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Prognostic analysis of concurrent *Pneumocystis jirovecii* pneumonia in patients with systemic lupus erythematosus: a retrospective study

Yujie Shi[1], Ruxuan Chen[1], Hongli Sun[2], Kai Xu[3], Zhiyi Li[1], Mengqi Wang[1], Chi Shao[1] and Hui Huang[1*]

Abstract

Background Systemic lupus erythematosus (SLE) has been less deadly since the advent of corticosteroid-sparing medications. SLE patients still have a higher mortality rate than the general population. Infectious disease is reported as one of the major causes of death in patients with SLE. Although bacteria are the most often isolated pathogens from patients with SLE, *Pneumocystis jirovecii* pneumonia (PJP) is more deadly than bacterial infection.

Methods We retrospectively enrolled consecutive patients with SLE concurrent with PJP (SLE-PJP) in our center between January 2014 and December 2022. The participants were classified into two groups: survivors and non-survivors. Cox regression models and Kaplan–Meier survival analyses were conducted to explore prognostic factors for survival.

Results There were 57 patients with SLE (42.0 ± 15.8 years old, 78.9% female) complicated with PJP, 22 (38.6%) of whom died. Compared with the survival group, the non-survival group had more patients with hyperglycemia or diabetes mellitus, invasive ventilation ($p < 0.01$), respiratory failure, intensive care unit admission, non-invasive ventilation, and hospital-acquired pneumonia ($p < 0.05$). The non-survival group showed a higher neutrophil percentage, lactate dehydrogenase, D-dimer ($p < 0.001$), urea, high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), and ferritin ($p < 0.05$). It also had lower minimal albumin, hemoglobin ($p < 0.001$), immunoglobulin G, complement 3, peripheral lymphocyte count, platelet, NK cell count, and CD4$^+$ T-cell count ($p < 0.05$). Multivariate analysis indicated that hyperglycemia or diabetes mellitus (HR = 4.25, $p < 0.01$, 95% CI: 1.51–11.97), thrombocytopenia (HR = 4.22, $p < 0.01$, 95% CI: 1.63–10.91) and lower complement 3 (C3) (HR = 4.06, $p < 0.01$, 95% CI: 1.60-10.33) were independent risk factors for the survival of SLE-PJP patients.

Conclusions The mortality rate of patients with SLE-PJP is still high. Hyperglycemia, decreased C3, and thrombocytopenia are independent survival risk factors.

Keywords *Pneumocystis jirovecii* pneumonia, Systemic lupus erythematosus, Prognosis

*Correspondence:
Hui Huang
pumchhh@126.com
Full list of author information is available at the end of the article

Introduction

Systemic lupus erythematosus (SLE) is a common chronic multisystemic autoimmune disease with heterogeneous clinical phenotypes that predominantly affects young females. Although the overall mortality rate of patients with SLE has improved dramatically since the 21st century thanks to improvements in early diagnosis and treatment, SLE patients still have a higher mortality than the general population [1]. The standardized mortality rate (SMR) of SLE has been 1.8-3.0 in epidemiologic studies [2–5]. Infectious diseases are some of the main causes of death [3, 6]. A case–control study showed that uncontrolled SLE (20%), infection (34.2%), and both together (24.8%) were common causes of death in hospitalized patients with SLE [6]. A Chinese nationwide cohort study of 29,510 hospitalized patients with SLE reported that infection (65.8%) was the most common cause of death, followed by lupus nephritis (48.6%) and hematological abnormalities (18.1%) [3]. The lower respiratory system is one of the most involved infection sites in SLE patients [7, 8]. Opportunistic pathogens such as pneumocystis, *Mycobacterium tuberculosis* and cytomegalovirus are common and are also associated with a high risk of in-hospital death among SLE patients [9].

Pneumocystis jirovecii pneumonia (PJP) is a fatal opportunistic infectious disease that predominantly occurs in immunosuppressed patients. PJP was first reported as the most common opportunistic infection in patients with human immunodeficiency virus (HIV), but with suggested preventive protocols and effective antiretroviral treatments, PJP incidence and mortality have fallen dramatically in HIV patients. However, immunosuppression treatments, including chemotherapy, radiotherapy, transplantation, corticosteroids and/or immunosuppressant medications, have been gradually reported as common risk factors for PJP. Non-HIV-PJP patients have different manifestations and prognoses than HIV-PJP patients, with rapid progression to hypoxemia and high mortality [10–12]. Both inherently associated SLE immunodeficiency and immunosuppressant treatment might be key risk factors for common opportunistic infections, e.g., PJP, in SLE patients. Patients with SLE-PJP have a mortality rate as high as 37–60% [13]. We conducted this retrospective analysis of hospitalized SLE-PJP patients to elucidate their clinical characteristics and prognostic factors, aiming to improve the identification of high-risk SLE-PJP patients with poor prognosis and improve their clinical management.

Materials and methods

Patients

All enrolled patients who were discharged with a diagnosis of PJP and negative HIV test from January 2014 to December 2022 were screened for eligibility from the electronic medical records system at Peking Union Medical College Hospital (PUMCH). There were 246 hospitalized patients with systemic autoimmune diseases who were complicated with PJP. Among them, there were 57 patients with SLE. Their complete medical records and radiological imaging data were retrospectively reviewed through the hospital's electronic banks. They were followed up from the day that the diagnosis PJP was confirmed. After discharge, they were followed up every 1 to 6 months, depending on the disease activity and severity. The final follow-up point was December 30, 2023. The follow-up information was obtained through outpatient records or telephone conversations. The following information was reviewed and analyzed: age, sex, the clinical manifestations, the serological results, chest high-resolution computed tomography (HRCT), treatments, and outcomes. Survival time was defined as the time from diagnosis of PJP to death or the final follow-up point.

During screening process, patient with any of following character were excluded from our study: (1) younger than 18 years old; (2) with positive HIV test; and (3) without chest CT imaging in our hospital's data bank.

Definitions

Diagnosis of SLE were coincide with 2012 SLE classification criteria of the Systemic Lupus International Collaborating Clinics (SLICC) [14] and/or 2019 SLE classification criteria of European League Against Rheumatism /American College of Rheumatology (EULAR/ACR) [15].

Diagnostic criteria of confirmed PJP were defined as follows: (1) new presence of relevant respiratory manifestations (cough, dyspnea, sputum, and/or hypoxia) or fever (temperature≥37.3 ℃); (2) new presence of pulmonary shadows (ground-glass opacities, consolidation, or patchy shadows) that were identified by chest CT; (3) Pneumocystis DNA fragments were confirmed by polymerase chain reaction (PCR) or metagenomic next-generation sequencing (mNGS), and/or Pneumocystis asci were observed at direct microscopic examination with Grocott's methenamine silver (GMS) stain in the respiratory samples, including qualified sputum specimens, aspirates, or bronchoalveolar lavage fluid (BALF).

Respiratory failure was defined as a room air pulse oxygenation of <90%, a room air arterial partial pressure oxygen level of <60 mmHg (1 mmHg=0.133 kPa), or the oxygenation index under oxygen inhalation is less than 300 mmHg.

Cytomegalovirus (CMV) viremia was defined as peripheral blood CMV-DNA>500 copies.

This study was approved by the Ethics Committee of Peking Union Medical College Hospital (K5596) in accordance with the Declaration of Helsinki. Our study was performed using anonymized health care data. The written informed consent from each patient was waived

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as this study met the PUMCH IRB's minimal risk waiver criteria.

Statistical analysis

All the data were analyzed using the IBM SPSS Statistics version 27.0 software package (IBM Corporation, North Castle Drive, MD-NC119, Armonk, NY 10504−1785, USA). The quantitative variables were presented as the means±standard deviations (SD) or medians (interquartile ranges [IQRs]), and the categorical variables were presented as frequencies and percentages. Comparison between groups was conducted using t test or rank sum test for quantitative variables, and the chi-square test for categorical variables. Cox regression models were used to identify factors associated with prognosis for SLE-PJP patients. The statistically significant variables selected via univariate analysis were finally assessed by multivariate analysis. And Kaplan–Meier survival curves were used to compare mortality of different groups. The difference was statistically significant when $p < 0.05$.

Results

General characteristics of the enrolled SLE patients with PJP (SLE-PJP)

Fifty-seven patients with a diagnosis of SLE-PJP were enrolled in our study after a detailed medical record review. Among them were 35 survival patients (61.4%) and 22 non-survival patients (38.6%), with a median follow-up period of 198 days. 12 were male (21.1%) and 45 were female (78.9%), and they were 42.0±15.8 years old (range 20 to 77 years). The average period of PJP infection was 7.7 years after the diagnosis of SLE. Among 22 patients in non-survival group, 8 (36.4%) died due to severe PJP infection, 10 (45.5%) died due to pulmonary mixed infection (CMV, bacteria, aspergillus, etc.) including PJP infection, 3 (13.6%) died due to septic shock, and 1 (4.5%) died due to the progression of the underlying ILD after PJP infection.

The SLE-PJP patients had several comorbidities (Fig. 1): 19 patients (33.3%) had ILD, about half of the patients (29, 50.9%) had hyperglycemia or diabetes, and most patients (41, 71.9%) had kidney disease. Among them, 36 SLE-PJP patients (63.2%) experienced respiratory failure, and 33 patients (57.9%) were transferred to intensive care unit (ICU) wards. Most patients were given glucocorticosteroids (56, 98.2%) and/or immunosuppressants/biological medications (44, 77.2%) before PJP. There were 29.5% (13/44) patients treated with mycophenolate mofetil, 25% (11/44) patients treated with cyclophosphamide, 20.5% (9/44) patients treated with other immunosuppressants (such as methotrexate, azathioprine, cyclosporine A, tacrolimus, etc.), and 25% (11/44) patients treated with the combination of the above two immunosuppressants. Some patients had coinfection with CMV viremia (38, 66.7%), hospital-acquired pneumonia (HAP) (19, 33.3%), oral candidiasis (7, 12.3%), aspergilli (10,17.5%), mycobacteria (1, 1.8%), and nocardia (1, 1.8%).

The main clinical manifestations of PJP were dyspnea (54, 94.7%), fever (52, 91.2%), cough (49, 86.0%), expectoration (40, 70.2%), and, rarely, hemoptysis (2, 3.5%). Hypoalbuminemia was common in the SLE-PCP patients; 55 patients (96.5%) had hypoalbuminemia, with minimal serum albumin (23.0±5.5) g/L. Many SLS-PJP patients (48, 84.2%) had a low peripheral lymphocyte
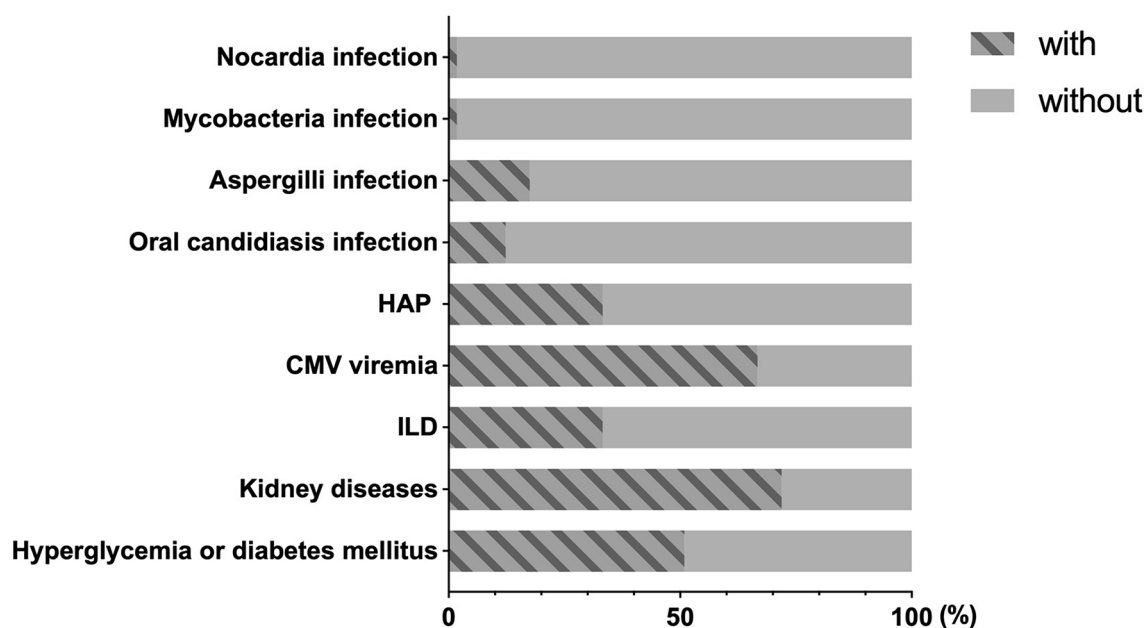
Fig. 1 The comorbidities of our enrolled patients with SLE-PJP. HAP, hospital-acquired pneumonia; CMV, cytomegalovirus; ILD, interstitial lung disease

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count, i.e., $0.8 \pm 1.4 \times 10^9$/L. Most patients (54, 94.7%) had a low peripheral $CD4^+$ T-cell count (129.7 ± 196.4)/ μL. Bilateral (56, 98.2%), ground-glass opacities (GGOs) (48, 84.2%), and patches (46, 80.7%) were the most common chest CT manifestations. Less common chest CT findings were consolidations (22, 38.6%), lymphadenopathy (22, 38.6%), pleural effusion (27, 47.4%), and pleural thickening (34, 59.6%).

After the diagnosis of PJP, all patients (57, 100%) were prescribed trimethoprim-sulfamethoxazole (TMPco), and about half of them (27, 47.4%) also received second-line treatment with second-line anti-PJ medications: caspofungin (21, 36.8%), clindamycin (13, 22.8%), or primaquine (1, 1.8%).

Differences between the survival and non-survival groups of SLE-PJP patients

The baseline characteristics of patients with SLE-PJP, subdivided according to prognosis, i.e., the survival group vs. the non-survival group, are listed in Table 1. There were no significant differences in age, sex, interval from diagnosis of SLE to diagnosis of PJP, or interval between onset and diagnosis of PJP between the two groups. Hyperglycemia or diabetes was more common in the non-survival group (72.7% vs. 37.1%, $p < 0.01$).

The clinical characteristics of patients with PJP in different prognostic groups are listed in Table 2. Patients in the non-survival group were more likely to suffer from respiratory failure (72.7% vs. 37.1%, $p < 0.01$), to be transferred to the ICU (77.3% vs. 45.7%, $p = 0.02$), to need invasive ventilation (77.3% vs. 34.3%, $p < 0.01$), and to need noninvasive ventilation (50.0% vs. 20.0%, $p = 0.02$). Both groups had some patients who suffered

Table 1 The baseline characteristics between survival group and non-survival group

Variables	Survival group	Non-survival group	t / Z /χ^2	P Value
Age (years) [a]	39.8 ± 15.5	45.4 ± 16.2	-1.29	0.20
Male [b]	27 (77.1)	18 (81.8)	0.01	0.93
ILD [b]	10 (28.6)	9 (40.9)	0.93	0.34
hyperglycemia or diabetes mellitus [b]	13 (37.1)	16 (72.7)	6.84	**< 0.01**
Kidney disease [b]	23 (65.7)	18 (81.8)	1.74	0.19
The interval between diagnosis of SLE and PJP (days) [a]	3122.4 ± 3126.9	2339.9 ± 2288.9	1.01	0.32
The interval between onset and diagnosis of PJP (days) [c]	6 (2.0, 17.0)	11 (6.8, 20.3)	-1.67	0.10

[a] mean±SD, [b] n (%), [c] median (IQR). Bold values mean *p* value<0.05. ILD, interstitial lung disease; SLE, systemic lupus erythematosus; PJP, *pneumocystis jirovecii* pneumonia

from mixed infectious diseases. There were significantly more patients with hospital-acquired pneumonia in the non-surviving group than in the surviving group (50.0% vs. 22.9%, $p = 0.03$). The two groups had similar chest CT features and received glucocorticosteroid or immunosuppressant administration. As for anti-PJP treatment, patients in the non-survival group were more likely to be prescribed combination with second-line antibiotics (63.6% vs. 37.1%, $p = 0.05$). In the non-survival group, all 14 patients were prescribed with second-line treatment because of poor therapeutic effect and progression of disease, and 4 patients among them reduced TMPco dose due to renal impairment.

The differences in laboratory data between the two groups of SLE-PJP patients were as follows. The non-survival group had a significantly higher neutrophil percentage ($89.6 \pm 8.0\%$ vs. $82.9 \pm 13.0\%$, $p < 0.001$), urea [10.5 (8.4, 24.8) mmol/L vs. 7.6 (4.8, 14.6) mmol/L, $p = 0.02$], lactate dehydrogenase [798.0 (683.5, 1200.5) U/L vs. 500.0 (327.8, 689.8) U/L, $p < 0.001$], high-sensitivity C-reactive protein (78.7 ± 72.8 mg/L vs. 36.5 ± 42.7 mg/L, $p = 0.02$), erythrocyte sedimentation rate (65.8 ± 31.4 mm/h vs. 46.5 ± 31.1 mm/h, $p = 0.03$), ferritin [1071.0 (516.0, 2455.0) μg/L vs. 459.0 (185.8, 1177.8) μg/L, $p < 0.05$], and D-dimer [6.7 (1.4, 13.5) mg/L vs. 0.9 (0.4, 1.8) mg/L, $p < 0.001$]. The non-survival group had significantly lower levels of PaO2/FiO2 ratio [116.5 (86.5, 211.8) vs. 250.0 (157.0, 375.0), $p < 0.001$], minimal albumin (19.3 ± 4.1 g/L vs. 25.4 ± 4.9 g/L, $p < 0.001$), immunoglobulin G (5.6 ± 3.0 g/L vs. 8.7 ± 4.3 g/L, $p < 0.01$), complement 3 (C3) (0.7 ± 0.3 g/L vs. 0.9 ± 0.3 g/L, $p = 0.02$), peripheral lymphocyte count ($0.4 \pm 0.3 \times 10^9$/L vs. $1.0 \pm 1.7 \times 10^9$/L, $p = 0.03$), hemoglobin (86.6 ± 20.2 g/L vs. 107.1 ± 19.7 g/L, $p < 0.001$), and platelets ($102.1 \pm 85.9 \times 10^9$/L vs. $169.5 \pm 92.5 \times 10^9$/L, $p < 0.01$). NK cell count (21.6 ± 33.5 /μL vs. 56.8 ± 75.4 /μL, $p = 0.04$), and $CD4^+$ T cell count (63.7 ± 43.3 /μL vs. 167.4 ± 237.3 /μL, $p = 0.03$).

Prognostic analysis for SLE-PJP patients

Univariate Cox regression analysis (Fig. 2A) indicated that hyperglycemia or diabetes mellitus, HAP, respiratory failure, non-invasive ventilation, invasive ventilation, ICU admission, thrombocytopenia, higher serum urea, lower immunoglobulin G and lower C3 were associated with non-survival. Finally, multivariate Cox regression analysis showed that hyperglycemia or diabetes mellitus (HR=4.25, χ^2=7.49, $p < 0.01$, 95% CI: 1.51–11.97), thrombocytopenia (HR=4.22, χ^2=8.84, $p < 0.01$, 95% CI: 1.63–10.91) and lower C3 (HR=4.06, χ^2=8.68, $p < 0.01$, 95% CI: 1.60-10.33) were independent risk factors for non-survival in patients with SLE-PJP.

Kaplan-Meier analysis (Fig. 3) also indicated that decreased C3 ($p < 0.001$) were associated with poor

Table 2 The clinical characteristics between survival group and non-survival group

Variables	Survival group	Non-survival group	t / Z /χ^2	P Value
Infection status				
Respiratory failure [b]	18 (51.4)	18 (81.8)	5.36	**0.02**
ICU admission [b]	16 (45.7)	17 (77.3)	5.52	**0.02**
Invasive ventilation [b]	12 (34.3)	17 (77.3)	9.99	**< 0.01**
Non-invasive ventilation [b]	7 (20.0)	11 (50.0)	5.63	**0.02**
Pneumomediastinum [b]	3 (8.6)	3 (13.6)	0.03	0.87
CMV viremia [b]	21 (60.0)	17 (77.3)	1.81	0.18
Oral candidiasis infection [b]	5 (14.3)	2 (9.1)	0.03	0.87
Mycobacteria infection [b]	0 (0.0)	1 (4.5)	-	0.39
Nocardia infection [b]	0 (0.0)	1 (4.5)	-	0.39
Aspergilli infection [b]	4 (11.4)	6 (27.3)	1.38	0.24
HAP [b]	8 (22.9)	11 (50.0)	4.48	**0.03**
Chest CT features				
Bilateral [b]	34 (97.1)	22 (100)	-	1.00
Sub-pleural distribution [b]	6 (17.1)	2 (11.1)	0.00	1.00
Peri-bronchial distribution [b]	4 (11.4)	0 (0.00)	1.24	0.27
GGO [b]	32 (91.4)	16 (72.7)	2.29	0.13
Patches [b]	30 (85.7)	16 (72.7)	0.75	0.39
Consolidation [b]	11 (31.4)	11 (50.0)	1.97	0.16
Reticular [b]	5 (14.3)	0 (0.0)	1.89	0.17
Honeycomb [b]	0 (0.00)	0 (0.00)	-	-
Septal thickening [b]	6 (17.1)	1 (4.5)	0.99	0.32
Nodular [b]	14 (40.0)	10 (45.5)	0.17	0.69
Pleural thickening [b]	21 (60.0)	13 (59.1)	0.01	0.95
Pleural effusion [b]	14 (40.0)	13 (59.1)	1.98	0.16
pericardial effusion [b]	15 (42.9)	12 (54.5)	0.74	0.39
Lymphadenopathy [b]	11 (31.4)	11 (50.0)	1.97	0.16
Primary treatment before hospitalization				
Glucocorticosteroids [b]	34 (97.1)	22 (100.0)	-	1.00
The interval between glucocorticosteroids treatment and PJP (days) [a]	2127.2±2643.9	1699.9±2315.6	0.60	0.55
Steroid pulse therapy [b]	13 (37.1)	9 (40.9)	0.00	1.00
Prednisone ≥ 1 mg/kg/d [b]	29 (85.3)	19 (86.4)	0.00	1.00
Prednisone dosage (mg/d) [c]	35 (20, 50)	45 (25, 60)	-1.58	0.11
Immunosuppressants [b]	25 (71.4)	19 (86.4)	1.71	0.19
The interval between immunosuppressants treatment and PJP (days) [c]	617.5 (93.3, 2426.3)	102 (66.3, 997.0)	-1.77	0.08
Biologics [b]	2 (5.7)	0 (0.0)	-	0.52
Treatment for PJP				
Therapeutic dose TMPco [b]	35 (100.0)	22 (100.0)	-	-
Combination with second-line treatment [b]	13 (37.1)	14 (63.6)	3.19	0.05
Caspofungin [b]	11 (31.4)	10 (45.5)	1.14	0.29
Clindamycin [b]	6 (17.1)	7 (31.8)	1.65	0.20
Primaquine [b]	1 (2.9)	0 (0.0)	-	1.00

[a] mean±SD, [b] n (%), [c] median (IQR). Bold values mean *p* value < 0.05. ICU, intensive care unit; CMV, cytomegalovirus; HAP, hospital-acquired pneumonia; GGO, ground-glass opacities; PJP, *Pneumocystis jirovecii* pneumonia; TMPco, trimethoprim-sulfamethoxazole

survival in SLE-PJP patients. The median survival time of non-survival group was thirty-three days.
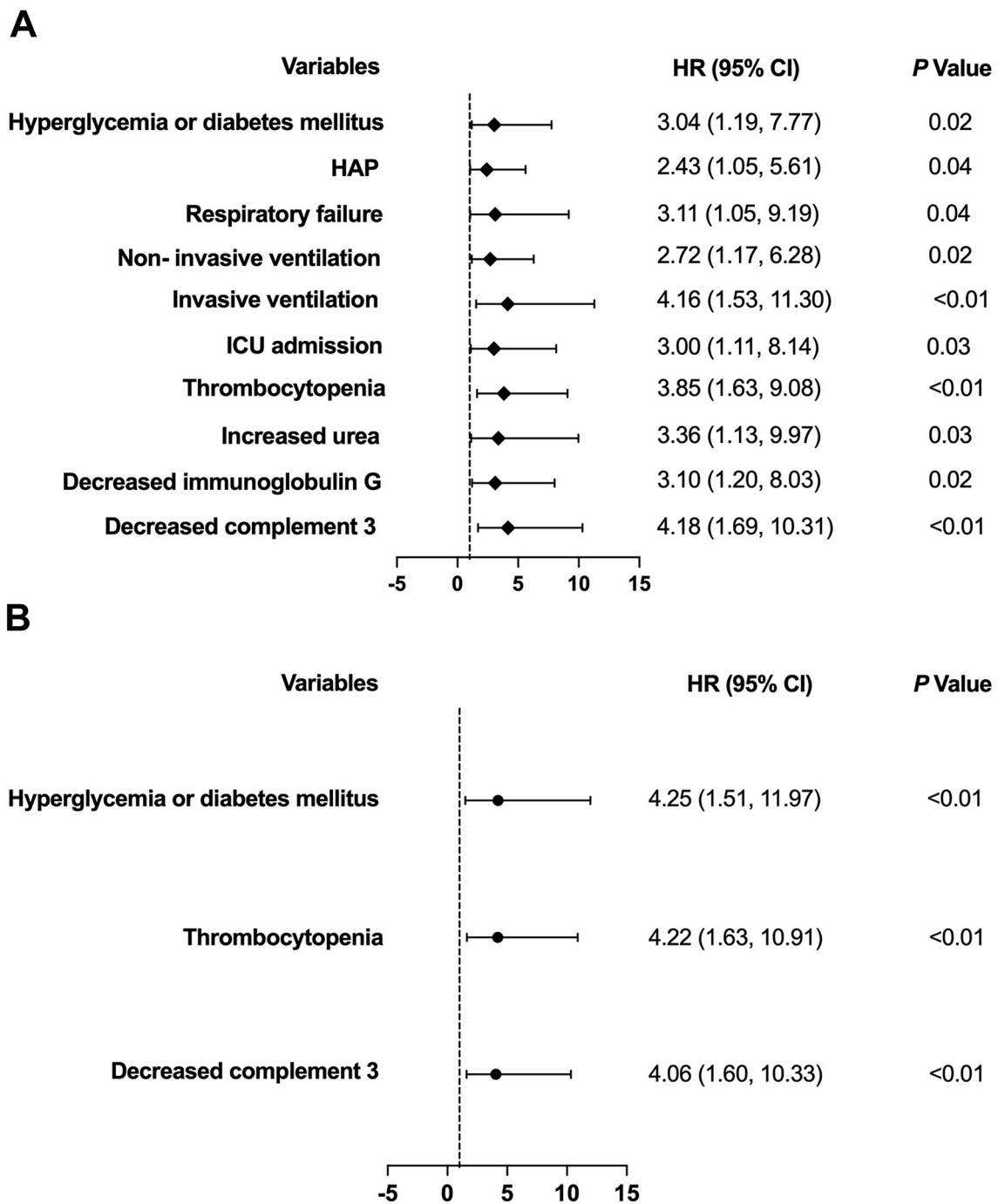
Discussion

Our retrospective study showed that the mortality rate of SLE-PJP patients was high (38.6%, 22 of 57), and hyperglycemia, diabetes mellitus, decreased C3, and thrombocytopenia were independent risk factors for their

survival. Neither corticosteroid and/or immunosuppressant administration before concurrent PJP nor peripheral CD4$^+$ T-cell count was associated with their survival.

Previous studies have reported that risk factors for SLE-PJP include long-term use of glucocorticoids and immunosuppressants, a low CD4$^+$ T-cell count, and renal dysfunction [16, 17]. There has not been much research on the prognostic factors of SLE-PJP. Advanced age,

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A

Variables	HR (95% CI)	*P* Value
Hyperglycemia or diabetes mellitus	3.04 (1.19, 7.77)	0.02
HAP	2.43 (1.05, 5.61)	0.04
Respiratory failure	3.11 (1.05, 9.19)	0.04
Non- invasive ventilation	2.72 (1.17, 6.28)	0.02
Invasive ventilation	4.16 (1.53, 11.30)	<0.01
ICU admission	3.00 (1.11, 8.14)	0.03
Thrombocytopenia	3.85 (1.63, 9.08)	<0.01
Increased urea	3.36 (1.13, 9.97)	0.03
Decreased immunoglobulin G	3.10 (1.20, 8.03)	0.02
Decreased complement 3	4.18 (1.69, 10.31)	<0.01

B

Variables	HR (95% CI)	*P* Value
Hyperglycemia or diabetes mellitus	4.25 (1.51, 11.97)	<0.01
Thrombocytopenia	4.22 (1.63, 10.91)	<0.01
Decreased complement 3	4.06 (1.60, 10.33)	<0.01

Fig. 2 Univariable (**A**) and multivariable (**B**) Cox regression analysis of survival associated risk factors for patients with SLE-PJP. HAP, hospital-acquired pneumonia; ICU, intensive care unit

pneumomediastinum, low PaO_2/FiO_2, high D (A-a) O_2, increased urea, decreased albumin, bacteremia, preexisting pulmonary underlying diseases and initial anti-PJP treatment failure were reported to be independent factors for poor prognosis in non-HIV PJP patients [18–20]. In our study, hyperglycemia or diabetes mellitus was one of the independent survival risk factors among SLE-PJP patients. A meta-analysis showed that diabetes mellitus (OR=3.89, *P*<0.001, 95% CI: 2.45–6.16) was associated with infection in SLE patients [21]. A retrospective nationwide study in Korea showed that diagnoses of diabetes (HR=2.51, 95% CI: 1.19–5.31) significantly associated with PJP risk in ulcerative colitis patients [22]. Hyperglycemia can lead to the suppression of neutrophils
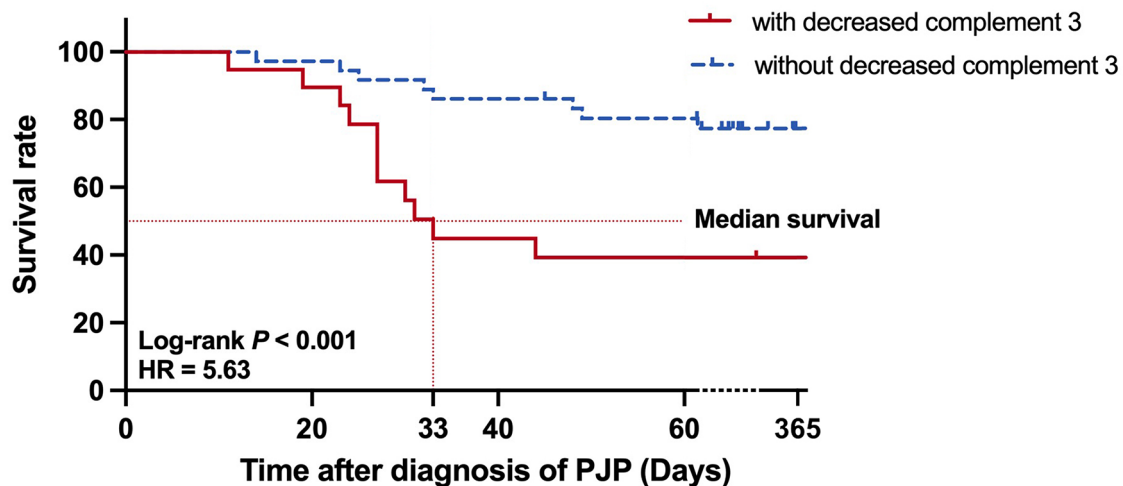
Fig. 3 Kaplan-Meier analysis of the effect of decreased complement 3 on cumulative survival

and mononuclear phagocyte systems [23]. Diabetes mellitus can also cause lymphocyte dysfunction, reduce the activity of NK cells, change T-cell differentiation, and damage the function of B cells [24]. Therefore, patients with hyperglycemia might suffer from an inability to overcome infections. In future diagnosis and treatment, we should pay attention to SLE patients with hyperglycemia and strictly control their blood glucose during follow-up.

Our study also revealed that thrombocytopaenia increased the risk of death in SLE-PJP patients in the non-survival group ($102.1 \pm 85.9 \times 10^9$/L) versus survival group ($169.5 \pm 92.5 \times 10^9$/L). A retrospective study on the short-term prognosis of patients with SLE with infection showed deceased patients had a lower platelet count than survivors ($93.0 \pm 64.0 \times 10^9$/L vs. $181.3 \pm 82.1 \times 10^9$/L, $P<0.001$) [25]. A meta-analysis found that compared to non-infected SLE patients, infected patients had significantly fewer platelets (OR=1.61, $P<0.001$, 95% CI: 1.40–1.85) [21].

The complement system not only participates in the pathogenesis of SLE but is also an important component of innate immunity and plays an important role in regulating adaptive immunity. In SLE patients with increased complement C3 consumption and decreased production, the risk of infection might significantly increase. According to our findings, lower complement C3 was an independent risk factor for mortality in SLE-PJP patients. The C3 concentration in the non-survival group of patients was 0.7 ± 0.3 g/L, while that in the survival group was 0.9 ± 0.3 g/L. Barrera et al. investigated risk factors for drug-resistant bacterial infections in patients with SLE and reported that low pre-infection C3 levels (OR=3.12, 95% CI: 1.91–8.22) were an independent risk factor [26]. One study investigated whether monitoring complement levels could predict the occurrence of infection in kidney transplant recipients and showed that decreased C3 at 1 month after transplantation was a risk factor for overall (AHR=1.91, $p<0.01$) and bacterial infection (AHR=2.13, $p<0.05$), while decreased C3 at 6 months predicted the occurrence of bacterial infection (AHR=3.35, $p=0.04$) in the late period (>6 months) [27]. Although complement 4 (C4) plays a crucial role in the classical activation pathway of the complement system, like our study, that study did not show that the serum level of C4 was associated with infectious disease [27]. Another study reported that 24-hour urinary protein, peripheral lymphocyte count, and low serum C3 (OR= 0.10, 95% CI: 0.01-0.95, $p<0.05$) were independent prognostic predictors of short-term mortality in SLE patients with concurrent pulmonary infection [28]. Therefore, C3 is an important component of the complement system that is involved in microbial clearance. The opsonophagocytic capacity of neutrophils is positively correlated with the level of serum complement factors, and C3a, which is liberated by C3 during complement activation, also has direct antimicrobial activity [29]. Defending against extracellular bacteria has been considered the main role of C3 [30], and it is also important in controlling intracellular microorganism infection [31]. Moreover, it has recently been found that viruses or intracellular bacteria can decrease defense by binding complement regulatory proteins and receptors, which increases their pathogenicity [32]. Animal experiments have shown the relevance of C3 in the activation and regulation of the immune system. In Yuan's septic model of peritonitis, exogenous C3 administration to mice at an early stage was associated with attenuated liver and kidney injuries, better bacterial clearance, and longer survival [33].

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Previous reports on the adverse effects of corticosteroid and/or immunosuppressant therapy on SLE-PJP patients are inconsistent. A retrospective study showed that higher doses of glucocorticoids increased the risk of PJP in SLE patients (5–10 mg/day, OR=25.88, 95% CI: 2.97-225.33; > 10 mg/day, OR=286.58, 95% CI: 28.58->999), as did a higher 3-month cumulative dose of cyclophosphamide (>1.4 g, OR=11.52, 95% CI: 1.97–67.39) [34]. Another study found that cyclophosphamide did not increase the risk of PJP infection in SLE patients [17]. A retrospective study of 95 SLE patients who were hospitalized for pulmonary infections showed that the average daily steroid dose before PJP infection and high-dose steroid pulse therapy did not increase patient mortality, and immunosuppressant therapy was not associated with patient mortality [35]. Our study also showed that corticosteroid or immunosuppressant administration was not associated with mortality in SLE-PJP patients. Some immunosuppressants even have anti-PJP effects. Hydroxychloroquine (HCQ) has been reported to have antibacterial activity, possibly through pH-dependent iron depletion and an increased pH of the phagosome, which in turn inhibits the growth of intracellular organisms and the hyperinflammatory state of peripheral blood mononuclear cells (PBMCs) [36]. In SLE patients, HCQ users have had a lower risk of infection than never-users [37]. Yeo KJ et al. also showed that a cumulative dose of HCQ for 3 months was associated with lower risk of PJP in SLE patients (≤14 g, OR=0.69, 95% CI: 0.21–2.24; > 14 g, OR=0.20, 95% CI: 0.05–0.71), suggesting that HCQ has a potential protective effect on PJP [34]. In patients and rats, mycophenolate mofetil (MMF) also seems to exhibit anti-PJP activity [38, 39].

Serum albumin is not only a factor related to nutrition but also related to the prognosis of many infectious diseases. A meta-analysis showed that hypoalbuminemia was an independent predictor of poor prognosis in patients with acute illness, with a 137% increased mortality rate for each 10 g/L decrease in the serum albumin concentration [40]. The mortality of non-HIV-surviving PJP patients was also negatively correlated with albumin concentration [20, 41]. Kumagai S et al. reviewed the clinical data of 61 non-HIV PJP patients at multiple institutions and found that both crazy paving GGOs (HR=10.80, 95% CI: 1.40–83.00, $p=0.02$) and low serum albumin (HR=0.20, 95% CI: 0.07–0.58, $p<0.01$) were independent risk factors for mortality [36]. Almost all our enrolled SLE patients had hypoalbuminemia (55/57, 96.5%). Furthermore, the non-survival group had significantly lower serum albumin than the survival group [(19.3±4.1) g/L vs. (25.4±4.9) g/L, $p<0.001$].

In our study, the peripheral lymphocyte count ($0.4±0.3×10^9$/L vs. $1.0±1.7×10^9$/L, $p=0.03$) and CD4$^+$ cell count (63.7±43.3/μL vs. 167.4±237.3/μL, $p=0.03$) were significantly lower in the non-survival group than the survival group. Peripheral lymphocytes play an important role in immune responses against infection. In clinical practice, we should pay more attention to patients treated with corticosteroids and immunosuppressant with lower peripheral lymphocyte count. Lymphocyte subset analysis in patients with peripheral lymphopenia could further evaluate patients' immune status. A significantly decreased CD4$^+$ cell count was associated with an immunosuppressive state, which predisposes patients to various infectious diseases. CD4$^+$ T lymphocytes include Th1, Th2, Th17, and Treg cells, which are critical components of adaptive immunity in the lung [42]. Low lymphocyte counts and low CD4$^+$ T lymphocyte counts have also been risk factors for PJP infection, and the number of CD4$^+$ cells might be negatively correlated with the pneumocystis load [43, 44].

The guidelines for the prevention and treatment of HIV-PJP patients are well known to physicians. TMPco prophylaxis effectively reduces morbidity and mortality in connective tissue disease (CTD)-PJP patients [45]. However, because of disease heterogeneity and the lack of randomized controlled trials with large samples, there is no established protocol for PJP prophylaxis in CTD patients. The overall incidence of PJP in common SLE patients is low [46], and there are several adverse effects related to TMPco in SLE patients [45]. TMPco prophylaxis is not suggested for every SLE patient. However, the mortality of SLE-PJP patients is high, and the cost of anti-PJP therapy is very high. Selective prevention of PJP should be considered for SLE patients with risk factors for suffering from PJP, including those with lymphopenia, low CD4$^+$ lymphocyte counts or specific immunosuppressant administration [47].

There are several limitations in our study. First, all patients were admitted to a famous tertiary medical center, which would lead to selective bias. Second, it was a retrospective study, therefore, much information could not be collected completely, especially detailed protocol of corticosteroids and immunosuppressants medications. Finally, due to the low incidence rate of SLE-PJP patients, the sample size is relatively limited. A multicenter, well-designed prospective study is expected in near future.

Conclusion

The mortality rate of patients with SLE-PJP was still high. Hyperglycemia or diabetes mellitus, decreased C3, thrombocytopenia were independent survival risk factors for them. For high-risk SLE-PJP patients with poor prognosis, early identification, active prevention medications, and early effective treatments might improve their prognosis.

Abbreviations

SLE	Systemic lupus erythematosus
SMR	Standardized mortality rate
PJP	*Pneumocystis jirovecii* pneumonia
HIV	Human immunodeficiency virus
PUMCH	Peking Union Medical College Hospital
HRCT	High-resolution computed tomography
SLICC	Systemic Lupus International Collaborating Clinics
EULAR	European League Against Rheumatism
ACR	American College of Rheumatology
PCR	Polymerase chain reaction
mNGS	Metagenomic next-generation sequencing
GMS	Grocott's methenamine silver
BALF	Bronchoalveolar lavage fluid
CMV	Cytomegalovirus
SD	Standard deviations
IQRs	Interquartile ranges
ICU	Intensive care unit
HAP	Hospital-acquired pneumonia
GGOs	Ground-glass opacities
TMPco	Trimethoprim-sulfamethoxazole
C3	Complement 3
C4	Complement 4
HCQ	Hydroxychloroquine
PBMCs	Peripheral blood mononuclear cells
MMF	Mycophenolate mofetil
CTD	Connective tissue disease

Data availability
Upon reasonable request, the corresponding author will provide the data.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Peking Union Medical College Hospital (K5596) in accordance with the Declaration of Helsinki. Written informed consent from each patient was waived because our study was conducted using anonymized health care data, which met the IRB's minimal risk waiver criteria.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, #1 Shuaifuyuan Street, Dongcheng District, Beijing 100730, China
[2]Department of Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, #1 Shuaifuyuan Street, Dongcheng District, Beijing, China
[3]Radiological Department, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, #1 Shuaifuyuan Street, Dongcheng District, Beijing, China

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