day mortality		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Septic shock	5.874	3.210-10.750	<0.001	4.900	2.685-8.941	<0.001
Respiratory failure	8.625	2.580-28.832	<0.001	8.757	2.554-30.024	0.001
Persistent lymphocytopenia	2.069	1.183-3.621	0.011	1.757	1.049-2.941	0.032
Invasive mechanical ventilation	-	-	-	2.240	1.251-4.010	0.007
High-dose steroids	1.989	1.145-3.456	0.015	-	-	-

Table 7 Cox regression analysis of prognostic factors in glucocorticoid and immunosuppressants users with community acquired pneumonia patients

Variables	30-day mortality			90-day mortality		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Septic shock	4.438	2.783-7.077	<0.001	4.030	2.549-6.370	<0.001
Interstitial lung disease	-	-	-	1.678	1.099-2.562	0.017
Respiratory failure	48.238	6.568-354.301	<0.001	35.106	4.560-270.244	0.001
Persistent lymphocytopenia	1.714	1.046-2.810	0.033	1.648	1.047-2.594	0.031
Mechanical ventilation				1.949	1.031-3.685	0.040

DISCUSSION

This study was the first large-scale retrospective investigation of the etiology and the prognostic risk factors of pneumonia in patients with glucocorticoid use. The main findings of the present study are summarized as follows: (1) more than 60% of the patients developed pneumonia within 6 months of glucocorticoid therapy initiation, especially those with PCP and CMV pneumonia; (2) persistent lymphocytopenia was associated with significantly higher rates of infection by opportunistic pathogens, mixed pathogen types, and MDR bacteria; (3) patients using high-dose glucocorticoids were significantly more likely to develop opportunistic pneumonia than those using low-dose glucocorticoids; (4) the 30-day and 90-day mortality of non-CMV and CMV viral pneumonia were similar, but lower than PCP; (5) septic shock, respiratory failure, mechanical ventilation, interstitial lung disease, and persistent lymphocytopenia were independent predictors of 90-day mortality in GP.

The use of glucocorticoid and other immunosuppressive agents are risk factors for the development of CMV, *Pneumocystis*, *Aspergillus*, and other opportunistic infections. [18-23] . A review of 33 pneumonia patients with long-term glucocorticoid use showed that *Staphylococcus aureus* was the most common pathogen, with a wide range of other causative pathogensincluding bacteria, fungi, viruses, *Pneumocystis*, and *Mycobacterium*. [1] In an international multicenter study of immunocompromised patients, with chronic steroid users accounted for 45% of the patients,[24] which found the main causative pathogens for pneumonia were *Streptococcus pneumoniae, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus*, influenza viruses, and PCP. In our study, the most common isolated pathogen types were bacterial, CMV, non-CMV viruses, PCP, *Aspergillus* or *Cryptococcus*, *Mycoplasma pneumoniae or Legionella, and Mycobacterium tuberculosis or Nontuberculosis mycobacteria.* For bacterial infections, *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae*, *and Staphylococcus aureus* were most common possibly due to antibiotic therapy before admission. In some patients, the timing of the BAL or sputum sampling was more than 48 hours after admission, which might increase the nosocomial etiology such as *Acinetobacter baumannii*.

The associations between mixed pulmonary infections and treatment with glucocorticoids for nephrotic syndrome, lung transplantation, and other disorders requiring immunosuppression

have reported.[25-27] We found mixed infections in more than 50% of the patients. The glucocorticoid use may also be a risk factor for MDR bacterial infection. We demonstrated that the MDR bacterial infection was significantly higher in the high-dose steroid and the persistent lymphocytopenia subgroups. When treating pneumonia in patients with high-dose steroids or those with persistent lymphocytopenia, MDR pathogens must be considered when selecting antimicrobial agents. A low $CD4^+$ T-lymphocyte count is known to associate with PCP infection.[30 31] Moreover, low absolute lymphocyte count and prolonged high-dose steroid therapy are predictors of PCP and CMV infections. [32-39] Yang demonstrated that the average time until the diagnosis of PCP was only 2.4 months after immunosuppressant initiation in glomerulonephritis patients. [40] Our results resonate with the importance of considering PCP infection in patients receiving chronic, high-dose glucocorticoid. This study also indicates that high-dose glucocorticoid use is associated with *Mycobacterium tuberculosis* and *Aspergillus* pneumonia. It has been shown that glucocorticoids have profound effects on the distributions and functions of immune cells, including decreasing macrophage antifungal activity through inhibiting reactive oxidant intermediates and directly stimulating the growth of *Aspergillus fumigatus*.[41]

Respiratory viruses have also been recognized as a potential cause of pneumonia and death in immunocompromised individuals with hematopoietic stem cell transplants or hematologic malignancies. Jacobs found a 25% overall 30-day mortality in 32 patients with hematologic malignancies with human rhinovirus lower respiratory tract infection. [42] Slightly higher mortality (27%) was observed by Dimpy in patients with lower respiratory tract infections caused by parainfluenza virus in hematopoietic cell transplant recipients and hematologic malignancy patients.[43] Chatzis showed that 21.3% of an immunocompromised adult cohort with RSV pneumonia required ICU transfer with nearly 20% mortality. [44] Crotty conducted an observational cohort study of 284 patients with viral pneumonia, in which the majority (51.8%) were immunocompromised and the overall in-hospital mortality was high (23.2%). [45] In our study, the 90-day mortality was 24.2% in non-CMV viral pneumonia which was similar to CMV (27.4%) but lower than PCP (38.1%, $P<0.05$). Therefore, it is important to include in viral etiology in the differential diagnosis in pneumonia of those on corticosteroid. The presence of ground-glass lesions on CT imaging should prompt the consideration of PCP and viral infections. Viral nucleic acid and PCP testing should be obtained, and targeted antimicrobial treatment should be started as

early as possible.

Overall mortality from pulmonary infections in patients receiving long-term glucocorticoid therapy can be as high as 45%, [1] with a similar rate in patients with other causes of immunosuppression. [21] Respiratory failure and the need for mechanical ventilation have been shown to be the strongest predictors of mortality in immunocompromised patients with or without pneumonia. [46 47] Lymphoctopniapenia is also significantly associated with increased mortality in non-HIV-infected patients with PCP or viral pneumonia. [32 48] Vial-Dupuy indicated high-dose steroids during ICU stay (OR=0.19; [95% CI, 0.04-0.99]) were independent determinants of in-hospital mortality in patients with interstitial lung disease admitted to the ICU[49]. Kotani's study indicated interstitial lung disease was a risk factor associated with the mortality of Pneumocystis jirovecii pneumonia (PCP) who required mechanical ventilation .[50] Our research pointed out that patients on high-dose glucocorticoid, persistent lymphocytopenia, and interstitial lung disease may convey a poor prognosis.

There are several limitations to this study. First, it had a retrospective design. Second, not all patients with pneumonia underwent a full array of pathogen testing, thus the pathogen identification and diagnosis might be incomplete. Third, some pathogens were not identified until at least 48 hours after admission, which increases the possibility of nosocomial infections. Despite these limitations, our results are consistent with the existing literature and provide more detailed insights into the clinical characteristics, pathogenic etiologies, and prognostic factors that should be carefully considered when managing patients on glucocorticoid therapy.

CONCLUSIONS

Patients receiving glucocorticoid therapy with pneumonia experience higher rates of infection with opportunistic pathogens, significant morbidity, and high mortality, especially with specific risk factors. This information should be carefully considered when determining treatment strategies for this patient population.

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JP, JL. Statistical analysis: LL, SH.H. GX. Writing: LL, BC, SH.H. 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.

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Patient consent: A consent was obtained from all patients. A waiver of consent was granted by the Ethic Committee of China-Japan Friendship Hospita in collaboration with all participating institutions to submit and collect anonymized data.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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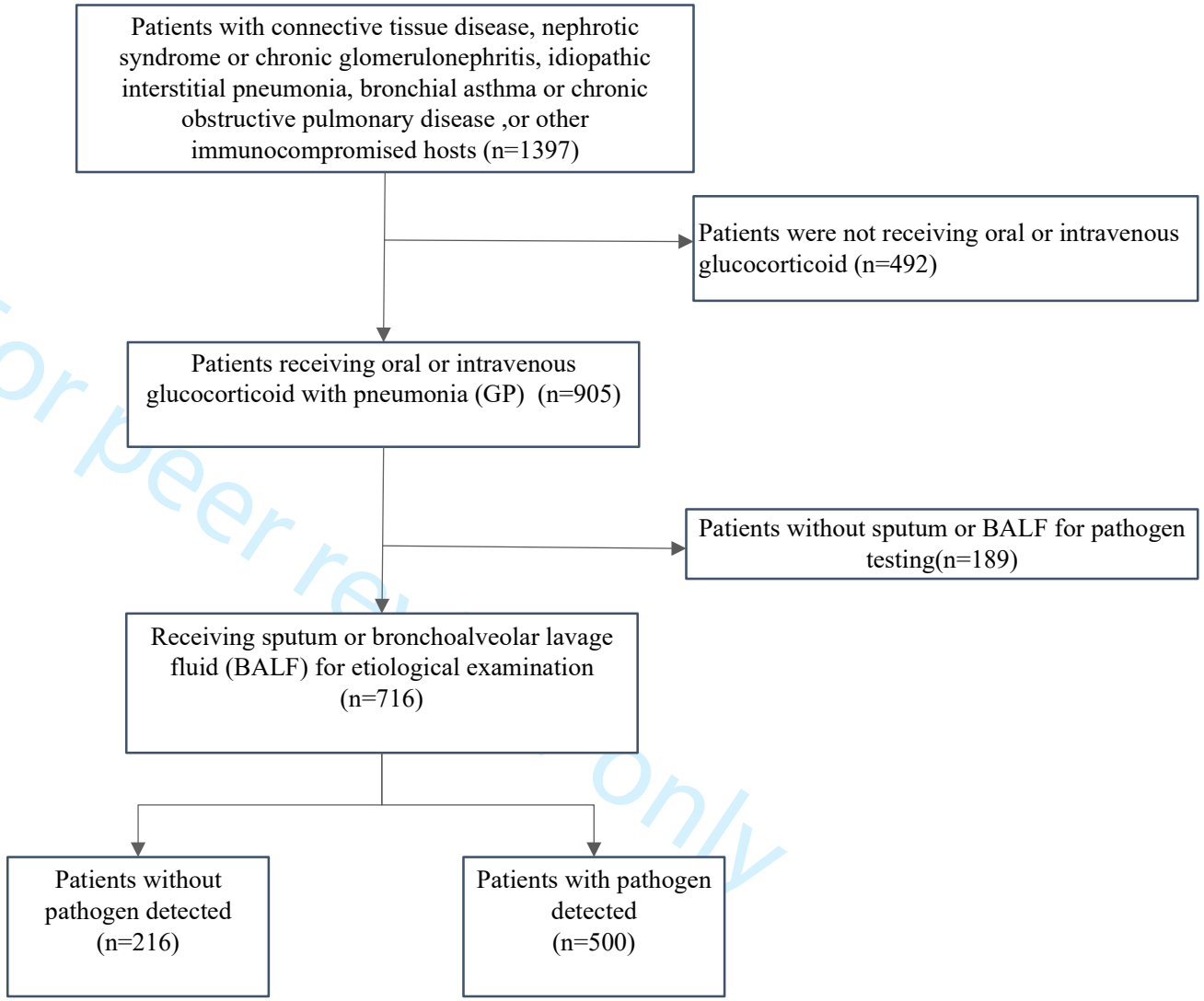
Figure legend/caption:

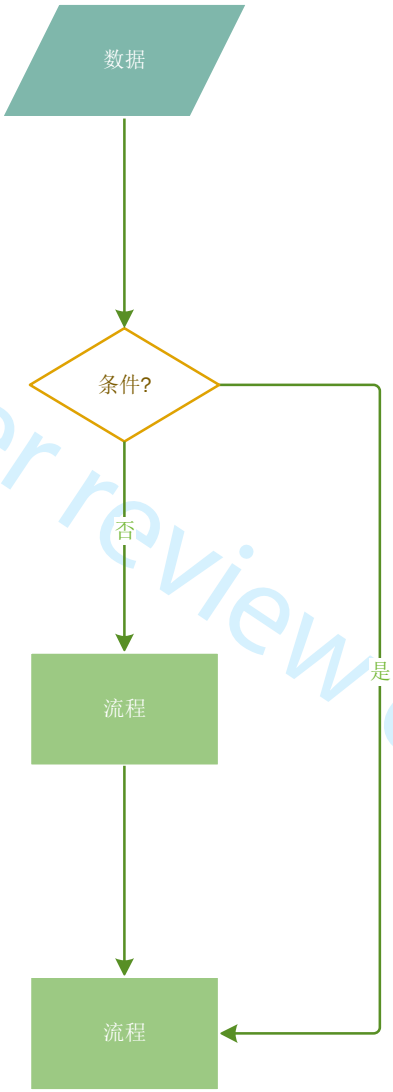
Figure1: Study flowchart

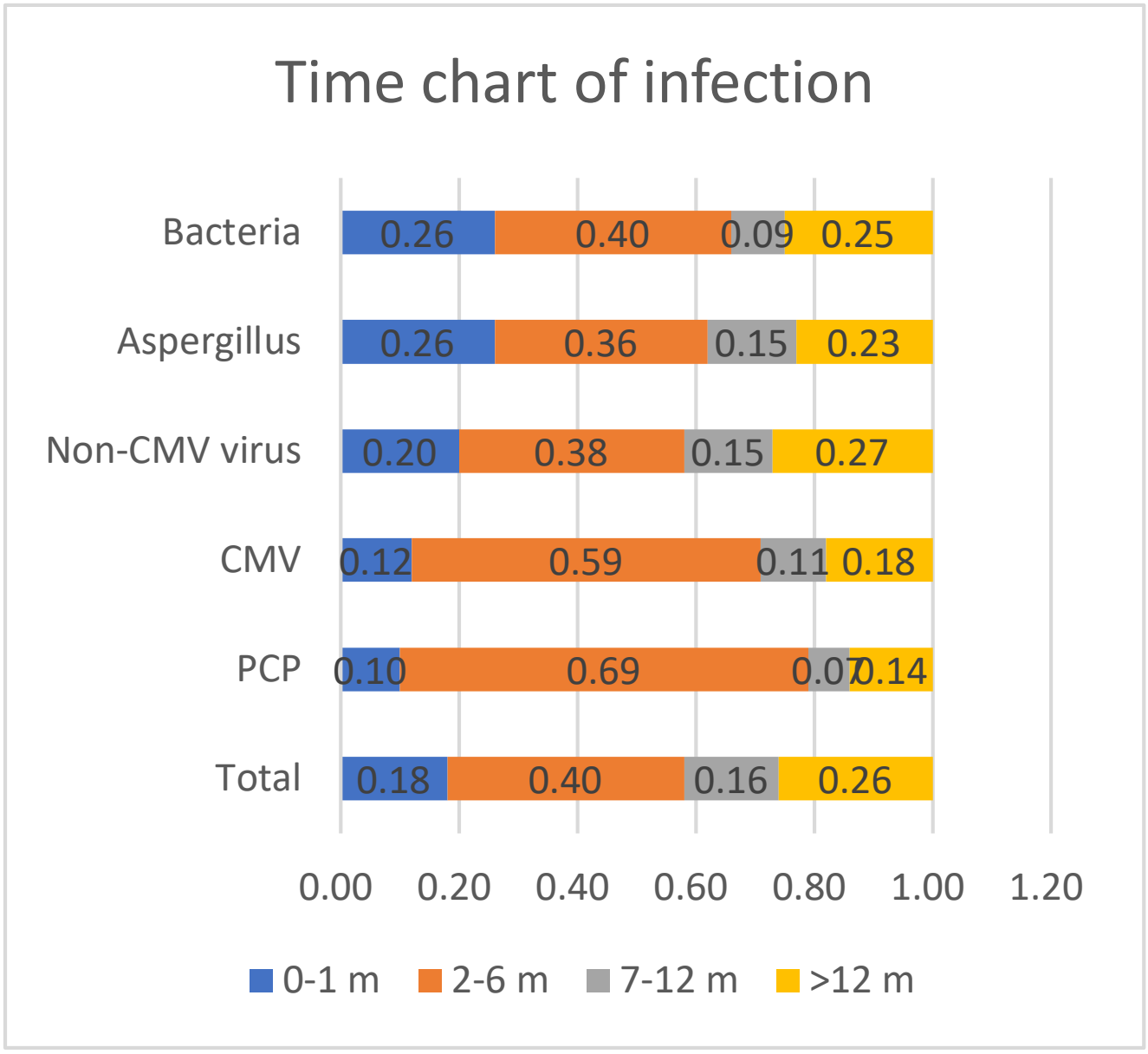
Figure2: Duration of glucocorticoid use among glucocorticoid users with pneumonia

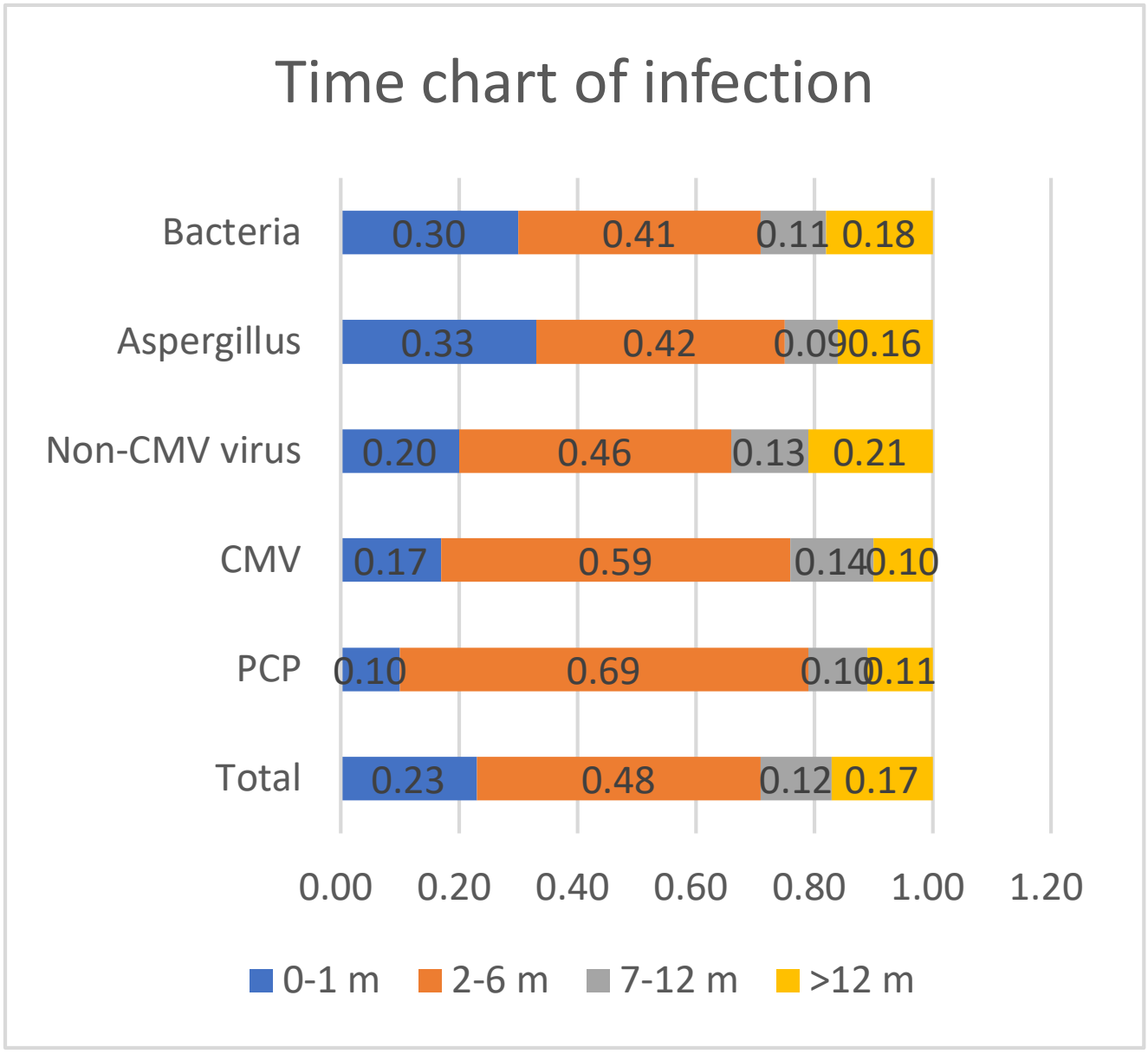
Figure3: Duration of glucocorticoid use among only glucocorticoid users with pneumonia

Figure4: Duration of glucocorticoid use among glucocorticoid and immunosuppressant users with pneumonia






Time chart of infection
Bacteria
0.26
0.40
0.09
0.25
Aspergillus
0.26
0.36
0.15
0.23
Non-CMV virus
0.20
0.38
0.15
0.27
CMV
0.12
0.59
0.11
0.18
PCP
0.10
0.69
0.07
0.14
Total
0.18
0.40
0.16
0.26
0.00
0.20
0.40
0.60
0.80
1.00
1.20
0-1 m
2-6 m
7-12 m
>12 m


Time chart of infection
Bacteria
0.30
0.41
0.11
0.18
Aspergillus
0.33
0.42
0.09
0.16
Non-CMV virus
0.20
0.46
0.13
0.21
CMV
0.17
0.59
0.14
0.10
PCP
0.10
0.69
0.10
0.11
Total
0.23
0.48
0.12
0.17
0.00
0.20
0.40
0.60
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1.00
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0-1 m
2-6 m
7-12 m
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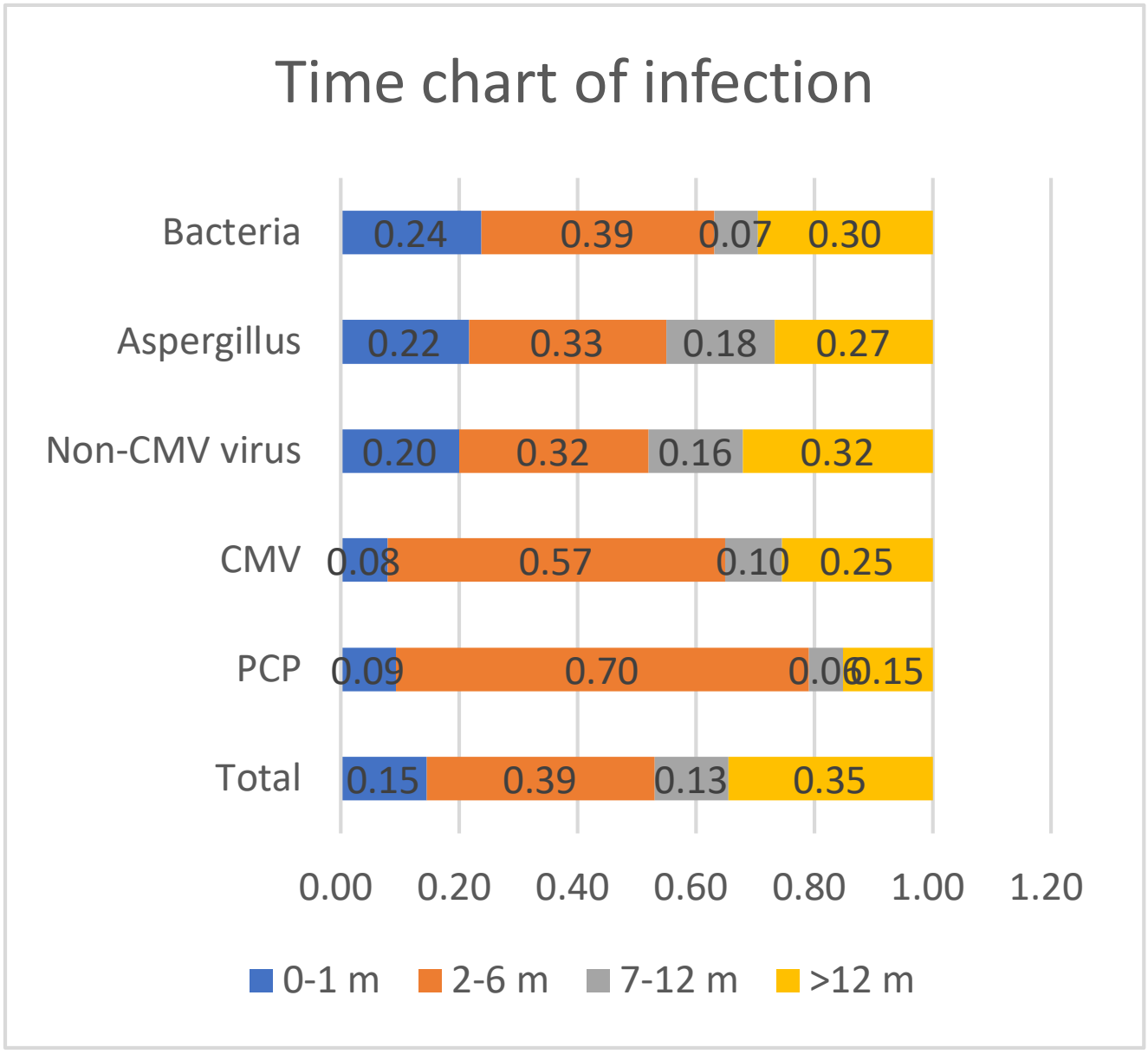
Time chart of infection
Bacteria
0.24
0.39
0.07
0.30
Aspergillus
0.22
0.33
0.18
0.27
Non-CMV virus
0.20
0.32
0.16
0.32
CMV
0.08
0.57
0.10
0.25
PCP
0.09
0.70
0.06
0.15
Total
0.15
0.39
0.13
0.35
0.00
0.20
0.40
0.60
0.80
1.00
1.20
0-1 m
2-6 m
7-12 m
>12 m

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	2-3
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7 and Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8,Table3
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Aetiology and prognostic risk factors of mortality in pneumonia patients receiving glucocorticoids alone or glucocorticoids and other immunosuppressants: a retrospective cohort study

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Aetiology and prognostic risk factors of mortality in pneumonia patients receiving glucocorticoids alone or glucocorticoids and other immunosuppressants: a retrospective cohort study

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ABSTRACT

Objectives: Long-term use of high-dose glucocorticoids can lead to severe immunosuppression and increased risk of treatment-resistant pneumonia and mortality. We investigated the aetiology

and prognostic risk factors of mortality in hospitalised patients who developed pneumonia while receiving glucocorticoid therapy alone or glucocorticoid and other immunosuppressant therapies.

Design: Retrospective cohort study

Setting: Six secondary and tertiary academic hospitals in China

Participants: Patients receiving glucocorticoids who were hospitalised with pneumonia between 1st January 2013 and 31st December 2019.

Main Outcomes: We analysed the prevalence of comorbidities, microbiology, antibiotic susceptibility patterns, 30-day and 90-day mortality rates, and prognostic risk factors.

Results: A total of 716 patients were included, with pneumonia pathogens identified in 69.8% of patients. Significant morbidities occurred, including respiratory failure (50.8%), intensive care unit (ICU) transfer (40.8%), and mechanical ventilation (36%), with a 90-day mortality rate of 26.0%. Diagnosis of pneumonia occurred within 6 months of glucocorticoid initiation for 69.7% of patients with *Cytomegalovirus* (CMV) pneumonia and 79.0% of patients with *Pneumocystis jirovecii* pneumonia (PCP). Pathogens, including *Pneumocystis*, CMV, and multidrug-resistant bacteria, were identified more frequently in patients with persistent lymphocytopenia and high-dose glucocorticoid treatment (≥ 30 mg/day of prednisolone or equivalent within 30 days before admission). The 90-day mortality rate was significantly lower for non-CMV viral pneumonias than for PCP ($P < 0.05$), with a similar mortality rate as CMV pneumonias (24.2% vs 38.1% vs 27.4%, respectively). Cox regression analysis indicated several independent negative predictors for mortality in this patient population, including septic shock, respiratory failure, persistent lymphocytopenia, interstitial lung disease, and high-dose glucocorticoid use.

Conclusions: Patients who developed pneumonia while receiving glucocorticoid therapy experienced high rates of opportunistic infections, with significant morbidity and mortality. These findings should be carefully considered when determining treatment strategies for this patient population.

KEYWORDS: Pneumonia; Immunocompromised; Glucocorticoids; Prognosis.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first large-scale investigation of the aetiologies and prognostic risk factors of pneumonia in patients using glucocorticoids.
- This study had several strengths, including a large sample size from multiple centres (six hospitals in China) and examinations of sputum or bronchoalveolar lavage samples in all patients.
- In this retrospective study, all pneumonia patients did not undergo the full array of pathogen testing, and some pathogens were not identified until at least 48 hours after admission, increasing the probability of nosocomial infections.

INTRODUCTION

Long-term use of glucocorticoids at high doses may result in severe immunosuppression and serious infections.[1] Pulmonary infections occur most commonly in this context and remain one of the leading causes of death in immunocompromised patients.[1-4] Infections caused by opportunistic pathogens, including *Cytomegalovirus* (CMV), *Pneumocystis jiroveccii*, and *Aspergillus*, have been reported in immunocompromised patients receiving glucocorticoids.[2-4] Mortality rates of up to 45% have been identified in patients with rheumatic diseases treated with long-term glucocorticoid therapy who develop pulmonary infections, with rates increasing to 93% for those requiring mechanical ventilation.[1] The paucity of studies related to patients who develop pneumonia while receiving glucocorticoid therapy may lead to an underestimation of pneumonia prevalence and an overestimation of disease burden in this patient population. These assumptions may result in mismanagement, with excessive use of broad-spectrum antibiotics and treatment failure due to absence of therapeutic guidance based on pathogenic data. Given the significant morbidity and mortality associated with glucocorticoid-induced immunosuppression, our study aimed to identify the clinical characteristics, pathogenic aetiologies, and prognostic risk factors of pneumonia in this population.

METHODS

Study design and participants

We retrospectively recruited patients with pneumonia who were hospitalised between 1st January 2013 and 31st December 2017 at six secondary and tertiary academic hospitals in China. Pneumonia diagnoses were based on the American Thoracic Society and Infectious Disease Society of America's (ATS/IDSA) guidelines.[5, 6] Pneumonia was defined as the presence of a new pulmonary infiltrate with infiltrative changes identified on chest radiography or computed tomography (CT) imaging combined with one or more of the following clinical manifestations: (1) recent cough, sputum production or aggravation of respiratory symptoms, and emergence of purulent sputum with or without chest pain; (2) fever (defined as an axillary temperature of ≥ 37.3°C) or hypothermia (defined as an axillary temperature < 36°C); (3) clinical signs of pulmonary consolidation and/or presence of moist crackles; or (4) white cell count > 10×10^9/L or < 4×10^9/L, with or without neutrophilic predominance. We identified patients with connective

tissue diseases, nephrotic syndrome or chronic glomerulonephritis, idiopathic interstitial pneumonia, bronchial asthma, chronic obstructive pulmonary disease, or other causes for immunosuppressive therapy. Study patients were then selected based on the following inclusion criteria: (1) oral or intravenous glucocorticoid treatment [7-9] before admission; (2) pneumonia diagnosis on admission or during hospitalisation; and (3) at least 16 years of age. The exclusion criteria were as follows: (1) diagnosis of noninfectious pulmonary diseases, including lung cancer, interstitial lung diseases without infection, pulmonary embolism, or heart failure; (2) inability to provide consent for procedures.

Study quality control

Key investigators, including clinicians, statisticians, microbiologists, and radiologists, worked together to draft the protocol and to 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 data were collected, CRFs were reviewed by a trained researcher to ensure completeness and data quality. The study was led and approved by the Ethics Committee at China-Japan Friendship Hospital with centralised collaboration between all participating hospitals, including anonymised data submission and collection.

Data collection

The following data were collected from medical records of patients during their hospitalisations: (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 noninvasive mechanical ventilation, pneumonia severity index [PSI] score, and/or CURB-65 score);[10-12] (5) laboratory and microbiological data (blood, sputum and/or bronchoalveolar lavage 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 and 90 days after admission. High-dose steroid use was defined as equal to or greater than 30 mg per day of prednisolone or an equivalent glucocorticoid within 30 days before admission. Persistent lymphocytopenia was defined as a peripheral blood lymphocyte count lower than 1×10^9/L for greater than 7 days.

Diagnostic procedures

After identification of pulmonary infiltrates on chest imaging, bronchoalveolar lavage (BAL) or sputum samples were obtained by treating physicians, and microorganisms were identified and tested for drug sensitivities. Bronchoscopic examinations were performed according to general guidelines. Lidocaine spray was applied to the upper airway and carina for local anaesthesia, and airways were thoroughly examined. BAL was performed by instilling 60 to 120 mL of a sterile saline solution 2 to 4 times into the distal bronchial tree, either at the affected lobe or in the middle lung lobe with more radiographic abnormalities. BAL specimens were aliquoted and immediately transported to laboratories. Bacterial cultures were incubated at 35℃ in 5% to 10% CO_2 for 48 hours. If *Nocardia* was suspected, the incubation time was prolonged. Fungal cultures were incubated at 27℃ for 5 days under ambient conditions. Species were identified using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (Brooks Instrument, Germany) or a BACTEC 9102 culture instrument (BD Biosciences, USA). Respiratory viral and atypical pathogens were detected by polymerase chain reactions (PCR) (Shanghai Zhijiang Biological Technology, China). The Platelia Aspergillus test was used for galactomannan detection (Bio-Rad Laboratories, Marnes-la-Coquette, France).

Pathogen-specific diagnostic information

We defined multidrug-resistance (MDR) in specific organisms using the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) criteria. We included the following species in this category: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBL). *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and other nonfermenting Gram-negative bacilli were considered to be MDR pathogens if not susceptible to at least one agent in three or more antimicrobial categories. [13, 14]

For diagnoses of pneumonias caused by atypical pathogens, including *Legionella* spp, *Mycoplasma pneumoniae*, and *Mycobacterium* spp, we used PCR to identify bacterial DNA. Diagnoses of viral pneumonias were based on positive nucleic acid tests. For diagnosis of an *Aspergillus* pneumonia, 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) positive *Aspergillus* culture from BAL, (3) galactomannan optical index on BAL of ≥ 1, (4) galactomannan optical index on serum of ≥ 0.5, or (5) *Aspergillus* species identified by culture characteristics and microscopic morphology.[15, 16]

Diagnosis of PCP required the following criteria: (1) high-resolution CT (HRCT) imaging showing diffuse ground-glass opacity (GGO) with a patchy distribution and (2) microscopic examination of respiratory samples demonstrating *Pneumocystis* cystic or trophic forms or *Pneumocystis* DNA identified using PCR.[17]

Statistical analysis

Demographics, clinical characteristics, and pathogen testing results were expressed as means (± standard deviation), medians (interquartile range), or numbers (percentage). Group comparisons were conducted using the Student's *t*-test or Wilcoxon rank-sum test for continuous variables with or without normal distributions, respectively. Categorical variables were compared between groups using the χ^2 test. Histogram charts were used to depict glucocorticoid application timelines. Distributions for the duration of glucocorticoid use in patients with different respiratory pathogens were also compared using the χ^2 test. Cox regression models were used to analyse the associations of septic shock, interstitial lung diseases, invasive and noninvasive mechanical ventilation, partial pressure of arterial oxygen and fraction of inspired oxygen ratio (PaO_2/FiO_2), and persistent lymphocytopenia with 30-day and 90-day mortality. In the Cox analysis, adjustments were made for age, gender, noninvasive mechanical ventilation, invasive mechanical ventilation, respiratory failure, septic shock, ICU admission, high-dose corticosteroid use, persistent lymphocytopenia, interstitial lung disease, PSI score, CURB65 score, PCP, and CMV and non-CMV viral infections.

Statistical analyses were performed using SPSS, version 19.0 (SPSS, Inc., Chicago, Illinois). All tests were two-sided, and a *P*-value of < 0.05 was considered to indicate statistical significance.

Patient and public involvement

Neither patients nor the public were involved in the development of the research question, study design, patient recruitment, nor the conduct of the study.

RESULTS

In total, 1,397 immunocompromised patients who developed pneumonia between 1st January

2013 and 31st December 2017 were identified. After excluding patients who were not receiving oral or intravenous glucocorticoids (N = 492) and those without sputum or BAL for pathogen testing (N = 189), 716 patients with pneumonia who were receiving glucocorticoids were included in the final analysis (Figure 1). Approximately 48% of study patients were female, with a median age of 60. The main presenting symptoms included fever (74.6%), cough (87.7%), and dyspnoea (60.2%). The most common underlying immune-related diseases were connective tissue diseases (52.1%), interstitial lung disease (45.3%), diabetes (25%), and nephrotic syndrome or chronic glomerulonephritis (12.8%). The average duration (IQR) of glucocorticoid use was 4 (2,18) months. The positivity rate for pathogen testing was 69.8% (500/716). Among the 292 (40.8%) patients who required ICU admission, 24.2% and 24% received noninvasive and invasive ventilation, respectively. The 30-day and 90-day mortality rates were 22.6% and 26.0%, respectively. Complication rates were similar between patients using glucocorticoids alone and patients using glucocorticoids with other immunosuppressants (Table 1).

Table1 Clinical characteristics of pneumonia between glucocorticoid users and those glucocorticoids with immunosuppressants users

Variables	Total, N=716	Glucocorticoid users, N=297	Glucocorticoid with immunosuppressants* users, N=419	P-Value
Sex, female, n (%)	341(47.6)	123(41.4)	218(52.0)	0.005
Age, median (IQR)	60(49, 68)	62.0(52.0, 70.0)	59.0(46.0, 67.0)	<0.001
Symptoms and signs, n (%)				
Fever	534(74.6)	225(75.8)	309(73.7)	0.543
Cough	628(87.7)	267(89.9)	361(86.2)	0.133
Sputum production	580(81.0)	239(80.5)	341(81.4)	0.829
Dyspnea	431(60.2)	185(62.3)	246(58.7)	0.335
Disturbance of consciousness	40(6.2)	11(3.7)	29(6.9)	0.065
Laboratory examination				
White blood cell, $\times 10^9$/L (IQR)	7.94(5.79, 11.60)	9.27 (6.37, 12.63)	7.51 (5.37, 10.97)	<0.001
Neutrophils, $\times 10^9$/L (IQR)	6.49(4.28, 10.08)	7.35(4.89, 10.83)	6.05 (4.10, 9.35)	<0.001
Lymphocyte, $\times 10^9$/L (IQR)	0.85(0.50, 1.38)	0.95 (0.60, 1.46)	0.80 (0.45, 1.30)	0.004
Persistent lymphocytopenia	304(42.7)	113(38.0)	191(45.6)	0.044
Mean hemoglobin±SD, g/L	111.8±23.9	113.1±24.2	108.4±22.8	0.034
Mean albumin±SD, g/L	32.4±6.4	33.3±6.2	29.9±6.1	<0.001
Lactate dehydrogenase, U/L	328.5(227.8, 506.0)	338.0 (226.0, 528.0)	312.0 (228.5, 495.0)	0.525
Blood urea nitrogen, mmol/L	6.28(4.60, 9.80)	6.24 (4.60, 9.40)	6.50 (4.63, 10.24)	0.372

Variables	Total, N=716	Glucocorticoid users, N=297	Glucocorticoid with immunosuppressants* users, N=419	P-Value
Serum creatinine, mmol/L	64.0(50.8, 90.2)	62.6 (50.0, 81.2)	65.9 (51.1, 99.1)	0.157
Procalcitonin, ng/ml	0.28(0.12, 0.77)	0.29 (0.14, 0.71)	0.27(0.11, 0.81)	0.613
Oxygenation index	241.4(126.6, 347.6)	228.0(128.1, 351.2)	243.1(122.4, 347.6)	<0.001
Severe pneumonia index score	76.5(59.3, 101.0)	77.0(60.0, 103.0)	76.0(57.0, 100.0)	0.845
CURB65 score>1	211(29.5)	88(29.6)	123(1.0, 2.0)	0.937
Underlying immune defect, n (%)				
Diabetes mellitus	179(25.0)	63(21.2)	116(27.7)	0.049
Tumor	43(6.0)	20(6.7)	23(5.5)	0.490
Connective tissue disease**	368(51.4)	111(37.4)	257(61.3)	<0.001
Interstitial lung disease	324(45.3)	115(38.7)	209(49.9)	0.003
Nephrotic syndrome or chronic glomerulonephritis	90(12.6)	42(14.1)	48(11.5)	0.286
Idiopathic interstitial pneumonia	73(10.2)	56(18.9)	17(4.1)	<0.001
Bronchial asthma or chronic obstructive pulmonary disease	30(4.2)	30(10.1)	0(0)	<0.001
Lymphoma	17(2.4)	8(2.7)	9(2.1)	0.628
Bone marrow or hematopoietic stem cell transplant	7(1.0)	1(0.3)	6(1.4)	0.144
Solid organ transplant	63(8.8)	0(0)	63(15.0)	<0.001
Radiation pneumonitis	8(1.1)	7(2.4)	1(0.2)	0.008
Other immunocompromised hosts†	65(9.1)	46(15.5)	19(4.5)	<0.001
Bronchoalveolar lavage, n (%)	366(51.1)	248(83.5)	118(28.2)	<0.001
Total pathogenic positive rate	500(69.8)	218(73.4)	282(67.3)	0.080
Treatment, before admission, n (%)				
High-dose steroids(>1mg/kg/day)	216(30.2)	134(45.1)	82(19.6)	<0.001
Time of steroids use, median (IQR), month	4.0(2.0, 18.0)	3.0(1.6, 9.0)	6.0(2.0, 24.0)	<0.001
Accumulated dose of glucocorticoids, methylprednisolone, g (IQR)	38(1.9, 8.8)	3.0(1.5, 5.4)	4.8(2.2, 12.5)	<0.001
Antibiotics	502(70.1)	219(73.7)	283(67.5)	0.074
Antiviral drugs	113(15.8)	44(14.8)	69(16.5)	0.550
Treatment, during hospitalization, n (%)				
Anti - Pseudomonas aeruginosa drugs	547(76.4)	220(74.1)	327(78.0)	0.218
Voriconazole or caspofungin	282(39.4)	105(35.4)	177(42.2)	0.063
Ganciclovir	336(46.9)	120(40.4)	216(51.6)	0.003
Trimethoprim	333(46.5)	111(37.4)	222(53.0)	<0.001
Complications, n (%)				
Noninvasive ventilation	173(24.2)	63(21.2)	110(26.3)	0.121
Invasive mechanical ventilation	172(24.0)	70(23.6)	102(24.3)	0.811
Mechanical ventilation	258(36.0)	106(35.7)	152(36.3)	0.872
Respiratory failure	364(50.8)	155(52.2)	209(49.9)	0.543

Variables	Total, N=716	Glucocorticoid users, N=297	Glucocorticoid with immunosuppressants* users, N=419	P-Value
ICU admission	292(40.8)	116(39.1)	176(42.0)	0.429
Septic shock during hospitalization	154(21.5)	64(21.5)	90(21.5)	0.982
CAP	635(88.7)	263(88.6)	372(88.8)	0.924
Extracorporeal membrane oxygenation	36(4.2)	15(5.1)	21(5.0)	0.981
30-day mortality	162(22.6)	66(22.2)	96(22.9)	0.828
90-day mortality	186(26.0)	76(25.6)	110(26.3)	0.842

* other immunosuppressants: methotrexate, cyclosporine, cyclophosphamide, tacrolimus, sirolimus, and azathioprine.

**Connective tissue disorders: rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, systemic sclerosis, Sjogren's syndrome, etc.@ Immunosuppressive drugs: glucocorticoid, tacrolimus, sirolimus, cyclosporine, methotrexate, etc.

†Other immunocompromised hosts: eczema, myelitis, autoimmune encephalitis, idiopathic thrombocytopenic purpura, etc.

MDR bacteria and CMV were more commonly identified in patients with hospital-acquired pneumonias (HAPs) than in those with community-acquired pneumonias (CAPs) ($P < 0.05$) (Table 2). For CAPs, more pathogens were detected in patients with persistent lymphocytopenia than in patients without lymphocytopenia ($P < 0.05$), including *Pneumocystis*, influenza A virus, CMV, and MDR bacteria. Patients on high-dose corticosteroids developed pneumonia more frequently than those on low-dose corticosteroids in both the CAP and HAP groups, with more frequent identification of *Klebsiella pneumoniae,* MDR bacteria, *Pneumocystis*, CMV, and *Mycobacterium tuberculosis* in patients on high-dose corticosteroids than in patients on low-dose corticosteroids in the CAP group ($P < 0.05$). Pathogen positivity rates were higher, and MDR bacteria were more commonly identified in nonsurvivors than in survivors of CAPs or HAPs ($P < 0.05$) (Tables 2 and 3). For non-CMV viral pneumonias, respiratory syncytial virus (RSV, 64 strains) was detected most frequently, followed by influenza A virus (62 strains), human parainfluenza virus (HPIV, 20 strains), influenza B virus (20 strains), human rhinovirus (HRV, eight strains), herpes simplex virus type 1 (HSV-1, four strains), and adenovirus (ADV, nine strains) (Table 2).

Table 2 The pathogen results of glucocorticoid users with community-acquired pneumonias according to different subgroup

Variables, n (%)	CAP, N=635	HAP, N=81	Simple glucocorticoid users, N=263	Glucocorticoid with immunosuppressants users, N=372	Patients discharged alive, N=479	Patients died during hospitalization, N=156	Persistent lymphocytopenia group, N=264	Non-lymphocytopenia group, N=371	Patients use high-dose steroids, N=219	Patients use low-dose steroids, N=416
Total pathogenic positive rate	438(69.0)	62(76.5)	190(72.2)	248(66.7)	321(67.0)	117(75.0)	190(72.0)	248(66.8)	181(82.6)	257(61.8) #
Pathogens covered by CAP therapy	167(26.3)	24(29.6)	79(30.3)	88(23.7)	126(26.3)	41(26.3)	77(29.2)	90(24.3)	70(32.0)	97(23.3) *
Streptococcus pneumoniae	6(0.9)	0(0)	2(0.8)	4(1.1)	6(1.3)	0(0)	2(0.8)	4(1.1)	1(0.5)	5(1.2)
Haemophilus influenzae	2(0.3)	0(0)	1(0.4)	1(0.3)	2(0.4)	0(0)	1(0.4)	1(0.3)	2(0.9)	0(0)
Staphylococcus aureus	18(2.8)	5(6.2)	10(3.8)	8(2.2)	13(2.7)	5(3.2)	10(3.8)	8(2.2)	7(3.2)	11(2.6)
Escherichia coli	16(2.5)	3(3.7)	6(2.3)	10(2.7)	12(2.5)	4(2.6)	7(2.7)	9(2.4)	6(2.7)	10(2.4)
Enterobacter aerogenes	2(0.3)	0(0)	0(0)	2(0.5)	1(0.2)	1(0.6)	1(0.4)	1(0.3)	0(0)	2(0.5)
Enterobacter cloacae	7(1.1)	3(3.7)	3(1.1)	4(1.1)	5(1.0)	2(1.3)	2(0.8)	5(1.3)	4(1.8)	3(0.7)
Klebsiella pneumoniae	43(6.8)	4(4.9)	25(9.5)	18(4.8)	29(6.1)	14(9.0)	20(7.6)	23(6.2)	21(9.6)	22(5.3) *
Pseudomonas	57(9.0)	9(11.1)	28(10.6)	29(7.8)	42(8.8)	15(9.6)	28(10.6)	29(7.8)	24(11.0)	33(7.9)
Proteus mirabilis	3(0.5)	0(0)	1(0.4)	2(0.5)	3(0.6)	0(0)	3(1.1)	0(0)	2(0.9)	1(0.2)
Mycoplasma pneumoniae	6(0.9)	0(0)	1(0.4)	5(1.3)	6(1.3)	0(0)	1(0.4)	5(1.3)	2(0.9)	4(1.0)
Legionella	7(1.1)	0(0)	2(0.8)	5(1.3)	7(1.5)	0(0.6)	2(0.8)	5(1.3)	1(0.5)	6(1.4)
Pathogens not covered by CAP therapy	98(15.4)	24(29.6) #	37(14.1)	61(16.4)	50(10.4)	48(30.8) #	47(17.8)	51(13.7)	35(16.0)	63(15.1)
Acinetobacter	45(7.1)	15(18.5) #	18(6.8)	27(7.3)	22(4.6)	23(14.7) #	27(10.2)	18(4.9)	14(6.4)	31(7.5)
Burkholderia	17(2.7)	2(2.5)	7(2.7)	10(2.7)	3(0.6)	14(9.0) #	6(2.3)	11(3.0)	9(4.1)	8(1.9)
Enterococcus	12(1.9)	2(2.5)	2(0.8)	10(2.7)	7(1.5)	5(3.2)	2(0.8)	10(2.7)	3(1.4)	9(2.2)
Stenotrophomonas maltophilia	13(2.0)	2(2.5)	5(1.9)	8(2.2)	10(2.1)	3(1.9)	7(1.5)	6(1.6)	4(1.8)	9(2.2)
Nocardia	8(1.3)	0(0)	4(1.5)	4(1.1)	6(1.3)	2(1.3)	4(1.5)	4(1.1)	4(1.8)	4(1.0)
Corynebacterium striatum	1(0.2)	2(2.5)	1(0.4)	0(0)	1(0.2)	0(0)	0(0)	1(0.6)	0(0)	1(0.2)
Comamonas acidovorans	1(0.2)	1(1.2)	0(0)	1(0.3)	0(0)	1(0.6)	1(0.4)	0(0)	1(0.5)	0(0)
Cupriavidus pauculus	1(0.2)	0(0)	0(0)	1(0.3)	1(0.2)	0(0)	0(0)	1(0.3)	0(0)	1(0.2)

Multidrug resistance bacteria/ bacteria	108(17.0)	40(49.4) #	68(13.3)	40(10.8)	57(11.9)	51(32.7) #	61(23.1)	47(12.7) #	51(23.3)	57(13.7) #
Fungus	212(33.3)	34(42.0)	80(30.4)	132(35.5)	141(29.4)	71(45.5) #	109(41.3)	103(27.8) #	105(47.9)	107(25.7) #
Pneumocystis	128(20.2)	21(25.9)	48(18.3)	80(21.5)	88(18.4)	40(25.6) *	70(26.5)	58(15.6) #	71(32.4)	57(13.7) #
Aspergillus	81(12.8)	13(16.0)	32(12.2)	49(13.2)	52(10.9)	29(18.6) *	38(14.4)	43(11.6)	33(15.1)	48(11.5)
Rhizopus/ Trichoderma	2(0.3)	0(0)	0(0)	2(0.5)	0(0)	2(1.3)	1(0.4)	1(0.3)	1(0.5)	1(0.2)
Cryptococcus	1(0.2)	0(0)	0(0)	1(0.3)	1(0.2)	0(0)	0(0)	1(0.3)	0(0)	1(0.2)
Virus	355(55.9)	51(63.0)	154(58.6)	201(54.0)	257(53.7)	98(62.8) *	167(63.3)	188(50.7) #	132(60.3)	223(53.6)
Cytomegalovirus	186(29.3)	33(40.7) *	79(30.0)	107(28.8)	133(27.8)	53(34.0)	93(35.2)	93(25.1) #	84(38.4)	102(24.5) #
Influenza A virus	55(8.7)	7(8.6)	29(11.0)	26(7.0)	36(7.5)	19(12.2)	30(11.4)	25(6.7) *	15(6.8)	40(9.6)
Influenza B virus	19(3.0)	1(1.2)	7(2.7)	12(3.2)	15(3.1)	4(2.6)	9(3.4)	10(2.7)	9(4.1)	10(2.4)
Rhinovirus	8(1.3)	0(0)	2(0.8)	6(1.6)	5(1.0)	3(1.9)	5(1.9)	3(0.8)	2(0.9)	6(1.4)
Respiratory syncytial virus	56(8.8)	8(9.9)	27(10.3)	29(7.8)	45(9.4)	11(7.1)	18(6.8)	38(10.2) *	14(6.4)	42(10.1)
Adenovirus	9(1.4)	0(0)	4(1.5)	5(1.3)	8(1.7)	1(0.6)	2(0.8)	7(1.9)	2(0.9)	7(1.7)
Parainfluenza virus	18(2.8)	2(2.5)	5(1.9)	13(3.5)	12(2.5)	6(3.8)	6(2.3)	12(3.2)	4(1.8)	14(3.4)
Herpes simplex virus type 1	4(0.6)	0(0)	1(0.4)	3(0.8)	3(0.6)	1(0.6)	4(1.5)	0(0)	2(0.9)	2(0.5)
Mycobacterium tuberculosis	12(1.9)	0(0)	3(1.1)	9(2.4)	10(2.1)	2(1.3)	5(1.9)	7(1.9)	8(3.7)	4(1.0) *
Nontuberculosis mycobacteria	3(0.5)	0(0)	3(1.1)	0(0)	1(0.2)	2(1.3)	3(1.1)	0(0)	1(0.5)	2(0.5)
Pathogenic types in different groups (Total)	847(133.4)	133(164.2)	356(135.4)	491(132.0)	585(122.1)	262(167.9)	408(154.5)	439(118.3)	351(160.3)	496(119.2)

#:P<0.01, *:P<0.05

Table 3 The pathogen testing result of glucocorticoid users with hospital-acquired pneumonia in different subgroup

Variables, n (%)	Patients discharged alive, N=51	Patients died during hospitalization, N=30	Persistent lymphocytopenia group, N=40	Non-lymphocytopenia group, N=41	Patients use high-dose steroids, N=30	Patients use low-dose steroids, N=51
Total pathogenic positive rate	34(66.7)	28(93.3) #	33(82.5)	29(70.7)	27(90.0)	35(68.6) *
Bacteria	22(43.1)	26(86.7) #	23(57.5)	25(61.0)	21(70.0)	27(52.9)
Staphylococcus aureus	2(3.9)	3(10.0)	2(5.0)	3(7.3)	3(10.0)	2(3.9)
Escherichia coli	2(3.9)	1(3.3)	0(0)	3(7.3)	2(6.7)	1(2.0)
Enterobacter cloacae	0(0)	3(10.0) *	1(2.5)	2(4.9)	1(3.3)	2(3.9)
Klebsiella pneumoniae	1(2.0)	3(10.0)	2(5.0)	2(4.9)	2(6.7)	2(3.9)
Pseudomonas	3(5.9)	6(20.0)	5(12.5)	4(9.8)	3(10.0)	6(11.8)
Acinetobacter	8(15.7)	7(23.3)	8(20.0)	7(17.1)	5(16.7)	10(19.6)
Burkholderia	1(2.0)	1(3.3)	1(2.5)	1(2.4)	1(3.3)	1(2.0)
Enterococcus	2(3.9)	0(0)	2(5.0)	0(0)	1(3.3)	1(2.0)
Stenotrophomonas maltophilia	2(3.9)	0(0)	1(2.5)	1(2.4)	2(6.7)	0(0)
Others bacteria	1(2.0)	2(6.7)	1(2.5)	2(4.9)	1(3.3)	2(3.9)
Multidrug resistance bacteria/ bacteria	11(21.6)	13(43.3) *	13(32.5)	11(26.8)	8(26.7)	16(31.4)
Fungus	21(41.2)	13(43.3)	21(52.5)	13(31.7)	14(46.7)	20(39.2)
Pneumocystis	15(29.4)	6(20.0)	14(35.0)	7(17.1)	10(33.3)	11(21.6)
Aspergillus	6(11.8)	7(23.3)	7(17.5)	6(14.6)	4(13.3)	9(17.6)
Virus	20(39.2)	31(103.3) #	25(62.5)	26(63.4)	20(66.7)	31(60.8)
Cytomegalovirus	16(31.4)	17(56.7) *	18(45.0)	15(36.6)	17(56.7)	16(31.4) *
Influenza A virus	1(2.0)	6(20.0) #	5(12.5)	2(4.9)	2(6.7)	5(9.8)
Influenza B virus	0(0)	1(3.3)	1(2.5)	0(0)	0(0)	1(2.0)
Respiratory syncytial virus	1(2.0)	7(23.3) #	1(2.5)	7(17.1) *	1(3.3)	7(13.7)
Parainfluenza virus	2(3.9)	0(0)	0(0)	2(4.9)	0(0)	2(3.9)

Pathogenic types in different groups (Total)	63(123.5)	70(233.3)	69(172.5)	64(156.1)	55(183.3)	78(152.9)

#:P<0.01, *:P<0.05

Patients with non-CMV viral pneumonias had higher PaO_2/FiO_2 ratios, lower rates of respiratory failure, and lower 30-day and 90-day mortality rates than patients with PCP or CMV pneumonias *(P* < 0.05) (Table 4). There were more PCP and CMV pneumonias in patients with nephrotic syndrome or chronic glomerulonephritis and more *Aspergillus* and non-CMV viral pneumonias in the solid organ transplant group; however, there were no statistically significant differences in mortality rates between patients with different underlying diseases (Table 5).

Time analysis showed that 58.0% of patients developed pneumonia within 6 months of starting glucocorticoid therapy, with 74.0% of patients developing pneumonia within 1 year (Figure 2). Of confirmed PCP cases, 79.0% developed pneumonia within 6 months of starting glucocorticoid therapy, with 86.0% developing pneumonia within 1 year. Of confirmed CMV pneumonia cases, 71.0% developed pneumonia within 6 months of starting glucocorticoid therapy, with 82.0% developing pneumonia within 1 year (Figure 3). For non-CMV viral, *Aspergillus*, and bacterial pneumonias, most patients developed pneumonia within 6 months of starting glucocorticoid therapy, though less frequently than in patients with CMV pneumonia or PCP (Figure 2). The trends in the incidences of these pneumonia types were similar in patients treated with glucocorticoids and other immunosuppressants and in patients treated with glucocorticoids alone (Figures 3 and 4).

Table 4 Comparative analysis of pneumocystis infection group and viral infection group

Variables	Pneumocystis infection group, N=134	Non-CMV viral infection group, N=157	CMV viral infection group, N=95	P-Value
Sex, female, n (%)	65(48.5)	56(35.7)	32(33.7)	0.033
Age, median (IGR)	56.0(45.8,65.0)	60.0(52.0, 68.0)	64.0(53.0, 71.0)	<0.001
Nephrotic syndrome or chronic glomerulonephritis	38(28.4)	10(6.4)	13(13.7)	<0.001
Solid organ transplant	7(5.2)	43(27.4)	5(5.3)	<0.001
Connective tissue disease	58(44.0)	50(33.1)	43(46.3)	0.051
Interstitial lung disease	49(36.6)	95(60.5)	42(44.2)	<0.001
Idiopathic interstitial pneumonia	12(9.1)	28(17.8)	14(14.7)	0.091
Laboratory examination				
White blood cell, $\times10^9$/L (IQR)	8.22 (5.50, 11.46)	8.45 (5.94, 11.59)	7.96(5.77, 12.65)	0.888
Neutrophils, $\times10^9$/L (IQR)	7.12(4.66, 10.50)	6.56 (4.47, 9.51)	6.47(4.39, 10.77)	0.438
Lymphocyte, $\times10^9$/L (IQR)	0.60 (0.40, 1.00)	0.99 (0.60, 1.55)	0.91(0.49, 1.57)	<0.001

Variables	Pneumocystis infection group, N=134	Non-CMV viral infection group, N=157	CMV viral infection group, N=95	P-Value
Persistent lymphocytopenia	74(55.2)	62(39.5)	39(41.1)	0.017
Oxygenation index	154.4(93.6, 251.4)	295.2(171.3, 403.3)	177.8(102.5, 321.0)	<0.001
Severe pneumonia index score	75.5(57.0,105.3)	79.0(61.0, 98.0)	89.0(68.0, 118.0)	0.017
CURB65 score>1	39 (29.1)	46(29.3)	34(35.8)	0.512
Imaging features, n (%), 35missing				
Consolidation or mass	57(42.5)	66(42.0)	41(43.2)	0.547
Ground-glass opacity	102(76.1)	83(52.9)	51(53.7)	<0.001
Treatment, before admission, n (%)				
High-dose steroids(>30mg/day)	73(54.5)	39(24.8)	41(43.2)	<0.001
Accumulated dose of glucocorticoids, methylprednisolone, g (IQR)	3.3(2.2, 5.8)	2.9(1.2, 6.8)	4.0(2.1, 7.4)	0.186
Time of steroids use (month)	3.0(2.0, 5.0)	5.0(2.0, 16.0)	4.0(2.0, 12.0)	0.291
Receiving other immunosuppressants	58(43.3)	67(42.7)	45(47.4)	0.749
Complications, n (%)				
Noninvasive ventilation	51(38.1)	29(18.5)	29(30.5)	0.001
Invasive mechanical ventilation	41(30.6)	43(27.4)	27(28.4)	0.831
Respiratory failure	104(77.6)	69(43.9)	55(57.9)	<0.001
ICU care	84(62.7)	52(33.1)	49(51.6)	<0.001
Septic shock	38(28.4)	40(25.5)	22(23.2)	0.667
Extracorporeal membrane oxygenation	6(4.5)	17(10.8)	6(6.3)	0.108
30-day mortality	45(33.6)	32(20.4)	23(24.2)	0.034
90-day mortality	51(38.1)	38(24.2)	26(27.4)	0.030

Non-CMV virus: respiratory syncytial virus (RSV), influenza A virus, influenza B virus, human parainfluenza virus (HPIV), human rhinovirus (HRV), and adenovirus.

Table 5 Clinical characteristics of pneumonia with glucocorticoid users in different underlying disease

Variables	Connective tissue disease, N=368	Nephrotic syndrome or chronic glomerulonephritis, N=90	Solid organ transplant, N=63	Bone marrow or HSCT, N=7	Lymphoma, N=17	Bronchial asthma or COPD, N=30	Idiopathic interstitial pneumonia, N=73	Radiation pneumonitis, N=8	*P* value
Sex, female, n (%)	228(62.0)	28(31.1)	15(23.8)	1(14.3)	4(23.5)	9(30.0)	28(38.4)	0(0)	<0.001
Age, median (IGR)	60.0(47.3,69.8)	57.0(41.8, 66.0)	56.0(46.0, 63.0)	33.0(32.0, 53.0)	65.0(53.5, 75.0)	62.0(57.0, 73.3)	65.0(55.0,71.0)	62.5(52.0, 66.8)	<0.001
Laboratory examination									
White blood cell, $\times 10^9$/L (IQR)	7.79 (5.72, 11.19)	8.31 (6.47, 11.81)	6.92(4.45, 9.93)	5.27(3.80, 11.6)	5.16(2.85, 9.23)	9.42(6.59, 12.82)	9.58(7.15, 12.91)	6.95(5.52, 10.82)	0.001
Neutrophils, $\times 10^9$/L (IQR)	6.36(4.29, 9.80)	7.48 (5.30, 10.81)	4.80(3.2, 7.7)	3.85(0.90, 7.05)	3.52(1.89, 7.91)	6.94(4.45, 9.13)	8.13(4.87, 11.07)	6.16(5.20, 9.50)	<0.001
Lymphocyte, $\times 10^9$/L (IQR)	0.83 (0.50, 1.34)	0.77 (0.40, 1.22)	0.80(0.33, 1.31)	0.61(0.43, 2.07)	0.86(0.38, 1.42)	1.15(0.76, 1.73)	1.10(0.70, 1.61)	0.50(0.09, 0.94)	0.014
Persistent lymphocytopenia	160(43.5)	39(43.3)	29(46.0)	3(42.9)	8(47.1)	8(26.7)	29(39.7)	5	0.634
Oxygenation index	243.1(126.6, 343.8)	176.5(103.4, 279.0)	323.8(207.1, 424.5)	265.5(148.8, 304.7)	197.8(80.0,350.7)	264.6(181.6, 444.0)	242.9(128.0, 364.3)	307.4(244.1, 442.0)	0.001
Severe pneumonia index score	73.0(54.0,96.0)	88.0(67.8, 113.5)	83.0(64.0, 100.0)	64.0(42.0, 86.0)	96.0(73.5, 141.5)	74.5(60.8, 92.5)	75.0(63.0, 96.5)	91.5(85.0, 131.0)	<0.001
CURB65 score>1	105 (28.5)	34(37.8)	15(23.8)	1(14.3)	4(23.5)	6(20.0)	25(34.2)	2(25.0)	0.391
Imaging features, n (%)	316(85.9)	74(82.2)	61(96.8)	5(71.4)	13(76.5)	21(70.0)	67(91.8)	6(75.0)	
Consolidation or mass	163(51.6	41(55.4)	23(37.7)	3(60.0)	5(38.5)	7(23.3)	19(28.4)	5(83.3)	0.005
Ground-glass opacity	203(64.2)	50(67.6)	29(47.5)	2((40.0)	8(61.5)	16(53.3)	51(76.1)	4(66.7)	0.04
Total pathogenic positive rate									
Bacteria	104(28.3)	29(32.2)	31(49.2)	2(28.6)	2(11.8)	11(36.7)	18(24.7)	4(50.0)	0.015
PCP	63(17.1)	40(44.4)	10(15.9)	0(0)	4(23.5)	3(10.0)	12(16.4)	3(37.5)	<0.001
Aspergillus	33(9.0)	9(10.0)	26(41.3)	0(0)	1(5.9)	5(16.7)	10(13.7)	2(25.0)	<0.001
CMV	85(23.1)	41(45.6)	15(23.8)	3(42.9)	8(47.1)	4(13.3)	26(35.6)	5(62.5)	<0.001
Non-CMV virus	56(15.2)	12(13.3)	47(74.6)	2(28.6)	4(23.5)	3(10.0)	28(38.4)	1(12.5)	<0.001

Variables	Connective tissue disease, N=368	Nephrotic syndrome or chronic glomerulonephritis, N=90	Solid organ transplant, N=63	Bone marrow or HSCT, N=7	Lymphoma, N=17	Bronchial asthma or COPD, N=30	Idiopathic interstitial pneumonia, N=73	Radiation pneumonitis, N=8	*P* value
Treatment, before admission, n (%)									
High-dose steroids use	140(38.0)	32(35.6)	3(4.8)	1(14.3)	9(52.9)	7(23.3)	27(37.0)	3(37.5)	<0.001
Accumulated dose of glucocorticoids, methylprednisolone, g (IQR)	5.4(2.4, 13.7)	3.8(2.5, 6.6)	1.9(0.9, 3.3)	1.3(0.6, 7.3)	2.9(2.4, 36)	0.6(0.3, 2.4)	3.6(2.0, 6.5)	5.9(3.1, 6.7)	<0.001
Time of steroids use (month)	5.9(2.0, 29.8)	3.0(3.0, 11.0)	7.0(2.0, 15.0)	6.0(3.0, 18.0)	3.5(2.0, 5.0)	1.0(1.0,13.5)	3.5(2.0, 12.0)	3.0(2.0, 8.0)	0.024
Receiving other immunosuppressants	257(69.8)	48(53.3)	63(100.0)	6	9(52.9)	0(0)	17(23.3)	1(12.5)	<0.001
Complications, n (%)									
Noninvasive ventilation	98(26.6)	25(27.8)	8(12.7)	1(14.3)	4(23.5)	3(10.0)	19(26.0)	2(25.0)	0.183
Invasive mechanical ventilation	89(24.2)	25(27.8)	10(15.9)	1(14.3)	4(23.5)	6(20.0)	24(32.9)	0(0)	0.237
Respiratory failure	179(48.6)	58(64.4)	24(38.1)	3(42.9)	6(35.3)	14(46.7)	41(56.2)	3(37.5)	0.040
ICU care	152(41.3)	49(54.4)	14(22.2)	3(42.9)	6(35.3)	6(20.0)	35(47.9)	1(12.5)	0.001
Septic shock	68(18.5)	25(27.8)	15(23.8)	2(28.6)	4(23.5)	5(16.7)	20(27.4)	2(25.0)	0.481
Extracorporeal membrane oxygenation	15(4.1)	4(4.4)	4(6.3)	0(0)	1(5.9)	0(0)	10(13.7)	0(0)	0.044
30-day mortality	88(23.9)	23(25.6)	8(12.7)	2(28.6)	3(17.6)	4(13.3)	17(23.3)	2(25.0)	0.509
90-day mortality	103(28.0)	25(27.8)	9(14.3)	2(28.6)	4(23.5)	6(20.0)	20(27.4)	2(25.0)	0.528

HSCT: hematopoietic stem cell transplant; COPD: chronic obstructive pulmonary disease

Cox regression analysis indicated that the following factors were independent predictors of 30-day and 90-day mortality in patients with CAP treated with glucocorticoids and other immunosuppressants and in patients with CAP treated with glucocorticoids only: septic shock, respiratory failure, and persistent lymphocytopenia. In the glucocorticoid-only group, high-dose corticosteroid use and invasive mechanical ventilation were independent negative predictors of 90-day mortality (Table 6). Interstitial lung disease and mechanical ventilation were independent negative predictors of 90-day mortality in the glucocorticoid and immunosuppressant group (Table 7).

Table 6 Cox regression analysis of prognostic factors in glucocorticoid users with community-acquired pneumonia patients

Variables	30-day mortality			90-day mortality		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Septic shock	5.874	3.210-10.750	<0.001	4.900	2.685-8.941	<0.001
Respiratory failure	8.625	2.580-28.832	<0.001	8.757	2.554-30.024	0.001
Persistent lymphocytopenia	2.069	1.183-3.621	0.011	1.757	1.049-2.941	0.032
Invasive mechanical ventilation	-	-	-	2.240	1.251-4.010	0.007
High-dose steroids	1.989	1.145-3.456	0.015	-	-	-

Table 7 Cox regression analysis of prognostic factors in glucocorticoid and immunosuppressants users with community-acquired pneumonia patients

Variables	30-day mortality			90-day mortality		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Septic shock	4.438	2.783-7.077	<0.001	4.030	2.549-6.370	<0.001
Interstitial lung disease	-	-	-	1.678	1.099-2.562	0.017
Respiratory failure	48.238	6.568-354.301	<0.001	35.106	4.560-270.244	0.001
Persistent lymphocytopenia	1.714	1.046-2.810	0.033	1.648	1.047-2.594	0.031
Mechanical ventilation				1.949	1.031-3.685	0.040

DISCUSSION

This study was the first large-scale retrospective investigation of the aetiology and prognostic risk factors of pneumonia in patients using glucocorticoids. The main findings of the present study are summarised as follows: (1) more than 60% of patients developed pneumonia within 6 months of glucocorticoid therapy initiation, especially for PCP and CMV pneumonias; (2) persistent lymphocytopenia was associated with significantly higher rates of infection by opportunistic pathogens, mixed pathogen types, and MDR bacteria; (3) patients using high-dose glucocorticoids were significantly more likely to develop opportunistic pneumonias than those using low-dose glucocorticoids; (4) 30-day and 90-day mortality rates of patients with non-CMV and CMV viral pneumonias were similar, though lower than those with PCP; (5) septic shock, respiratory failure, mechanical ventilation, interstitial lung disease, and persistent lymphocytopenia were independent predictors of 90-day mortality in patients receiving glucocorticoids.

Use of glucocorticoids and other immunosuppressive agents have been shown to increase risk of infections caused by CMV, *Pneumocystis*, *Aspergillus*, and other opportunistic pathogens.[18-23] A review of 33 pneumonia patients undergoing long-term glucocorticoid therapy showed that *Staphylococcus aureus* was the most common pathogen identified, with a wide range of other causative pathogens, including bacteria, fungi, viruses, *Pneumocystis*, and *Mycobacterium*.[1] In an international multicentre study of immunocompromised patients, chronic steroid users accounted for 45% of patients,[24] with the main causative pathogens for pneumonia including *Streptococcus pneumoniae, Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus*, influenza viruses, and *Pneumocystis.* In our study, the most common pathogens isolated were bacteria, CMV, non-CMV viruses, *Pneumocystis*, *Aspergillus* or *Cryptococcus*, *Mycoplasma pneumoniae* or *Legionella,* and *Mycobacterium tuberculosis* or nontuberculous *Mycobacteria.* For bacterial pneumonias, *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae*, and *Staphylococcus aureus* were most commonly identified, possibly due to antibiotic therapy before admission. In some patients, BALs or sputum sampling occurred more than 48 hours after admission, increasing the risk of nosocomial aetiologies for pneumonia, including infection with *Acinetobacter baumannii*.

An association between mixed pulmonary infections and treatment with glucocorticoids for

nephrotic syndrome, lung transplantation, or other disorders requiring immunosuppression has previously been reported. [25-27] We found mixed infections in more than 50% of our study patients. Glucocorticoid use may also be a risk factor for MDR bacterial infections. We demonstrated that MDR bacterial infections were significantly more common in patients treated with high-dose steroids and in patients with persistent lymphocytopenia. Therefore, MDR pathogens must be considered when selecting antimicrobial agents for pneumonia in patients who are receiving high-dose steroids or in those with persistent lymphocytopenia.

A low $CD4^+$ T-lymphocyte count has previously been shown to be associated with PCP.[28-29] Moreover, a low absolute lymphocyte count and prolonged high-dose steroid therapy have also been shown to be predictors of PCP and CMV infections.[30-36] Yang et al. demonstrated that the average time until diagnosis of PCP was only 2.4 months after immunosuppressant initiation in patients with glomerulonephritis.[37] Our results underscore the importance of considering PCP in the differential diagnosis of patients receiving chronic high-dose glucocorticoids. This study also indicated that high-dose glucocorticoid use is associated with *Mycobacterium tuberculosis* and *Aspergillus* pneumonias. It has been shown that glucocorticoids have profound effects on the distribution and function of immune cells, including a decrease in macrophage antifungal activity through inhibition of reactive oxidant intermediates and direct stimulation of growth of *Aspergillus fumigatus*.[38]

Respiratory viruses have also been recognised to be potential causes for pneumonia and death in immunocompromised individuals with haematologic malignancies and those undergoing haematopoietic stem cell transplants. Jacobs et al. found a 25% overall 30-day mortality in 32 patients with haematologic malignancies and human rhinovirus lower respiratory tract infections.[39] A slightly higher mortality rate (27%) was observed in a study by Shah of patients with lower respiratory tract infections caused by parainfluenza virus who were undergoing haematopoietic cell transplants or had haematologic malignancies.[40] Chatzis et al. showed that 21.3% of an immunocompromised adult cohort with RSV pneumonia required ICU transfer, with nearly a 20% mortality rate.[41] Crotty et al. conducted an observational cohort study of 284 patients with viral pneumonias, in which the majority (51.8%) were immunocompromised, with a high overall in-hospital mortality rate (23.2%).[42] In our study, the 90-day mortality rate was 24.2% for patients with non-CMV viral pneumonias, which was similar to patients with CMV

pneumonia (27.4%), but significantly lower than patients with PCP (38.1%, $P < 0.05$). Therefore, it is of vital importance to include viral pathogens in the differential diagnosis of pneumonia in patients on glucocorticoids. Also, the presence of ground-glass lesions on CT imaging should prompt consideration of PCP and viral infections. Viral nucleic acid and PCP testing should be obtained, and targeted antimicrobial treatment should be started as early as possible.

Overall mortality from pulmonary infections in patients receiving long-term glucocorticoid therapy can be as high as 45%,[1] with similar rates in patients with other causes for immunosuppression.[21] Development of respiratory failure and the need for mechanical ventilation have been shown to be the strongest predictors of mortality in immunocompromised patients with or without pneumonia.[43, 44] Lymphocytopenia has also been shown to be significantly associated with increased mortality rates in non-HIV-infected patients with PCP or viral pneumonias.[29, 45] Vial-Dupuy et al. indicated that high-dose steroid use during an ICU stay (OR = 0.19; [95% CI, 0.04-0.99]) was an independent determinant of in-hospital mortality in patients with interstitial lung disease admitted to the ICU.[46] Kotani et al.'s study indicated that interstitial lung disease was a risk factor associated with mortality in patients with PCP who required mechanical ventilation.[47] Our study demonstrated that several factors conveyed a poor prognosis in this patient population, including high-dose glucocorticoid use, persistent lymphocytopenia, and interstitial lung disease.

There were several limitations to this study. First, it had a retrospective observational design, which might have introduced some bias by indication. Second, not all patients with pneumonia underwent a full array of pathogenic testing; thus, pathogen identification and diagnosis may have been incomplete. Third, some pathogens were not identified until at least 48 hours after admission, increasing the possibility of nosocomial infections. Despite these limitations, our results are consistent with the existing literature and provide more detailed insights into the clinical characteristics, pathogenic aetiologies, and prognostic factors that should be carefully considered when managing patients on glucocorticoid therapy who develop pneumonia.

CONCLUSIONS

Patients who develop pneumonia while receiving glucocorticoid therapy experience high rates of infection by opportunistic pathogens, significant morbidity, and high mortality rates,

especially with specific risk factors. This information should be carefully considered when determining treatment strategies for this patient population.

DISCLOSURES

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Contributors: Study design: LL, BC. Data collection: LL, JS, LS, GS, LS, LZ, CW, YR, JW, JP, JL. Statistical analysis: LL, SH.H, GX. Writing: LL, BC, SH.H. 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.

Competing interests: None declared.

Ethics approval: The Ethics Committee of China-Japan Friendship Hospital (no. 2015-86) granted approval for this retrospective study and orchestrated centralised collaboration and approval of all participating institutions.

Patient consent: Consent for procedures was obtained from all patients. The need for written informed patient consent for participation in this study was waived by the Ethics Committee of China-Japan Friendship Hospital in collaboration with all participating institutions, with submission and collection of anonymised data.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.mkkwh70x2

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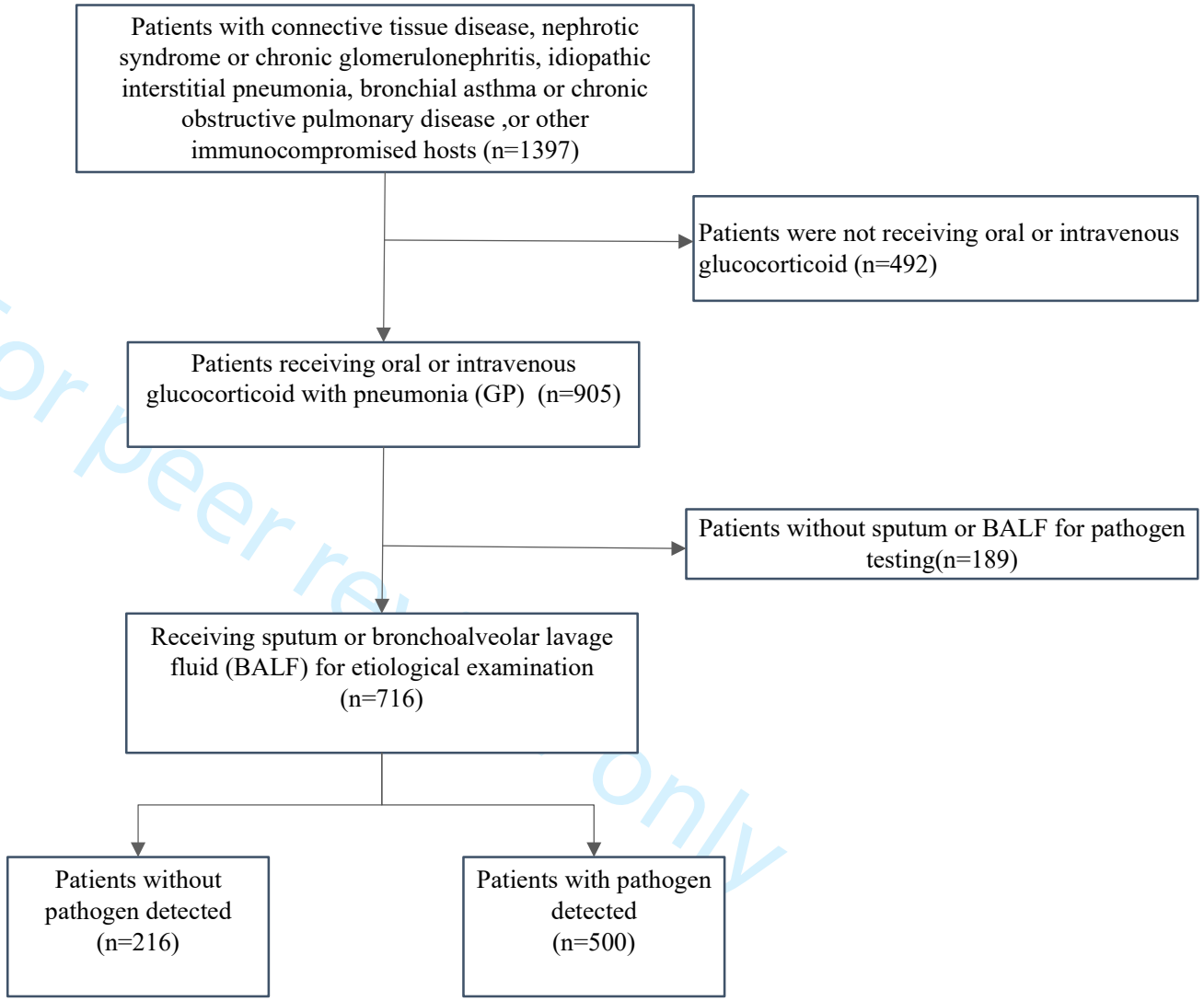
FIGURE LEGENDS

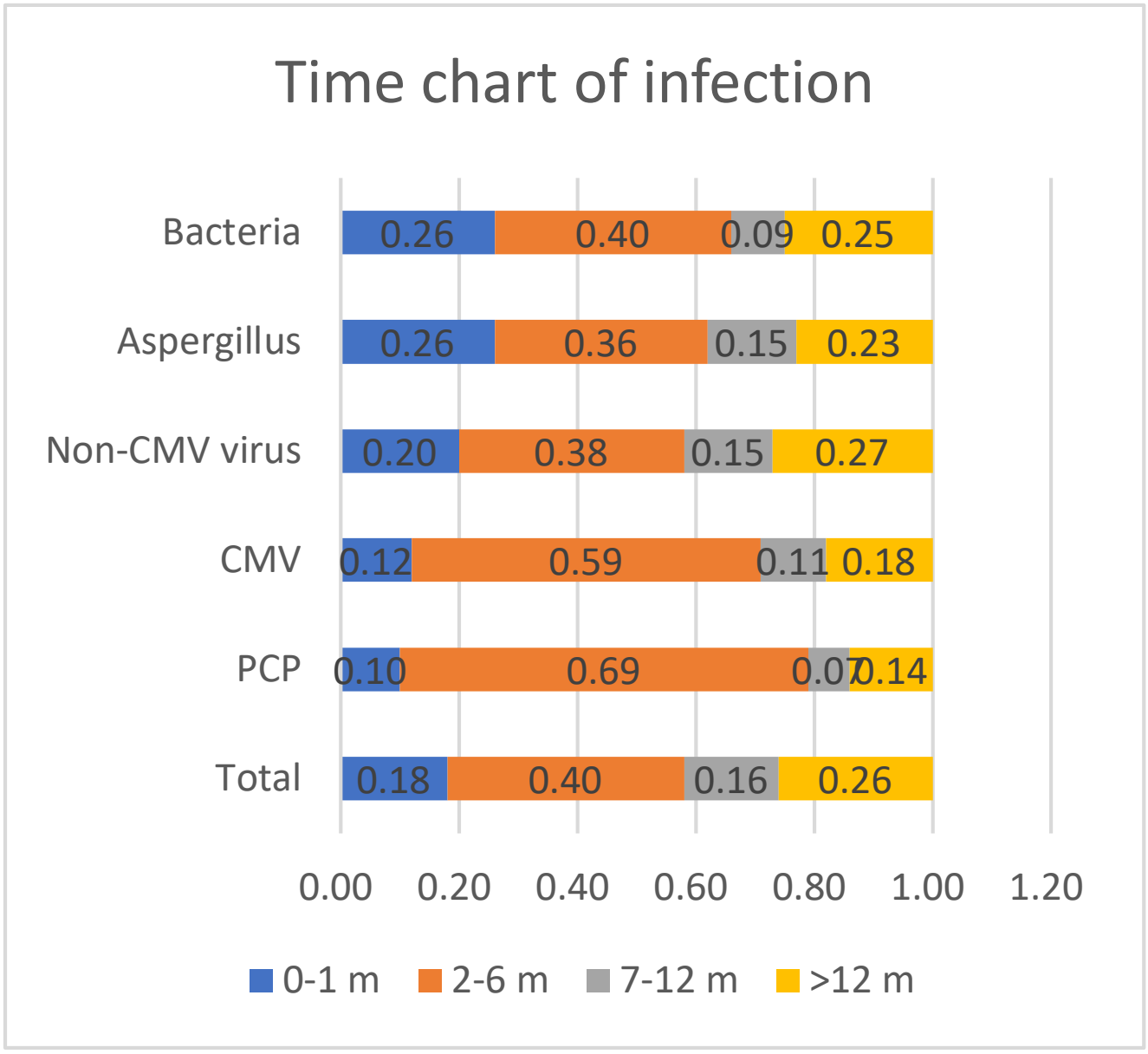
Figure 1: Study flowchart

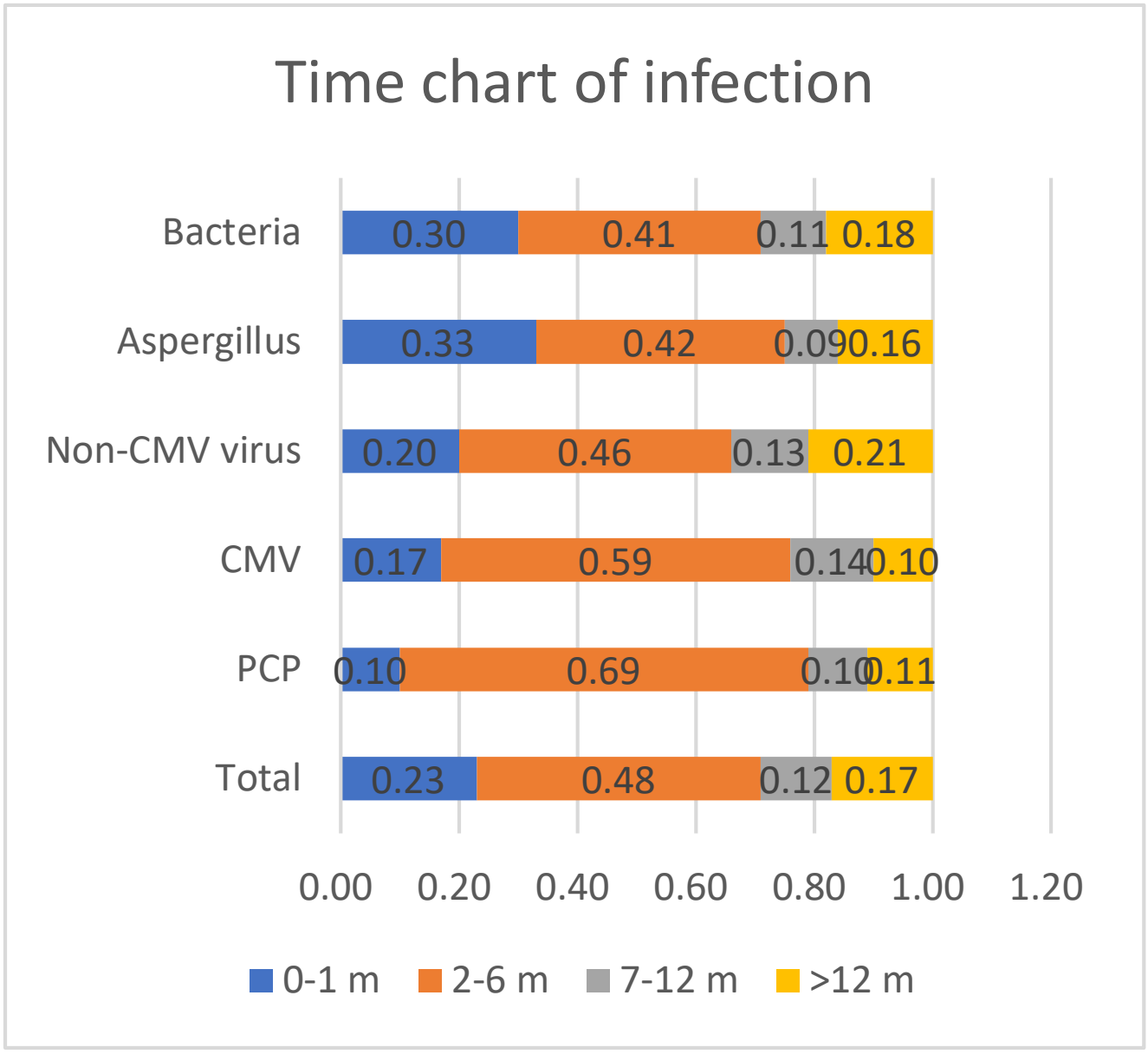
Figure 2: Duration of glucocorticoid use among glucocorticoid users with pneumonia

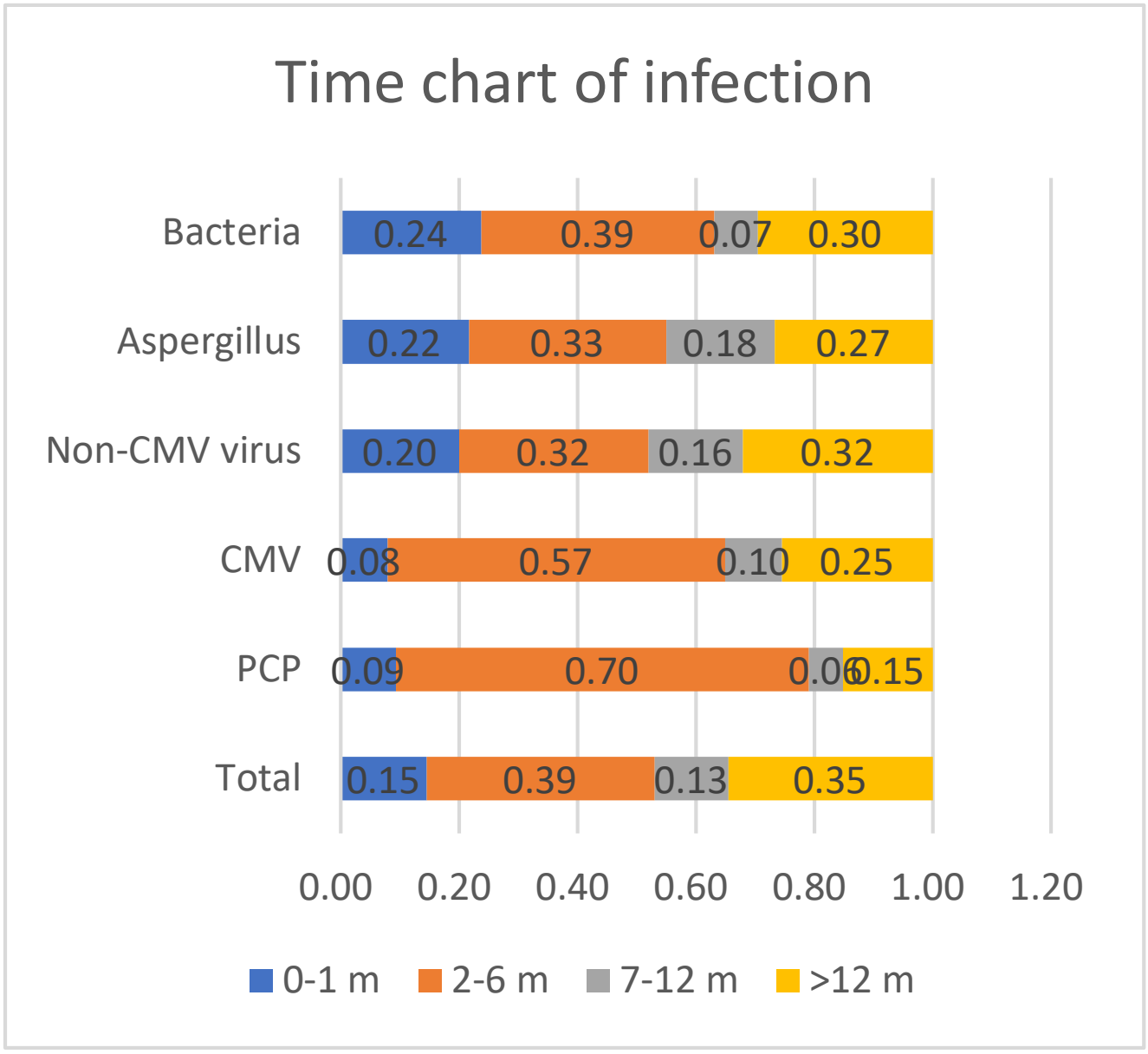
Figure 3: Duration of glucocorticoid use among glucocorticoid only users with pneumonia

Figure 4: Duration of glucocorticoid use among glucocorticoid and immunosuppressant users with pneumonia




Time chart of infection
Bacteria
0.26
0.40
0.09
0.25
Aspergillus
0.26
0.36
0.15
0.23
Non-CMV virus
0.20
0.38
0.15
0.27
CMV
0.12
0.59
0.11
0.18
PCP
0.10
0.69
0.07
0.14
Total
0.18
0.40
0.16
0.26
0.00
0.20
0.40
0.60
0.80
1.00
1.20
0-1 m
2-6 m
7-12 m
>12 m


Time chart of infection
Bacteria
0.30
0.41
0.11
0.18
Aspergillus
0.33
0.42
0.09
0.16
Non-CMV virus
0.20
0.46
0.13
0.21
CMV
0.17
0.59
0.14
0.10
PCP
0.10
0.69
0.10
0.11
Total
0.23
0.48
0.12
0.17
0.00
0.20
0.40
0.60
0.80
1.00
1.20
0-1 m
2-6 m
7-12 m
>12 m


Time chart of infection
Bacteria
0.24
0.39
0.07
0.30
Aspergillus
0.22
0.33
0.18
0.27
Non-CMV virus
0.20
0.32
0.16
0.32
CMV
0.08
0.57
0.10
0.25
PCP
0.09
0.70
0.06
0.15
Total
0.15
0.39
0.13
0.35
0.00
0.20
0.40
0.60
0.80
1.00
1.20
0-1 m
2-6 m
7-12 m
>12 m

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	2-3
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7 and Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8,Table3
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.