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Aetiology and prognostic risk factors of mortality in patients with pneumonia 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 1 January 2013 and 31 December 2019.

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

Results

Conclusions 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 transfer (40.8%) and mechanical ventilation (36%), with a 90-day mortality 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 was significantly lower for non-CMV viral pneumonias than for PCP ($p<0.05$), with a similar mortality 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.

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.

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 patients with pneumonia 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 jirovecii* 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 1 January 2013 and 31 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 guidelines.[5 6] Pneumonia was defined as the presence of a new pulmonary infiltrate with infiltrative changes identified on chest radiography or 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[4 7 8] 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 non-infectious 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 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 non-invasive mechanical ventilation, pneumonia severity index (PSI) score and/or Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older (CURB-65 score))[9–11]; (5) laboratory and microbiological data (blood, sputum and/or bronchoalveolar lavage (BAL) 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 and 90 days after admission. High-dose steroid use was defined as equal to or greater than 30 mg/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.

Data collection

Diagnostic procedures

After identification of pulmonary infiltrates on chest imaging, 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 60–120 mL of a sterile saline solution two to four 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°C in 5%–10% carbon dioxide for 48 hours. If *Nocardia* was suspected, the incubation time was prolonged. Fungal cultures were incubated at 27°C 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 PCRs (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

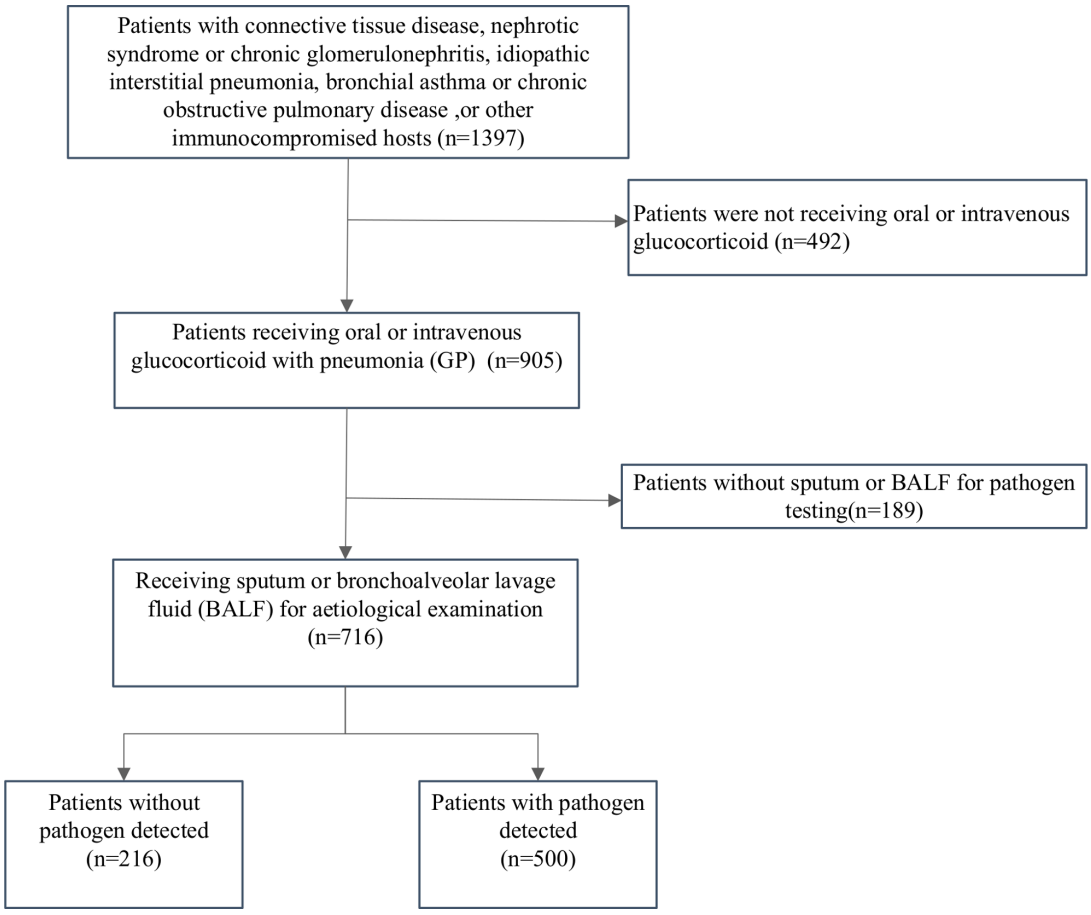

Figure 1 Study flow chart.

and Control and the Centers for Disease Control and Prevention criteria. We included the following species in this category: methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* and *Enterobacteriaceae* producing extended-spectrum beta-lactamases. *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and other non-fermenting Gram-negative bacilli were considered to be MDR pathogens if not susceptible to at least one agent in three or more antimicrobial categories.[12 13]

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 ≥1, (4) galactomannan optical index on serum ≥0.5, or (5) *Aspergillus* sp identified by culture characteristics and microscopic morphology.[14 15]

Diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) required the following criteria: (1) high-resolution CT imaging showing diffuse ground-glass opacity with a patchy distribution and (2) microscopic examination of respiratory samples demonstrating *Pneumocystis* cystic or trophic forms or *Pneumocystis* DNA identified using PCR.[16]

Statistical analysis

Demographics, clinical characteristics and pathogen testing results were expressed as means (±SD), medians (IQR) 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 non-invasive 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, non-invasive mechanical ventilation, invasive mechanical ventilation, respiratory failure, septic shock, ICU admission, high-dose corticosteroid use, persistent lymphocytopenia, interstitial lung disease, PSI score, CURB-65 score, PCP, and CMV and non-CMV viral infections.

Table 1 Clinical characteristics of pneumonia between glucocorticoid users and those glucocorticoids with immunosuppressant users

Variables	Total, n=716	Glucocorticoid users, n=297	Glucocorticoid with immunosuppressant* 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
Dyspnoea	431 (60.2)	185 (62.3)	246 (58.7)	0.335
Disturbance of consciousness	40 (5.6)	11 (3.7)	29 (6.9)	0.065
Laboratory examination				
White cell, $\times10^9$/L (IQR)	7.94 (5.79, 11.60)	9.27 (6.37, 12.63)	7.51 (5.37, 10.97)	<0.001
Neutrophils, $\times10^9$/L (IQR)	6.49 (4.28, 10.08)	7.35 (4.89, 10.83)	6.05 (4.10, 9.35)	<0.001
Lymphocyte, $\times10^9$/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 (42.5)	113 (38.0)	191 (45.6)	0.044
Mean haemoglobin±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
CURB-65 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
Tumour	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 haematopoietic 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 (>1 mg/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

Continued

Table 1 Continued

Variables	Total, n=716	Glucocorticoid users, n=297	Glucocorticoid with immunosuppressant* users, n=419	P value
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 hospitalisation, 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 (%)				
Non-invasive 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 hospitalisation	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 (5.0)	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, and so on. Immunosuppressive drugs: glucocorticoid, tacrolimus, sirolimus, cyclosporine, methotrexate, and so on.
‡Other immunocompromised hosts: eczema, myelitis, autoimmune encephalitis, idiopathic thrombocytopenic purpura, and so on.
CAP, community-acquired pneumonia; CURB-65, Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older; ICU, intensive care unit.

Statistical analyses were performed using SPSS V.19.0 (SPSS). All tests were two sided, and a p value <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, 1397 immunocompromised patients who developed pneumonia between 1 January 2013 and 31 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 non-invasive and invasive ventilation, respectively. The 30-day and 90-day mortality 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).

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).

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 immunosuppressant users, n=372	Patients discharged alive, n=479	Patients died during hospitalisation, 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 (2.7)	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 (0.3)	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)*	40 (15.2) ()	68 (18.3)	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)

Continued

Table 2 Continued

Variables, n (%)	CAP, n=635	HAP, n=81	Simple glucocorticoid users, n=263	Glucocorticoid with immunosuppressant users, n=372	Patients discharged alive, n=479	Patients died during hospitalisation, 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
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)†
Non-tuberculosis 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.
CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia.

Pathogen positivity rates were higher, and MDR bacteria were more commonly identified in non-survivors 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 (20 strains), influenza B virus (20 strains), human rhinovirus (HRV, 8 strains), herpes simplex virus type 1 (4 strains) and adenovirus (9 strains) (table 2).

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 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 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).

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).

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

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 hospitalisation, 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.

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 (IQR)	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 (43.3)	50 (31.8)	43 (45.3)	0.051
Interstitial lung disease	49 (36.6)	95 (60.5)	42 (44.2)	<0.001
Idiopathic interstitial pneumonia	12 (9.0)	28 (17.8)	14 (14.7)	0.091
Laboratory examination				
White 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
CURB-65 score >1	39 (29.1)	46 (29.3)	34 (35.8)	0.512
Imaging features, n (%), 35 missing				
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 (>30 mg/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 (%)				
Non-invasive 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.
CMV, Cytomegalovirus; CURB-65, Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older; ICU, intensive care unit.

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 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.

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 (IQR)	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 cell, $\times10^9$/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, $\times10^9$/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, $\times10^9$/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 (62.5)	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
CURB-65 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
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 (85.7)	9 (52.9)	0 (0)	17 (23.3)	1 (12.5)	<0.001
Complications, n (%)									
Non-invasive 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

Continued

Table 5 Continued

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
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

CMV, Cytomegalovirus; COPD, chronic obstructive pulmonary disease; CURB-65, Confusion, uremia, elevated respiratory rate, hypotension, and aged 65 years or older; HSCT, haematopoietic stem cell transplant; ICU, intensive care unit; PCP, Pneumocystis jirovecii pneumonia.

Figure 2 Duration of glucocorticoid use among glucocorticoid users with pneumonia. CMV, *Cytomegalovirus*; PCP, *Pneumocystis jirovecii* pneumonia.

Figure 3 Duration of glucocorticoid use among glucocorticoid-only users with pneumonia. CMV, *Cytomegalovirus*; PCP, *Pneumocystis jirovecii* pneumonia.

Figure 4 Duration of glucocorticoid use among glucocorticoid and immunosuppressant users with pneumonia. CMV, *Cytomegalovirus*; PCP, *Pneumocystis jirovecii* pneumonia.

Use of glucocorticoids and other immunosuppressive agents has been shown to increase risk of infections caused by CMV, *Pneumocystis*, *Aspergillus* and other opportunistic pathogens.[2 17–21] A review of 33 patients with pneumonia

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

	30-day mortality			90-day mortality		
Variables	OR	95% CI	P value	OR	95% CI	P value
Septic shock	5.874	3.210 to 10.750	<0.001	4.9	2.685 to 8.941	<0.001
Respiratory failure	8.625	2.580 to 28.832	<0.001	8.757	2.554 to 30.024	0.001
Persistent lymphocytopenia	2.069	1.183 to 3.621	0.011	1.757	1.049 to 2.941	0.032
Invasive mechanical ventilation	–	–	–	2.24	1.251 to 4.010	0.007
High-dose steroids	1.989	1.145 to 3.456	0.015	–	–	–

undergoing long-term glucocorticoid therapy showed that *S. 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,[22] with the main causative pathogens for pneumonia including *Streptococcus pneumoniae, P. aeruginosa, K. pneumoniae, S. aureus*, influenza viruses and *Pneumocystis*. In our study, the most common pathogens isolated were bacteria, CMV, non-CMV viruses, *Pneumocystis*, *Aspergillus* or *Cryptococcus*, *M. pneumoniae* or *Legionella*, and *M. tuberculosis* or non-tuberculous mycobacteria. For bacterial pneumonias, *P. aeruginosa, A. baumannii, K. pneumoniae* and *S. 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 *A. 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.[23–25] 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.[26 27] Moreover, a low absolute lymphocyte count and prolonged high-dose steroid therapy have also been shown to be predictors of PCP and CMV infections.[28–34] Yang *et al* demonstrated that the average time until diagnosis of PCP was only 2.4 months after immunosuppressant initiation in patients with glomerulonephritis.[35] 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 *M. 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*.[36]

Respiratory viruses have also been recognised to be potential causes for pneumonia and death in immunocompromised individuals with haematological malignancies and those undergoing haematopoietic stem cell transplants. Jacobs *et al* found a 25% overall 30-day mortality in 32 patients with haematological malignancies and HRV lower respiratory tract infections.[37] A slightly higher mortality (27%) was observed in a study by Shah *et al* of patients with lower respiratory tract infections caused by parainfluenza virus who were undergoing haematopoietic cell transplants or had haematological malignancies.[38] Chatzis *et al* showed that 21.3% of an immunocompromised adult cohort with RSV pneumonia required ICU transfer, with nearly a 20% mortality .[39] 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 (23.2%).[40]

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

	30-day mortality			90-day mortality		
Variables	OR	95% CI	P value	OR	95% CI	P value
Septic shock	4.438	2.783 to 7.077	<0.001	4.03	2.549 to 6.370	<0.001
Interstitial lung disease	–	–	–	1.678	1.099 to 2.562	0.017
Respiratory failure	48.238	6.568 to 354.301	<0.001	35.106	4.560 to 270.244	0.001
Persistent lymphocytopenia	1.714	1.046 to 2.810	0.033	1.648	1.047 to 2.594	0.031
Mechanical ventilation				1.949	1.031 to 3.685	0.04

In our study, the 90-day mortality 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.[19] 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.[41 42] Lymphocytopenia has also been shown to be significantly associated with increased mortality in non-HIV-infected patients with PCP or viral pneumonias.[27 43] Vial-Dupuy *et al* indicated that high-dose steroid use during an ICU stay (OR=0.19; 95% CI 0.04 to 0.99) was an independent determinant of in-hospital mortality in patients with interstitial lung disease admitted to the ICU.[44] 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.[45] 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, especially with specific risk factors. This information should be carefully considered when determining treatment strategies for this patient population.

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