Infection and Drug Resistance Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Comparative Dosing of Adjunctive Corticosteroids Therapy for *Pneumocystis* Pneumonia with ARDS in Non-HIV Immunocompromised Patients

Xuyan Li[1], Lujia Guan[1], Dong Wang[1], Xiao Tang[1], Rui Wang[1], Ying Li[1], Zhaohui Tong[1], Bing Sun[1], Chen Wang[2–5]

[1]Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, 100020, People's Republic of China; [2]Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, 100029, People's Republic of China; [3]National Clinical Research Center for Respiratory Diseases, Beijing, 100029, People's Republic of China; [4]Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, People's Republic of China; [5]Department of Respiratory Medicine, Capital Medical University, Beijing, 100069, People's Republic of China

Correspondence: Bing Sun; Chen Wang, Email sunbing20002023@163.com; birm2022@126.com

Background: Adjuvant corticosteroids are effective in patients with human immunodeficiency virus (HIV)-associated *Pneumocystis jirovecii* pneumonia (PCP) patients, but the effectiveness of adjuvant corticosteroids in non-HIV PCP remained controversial. This study aimed to evaluate the effectiveness of standard-dose compared with low-dose steroids in non-HIV PCP patients with acute respiratory distress syndrome (ARDS).

Methods: This retrospective observational study included non-HIV PCP patients with ARDS admitted to the respiratory intensive care unit (RICU) of Beijing Chao-Yang Hospital from 2015 to 2022. Demographics, clinical characteristics, and outcomes were compared between patients receiving standard-dose and those receiving low-dose steroids. Survival times were assessed using Kaplan-Meier curves and compared with the Log rank test. Cox proportional hazards regression analysis was conducted to identify independent risk factors for 28-day and 60-day mortality.

Results: A total of 105 non-HIV PCP with ARDS were included, with 48 patients in the standard-dose steroid group (66.7% male, 50.5±12.6 years) and 57 in the low-dose steroid group (61.4% male, 55.5±14.2 years). The 60-day mortality was lower in the standard-dose group than in the low-dose group (63.2% vs 48.3%, p=0.04), while 28-day mortality showed no significant difference (50.8% vs 35.4%, p=0.11). After adjusting for confounders, standard-dose steroids reduced 28-day mortality (aHR: 0.339, 95% CI: 0.147–0.780) and 60-day mortality (aHR: 0.328, 95% CI: 0.152–0.709), particularly in patients aged <65 years, non-smokers, those requiring mechanical ventilation, with albumin<30 g/L, or a PaO_2/FiO_2 ratio <150 mmHg. No differences in co-infections or gastrointestinal bleeding were observed.

Conclusion: The standard-dose steroid therapy significantly reduced 28-day and 60-day mortality without major complications in the non-HIV immunocompromised population with severe PCP with ARDS. These findings highlight the potential survival benefit of standard-dose corticosteroid regimen in this population.

Keywords: adjuvant corticosteroids, *Pneumocystis jirovecii* pneumonia, acute respiratory distress syndrome, non-human immunodeficiency virus

Introduction

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic pulmonary fungal infection caused by *Pneumocystis jirovecii*, and it is a major cause of acute respiratory distress syndrome (ARDS) in immunocompromised patients.[1] Recent epidemiological data show that the incidence of PCP is increasing in immunocompromised patients without human immunodeficiency virus (HIV), such as those who have undergone organ or bone marrow transplantation or those

Received: 27 September 2024
Accepted: 4 December 2024
Published: 11 December 2024

using corticosteroids or cytotoxic drugs.[2] Compared to HIV-infected PCP patients, non-HIV immunocompromised PCP patients rapidly progress to respiratory failure, with more than 50% requiring intensive care unit (ICU),[3] and mortality rates ranging from 50% to 60%.[3,4] An overactive inflammatory response is considered to contribute to lung lesions in non-HIV immunocompromised PCP patients. The accumulation of inflammatory factors and robust neutrophil recruitment in the lung interstitial and alveolar cavities, combined with unmodifiable risks from previous diseases, are the main cause of mortality in patients.[5]

It has been hypothesized that corticosteroids may attenuate the inflammatory response induced by anti-*pneumocystis* treatment. The two largest trials conducted among hypoxemic HIV-positive patients showed that corticosteroid therapy significantly reduced the need for mechanical ventilation and mortality during PCP episodes.[6–8] Unfortunately, there is no corresponding evidence for the efficacy of adjunctive corticosteroids in HIV-negative patients with PCP, and results from available retrospective studies are conflicting.[9–11] Furthermore, the majority of the published data did not focus on patients with respiratory failure nor provided detailed corticosteroid regimens.

Based on this limited and conflicting evidence from available studies, this study aimed to assess the effectiveness of standard-dose steroid therapy in non-HIV PCP patients with ARDS compared with low-dose steroids.

Methods

Study Design and Patients

The study was a retrospective cohort analysis conducted in the respiratory intensive care unit (RICU) of Beijing Chao-Yang Hospital. And this study used anonymized historical data, making informed consent unnecessary (informed consent was waived), and had received approval from the Ethics Committee of Beijing Chao-Yang Hospital (No.2022-ke-65) in compliance with ethical and privacy standards.

We selected all non-HIV PCP patients with ARDS admitted to RICU from 1 October 2015 to 31 July 2022. Eligible patients met the following inclusion criteria: (1) negative HIV serology test confirming non-HIV status; (2) diagnosis of ARDS; and (3) diagnosis of Pneumocystis pneumonia (PCP) based on established clinical and microbiological criteria. Patients younger than 18 years, those with incomplete clinical data, or those with concurrent COVID-19 infection were excluded from this study.

The diagnosis of ARDS was based on the Berlin definition criteria.[12] The diagnostic criteria for PCP include: (1) an underlying immunosuppressive condition, such as malignancy, bone marrow or solid organ transplantation, autoimmune disease, or the use of corticosteroids or immunosuppressive therapy; (2) consistent clinical symptoms, including fever, cough, and dyspnea; (3) chest CT findings of bilateral diffuse ground-glass opacities; (4) positive identification of *Pneumocystis jirovecii* in respiratory specimens confirmed by nucleic acid testing through metagenomic next-generation sequencing or polymerase chain reaction (PCR); and (5) elevated serum 1.3-β-glucan levels (BDG).[13] Patients with *Pneumocystis jirovecii* colonization, defined as a positive nucleic acid test result in respiratory specimens without typical PCP symptoms, characteristic imaging findings, or elevated BDG levels, were excluded.[14]

Definitions

Patients in this study were categorized based on corticosteroid dosage into the standard-dose and low-dose groups. The standard-dose group received intravenous methylprednisolone at 40 mg twice daily for the initial 5 days, followed by 40 mg once daily for the subsequent 5 days, and then tapered to 20 mg daily over the remaining 11 days. In contrast, the low-dose methylprednisolone regimen involved a daily administration of less than 40 mg of methylprednisolone. The entire corticosteroid treatment course spanned 21 days,[3] with adjustments made as clinically indicated to accommodate individual patient needs. Extracorporeal membrane oxygenation (ECMO) was considered if PFR<50 mmHg over 30 minutes or if patients developed barotrauma, including pneumothorax, pneumomediastinum, or pneumoderma.

Data Collection

The data were obtained from electronic medical records (EMR), including daily prescription information for corticosteroids and trimethoprim-sulfamethoxazole (TMP-SMX), verified by two individuals. Baseline characteristics and medical

history data collected included age, sex, smoke status, body mass index, comorbidities, immunocompromised status, corticosteroid and immunosuppressant treatment regimens (within 30 days). Serum BDG levels, respiratory *Pneumocystis* PCR results, and additional respiratory pathogens detected from the same sample (BAL fluid or aspiration) used for PCP diagnosis were collected to identify potential respiratory coinfections. Clinical data collected at the time of admission included symptoms, oxygen requirements, severity evaluation [sequential organ failure assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), and Murray Score], laboratory results, blood gas analysis, and lymphocyte subsets (CD3+ T cell, CD4+ T cell, CD8+ T cell).

Outcome

The primary outcomes were 28-day mortality and 60-day mortality. Secondary outcomes investigated were length of ICU stay, ICU mortality, the incidence and duration of invasive mechanical ventilation (IMV), the need for ECMO, and complications.

Statistical Analysis

Continuous variables, presented as mean (±standard deviation) or median (interquartile range), were compared between groups using unpaired Student's *t*-tests or Mann–Whitney *U*-tests. Categorical variables, presented as frequencies and percentages, were compared using chi-squared tests or Fisher's exact tests. Univariate and multivariate Cox regression models were used to examine the association between participant demographics, laboratory tests, steroid therapy, and mortality. The Kaplan-Meier method and Log rank test were used to compare survival differences between groups. Analyses were performed on the complete cases without imputation of missing data. ECMO and IMV were analyzed separately due to their distinct mechanisms and clinical implications. Stratified analyses were conducted in subgroups defined by age, sex, smoke, IMV, albumin, lactic dehydrogenase (LDH), PFR, and bacterial infection. Sensitivity analyses were performed as follows: first, to account for the potential impact of chronic pulmonary disease on primary outcomes, we restricted analyses to patients without chronic pulmonary disease at baseline; second, given that a longer interval between the onset of respiratory symptoms and ICU admission is associated with worse prognosis,[15] we excluded patients with an interval exceeding 14 days. All analyses were performed using SPSS software version 25.0 and GraphPad Prism version 7.0. Two-tailed p-values < 0.05 were considered statistically significant.

Results

Baseline Characteristics of the Study Cohort

Between 1 October 2015 and 31 July 2022, 141 non-HIV PCP patients with ARDS were screened. Of these, 105 patients were included in the analysis: 57 in the low-dose steroid therapy group and 48 in the standard-dose steroid group (Figure 1).

Of the 105 patients, the mean age was 52.9±13.9 years, and 67 (63.8%) were male. The main causes of immunocompromised status were solid organ transplantation, connective tissue disease, and hematologic malignancy. Among the connective tissue diseases, rheumatoid arthritis was the most common (9 cases, 8.6%), followed by dermatomyositis/polymyositis (6 cases, 5.7%), Sjögren's syndrome (6 cases, 5.7%), and systemic lupus erythematosus (4 cases, 3.8%). A total of 69 cases (65.7%) cases were treated with immunosuppressants prior to admission, and 83 cases (79.0%) cases were treated with corticosteroids. The baseline demographic of the two groups were similar, as expected for age (55.5 ±14.2 years in the low-dose steroid group vs 50.5±12.6 years in the standard-dose steroid group, p=0.04) (Table 1).

Clinical Characteristics on Admission

Fever (95 cases, 90.5%), cough (86 cases, 91.4%), and sputum (62 cases, 59.0%) were common clinical manifestations in our cohort (Table 2). In terms of respiratory support, 21 patients (20.0%) required IMV upon admission. Additionally, 38 patients (36.2%) used non-IMV to maintain oxygenation, and 14 patients (13.3%) used nasal high-flow oxygen therapy. The median SOFA score on admission was 4(3–6), the acute APACHE II score was 14(11–16), and the Murray score was 2.75(2.25–3). No difference was found in the duration between admission and initiation of treatment (p=0.93) or in the

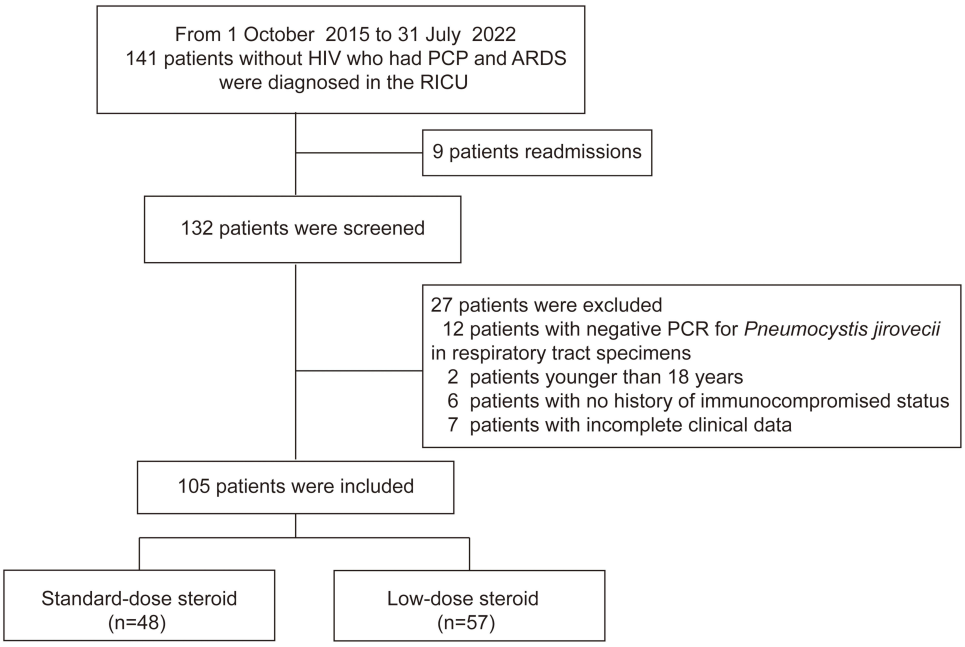

Figure 1 Study flow.
Abbreviations: HIV, human immunodeficiency virus; PCP, *Pneumocystis jirovecii* pneumonia; ARDS acute respiratory distress syndrome; RICU respiratory intensive care unit; PCR polymerase chain reaction.

proportion of patients starting treatment after 96 hours (p=0.76) between the two groups. However, Delayed TMP-SMX treatment (≥96 hours after admission) was associated with significantly higher ICU mortality compared to early treatment (<96 hours after admission) (64.3% vs 34.1%, p=0.03). (Table S1) The median PFR and CD4+T cell count were 143 (108–200) vs 144(104–174) mmHg and 97(62–158) vs 94(46–230) cells/ul, respectively.

Table 1 Comparison of Baseline Characteristics Between Standard-steroid and Low-dose Steroid Groups

Baseline Characteristics	Overall (n=105)	Low-dose Steroid Group (n=57)	Standard-dose Steroid Group (n=48)	*P*
Age, mean±SD, year	52.9±13.9	55.5±14.2	50.5±12.6	0.04
Male, n (%)	67(63.8)	35(61.4)	32(66.7)	0.58
Smoking, n (%)	23(21.9)	13(22.8)	10(20.8)	0.81
BMI, median (IQR), kg/m^2	23.2(20.4–25.7)	22.9(20.8–26.0)	22.8(20.2–25.3)	0.35
Comorbidity, n (%)				
Hypertension	44(41.9)	28(49.1)	16(33.3)	0.12
Diabetes	23(21.9)	16(28.1)	7(14.5)	0.10
Chronic pulmonary disease	5(4.8)	4(7.0)	1(2.1)	0.08
Coronary heart disease	8(7.6)	6(10.5)	2(4.2)	0.22
Chronic kidney disease	30(28.6)	18(31.6)	12()	0.46
Chronic liver disease	9(8.6)	4(7.0)	5(10.4)	0.54
Stroke	5(4.8)	2(3.5)	2(4.2)	0.86
Immunocompromised status, n (%)				
Connective tissue disease				0.65
RA	9(8.6)	6(10.5)	3(6.3)	
SLE	4(3.8)	2(3.5)	2(4.2)	
DM/PM	6(5.7)	3(5.3)	3(6.3)	
Sjogren's syndrome	6(5.7)	2(3.5)	4(8.3)	

(*Continued*)

Table 1 (Continued).

Baseline Characteristics	Overall (n=105)	Low-dose Steroid Group (n=57)	Standard-dose Steroid Group (n=48)	*P*
Idiopathic pulmonary fibrosis	7(6.7)	3(5.3)	4(8.3)	0.53
Nephrotic syndrome	14(13.3)	8(14.0)	6(12.5)	0.82
Solid organ transplantation	32(30.5)	16(28.1)	16(33.3)	0.56
Solid cancer	8(7.6)	3(5.3)	5(10.4)	0.32
Hematological malignancy	19(18.1)	13(22.8)	6(12.5)	0.17
Immunosuppressive drugs before admission, n (%)				
Corticosteroids	83(79.0)	41(71.2)	42(87.5)	0.05
Immunosuppressant				
One immunosuppressant	30(28.6)	19(33.3)	11(22.9)	0.24
Two immunosuppressants	34(32.4)	18(31.6)	14(29.2)	0.79
Three immunosuppressants	5(4.8)	2(3.5)	3(6.3)	0.51

Note: Data are presented as median (interquartile range), mean (standard deviation) or n (%).
Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; DM/PM, dermatomyositis/polymyositis.

Table 2 Differences in Clinical Characteristics on Admission

Clinical Characteristics	Overall (n=105)	Low-dose Steroid Group (n=57)	Standard-dose Steroid Group (n=48)	*P*
Symptoms, n (%)				
Fever	95(90.5)	50(87.7)	45(93.7)	0.29
Shiver	22(20.9)	9(15.8)	13(27.1)	0.16
Cough	86(91.4)	50(87.7)	36(75.0)	0.09
Sputum	62(59.0)	38(66.7)	24(50.0)	0.08
Chest distress	42(40.0)	24(42.1)	18(37.5)	0.63
Chest pain	6(5.7)	5(8.8)	1(2.1)	0.14
Dyspnea	71(67.6)	35(61.4)	36(75.0)	0.14
Fatigue	18(17.1)	10(17.5)	8(16.7)	0.91
Time from onset symptoms to ICU, median (IQR), day	11(7–11)	7(5–10)	9(6–12)	0.23
Vital signs, median (IQR)				
SBP, mmHg	125(110–139)	124(111–138)	128(108–140)	0.89
DBP, mmHg	73(60–82)	70(60–80)	75(60–83)	0.65
RR, rate/minute	26(22–30)	26(21–30)	25(22–31)	0.67
HR, rate/minute	95(81–109)	95(80–107)	96(83–111)	0.43
Oxygen requirements, n (%)				0.21
Venturi mask	32(30.4)	22(35.6)	10(20.8)	
HFNC	14(13.3)	6(10.5)	8(16.7)	
NPPV	38(36.2)	20(35.1)	18(37.5)	
Mechanical ventilation	21(20.0)	9(8.6)	12(25.0)	
Severity evaluation, median (IQR)				
Murray Score	2.75(2.25–3)	2.75(2.5–3)	2.75(2–3)	0.20
APACHE II Score	14(11–16)	14(11–16)	13(10.5–17)	0.76
SOFA score	4(3–6)	5(3–8)	4(3–7)	0.41
Co-infections				
Cytomegalovirus	41(39.0)	25(43.9)	16(33.3)	0.27
Bacteria	32(30.5)	17(29.8)	15(31.3)	0.87
Fungi	7(6.7)	5(10.4)	2(3.5)	0.16

(*Continued*)

Table 2 (Continued).

Clinical Characteristics	Overall (n=105)	Low-dose Steroid Group (n=57)	Standard-dose Steroid Group (n=48)	*P*
Treatment of PCP				
Duration between admission and initiation of treatment, days, median (IQR)	2(1–3)	1(1–3)	2(1–3)	0.93
Initiation of treatment after 96 hours, n (%)	14(13.3)	8(14.0)	6(12.5)	0.76
Laboratory results, median (IQR)				
WBC, median, 10^9/L	8.5(5.6–11.2)	8.4(5.6–10.3)	8.6(5.6–12.2)	0.43
Neutrophil count, 10^9/L	7.3(5.0–9.9)	7.3(4.8–9.7)	7.2(5.2–11.5)	0.55
Lymphocyte count, 10^9/L	0.4(0.30–0.60)	0.43(0.27–0.75)	0.43(0.30–0.84)	0.83
AST, U/L	37(24–60)	37(23–63)	35(26–53)	0.86
ALT, U/L	23(16–38)	21(16–34)	24(15–40)	0.55
BUN, mmol/L	8.3(5.9–14.0)	8.3(6.1–14.8)	7.8(5.6–14.0)	0.65
Creatinine, umol/L	77.4(53.7–143.4)	84.5(53.7–141.8)	68.7(50.6–151.7)	0.89
TBIL, umol/L	8.4(5.9–14.4)	8.7(5.9–14.3)	7.9(5.9–14.4)	0.34
DBIL, umol/L	3.7(2.3–6.3)	3.8(2.3–6.4)	3.4(2.3–6.2)	0.98
Hemoglobin, g/L	108(94–121)	109(92–124)	106(97–120)	0.86
Platelet, 10^9/L	174(120–244)	159(108–245)	187(145–243)	0.12
Albumin, g/L	26.4(23.5–30.2)	27(23.4–29.5)	25.6(23.9–30.5)	0.96
LDH, U/L	557(456–750)	549(465–698)	547(423–751)	0.81
Blood gas analysis				
PH	7.44(7.40–7.47)	7.45(7.40–7.47)	7.43(7.40–7.46)	0.13
P_aCO_2, mmHg	35(31–39)	34(30–38)	35(32–41)	0.17
P_aO_2, mmHg	83(64–97)	84(63–97)	82(65–98)	0.81
PFR, mmHg	143(105–192)	143(108–200)	144(104–174)	0.64
Lymphocyte subsets, cell/ul				
$CD3^+$ T cell	231(124–415)	249(127–423)	225(122–387)	0.86
$CD4^+$ T cell	96(50–169)	97(62–158)	94(46–230)	0.87
$CD8^+$ T cell	107(54–173)	98(47–172)	115(65–193)	0.38

Note: Data are presented as median (interquartile range), mean (standard deviation) or n (%).

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; HR, heart rate; HFNC, high-flow nasal cannula; NPPV, non-invasive positive pressure ventilation; APACHEII, acute physiology and chronic health evaluation II; SOFA, sepsis-related organ failure assessment; WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; TBIL, total bilirubin; DBIL, direct bilirubin; LDH, lactate dehydrogenase; PFR, PaO2/FiO2 ratio.

Comparison of Outcomes Between Standard-dose and Low-dose Steroid Groups

As shown in Table 3, there was no significant difference in 28-day mortality (50.8% vs 35.4%, p=0.11) and time from onset of symptoms to ICU [7(5–10) days vs 9(6–12) days, p=0.23]. However, there was a significant difference in the 60-day mortality across groups, with rates of 63.2% (36/57) in the low-dose steroid group and 43.8% (21/48) in the standard-dose steroid group (p=0.04). There was no significant difference in ICU mortality, length of ICU stay, IMV, and other secondary outcomes between the two groups. The overall incidence of complications was similar in both groups (Table 3).

After adjustment for potential confounders (age, BMI, Murray score, APACHEII score, SOFA score, oxygen requirement, immunocompromised status albumin, LDH, PFR, and $CD4^+$T cell), the 28-day mortality (adjusted hazard ratio [aHR]: 0.339, 95% confidence interval [CI]:0.147–0.78), p=0.011) and 60-day mortality (aHR: 0.328, 95% CI:0.152–0.760), p=0.005) was significantly lower in the standard-dose group than in the low-dose group (Table 4). The Kaplan-Meier curves for 60-day mortality observed in different groups of this cohort are illustrated in Figure 2 (p=0.04).

Subgroup Analysis

The standard-dose steroid therapy was associated with lower 60-day mortality in patients aged <65 years (aHR: 0.290, 95% CI:0.125–0.697), in no-smokers (aHR:0.410, 95% CI: 0.174–0.962), in patients requiring IMV (aHR: 0.232, 95% CI: 0.075–0.716), in those with albumin<30 g/L (aHR: 0360, 95% CI: 0.153–0.848), and in patients with PFR<150mmHg (aHR: 0.316, 95% CI: 0.122–0.814), while no interaction was observed (Table 5).

Table 3 Clinical Outcomes and Complications in Patients Receiving Low-dose versus Standard-dose Steroid Therapy

	Overall (n=105)	Low-dose Steroid Group (n=57)	Standard-dose Steroid Group (n=48)	*P*
Primary outcomes, n (%)				
28-day mortality	46(43.8)	29(50.8)	17(35.4)	0.11
60-day mortality	57(54.3)	36(63.2)	21(43.8)	0.04
Secondary outcomes				
ICU mortality, n (%)	39(37.1)	25(43.8)	14(29.2)	0.12
Length of ICU stay, median (IQR), day	18(11–27)	18(11–27)	17(12–27)	0.96
IMV, n (%)	59(56.2)	32(56.1)	27(56.2)	0.99
Duration of IMV, median (IQR), day	8(5–18)	8(5–15.5)	8.5(5.5–21)	0.53
ECMO, n (%)	15(14.3)	6(10.5)	9(18.8)	0.63
Complications, n (%)				
Bacterial infection	54(51.4)	30(52.6)	24(50.0)	0.78
Cytomegalovirus infection	79(75.2)	44(77.2)	35(72.9)	0.61
Fungal infection	46(43.8)	22(38.6)	24(50.0)	0.24
Barotrauma	19(18.1)	9(15.8)	10(20.8)	0.50
Gastrointestinal hemorrhage bleeding	8(7.6)	4(7.0)	4(8.3)	0.80

Note: Data are presented as median (interquartile range) or n (%).
Abbreviations: ICU, intensive care unit; IQR, interquartile range; IMV, invasive mechanical ventilation; ECMO, Extracorporeal Membrane Oxygenation.

Table 4 Multivariate Cox Regression Analysis of Steroid Therapy on 28-Day Mortality and 60-Day Mortality

	Low-dose Steroid	28-day Mortality		60-day Mortality	
		Standard-dose Steroid		Standard-dose Steroid	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Crude	Reference	0.655(0.360–1.189)	0.164	0.582(0.340–0.998)	0.049
Model 1[a]	Reference	0.546(0.300–1.059)	0.075	0.522(0.297–0.916)	0.023
Model 2[b]	Reference	0.463(0.221–0.972)	0.042	0.445(0.226–0.875)	0.019
Model 3[c]	Reference	0.339(0.147–0.780)	0.011	0.328(0.152–0.709)	0.005

Notes: [a]Model 1 was adjusted for age, BMI, oxygen requirement, immunocompromised status; [b]Model 2 was adjusted for the factors in Model 1 and Murray score, APACHEII score, and SOFA score; [c]Model 3 was adjusted for the factors in Model 2 and albumin, LDH, PFR, $CD4^+$T cell.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Sensitivity Analysis

Sensitivity analyses showed essentially similar results after excluding patients with chronic pulmonary disease (28-day mortality: aHR 0.396, 95% CI: 0.172–0.911, p=0.029; 60-day mortality: aHR 0.370, 95% CI: 0.171–0.803, p=0.014) (Table S2) or excluding patients with an interval of more than 14 days at inclusion (28-day mortality: aHR:0.258, 95% CI: 0.093–0.711, p=0.009; 60-day mortality: aHR: 291, 95% CI: 0.117–0.728, p=0.008) (Table S3).

Discussion

The main finding of our study is that the standard-dose steroid therapy significantly reduced 60-day mortality without major complications in non-HIV PCP patients with ARDS, particularly among patients < 65 years, non-smokers, those requiring IMV, those with albumin<30 g/L, and those with a PFR <150 mmHg.

Corticosteroids have been suggested for the treatment of community-acquired Pneumonia, as they reduce the time to clinical cure, the length of hospital and ICU stays, the development of respiratory failure or shock not present at the onset of pneumonia, and the rate of pneumonia complications.[16] However, in immunosuppressed patients, *Pneumocystis*

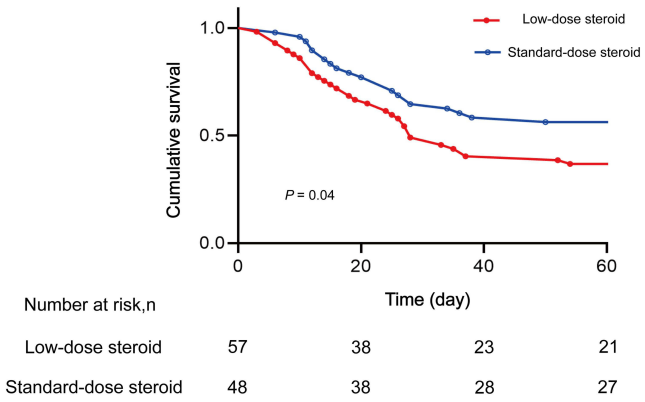

Figure 2 Kaplan-Meier overall survival curves and number at risk table for patients receiving low-dose and standard-dose steroid treatments.

jirovecii releases exogenous pro-inflammatory substances that trigger intense pulmonary and systemic inflammation, leading to severe respiratory impairment. Given the potent anti-inflammatory and immunomodulatory effects of corticosteroids, these agents may help mitigate the imbalance between immune and inflammatory responses.[17]

Few large, retrospective studies have evaluated glucocorticoids in non-HIV PCP patients with severe respiratory conditions admitted to the ICU. While the adjunctive use of steroids in HIV patients with PCP has shown significant efficacy, evidence supporting their use in non-HIV patients remains limited.[18] Since Pareja et al[19] demonstrated that steroids were associated with shorter ICU stays and reduced IMV duration in non-HIV patients, an increasing number of studies have focused on the role of adjunctive steroids in clinical outcomes. Unfortunately, the current evidence so far is not convincing. In a 2013 study of 139 patients, the 72 patients who received adjunctive high-dose steroids (≥1mg/kg/

Table 5 Subgroup Analysis of the Association Between Steroid Treatment and 60-Day Mortality

Variables	Low-dose Steroid	Standard-dose Steroid	Adjusted HR (95% CI)	*P*
	Death/Patients	Death/Patients		
Age				0.523
<65 years (n=81)	23/38	18/43	0.290(0.125–0.697)	
≥65 years (n=24)	13/19	3/5	0.182 (0.007–4.870)	
Smoke status				0.323
Yes (n=23)	9/13	3/10	0.316(0.101–1.203)	
No (n=82)	27/44	18/38	0.410(0.174–0.962)	
IMV				0.083
Yes (n=59)	21/32	14/27	0.232(0.075–0.716)	
No (n=46)	15/25	7/21	0.316(0.116–1.065)	
Albumin				0.496
<30 g/L (n=72)	30/43	17/29	0.360(0.153–0.848)	
≥30 g/L (n=33)	6/14	4/19	0.113(0.006–2.116)	
LDH				0.776
<495 U/L (n=40)	10/19	8/21	0.671(0.095–4.724)	
≥495 U/L (n=65)	26/38	13/27	0.131(0.045–0.377)	
PFR				0.599
<150 mmHg (n=46)	23/31	15/28	0.316(0.122–0.814)	
≥150 mmHg (n=59)	13/26	6/20	0.190(0.361–1.484)	
Bacterial infection				0.860
Yes (n=54)	19/30	11/24	0.260(0.083–2.161)	
No (n=51)	17/27	10/24	0.289(0.072–1.157)	

Abbreviations: HR, hazard ratio; CI, confidence interval; IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase; PFR, PaO_2 /FiO_2 ratio.

day) had an increased risk of death.[11] Wieruszewski et al[9] found no differences in 30-day mortality, length of stay, or need for IMV between early (within 48 hours) steroid recipients and non-recipients. A real-world study using the national database reported a lower risk of mortality rate in non-HIV PCP patients with severe respiratory status (P_aO_2 ≤60 mmHg) treated with adjunctive corticosteroid group. Furthermore, a meta-analysis of 16 studies suggested that corticosteroid combination therapy may be associated with higher mortality in non-HIV PCP patients (OR: 1.37; 95% CI: 1.07–1.75; p= 0.01). However, subgroup analyses indicated lower mortality in patients with hypoxia (OR: 0.69; 95% CI: 0.47–1.01; p = 0.05) and respiratory failure (OR: 0.63; 95% CI 0.41–0.95; p = 0.03).[20]

There were no differences between the two groups in baseline demographics (sex, BMI) or disease severity scores (SOFA score, APACHE II score, Murray score), except for age in our study, which may reduce the bias of the findings. Furthermore, multivariable Cox logistic models, adjusted for baseline demographics, immunocompromised status, disease severity, and risk factors for poor outcome, confirm previous research showing that standard-dose steroids reduce 28-day and 60-day mortality in these patients. Contrary to the findings by Pareja and inoue, who reported that adjunctive corticosteroids shortened the duration of IMV in non-HIV PCP,[10,19] our study found no statistically significant differences in the length of ICU stay, the need for IMV, or the duration of IMV between the standard-dose corticosteroid group and the control group. This discrepancy may be related to the greater severity of respiratory failure in the participants included in our study. Furthermore, we did not include patients with COVID-19 infection, as ICU admission policies during the pandemic prioritized COVID-19-related cases, which limited the inclusion of non-COVID-19 respiratory diseases. The overlapping symptoms and signs of PCP and COVID-19 made distinguishing between the two conditions particularly challenging in patients outside high-risk groups, who were often managed under the assumption of COVID-19 infection.[21]

Glucocorticoid therapy is not recommended for non-HIV patients with mild respiratory failure. The results of the above meta-analysis showed that adjunctive corticosteroid treatment had no significant effect on outcomes in non-HIV PCP patients with hypoxemia. Similarly, Inoue et al also found that adjunctive corticosteroids had no significant differences in mortality in the moderate non-HIV PCP. Consistent with the above studies, subgroup analysis in our study showed that standard-dose steroids were associated with lower 60-day mortality in patients requiring IMV, those with albumin< 30 g/L, and those with PFR<150mmHg. Our findings suggest that patients with a strong inflammatory response and severe respiratory failure may derive greater benefit from standard-dose glucocorticoid therapy.

Delayed treatment of *Pneumocystis jirovecii* has been consistently associated with worse outcomes, particularly in non-HIV immunocompromised patients. Li et al[22] demonstrated that delayed diagnosis and treatment of PCP led to significantly higher mortality rates in non-HIV-infected individuals. Kamel et al highlighted the critical impact of timely prophylaxis and early initiation of therapy on improving survival in intensive care patients with PCP, emphasizing the detrimental effects of treatment delay.[23] Consistent with these findings, our study observed that delayed initiation of TMP-SMX (≥96 hours after admission) was associated with higher ICU mortality. This underscores the importance of early clinical recognition and treatment of PCP, particularly in non-HIV patients, who often experience rapid disease progression and worse prognoses. When considering the use of corticosteroids in these patients, it is crucial to account for short-term side effects such as hyperglycemia, delirium, and secondary infections. Hyperglycemia, the most significant adverse effect of glucocorticoids, has been demonstrated in several studies, and reactive hyperglycemia was also observed in our study. Long-term side effects, such as myopathy and osteoporosis, should also be considered, although these are less likely to occur with a standard 21-day course.[24] Notably, the standard-dose steroid therapy was not associated with an increased incidence of nosocomial infections or gastrointestinal hemorrhage.

We recognize several limitations in our study. First, clinicians tend to prescribe steroids during acute exacerbations of comorbidities or severe disease episodes. To minimize this bias, we included only patients who received steroids within 24 hours of admission. Second, the broad spectrum of immunosuppressive disorders highlights the challenge of grouping a highly heterogeneous population of non-HIV PCP patients. Third, the sample size of our study is relatively small. Finally, the extended time span of this single-center study may introduce time-related bias. However, to ensure accuracy, two experienced respiratory physicians thoroughly reviewed each case in detail.

Conclusions

The standard-dose methylprednisolone therapy was associated with a significant reduction in 28-day and 60-day mortality without increasing the risk of major complications in *Pneumocystis* pneumonia with ARDS in non-HIV

immunocompromised patients. These findings underscore the potential benefits of optimized corticosteroid dosing, which should be further validated in prospective cohorts or randomized controlled studies to confirm its efficacy and safety.

Abbreviation

PCP, *Pneumocystis jirovecii* pneumonia; ARDS, acute respiratory distress syndrome; HIV, human immunodeficiency virus; ICU, intensive care unit; PFR, PaO_2/FiO_2 ratio; PCR, polymerase chain reaction; IMV, invasive mechanical ventilation; LRT, lower respiratory tract; TMP-SMX, trimethoprim-sulfamethoxazole; ECMO, extracorporeal membrane oxygenation; LDH, lactic dehydrogenase; SOFA, sequential organ failure assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; OR, odd ratio.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital (No.2022-ke-65), and complies with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the cohort study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

No funding was received.

Disclosure

The authors declare that they have no conflicts of interest.

This paper has been uploaded to ResearchSquare as a preprint: https://www.research-square.com/article/rs-4423359/v1.

References

1. Wickramasekaran RN, Jewell MP, Sorvillo F, Kuo T. The changing trends and profile of pneumocystosis mortality in the United States, 1999–2014. *Mycoses*. 2017;60(9):607–615. doi:10.1111/myc.12636
2. Ghembaza A, Vautier M, Cacoub P, Pourcher V, Saadoun D. Risk factors and prevention of Pneumocystis jirovecii Pneumonia in patients with autoimmune and inflammatory diseases. *Chest*. 2020;158(6):2323–2332. doi:10.1016/j.chest.2020.05.558
3. Cillóniz C, Dominedò C, Álvarez-Martínez MJ, et al. Pneumocystis pneumonia in the twenty-first century: HIV-infected versus HIV-uninfected patients. *Expert Rev Anti Infect Ther*. 2019;17(10):787–801. doi:10.1080/14787210.2019.1671823
4. Schmidt JJ, Lueck C, Ziesing S, et al. Clinical course, treatment and outcome of Pneumocystis pneumonia in immunocompromised adults: a retrospective analysis over 17 years. *Crit Care*. 2018;22(1):307. doi:10.1186/s13054-018-2221-8
5. Swain SD, Meissner N, Han S, Harmsen A. Pneumocystis infection in an immunocompetent host can promote collateral sensitization to respiratory antigens. *Infect Immun*. 2011;79(5):1905–1914. doi:10.1128/iai.01273-10
6. Bozzette SA, Sattler FR, Chiu J; California Collaborative Treatment Group, et al. A controlled trial of early adjunctive treatment with corticosteroids for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med*. 1990;323(21):1451–1457. doi:10.1056/nejm199011223232104
7. Nielsen TL, Eeftinck Schattenkerk JK, Jensen BN, et al. Adjunctive corticosteroid therapy for Pneumocystis carinii pneumonia in AIDS: a randomized European multicenter open label study. *J Acquir Immune Defic Syndr*. 1992;5(7):726–731.
8. Walmsley S, Levinton C, Brunton J, et al. A multicenter randomized double-blind placebo-controlled trial of adjunctive corticosteroids in the treatment of Pneumocystis carinii pneumonia complicating the acquired immune deficiency syndrome. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;8(4):348–357. doi:10.1097/00042560-199504000-00005
9. Wieruszewski PM, Barreto JN, Frazee E, et al. Early corticosteroids for Pneumocystis pneumonia in adults without HIV are not associated with better outcome. *Chest*. 2018;154(3):636–644. doi:10.1016/j.chest.2018.04.026
10. Inoue N, Fushimi K. Adjunctive corticosteroids decreased the risk of mortality of non-HIV Pneumocystis pneumonia. *Int J Inf Dis*. 2019;79:109–115. doi:10.1016/j.ijid.2018.12.001

11. Lemiale V, Debrumetz A, Delannoy A, Alberti C, Azoulay E. Adjunctive steroid in HIV-negative patients with severe Pneumocystis pneumonia. *Respir Res*. 2013;14(1):87. doi:10.1186/1465-9921-14-87
12. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526–2533. doi:10.1001/jama.2012.5669
13. Lagrou K, Chen S, Masur H, et al. Pneumocystis jirovecii disease: basis for the revised EORTC/MSGERC invasive fungal disease definitions in individuals without human immunodeficiency virus. *Clin Infect Dis*. 2021;72(Suppl 2):S114–s120. doi:10.1093/cid/ciaa1805
14. Jiang Y, Huang X, Zhou H, et al. Clinical characteristics and prognosis of patients with severe pneumonia With Pneumocystis jirovecii colonization: a multicenter, retrospective study. *Chest*. 2024. doi:10.1016/j.chest.2024.07.140
15. Azoulay E, Roux A, Vincent F, et al. A multivariable prediction model for Pneumocystis jirovecii pneumonia in hematology patients with acute respiratory failure. *Am J Respir Critical Care Med*. 2018;198(12):1519–1526. doi:10.1164/rccm.201712-2452OC
16. Stern A, Skalsky K, Avni T, et al. Corticosteroids for pneumonia. *Cochrane Database Syst Rev*. 2017;12(12):Cd007720. doi:10.1002/14651858.CD007720.pub3
17. Charpentier E, Marques C, Ménard S, et al. New insights into blood circulating lymphocytes in human Pneumocystis pneumonia. *J Fungi*. 2021;7(8):652. doi:10.3390/jof7080652
18. National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. *New Engl Med*. 1990;323(21):1500–1504. doi:10.1056/nejm199011223232131
19. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV Pneumocystis carinii pneumonia. *Chest*. 1998;113(5):1215–1224. doi:10.1378/chest.113.5.1215
20. Ding L, Huang H, Wang H, He H. Adjunctive corticosteroids may be associated with better outcome for non-HIV Pneumocystis pneumonia with respiratory failure: a systemic review and meta-analysis of observational studies. *Ann Intensive Care*. 2020;10(1):34. doi:10.1186/s13613-020-00649-9
21. Szydłowicz M, Matos O. Pneumocystis pneumonia in the COVID-19 pandemic era: similarities and challenges. *Trends Parasitol*. 2021;37(10):859–862. doi:10.1016/j.pt.2021.07.010
22. Li MC, Lee NY, Lee CC, et al. Pneumocystis jiroveci pneumonia in immunocompromised patients: delayed diagnosis and poor outcomes in non-HIV-infected individuals. *J Microbiol Immunol Infect*. 2014;47(1):42–47. doi:10.1016/j.jmii.2012.08.024
23. Kamel T, Janssen-Langenstein R, Quelven Q, et al. Pneumocystis pneumonia in intensive care: clinical spectrum, prophylaxis patterns, antibiotic treatment delay impact, and role of corticosteroids. A French multicentre prospective cohort study. *Intensive Care Med*. 2024;50(8):1228–1239. doi:10.1007/s00134-024-07489-2
24. Weyant RB, Kabbani D, Doucette K, Lau C, Cervera C. Pneumocystis jirovecii: a review with a focus on prevention and treatment. *Expert Opin Pharmacother*. 2021;22(12):1579–1592. doi:10.1080/14656566.2021.1915989