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ORIGINAL RESEARCH

Clinical Characteristics and Prognostic Predictors of Pneumocystis *Jirovecii* Pneumonia in Patients with and without Chronic Pulmonary Disease: A Retrospective Cohort Study

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Objective: Pneumocystis *jirovecii* pneumonia (PJP) is a severe respiratory infection caused by Pneumocystis *jirovecii* in immunocompromised hosts. The role of P. *jirovecii* colonization in the development or progression of various pulmonary diseases has been reported. Our aim was to explore serial change in serum biomarkers and the independent risk factors for mortality in patients with and without chronic pulmonary diseases who developed PJP.

Methods: We performed a retrospective study to select patients with Pneumocystis *jirovecii* pneumonia between January 1, 2012, and December 31, 2021. Information regarding demographics, clinical characteristics, underlying diseases, laboratory tests, treatment, and outcomes was collected. Univariate and multivariate logistic regression analyses were used to identify independent predictors of in-hospital mortality.

Results: A total of 167 patients diagnosed with PJP were included in the study: 53 in the CPD-PJP group and 114 in the NCPD-PJP group. The number of patients with PJP showed an increasing trend over the 10-year period. A similar trend was observed for in-hospital mortality. Independent risk factors associated with death in the NCPD-PJP group were procalcitonin level (adjusted OR 1.08, 95% CI 1.01–1.16, P=0.01), pneumothorax (adjusted OR 0.07, 95% CI 0.01–0.38, P=0.002), neutrophil count (adjusted OR 1.27, 95% CI 1.05–1.53, P=0.01) at 14 days, and hemoglobin level (adjusted OR 0.94, 95% CI 0.91–0.98; P=0.002) at 14 days after admission. The risk factor associated with death in the CPD-PJP group was neutrophil count (adjusted OR 1.19, 95% CI 0.99–1.43; P=0.05) at 14 days after admission.

Conclusion: The risk factors for death were different between patients with PJP with and without chronic pulmonary disease. Early identification of these factors in patients with PJP and other underlying diseases may improve prognosis.

Keywords: Pneumocystis *jirovecii*, pneumonia, chronic pulmonary disease, prognostic factors

Introduction

Pneumocystis *jirovecii* pneumonia (PJP), also known as Pneumocystis carinii pneumonia, is a fungal disease of the lower respiratory tract caused by Pneumocystis *jirovecii*. As one of the most serious complications in patients with HIV infection, PJP happened in immunosuppressed and immunocompetent individuals. In recent years, the incidence of PJP in certain non-AIDS immunocompromised patients has increased significantly with the application of massive doses of hormones and novel immunosuppressants. The discovery of the correlation between pneumocystis infection and chronic pulmonary disease has drawn more attention from the medical community. Molecular epidemiological investigations have found that the positive rate of Pneumocystis gene testing in patients with chronic pulmonary diseases such as

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chronic obstructive pulmonary disease (COPD) was relatively high; therefore, some scholars suspected that Pneumocystis infection was related to the occurrence and development of COPD and other chronic pulmonary diseases,[1] but the cause-and-effect relationship is unclear.[1–3] Several studies have found that infection or colonization of Pneumocystis has an impact on the progression and prognosis of various respiratory diseases, such as chronic airway inflammation, pulmonary cystic fibrosis, and interstitial lung disease.[4–6] Morris et al found that the probability of pulmonary fibrosis and obstructive pulmonary disease was significantly higher in patients with PJP than in those without PJP.[3] Pneumocystis infection increases airway dilation and inflammation in the host, which is aggravated by persistent pneumocystis infection.[7,8] Even a small number of pneumocystis-colonized lungs can stimulate the immune response and cause lung injury. Studies have shown that Pneumocystis colonization is a risk factor for PJP development.[9]

The colonization rate of Pneumocystis in the respiratory secretions of chronic bronchitis patients was as high as 41–100%,[10,11] that of Pneumocystis in COPD patients was as high as 10–54.9%,[11,12] and that of Pneumocystis in patients with interstitial lung disease was as high as 30–34%.[13] Cases of PJP have also been diagnosed in less typical scenarios, such as in non-HIV individuals with pre-existing lung disease.[14] To date, in-hospital mortality due to PJP in patients with chronic pulmonary disease before the onset of PJP has received little attention. Some studies have indicated the significance of coexisting chronic lung diseases in the development and progression of PJP.

In the real world, many patients with chronic pulmonary diseases, such as COPD, bronchial asthma, interstitial lung disease, and bronchiectasis, are at risk of Pneumocystis infection, and Pneumocystis is becoming a new pathogen in this group of patients with aggravating conditions.[15] Wang et al found a high prevalence of PJ in patients with chronic pulmonary disease in the People's Republic of China.[1] Currently, some studies need to be conducted in mainland China to effectively guide the treatment and early assessment of the prognosis of patients by identifying the clinical characteristics and risk factors of PJP patients with and without chronic pulmonary disease.

Patients and Methods

Objects of Study

We retrospectively screened the medical records of inpatients with confirmed PJP for the first time between January 2012 and December 2021 at Beijing Chaoyang Hospital and Beijing Huairou Hospital, two tertiary care teaching hospitals. After reviewing adult inpatients (age ≥18 years) from the hospital's electronic banks, 167 patients were included in our study. Medical information was reviewed and analyzed. Chest radiography patterns were assessed by two pulmonologists. Data collected from days 6 to 8 were classified as "day 7", and data collected from days 13 through 15 were classified as "day 14" after admission.

Diagnosis

The inclusion criteria were as follows: (1) confirmed PJP, and (2) only patients with a first episode of PJP. The exclusion criteria were as follows: HIV-1 positive, younger than 18 years of age or pregnant, allergic to sulfa drugs, and less than 2 weeks after hospitalization. The criteria for a definitive diagnosis of PJP were as follows: (1) clinical criteria, including fever, dry cough (occasionally expectorant), progressive dyspnea, fatigue, night sweats, wasting, and chest pain. Main Signs: Cyanosis, thrush, diffuse rale, or normal in the lungs. (2) Common manifestations on chest radiography, including bilateral interstitial infiltrates or bilateral diffuse ground-glass opacity on high-resolution computed tomography of the lungs. (3) Identification of active P. *jirovecii* infection, that is, positive P. jirovecii deoxyribonucleic acid in lung tissue or respiratory tract specimens, confirmed by quantitative real-time polymerase chain reaction (PCR) and elevated beta-D-glucan (β-DG) assay(cut-off value> 100 pg/mL), and/or ii. P. jirovecii cysts were positive for direct Grocott's methenamine silver (GMS) stain in bronchoalveolar lavage fluid (BALF) or sputum. The diagnostic criterion for HIV/AIDS was the use of Western blot to detect HIV-1 antibody positivity. Chronic pulmonary diseases (CPD) included COPD (6), asthma(2), interstitial lung diseases(32), chronic bronchitis(4), pneumoconiosis(1), and bronchiectasis(8). These diseases were diagnosed according to the disease diagnostic criteria of the People's Republic of the China Ministry of Health in 2011.[1]

Data Collection

Patient demographics, underlying diseases, corticosteroid or immunosuppressant use, symptoms and signs, radiological patterns, laboratory findings, treatment, and in-hospital mortality. The following laboratory values were collected: white blood cells, neutrophils, lymphocytes, platelets, and hemoglobin at 48–72h, day 7, and day 14 after admission. In addition, we collected β-D-glucan, CD4+T count, CD8+T count, serum procalcitonin (PCT), C-reactive protein (CRP), lactate dehydrogenase (LDH), serum albumin, PaO_2/FiO_2, ferritin, serum assay for pp65(cytomegalovirus, CMV), and Epstein-Barr virus (EBV) DNA results.

Statistical Methods

SPSS 20.0 statistical software was used. Means ± SD were expressed as continuous data with a normal distribution, whereas medians and interquartile ranges were used for continuous data with a non-normal distribution. Continuous or grade variables were compared using the Mann–Whitney *U*-test. Continuous numerical variables obeying a normal distribution were compared using an independent sample *T* test. Categorical data were expressed as percentages (%). Categorical data were compared using the chi-square test and Fisher's exact test. The correlation between variables and in-hospital mortality was evaluated using univariate and multivariate logistic regression analyses. In the univariate analysis, variables with P<0.05, were included in the multivariate logistic regression. All P values were two-tailed, and statistical significance was set at P <0.05.

Results

We reviewed the data of 502 patients with PJP, with the first episode occurring from 2012 to 2021. A total of 335 patients were not eligible for inclusion and were excluded for the following reasons: HIV-PJP (73), TMP-SMZ allergy (26), hospitalization less than 2 weeks (34), and suspected PJP (202). In total, 167 confirmed individuals were included in this study. The number of patients with PJP showed an increasing trend, and a similar trend was observed for mortality during 10 years (Figure 1). The 167 patients were divided into two groups according to chronic pulmonary disease (CPD). The study flow chart is shown in Figure 2, with 53 cases in the CPD-PJP group and 114 in the NCPD-PJP group.

Baseline Materials and Clinical Manifestations

We compared the demographics, clinical manifestations, and underlying diseases of both the groups (Table 1). NCPD-PJP patients were younger (49.76±16.22 vs 62.15±13.11, P<0.001), had lower rates of smoking (28.07% vs 50.94%, P=0.004), longer duration from fever onset to admission[7 (4–12) vs 4 (1.5–10) days, P= 0.019], higher highest body

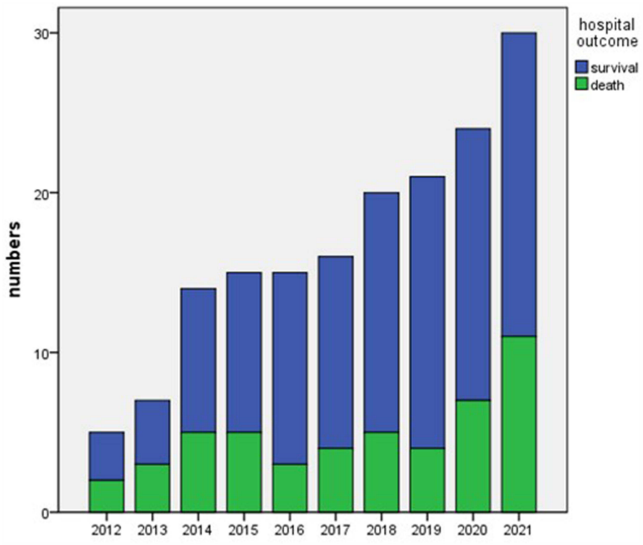

Figure 1 Number of PJP cases from 2012 to 2021.

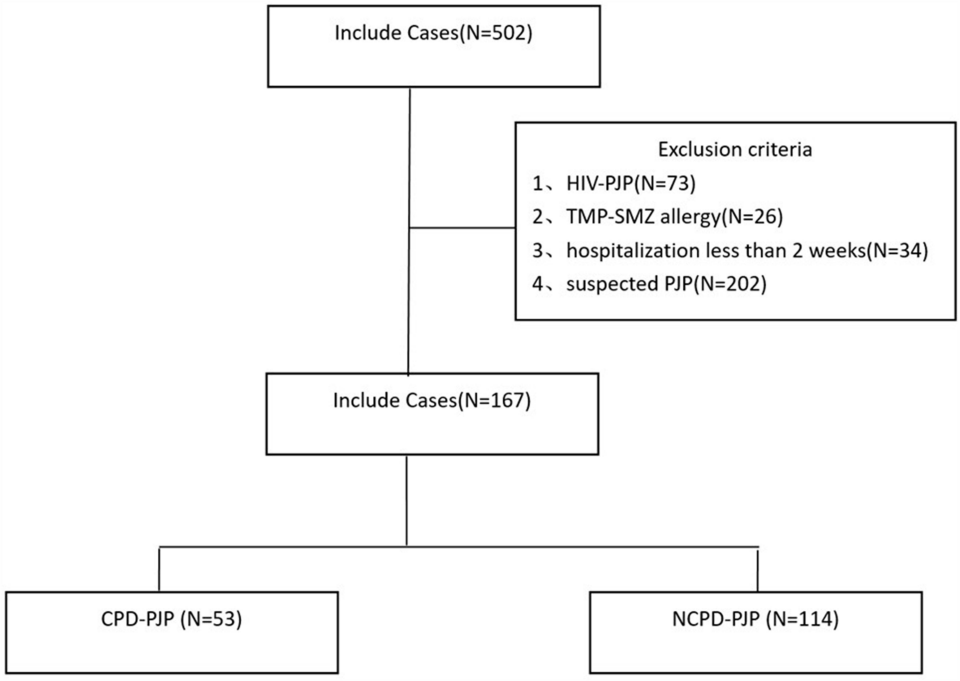

Figure 2 Study flowchart.

temperature[39.0 (38.5–39.5) vs 38.6 (38–39.3) °C, P= 0.040], higher rates of lung rale(66.03% vs 49.12%, P= 0.041), and use of IS (including CS) (76.32% vs 52.83%, P= 0.002) compared to CPD-PJP patients. There were no statistically significant differences in sex, BMI, weight loss, or blood type between the CPD and NCPD groups.

The underlying diseases in the CPD-PJP group included autoimmune inflammatory diseases (n =23), hematological malignancy (non-Hodgkin's lymphoma, 1), solid organ malignant tumor (n=7), solid organ transplant (kidney, 3), and nephrotic syndrome (n=1). The NCPD-PJP group included patients with solid organ transplant (kidney, n=40; liver, n=5; cornea, n=1), autoimmune inflammatory diseases (n=23), nephrotic syndrome (n=13), hematological malignancy (n=7), and solid organ malignant tumor (n =7).

Laboratory Examination and Radiological Findings

At 48–72h after admission, the WBC levels were not significantly different between the groups (P>0.05). At 7 days and 14 days after admission, the WBC levels were significantly higher among CPD-PJP patients than among NCPD-PJP

Table 1 Comparison of Demographics, Clinical Characteristics, Underlying Diseases of CPD-PJP and NCPD-PJP

Characteristics	NCPD- PJP (n=114)	CPD- PJP (n=53)	*P*-value
Demographics			
Male gender	70 (61.40)	33 (62.26)	0.915
Age, y	49.76±16.22	62.15±13.11	**<0.001**
BMI, kg/m^2	24.50±3.27	23.85±3.21	0.232
Blood type, Rh+			
A	32(28.07)	19 (35.85)	0.310
B	34 (29.82)	16 (30.19)	0.962
O	37 (32.46)	13 (24.53)	0.298
AB	11 (9.65)	5(9.43)	0.965
Smoking history	32 (28.07)	27(50.94)	**0.004**

(*Continued*)

Table 1 (Continued).

Characteristics	NCPD- PJP (n=114)	CPD- PJP (n=53)	*P*-value
Patients according to underlying diseases			
Malignant hematological diseases	7(6.14)	1(1.89)	
Solid tumors	7(6.14)	7(13.21)	
Renal transplant recipients	40(35.09)	3(5.66)	
Hepatic transplant recipients	5(4.38)	0	
Connective tissue diseases	23(20.18)	23(43.40)	
Nephrotic syndrome	13(11.40)	1(1.89)	
Clinical manifestations			
Duration from fever onset to admission, d	7(4–12)	4(1.5–10)	**0.019**
Highest temperature,°C	39.0(38.5–39.5)	38.6(38–39.3)	**0.040**
Loss of weight	18(15.79)	13(24.52)	0.176
Lung rale	56(49.12)	35(66.03)	**0.041**
Induction regimen			
CS	102(89.47)	45(84.91)	0.397
IS (combining CS)	87(76.32)	28(52.83)	**0.002**

Note: P value less than 0.05 is indicated by bold.
Abbreviations: BMI, body mass index; Rh, Rhesus; CS, corticosteroid; IS, immunosuppressor.

patients (9.04±3.29 vs 7.34±4.04, respectively, for day 7, P=0.008; 9.26±4.88 vs 6.78±4.02, respectively, for day 14, P=0.001) (Figure 3).

At 48–72h and 7 days after admission, the lymphocyte levels were significantly higher among CPD-PJP patients than among NCPD-PJP patients (1.02±0.63 vs 0.72±0.50, respectively, for 48–72h, P=0.001; 1.01±0.70 vs 0.75±0.72, respectively, for day 7, P=0.034). Fourteen days after admission, lymphocyte levels did not differ significantly between the groups (P>0.05) (Figure 4).

At 48–72h after admission, neutrophil levels did not differ significantly between the groups (P>0.05). At 7 days and 14 days after admission, the neutrophil levels were significantly higher among CPD-PJP patients than among NCPD-PJP patients (7.64±3.03 vs 6.33±3.76, respectively, for day 7, P=0.027; 7.72±4.77 vs 5.29±3.59, respectively, for day 14, P=0.000) (Figure 5).

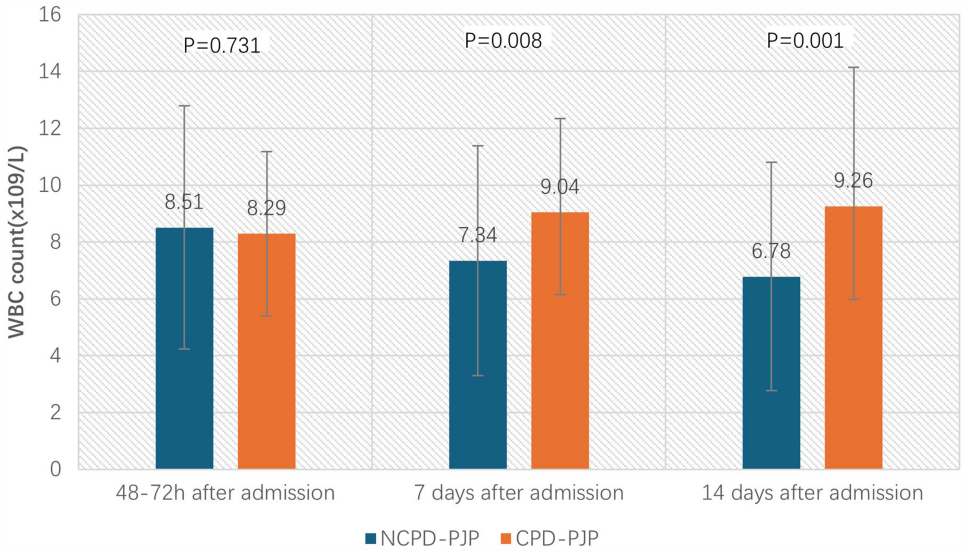

Figure 3 The red bar chart showed change in WBC count in CPD-PJP patients after admission. The blue bar chart showed change in WBC count in NCPD-PJP patients after admission. The paired *t*-test was used to compare values between the two groups.

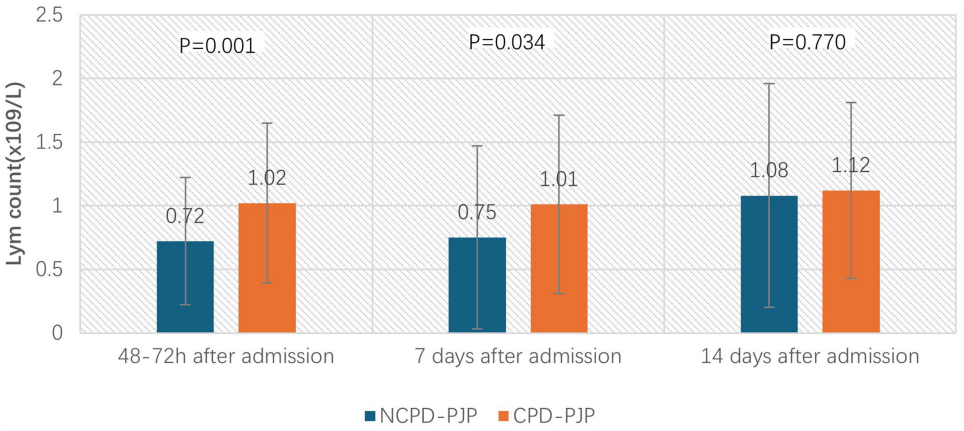

Figure 4 The red bar chart showed change in Lym count in CPD-PJP patients after admission. The blue bar chart showed change in Lym count in NCPD-PJP patients after admission. The paired *t*-test was used to compare values between the two groups.

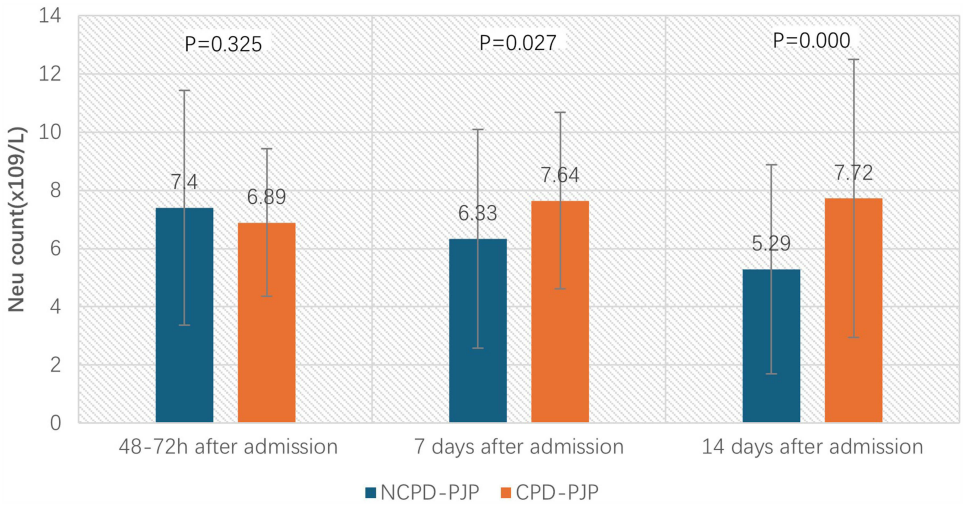

Figure 5 The red bar chart showed change in Neu count in CPD-PJP patients after admission. The blue bar chart showed change in Neu count in NCPD-PJP patients after admission. The paired *t*-test was used to compare values between the two groups.

The platelet levels did not significantly differ between the groups after admission(178.70±86.31 vs 179.61±76.81, respectively, for 48–72h, P=0.946; 198.79±102.89 vs 174.42±85.43, respectively, for day 7, P=0.110; 181.81±82.33 vs 172.95±101.95, respectively, for day 14, P=0.580)(Figure 6).

The hemoglobin levels were significantly higher among CPD-PJP patients than among NCPD-PJP patients after admission(121.68±22.00 vs 108.57±27.07, respectively, for 48–72h, P=0.002; 115.74±27.32 vs 98.05±25.12, respectively, for day 7, P=0.000; 112.04±29.03 vs 98.04±22.56, respectively, for day 14, P=0.001) (Figure 7).

Other examinations, serum β-D-glucan concentration[16.06 (10.00–121.90) vs115.40 (19.37–348.15) pg/mL, P=0.000]and procalcitonin [0.10 (0.05–0.71) vs 0.38 (0.09–2.14) ng/mL, P=0.002] were much lower among CPD-PJP group than among NCPD-PJP group. CD8+ T cell counts[185.00 (97–361) vs117.00 (69.5–233.5) cells/μL, P=0.022] were much higher in the CPD-PJP group than in the NCPD-PJP group. Albumin, LDH, CD4+T cell counts, oxygenation index, and C-reactive protein levels were not statistically significant among the groups (P>0.05). Microbiological findings showed that the proportion of coinfection with EBV was significantly higher among CPD-PJP than among NCPD-PJP patients (71.7% vs 51.75%, P= 0.015), but the proportion of coinfection with CMV did not significantly differ between the groups (64.15% vs 68.42%, P= 0.585).

A comparison of computed tomography (CT) scans between the two groups revealed that the proportion of patients with pneumothorax was significantly higher in the NCPD-PJP group than in the CPD-PJP group (14.04% vs 1.89%, P=

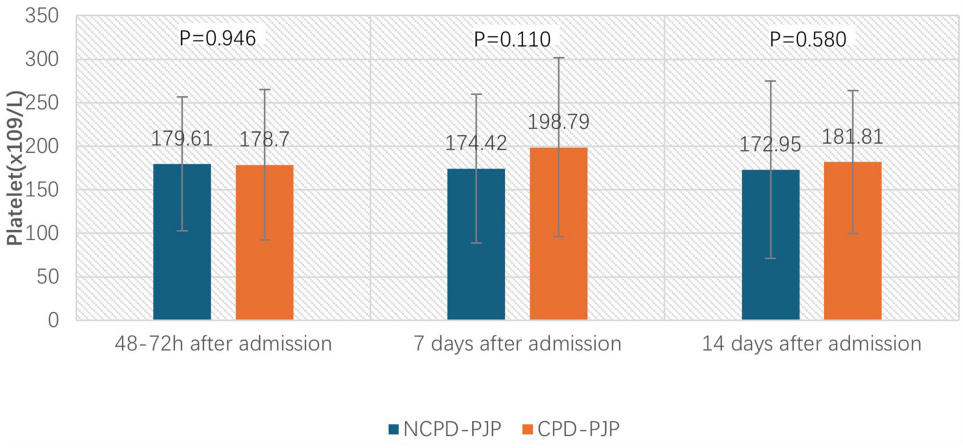

Figure 6 The red bar chart showed change in Platelet count in CPD-PJP patients after admission. The blue bar chart showed change in Platelet count in NCPD-PJP patients after admission. The paired *t*-test was used to compare values between the two groups.

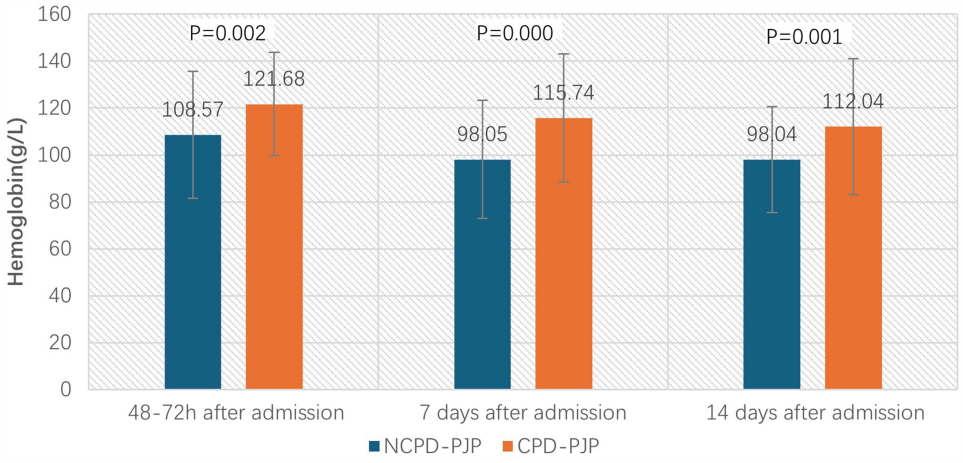

Figure 7 The red bar chart showed change in HGB in CPD-PJP patients after admission. The blue bar chart showed change in HGB in NCPD-PJP patients after admission. The paired *t*-test was used to compare values between the two groups.

0.016). The proportion of patients who received pleural infusion did not differ significantly between the groups (31.58% vs 26.42%, P= 0.498) (Table 2).

Treatment and Outcome

Compared with NCPD-PJP patients, the median ICU stay duration was significantly shorter among CPD-PJP patients [0 (0–6) days vs 10 (0–19) days, P=0.00]. A total of 164 patients received trimethoprim-sulfamethoxazole (TMP-SMX), and 2 patients experienced adverse effects of TMP-SMX requiring discontinuation. A total of 102 patients received sulfa combined with caspofungin: 27(50.9%) in the CPD-PJP group and 75(65.8%) in the NCPD-PJP group. Adverse effects of sulfa, including gastrointestinal symptoms (n = 3), rash (n = 8), and renal dysfunction (n = 11), were recorded in 22 patients (13.2%) during TMP-SMX treatment. The proportion of adverse effects associated with TMP-SMX was the same among the groups (7/53 and 15/114, 13.2%). A total of 162 patients received appropriate antibiotic treatment according to the standard bacterial cultures of respiratory specimens or empiric antibiotic therapy. A total of 147 patients received systemic hormone therapy as adjunctive therapy.

One hundred patients presenting with hypoxemia required mechanical ventilation, 39 patients were supported with noninvasive ventilation, 47 patients required intubation for ventilatory support, 12 patients received ECMO, and two patients received high-flow nasal cannula oxygen therapy. The hospital mortality was 37.74% in CPD-PJP patients and 25.44% in NCPD-PJP patients (Table 3).

Table 2 Comparison of Laboratory Data and Chest Computed Tomography of CPD-PJP and NCPD-PJP

Characteristics	NCPD- PJP (n=114)	CPD- PJP (n=53)	*P*-value
48–72h after admission			
WBC counts(x10^9/L)	8.51±4.28	8.29±2.89	0.731
Lymphocyte counts(x10^9/L)	0.72±0.50	1.02±0.63	**0.001**
Neutrophils counts(x10^9/L)	7.40±4.03	6.89±2.54	0.325
PLT(x10^9/L)	179.61±76.81	178.70±86.31	0.946
HGB(g/L)	108.57±27.07	121.68±22.00	**0.002**
7 days after admission			
WBC counts(x10^9/L)	7.34±4.04	9.04±3.29	**0.008**
Lymphocyte counts(x10^9/L)	0.75±0.72	1.01±0.70	**0.034**
Neutrophils counts(x10^9/L)	6.33±3.76	7.64±3.03	**0.027**
PLT(x10^9/L)	174.42±85.43	198.79±102.89	0.110
HGB(g/L)	98.05±25.12	115.74±27.32	**0.000**
14 days after admission			
WBC counts(x10^9/L)	6.78±4.02	9.26±4.88	**0.001**
Lymphocyte counts(x10^9/L)	1.08±0.88	1.12±0.69	0.770
Neutrophils counts(x10^9/L)	5.29±3.59	7.72±4.77	**0.000**
PLT(x10^9/L)	172.95±101.95	181.81±82.33	0.580
HGB(g/L)	98.04±22.56	112.04±29.03	**0.001**
β-D-Glucan(pg/mL)	115.40 (19.37–348.15)	16.06 (10.00–121.90)	**0.000**
CD4+T count(cells/μL)	138.00 (64.5–249)	148.00 (97–361)	0.191
CD8+T count(cells/μL)	117.00 (69.5–233.5)	185.00 (97–361)	**0.022**
PCT (ng/mL)	0.38 (0.09–2.14)	0.10 (0.05–0.71)	**0.002**
CRP(mg/dl)	8.42 (2.96—13.95)	6.61 (1.88—11.55)	0.056
LDH(U/L)	510.50±307.93	528.09±433.41	0.991
ALB(g/L)	28.05±6.62	29.86±6.29	0.196
Oxygenation index	265.69 (182.84–365.25)	303.44(216.19–368.55)	0.286
EBV coinfection	59(51.75)	38(71.70)	**0.015**
CMV coinfection	78(68.42)	34(64.15)	0.585
Ferritin(ng/mL)	864.23(512.28–1894.81)	684.20(484.05–1333.20)	0.183
Pneumothorax	16(14.04)	1(1.89)	**0.016**
Pleural infusion	36(31.58)	14(26.42)	0.498

Note: P value less than 0.05 is indicated by bold.
Abbreviations: WBC, white blood cell; PLT, platelet; HGB, hemoglobin; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALB, albumin; EBV, Epstein–Barr virus; CMV, cytomegalovirus.

Table 3 Comparison of Treatment and Outcome of CPD-PJP and NCPD-PJP

Characteristics	NCPD- PJP (n=114)	CPD- PJP (n=53)	*P*-value
RICU stay(days)	10(0–19)	0(0–6)	**<0.001**
NIV	29(25.43)	10(18.86)	0.350
IMV	35(30.70)	12(22.64)	0.281
ECMO	11(9.64)	1(1.88)	0.071
Hospital mortality	29 (25.44)	20 (37.74)	0.104

Note: P value less than 0.05 is indicated by bold.
Abbreviations: RICU, respiratory intensive care unit; NIV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

Univariate and Multivariate Analyses for Mortality

Table 4 and 5 presented univariate and multivariate regression analyses of the clinical outcomes for survivors and non-survivors in NCPD-PJP and CPD-PJP groups. In the multivariate regression analysis, corrections were made for age, sex,

Table 4 Characteristics Associated with Hospital Mortality in a Univariate Regression Analysis

	NCPD-PJP	*P*-value	CPD-PJP	*P*-value
	Crude OR (95% CI)		Crude OR (95% CI)	
Age, y	1.01 (0.98–1.03)	0.64	0.99 (0.95–1.04)	0.73
Male gender	0.58 (0.25–1.37)	0.58	0.86 (0.27–2.68)	0.79
Smoking history	0.66 (0.27–1.64)	0.38	1.06 (0.35–3.23)	0.92
CS combine IS before onset	1.03 (0.39–2.78)	0.95	1.20 (0.39–3.65)	0.75
PCT	1.08 (1.02–1.15)	**0.01**	14.9 (1.73–129.23)	**0.01**
β-D-Glucan	1.01 (1.00–1.02)	0.13	1.04 (1.00–1.08)	0.05
Pneumothorax	0.07 (0.02–0.24)	**0.00**	-	-
RICU stay(days)	1.03 (1.01–1.06)	**0.02**	1.11 (1.01–1.23)	**0.03**
Lymphocyte counts(48–72h)	0.49 (0.18–1.32)	0.16	0.78 (0.31–1.95)	0.59
HGB (48–72h)	0.98 (0.96–0.99)	**0.03**	0.98 (0.95–1.01)	0.20
WBC counts (day 7)	1.04 (0.94–1.15)	0.44	0.94 (0.79–1.13)	0.52
Neutrophils counts (day 7)	1.07 (0.96–1.19)	0.20	1.02 (0.85–1.22)	0.87
Lymphocyte counts (day 7)	0.60 (0.29–1.27)	0.18	0.17 (0.05–0.65)	**0.01**
HGB (day 7)	0.97 (0.95–0.99)	**0.01**	0.96 (0.94–0.99)	**0.01**
WBC counts (day 14)	1.06 (0.96–1.18)	0.21	1.08 (0.96–1.21)	0.21
Neutrophils counts (day 14)	1.13 (1.00–1.27)	**0.03**	1.12 (0.94–0.99)	0.08
HGB (day 14)	0.94 (0.92–0.97)	**0.00**	0.97 (0.94–0.99)	**0.01**
EBV coinfection	0.46 (0.19–1.12)	0.08	0.31 (0.08–1.28)	0.10

Note: P value less than 0.05 is indicated by bold.
Abbreviations: CS, corticosteroid; IS, immunosuppressor; PCT, procalcitonin; RICU, respiratory intensive care unit; EBV, Epstein–Barr virus; WBC, white blood cell; HGB, hemoglobin.

Table 5 Multivariate Analyses of Independent Factors Associated with Hospital Mortality

	NCPD-PJP	*P*-value	CPD-PJP	*P*-value
	Adjusted OR (95% CI)		Adjusted OR (95% CI)	
Age, y	1.02(0.98–1.05)	0.30	0.97 (0.91–1.03)	0.41
Male gender	0.57(0.17–1.89)	0.35	1.94 (0.30–12.27)	0.47
PCT	1.08(1.01–1.16)	**0.01**	4.93 (0.67–36.03)	0.11
Pneumothorax	0.07(0.01–0.38)	**0.002**	-	-
RICU stay(days)	0.98(0.94–1.02)	0.48	1.03(0.92–1.17)	0.53
Neutrophils counts (day 14)	1.27(1.05–1.53)	**0.01**	1.19(0.99–1.43)	0.05
HGB (day 14)	0.94(0.91–0.98)	**0.002**	0.96(0.93–1.00)	0.09

Note: P value less than 0.05 is indicated by bold.
Abbreviations: PCT, procalcitonin; RICU, respiratory intensive care unit; HGB, hemoglobin.

procalcitonin, hemoglobin, lymphocytes, neutrophils, and pneumothorax. Pneumothorax was not an independent predictor of death after admission in the PD–PJP group. In the NCPD-PJP group, procalcitonin (adjusted OR 1.08, 95% CI 1.01–1.16, P= 0.01), HGB at 14 days (adjusted OR 0.94, 95% CI 0.91–0.98, P= 0.002), neutrophil count at 14 days (adjusted OR 1.27, 95% CI 1.05–1.53; P= 0.01), and pneumothorax (adjusted OR 0.07, 95% CI 0.01–0.38, P= 0.002) were independently associated with mortality after admission (Figure 8).

Discussion

P. jirovecii colonization has been reported in non-HIV cases with various pulmonary diseases has been reported.[16–20] A high prevalence of Pneumocystis *jirovecii* colonization has been observed in patients with chronic lung diseases and various underlying respiratory diseases. Researchers have focused on the important role of *P. jirovecii* colonization in the development and progression of various pulmonary diseases. Patients carrying *P. jirovecii* are at a higher risk of

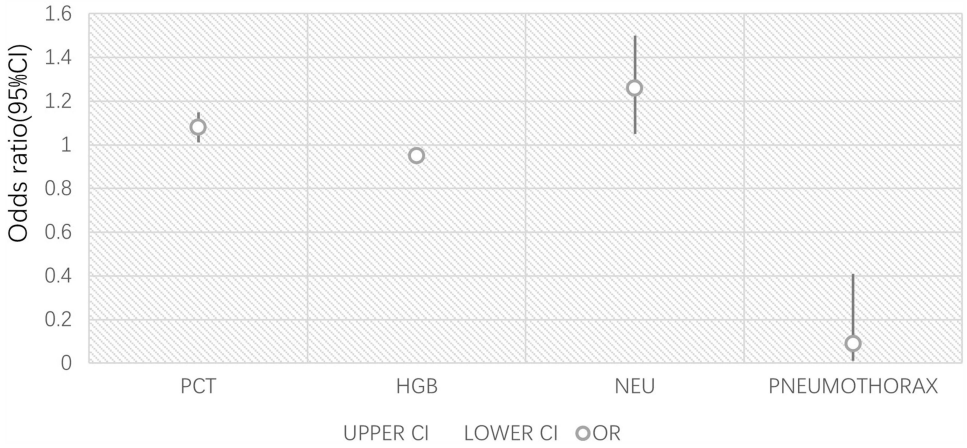

Figure 8 Risk factor of the fatal outcome in the multivariate regression model among NCPD-PJP patients after admission. The figure presents the OR and the 95% CIs associated with the end point.

P. jirovecii pneumonia.[1] The correlation between lower respiratory tract microbes and *P. jirovecii* colonization and its effect on pulmonary disease has drawn attention.[21,22] Several studies have reported that pre-existing lung disease or accompanied with CPD, or coexisting lung disease prior to PJP is associated with poor prognosis in non-HIV patients with PJP.[23–25] Our data also demonstrated that the overall prognosis of PJP in CPD patients was poor. In our study, the smoking and mortality rates were higher in the group of patients with chronic lung disease. Harmful substances in smoke can damage the mucosal barriers of the throat and airway. Lack of protection of the airway mucosa can easily lead to bacterial or fungal colonization. After the colonization of Pneumocystis, it aggravated the damage to the anatomical structure of the airway. These processes may be the first step in the development of pneumocystis pneumonia. The above results suggest that smoking cessation could reduce Pneumocystis colonization, prevent airway damage, and prevent Pneumocystis pneumonia, which is beneficial to the prognosis of the disease.[26]

Age was usually chosen as a predictor of risk evaluated rules for community-acquired pneumonia, and older age was associated with worse PJP prognosis among immunosuppressed patients.[25] Kageyama et al found that coexisting lung disease at an advanced age was an independent risk factor for death.[24] Roux et al confirmed a correlation between older age and death due to PJP in a large prospective cohort study.[27] In a prospective observational study that enrolled 107 cases with PJP, Gaborit et al reported that older age (OR 3.36 [95% CI 1.4–8.5]) was independently associated with disease prognosis.[28] In our study, patients with PJP and CPD were older and had higher in-hospital mortality than NCPD-PJP patients, the differences for age reach statistical significance (62.15±13.11 vs 49.76±16.22, P<0.001), but for mortality (37.7% versus 25.4%), the difference was not significant. Although our multivariate logistic regression analysis indicated that age was not independently associated with mortality (OR 1.02 [95% CI 0.98–1.05], P=0.30), consideration was related to sample size, but together with previous studies, we also should devote close attention to advanced age patients with PJP, especially PJP combined CPD.

Tobacco smoke results in weakened mucociliary clearance, which could facilitate *P. jirovecii* colonization. In short, pneumocystis present in the lung, together with smoking, could be a cofactor that accelerates or maintains an inflammatory response, improving CPD progression. *P. jirovecii* induces inflammatory changes that result in chronic pulmonary injury during chronic pulmonary diseases but also interacts with other agents, such as tobacco and pathogenic bacteria.[13] In this study, the proportion of smoking patients and mortality in the CPD group was higher than that in the NCPD group, suggesting that smoking aggravated the disease and related to the in-hospital mortality.

Important risk factors for PJP include deficiencies in cellular immunity and use of immunosuppressive agents. Steroid therapy may increase the rates of viral reactivation and bacterial infection in immunocompromised patients.[29] The direct pathogenic effect of *P. jirovecii* is not strong, and lung injury and respiratory impairment in cases of PJP are closely correlated with the host immune response.[30] A published study reported that HIV-negative PJP is a systemic inflammatory reaction caused by neutrophilic lung inflammation, and that neutrophilic overactivation results in alveolar damage

owing to the release of inflammatory cytokines.[31] Limper et al reported that respiratory failure and mortality were associated with neutrophil counts in the lower respiratory tract but not with the organism burden.[30] In PJ-infected patients, the higher the number of neutrophils, the more patients die, because neutrophilic lung inflammation may result in diffuse alveolar damage, impaired gas exchange, and poor survival.[15,32] The neutrophil count was identified as an independent risk factor for death in our study. We assumed that neutrophil count represented the overall effect of immunosuppressive treatment and could be a good biomarker. Finally, consistent with previous studies, we observed that a high neutrophil count was associated with a poor prognosis in patients with PJP without CPD. The NCPD group had the highest PCT levels and neutrophil counts at the most severe end of the spectrum, suggesting that anti-inflammatory treatment might improve patient outcomes.

PCT is a sensitive biomarker of bacterial infections. Significant differences in PCT levels were not observed between the patients with and without *P.* jirovecii infection.[33] This indicates that *P.* jirovecii may contribute to the risk of COPD exacerbation and other pulmonary diseases. Previous studies have not shown that PCT can independently affect the prognosis of NHIV-PJP infections. The use of PCT serum concentrations to differentiate PJP from other respiratory infections and/or colonization is clear.[34] One meta-analysis showed that PCT was 88% sensitive and 81% specific in determining bacterial infectivity.[35] PCT can be used as an indicator to differentiate bacterial pneumonia from tuberculosis and PJP.[36] In our study, we found that PCT levels could be a poor prognostic indicator in the CPD-PJP group. In the univariate regression analysis, the risk of death was 14.9 times for each unit increase in PCT level. In the NCPD-PJP group, the PCT level was an independent risk factor for in-hospital mortality. There are no reports on the relationship between PCT levels and prognosis of patients with NCPD-PJP. Further prospective studies are required to confirm these findings.

Mechanical ventilation can cause pneumothorax, pneumomediastinum and pneumohypoderma, called barotrauma.[37,38] Barotrauma is usually a warning of poor prognosis and a high mortality rate 50–100%.[39–41] Pneumothorax is currently difficult to treat in patients with PJP. The development of pneumothorax is independently associated with increased mortality in non-HIV PJP patients.[38] In our study, pneumothorax was a poor prognostic indicator in the NCPD-PJP group, which is in agreement with a previous report. In contrast to previous results, our study showed no relationship between pneumothorax and mortality in the CPD-PJP group. That the difference may be related to the relatively less sample numbers, or perhaps chronic pulmonary diseases might cause the destruction of the lung tissue, leading pneumocystis in lower respiratory tract more likely to progress, thereby increasing mortality and shortening survive duration, no pneumothorax developed before death.

Hemoglobin has rarely been used as an independent risk factor for death in previous studies,[42] but it has been reported[43] that anemia is a risk factor for disease progression and mortality in HIV/AIDS patients. Anemia is often present in HIV/AIDS patients with opportunistic infections, including PJP, and is treated as an indicator of increased severity of opportunistic infections.[44] An important finding of our study is the clear association between hemoglobin levels at 14 days and in-hospital mortality. The results of multivariate regression analysis showed that the risk of death decreased with the increase of HGB, and the correction of anemia had a protective effect on avoiding death. Different to the findings of previous studies, considering reasons were that hemoglobin was collected only one time in previous studies, however, blood routine tests will be done several times throughout the hospital stay, and few reports evaluated serial change in serum biomarkers after admission for PJP patients. Hemoglobin values were collected three times for each enrolled patient and it was found that hemoglobin at 14 days after admission was an independent predictor of death among NCPD-PJP patients. In our study cohort, hemoglobin levels at 14 days were associated with mortality in univariate and multivariate analyses.

There are several limitations to our retrospective, nonrandomized, observational study design without a standardized treatment. First, our study was relatively small, and the participants were recruited from two medical centers. Second, all patients were diagnosed with proven PJP and admitted to the hospital for more than 14 days, which could lead to selection bias. Third, some participants were diagnosed with PJP based on positive PCR results. PCR detection may indicate PJ colonization rather than PJ infection. However, our diagnostic rules for PJP included clinical manifestations, new pulmonary infiltrates on radiographic images, and elevated beta-D-glucan levels to reduce false positive results. In relatively rare diseases, such as CPD-PJP, research has been insufficient to evaluate its validity. Therefore, further multicenter prospective investigations are warranted.

Conclusions

In conclusion, procalcitonin level, pneumothorax, neutrophil count at 14 days, and hemoglobin level at 14 days after admission were poor prognostic indicators among patients with NCPD-PJP. Neutrophil count was related with poor prognosis among CPD-PJP patients. The all-cause mortality rate of CPD-PJP patients was higher than that of NCPD-PJP patients, with no significant difference. Early identification of these factors in patients with PJP and other underlying diseases may improve prognosis.

Data Sharing Statement

The data used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

The Medical Ethics Committee of Beijing Chaoyang Hospital approved this study and waived the requirement for informed written consent, given its observational nature. This study kept patient data confidential and complied with the Declaration of Helsinki.

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Disclosure

The authors declare no competing interests in this work.

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