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## Meta-Analysis

# Clinical Features of Pneumocystis Pneumonia in Non-Human Immunodeficiency Virus-Infected Patients: A Systemic Review and Meta-Analysis

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### Clinical Question Box

What are the clinical features of pneumocystis pneumonia in non-human immunodeficiency virus-infected patients?

Pneumocystis pneumonia was more likely to occur in men than in women at the age of 60, with a sex ratio of about 3 to 2 (males to females). The main symptoms were dyspnea and fever, which were observed in >70% of patients, accompanied by cough in >50% of patients. Ground glass opacity might offer a clue to diagnosing pneumocystis pneumonia in high-risk patients.

## Abstract

**Objectives:** Pneumocystis pneumonia (PCP) is an opportunistic disease that causes potentially fatal pneumonia in immunocompromised individuals. The clinical features of PCP without HIV remain incompletely understood. **Methods:** This study aimed to identify the clinical features of PCP without HIV in a systematic review following a meta-analysis. **Results:** 65 articles that included 10,133 PCP patients without HIV infection were enrolled. PCP occurred most commonly at age 59.2 years (95% CI: 57.7, 60.7) in a gender ratio of approximately 3 to 2 (males to females). Dyspnea, fever, cough, and sputum were nonspecific clinical findings in 73% (95% CI: 69, 79), 73% (95% CI: 65, 81), 56% (95% CI: 48%, 64%), and 32% (96%CI: 16, 48) of patients, respectively. Viral, bacterial, and fungal co-infection were observed in 28% (95% CI: 13, 44), 19% (95% CI: 13, 25), and 11% (95% CI: 6, 16) of patients, respectively. Laboratory data showed a trend of elevated WBC, LDH, CRP, β-D glucan, and KL-6. Ground glass opacity (GGO) was found in 87% (95% CI: 83, 91) of patients. In-hospital mortality was 41% (95% CI: 35, 46). **Conclusions:** PCP is a life-threatening disease in immune-compromised patients. Despite being a nonspecific clinical finding, GGO might offer a clue to diagnosing PCP in high-risk patients.

**Keywords:** Pneumocystis pneumonia, clinical features, non-HIV, ground glass opacity.

## Introduction

In individuals who are immunocompromised, the opportunistic fungal pathogen *Pneumocystis jirovecii* is capable of causing life-threatening pneumonia as the causative agent of pneumocystis pneumonia (PCP).[1] Human immunodeficiency virus (HIV)-infected patients are at the highest risk of PCP; however, non-HIV-infected immunocompromised patients, including those with chronic corticosteroid use, hematological or solid malignancies, organ transplantation, and immunomodulatory or biological therapy have a substantial risk of developing PCP.[2,3]

HIV-infected patients usually develop a subacute course of the disease, whereas respiratory insufficiency is usually more severe in non-HIV patients than in the HIV-infected population. Pneumocystis is more challenging to detect in non-HIV patients because of the smaller numbers of organisms in the lungs.[4] In addition, the mortality rate is 30%–50% in patients without HIV and 10%–12% in patients with HIV.[5] The diagnosis of PCP relies on a critical evaluation of clinical symptoms, risk factors, radiologic features, and microbiological tests. Computed tomography (CT) examination is helpful if there is clinical suspicion of PCP.

A clear overview of PCP in non-HIV patients is essential for diagnostic progress and treatment in clinical practice; however, this is currently lacking, and no meta-analysis has appraised the clinical features in this group. Therefore, we conducted a systematic review and meta-analysis to explore the general characteristics, comorbidity, co-infection, and laboratory and radiographic findings of PCP obtained in observational studies of non-HIV patients.

## Methods

### *Study Overview*

The protocol of this systematic review and meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. It was registered on the website of the University Hospital Medical Information Network Clinical Trials Registration (UMIN 000046230).[6,7] Because of the nature of the study, Institutional Review Board approval was not required.

### *Study Search*

Four major online databases (PubMed, Web of Science, Cochrane, and Embase) were searched from January 1, 2000 to October 30, 2022. The following search strategy was used for PubMed: (((((pneumocystis pneumonia) OR (pneumocystis jirovecii)) OR (pneumocystis infections)) OR (pneumocystis carinii)) AND (((((non-HIV) OR (non-AIDS)) OR (non-HIV-infected)) OR (HIV-uninfected)) OR (HIV-negative))) AND (((symptom) OR (clinical feature)) OR (diagnosis)). Two authors (H.C. and M.I.) independently screened the titles and abstracts and carefully evaluated the full text to select eligible articles; in cases of discrepancy, a consensus was reached through discussion. Review articles and the included original articles were hand-searched (H.C. and M.I.) for additional research papers that met the inclusion criteria.

### *Inclusion and Exclusion Criteria*

Full-length articles published in any language that provided data regarding the clinical features of PCP were included. The inclusion criteria were: (1) patients with PCP, (2) patients without HIV, and (3) age $\geq$16 years. The exclusion criteria were: (1) detailed data not available, (2) fewer than 10 cases, and (3) limited information regarding clinical features.

### *Risk of Bias*

Two reviewers independently assessed the methodological quality of the selected studies using the Newcastle–Ottawa quality assessment to evaluate the quality of observational studies.[8] Due to the nature of single-arm studies, the "selection of the non-exposed cohort" and "comparability" domains were not applicable in this study. The modified Newcastle–Ottawa quality assessment scored six stars. Any disagreement between the reviewers was discussed, and agreement was reached by consensus.[9]

### *Outcomes*

The clinical features of PCP were appraised in terms of the following five aspects: general characteristics, laboratory findings, comorbidity, existence of other microorganisms, and radiographic findings. General characteristics included age, sex, body mass index (BMI), prophylaxis, time from symptom onset to treatment, and hospital mortality. The following laboratory findings were collected: white blood cells (WBC), lactase dehydrogenase (LDH), albumin, c-reactive protein (CRP), β-D glucan, and sialylated carbohydrate antigen 6 (KL-6). Comorbidities included hematologic malignancies, solid tumors, immunosuppression (immunosuppressive drugs for nonmalignant diseases), and any transplant. Symptoms included dyspnea, fever, cough, and sputum. Although it is difficult to distinguish between co-infection and detection of the existence of other microorganisms, most previous studies have reported co-infection. Co-infection was classified as bacterial, viral, cytomegalovirus (CMV), and fungal. The radiographic findings were classified as ground glass opacity (GGO), consolidation, lung nodules, septal thickening, pleural effusion, and pneumothorax.

### *Data Extraction and Statistics*

Two authors (M.I. and S.T.) independently extracted the following data from the studies: first author, publication year, country of publication, number of patients with PCP, clinical features, and Newcastle–Ottawa quality assessment-related information. All analyses were performed using Review Manager software version 5.3 (Cochrane Collaboration, Oxford, UK). Figures illustrated using Review Manager were adjusted as necessary. Heterogeneity was evaluated with the $I^2$ statistic and interpreted as follows: $I^2 = 0\%$, no heterogeneity; $0\% < I^2 < 25\%$, the least heterogeneity; $25\% \leq I^2 < 50\%$, mild heterogeneity; $50\% \leq I^2 < 75\%$, moderate heterogeneity; and $75\% \leq I^2$, strong heterogeneity.[10] A p-value of $<0.05$ was considered significant.

## Results

### *Study Search and Study Characteristics*

A total of 581 articles were identified, including 578 articles by database search and three articles by hand search. Of the 581 articles, 416, 179, and 65 remained after removing duplication, screening for eligibility, and full-length article reading, respectively (Fig. S1). The analysis included 65 retrospective studies (Table 1).[11–75] All but two were written in English.[19,32] Of the 65 reports, 15 were from Japan, 13 were from China, 12 were from France, 5 were from Korea and the USA, 3 were from Germany, and 2 were from Israel and Spain. These studies included a total of 10,133 PCP patients without HIV infection. Among the studies, the modified Newcastle–Ottawa scale ranged from 5 to 6 stars. The method for diagnosis of PCP showed some variation among studies (Table S1). Polymerase chain reaction (PCR) was conducted in 43 studies. Clinical and/or radiological findings were also included as diagnostic criteria for PCP in 39 studies. Elevation of β-D-glucan was considered necessary in 6 studies, and no diagnostic criteria were provided in 5 studies.

**Table 1.** Characteristics of the enrolled studies

| Author | Year | Country | Cases | Male | Age | Prophylaxis | Mortality | NOS |
|---|---|---|---|---|---|---|---|---|
| Ainoda | 2012 | Japan | 24 | 10 | 66.5 | ND | 45.8%‡ | 6 |
| Asai | 2017 | Japan | 38 | 20 | | ND | 34.2% | 6 |
| Assal | 2021 | France | 133 | 100 | 65.0 | ND | 24.1%† | 6 |
| Azoulay | 2009 | France | 39 | | | ND | NA | 6 |
| Bienvenu | 2016 | France | 461 | 288 | | 27 | 20.6%‡ | 6 |
| Bollee | 2007 | France | 56 | 36 | 49.3 | ND | 19.6%‡ | 6 |
| Burghi | 2021 | France | 321 | 193 | 57.7 | 55 | 24.3%† | 5 |

(Continued)

**Table 1.** Continued

| Author | Year | Country | Cases | Male | Age | Prophylaxis | Mortality | NOS |
|---|---|---|---|---|---|---|---|---|
| Calero-Bernal | 2016 | Spain | 128 | 86 | | 7 | 28.9% | 6 |
| Cerón | 2014 | Chile | 45 | 42 | | ND | 33.0% | 6 |
| Choi | 2018 | Korea | 81 | 51 | 60.8 | ND | 64.2% | 5 |
| Chou | 2014 | Taiwan | 65 | 34 | 49.5 | ND | 44.6% | 6 |
| de Boer | 2011 | Netherlands | 21 | 11 | 56.3 | ND | 9.5%† | 5 |
| Deodhar | 2018 | India | 29 | | | ND | 34.5% | 6 |
| Enomoto | 2010 | Japan | 17 | 9 | 68.0 | 0 | 35.3%† | 6 |
| Festic | 2005 | USA | 30 | 13 | | ND | 66.7% | 6 |
| Fillatre | 2014 | France | 154 | | | ND | 59.2%‡ | 5 |
| Gilmartin | 2002 | USA | 33 | 22 | 57.8 | 3 | 27.3% | 6 |
| Grønseth | 2021 | Norway | 297 | 180 | 66.3 | ND | 21.5% | 6 |
| Guo | 2014 | China | 46 | 28 | 54.7 | ND | 15.2% | 6 |
| Hamada | 2020 | Japan | 74 | 40 | 73.2 | 1 | NA | 5 |
| Hardak | 2012 | Israel | 58 | 28 | 55.9 | ND | 17.2% | 6 |
| Huang | 2016 | China | 92 | 40 | 53.1 | ND | 76.1% | 6 |
| Ideguchi | 2020 | Japan | 50 | 27 | 66.3 | 0 | NA | 5 |
| Inoue | 2019 | Japan | 562 | 324 | 62.9 | ND | 44.0%‡ | 6 |
| Issa | 2018 | France | 112 | 74 | 63.8 | ND | 33.0% | 6 |
| Jin | 2019 | China | 126 | 71 | 53.7 | ND | 34.1%‡ | 5 |
| Kanj | 2021 | USA | 2780 | 1496 | 60.2 | ND | 16.0% | 6 |
| Kato | 2019 | Japan | 44 | 25 | 62.7 | ND | NA | 6 |
| Kim | 2014 | Korea | 173 | 116 | 56.0 | 6 | 35.8% | 5 |
| Ko | 2019 | Korea | 51 | 35 | 52.8 | 2 | 74.5% | 6 |
| Kofteridis | 2014 | Greece | 62 | 43 | 65.2 | 21 | 29.0% | 6 |
| Korkmaz Ekren | 2018 | Turkey | 45 | 43 | 56.7 | 3 | 64.4% | 6 |
| Kosaka | 2017 | Japan | 77 | 47 | 66.1 | 1 | 22.1% | 5 |
| Kumagai | 2019 | Japan | 61 | 28 | 69.0 | ND | 31.1% | 6 |
| Kunihiro | 2015 | Japan | 70 | 34 | 56.4 | ND | NA | 6 |
| Lahmer | 2017 | Germany | 50 | 29 | 59.0 | ND | 66.0% | 6 |
| Lee | 2019 | Korea | 362 | 211 | 51.0 | 94 | 32.6% | 6 |
| Lemiale | 2013 | France | 139 | 79 | 49.3 | 5 | 25.9%‡ | 6 |
| Li | 2014 | Taiwan | 20 | 9 | 50.2 | ND | 60.0% | 5 |
| Liu | 2019 | China | 84 | 71 | | ND | 46.4%‡ | 5 |
| Mansharamani | 2000 | Canada | 33 | 22 | 57.8 | ND | 39.4% | 6 |
| Matsumura | 2011 | Japan | 82 | 51 | | ND | 24.0%† | 6 |
| Moon | 2011 | Korea | 88 | 46 | 55.5 | ND | 31.8%† | 6 |
| Mu | 2016 | China | 105 | 62 | | ND | 34.3% | 5 |
| Mundo | 2020 | USA | 28 | 15 | 62.1 | ND | 71.4% | 6 |
| Nakamura | 2009 | Japan | 16 | 9 | 58.5 | ND | 43.8% | 5 |
| Nakashima | 2017 | Japan | 54 | 34 | 72.7 | ND | 4.2%† | 6 |
| Pereira-Díaz | 2019 | Spain | 1204 | 728 | 58.0 | ND | 25.5% | 6 |
| Roblot | 2002 | France | 103 | 61 | 57.4 | 4 | 37.9% | 5 |
| Roembke | 2014 | Germany | 30 | 19 | 56.4 | ND | 36.7%† | 6 |
| Roux | 2014 | France | 321 | | | 12 | 23.4% | 6 |

(Continued)

**Table 1.** Continued

| Author | Year | Country | Cases | Male | Age | Prophylaxis | Mortality | NOS |
|---|---|---|---|---|---|---|---|---|
| Sheikholeslami | 2013 | Iran | 89 | 89 | 66.5 | ND | NA | 5 |
| Sun | 2021 | China | 24 | 12 | 51.3 | ND | 25.0%† | 5 |
| Tamai | 2014 | Japan | 29 | 14 | 58.7 | ND | 41.4% | 6 |
| Tang | 2021 | China | 40 | 26 | 52.3 | ND | NA | 6 |
| Tasaka | 2010 | Japan | 21 | 13 | 50.7 | ND | 52.4% | 6 |
| Toper | 2011 | France | 41 | | 56.0 | 7 | 29.3% | 5 |
| Vogel | 2007 | Germany | 27 | 17 | | 0 | NA | 6 |
| Wang | 2017 | China | 35 | 24 | 54.5 | ND | NA | 5 |
| Weng | 2016 | China | 82 | 34 | 52.6 | ND | 75.6% | 6 |
| Wieruszewski | 2020 | USA | 323 | 202 | 63.7 | 8 | NA | 5 |
| Wu | 2021 | Taiwan | 62 | 38 | 59.7 | ND | 43.5% | 6 |
| Yu | 2017 | China | 70 | 43 | | ND | 37.1% | 6 |
| Zahar | 2002 | France | 39 | 20 | | 5 | NA | 6 |
| Zalmanovich | 2020 | Israel | 77 | 49 | 65.3 | 5 | 44.2% | 6 |

Note: †, 30-day mortality; ‡ 60-day mortality; ¶, Ainoda 2012, 90-day mortality; Bienvenu 2016, 14-day mortality; Fillatre 2014 and Lemiale 2013, ICU mortality; ND, not described; NA, not available; NOS, Newcastle–Ottawa Scale.

### *General Characteristics and Laboratory Findings*

Table 2 lists the general characteristics of patients with PCP without HIV. In an analysis of 50 studies, the mean age was 59.2 years (95% confidence interval (CI): 57.7, 60.7; $I^2 = 95\%$; Fig. S2). Males comprised 60% of patients (95% CI: 58, 63; $I^2 = 85\%$; Fig. S3). Mean BMI was 22.1 kg/m$^2$ (95% CI: 20.0, 24.1; $I^2 = 0\%$; Fig. S4), and 8% of patients underwent prophylaxis for PCP (95% CI: 5, 11; $I^2 = 92\%$; Fig. S5). Trimethoprim/sulfamethoxazole was used as prophylaxis in 11 studies. However, detailed information should have been provided. The other eight studies (Table S2) did not state the length of prophylaxis. The mean time from symptom onset to treatment was 8.9 days (95% CI: 6.8, 10.9; $I^2 = 94\%$; Fig. S6), and mean in-hospital mortality due to PCP was 41% (95% CI: 35, 46; $I^2 = 95\%$; Fig. S7) in 34 studies.

**Table 2.** General characteristics and laboratory findings in patients with PCP without HIV

| | Studies (n) | Statistical method | Estimated effect | 95% CI |
|---|---|---|---|---|
| Age (years) | 50 | IV, random | 59.2 | 57.7, 60.7 |
| Sex (male) | 60 | IV, random | 60 | 58, 63 |
| BMI (kg/m$^2$) | 10 | IV, random | 22.1 | 20.0, 24.1 |
| Prophylaxis (%) | 18 | IV, random | 8 | 5, 11 |
| WBC (/μL) | 18 | IV, random | 8210 | 7810, 8610 |
| LDH (IU/L) | 31 | IV, random | 496.4 | 454, 538 |
| Albumin (mg/dL) | 19 | IV, random | 2.86 | 2.76, 2.97 |
| CRP (mg/dL) | 17 | IV, random | 11.1 | 9.5, 12.8 |
| (1,3) β-D glucan (pg/mL) | 13 | IV, random | 137.1 | 95.1, 179.2 |
| KL-6 (U/mL) | 7 | IV, random | 1073 | 724, 1423 |
| Time from onset (days) | 9 | IV, random | 8.9 | 6.8, 10.9 |
| Mortality (%) | 34 | IV, random | 41 | 35, 46 |

Note: PCP, pneumocystis pneumonia; HIV, human immunodeficiency virus; CI, confidence interval; IV, inverse variance; BMI, body mass index; WBC, white blood cell; LDH, lactase dehydrogenase; CRP, c-reactive protein; KL-6, sialylated carbohydrate antigen 6.

The laboratory findings revealed elevated WBC, LDH, CRP, β-D glucan, and KL-6 and a decreased albumin value in the overall patients. The average values were as follows: WBC, 8,210/μL (95% CI: 7,810, 8,610; $I^2 = 52\%$; Fig. S8); LDH, 496 IU/L (95% CI: 454, 538; $I^2 = 94\%$; Fig. S9); albumin, 2.86 mg/dL (95% CI: 2.76, 2.97; $I^2 = 91\%$; Fig. S10); CRP, 11.1 mg/dL (95% CI: 9.5, 12.8; $I^2 = 89\%$; Fig. S11); β-D glucan, 137.1 pg/dL (95% CI: 95.1, 179.2; $I^2 = 100\%$; Fig. S12); and KL-6, 1073 (95% CI: 724, 1423; $I^2 = 91\%$; Fig. S13).

### *Comorbidity*

The frequencies of comorbidities in patients with PCP without HIV infection are listed in Table S1. The most frequent comorbidities were hematologic malignancies and use of immunosuppressive drugs for nonmalignant diseases, followed by transplant and solid tumor, as follows: 32% (95% CI: 27, 36; $I^2 = 97\%$; Fig. S14); 32% (95% CI: 27, 36; $I^2 = 96\%$; Fig. S15), 19% (95% CI: 16, 23; $I^2 = 95\%$; Fig. S16), and 16% (95% CI: 14, 18; $I^2 = 81\%$; Fig. S17).

### *Symptoms*

Table 3 lists the symptoms reported in at least two studies. The most frequently reported symptoms were dyspnea and fever, followed by cough, sputum, hemoptysis and chest pain, as follows: 73% (95% CI: 68, 79; $I^2 = 94\%$; Fig. S18), 73% (95% CI: 65, 81; $I^2 = 97\%$; Fig. S19), 56% (95% CI: 48, 64; $I^2 = 96\%$; Fig. S20), 32% (95% CI: 16, 48; $I^2 = 95\%$; Fig. S21), 9% (95% CI: 2, 16; $I^2 = 49\%$; Fig. S22), and 17% (95% CI: 0, 37; $I^2 = 85\%$; Fig. S23), respectively. The meta-analysis did not include articles that reported limited fatigue and body-weight loss data.

**Table 3.** Symptoms of PCP in non-HIV patients

| Symptoms | Studies (n) | Statistical method | Effect estimate | 95% CI |
|---|---|---|---|---|
| Dyspnea (%) | 29 | IV, random | 73 | 68, 79 |
| Fever (%) | 27 | IV, random | 73 | 65, 81 |
| Cough (%) | 29 | IV, random | 56 | 48, 64 |
| Sputum (%) | 7 | IV, random | 32 | 16, 48 |
| Hemoptysis (%) | 2 | IV, random | 9 | 2, 16 |
| Chest pain (%) | 2 | IV, random | 17 | 0, 37 |

Note: PCP, pneumocystis pneumonia; HIV, human immunodeficiency virus; CI, confidence interval; IV, inverse variance.

### *Co-infection*

Table 4 lists data regarding the detected microorganisms. In patients with PCP without HIV infection, viral microorganisms were detected most frequently, followed by bacterial and fungal, as follows: 28% (95% CI: 13, 44; $I^2 = 97\%$; Fig. S24), 19% (95% CI: 13, 25; $I^2 = 89\%$; Fig. S25), and 11% (95% CI: 13, 44; $I^2 = 97\%$; Fig. S26), respectively. Cytomegalovirus (CMV) was observed in 26% (95% CI: 16, 36; $I^2 = 97\%$; Fig. S27) of PCP patients. The methods used to identify CMV, viruses, and bacteria are shown in Tables S3, S4, and S5, respectively. A total of 14 studies reported a positive result for CMV, but only eight described the identification method. Among these, CMV antigenemia assay and real-time PCR were used in three studies each. Positive results were found for CMV in 25.5% and 47.3% of antigenemia assay and real-time PCR, respectively. The co-infection of viruses and bacteria was reported in 7 and 15 studies, respectively. Microbiological confirmation was used as the detection method in most of these studies.

### *Radiographic Findings*

Table 5 summarizes the radiographic findings. GGO was most the frequent radiographic finding, followed by septal thickening, consolidation, pleural effusion, lung nodules, and pneumothorax, as follows: 87% (95% CI: 83, 91; $I^2 = 95\%$; Fig. S28), 41% (95% CI: 24, 58; $I^2 = 91\%$; Fig. S29), 29%

(95% CI: 19, 38; $I^2 = 94\%$; Fig. S30), 20% (95% CI: 13, 28; $I^2 = 90\%$; Fig. S31), 14% (95% CI: 7, 21; $I^2 = 91\%$; Fig. S32), and 4% (95% CI: 2, 7; $I^2 = 63\%$; Fig. S33), respectively.

**Table 4.** Co-infection of PCP in non-HIV patients

| Co-infection | Studies (n) | Statistical method | Effect estimate | 95% CI |
|---|---|---|---|---|
| Viral (%) | 7 | IV, random | 28 | 13, 44 |
| Cytomegalovirus (%) | 14 | IV, random | 26 | 16, 36 |
| Bacterial (%) | 15 | IV, random | 19 | 13, 25 |
| Fungal (%) | 11 | IV, random | 11 | 6, 16 |

Note: PCP, pneumocystis pneumonia; HIV, human immunodeficiency virus; CI, confidence interval; IV, inverse variance.

**Table 5.** Radiographic findings of PCP in non-HIV patients

| Finding | Studies (n) | Statistical method | Effect estimate | 95% CI |
|---|---|---|---|---|
| GGO (%) | 19 | IV, random | 87 | 83, 91 |
| Septal thickening (%) | 5 | IV, random | 41 | 24, 58 |
| Consolidation (%) | 13 | IV, random | 29 | 19, 38 |
| Pleural effusion (%) | 12 | IV, random | 20 | 13, 28 |
| Lung nodules (%) | 9 | IV, random | 14 | 7, 21 |
| Pneumothorax (%) | 7 | IV, random | 4 | 2, 7 |

Note: PCP, pneumocystis pneumonia; HIV, human immunodeficiency virus; GGO, ground glass opacity; IV, inverse variance; CI, confidence interval.

## Discussion

The general features of PCP, including clinical presentation and laboratory and radiographic findings, were identified after analysis of 10,133 cases of PCP in patients without HIV. PCP was more likely to occur in men than in women at the age of 60 years, with a sex ratio of about 3 to 2 (males to females). The main symptoms were dyspnea and fever, which were observed in >70% of patients, accompanied by cough in >50% of patients. Most studies did not specify the type of cough; however, cough was accompanied by sputum in >30% of patients. The co-infection was frequently observed, and CMV was detected in >25% of patients. The laboratory findings revealed decreased albumin but no apparent weight loss in PCP patients. Elevated WBC, LDH, CRP, β-D glucan, and KL-6 were also observed in these patients. More than 60% of patients had a comorbidity of either hematologic malignancy or immunosuppressive drug use for nonmalignant disease. Eight percent of PCP patients underwent prophylaxis for PCP, and in-hospital mortality was high (~41%), which is in agreement with the results of previous studies.[3,34,76]

PCP is of increasing importance in non-HIV immunocompromised patients who present with severe respiratory distress and low fungal loads. β-D glucan level was found to be very useful in the diagnosis of PCP, and seven studies included β-D glucan positivity as a condition for the diagnosis of PCP. In contrast, three studies have reported negative β-D glucan in non-HIV patients, ranging from 12% to 27.2%.[38,52,56] These reports were all from Japan, which suggests possible racial differences or differences in laboratory examination methods between countries. The high rate of CMV positivity was surprising. CMV generally produces an asymptomatic or minimally symptomatic acute illness in immunocompetent patients. Detecting viral DNA/RNA does not necessarily mean clinically relevant disease but may also indicate viral 'dead' material.

Most importantly, CMV reactivation can be found in sick airways, and low levels of CMV can be found in peripheral blood. However, the enrolled articles provided limited information that

would enable differences to be identified between genetic information and CMV infection. The exact proportion of patients with the existence of CMV and how CMV infection affects the clinical progress of PCP in non-HIV patients remains unclear.

GGO was observed in almost 90% of PCP patients. Given the nonspecific nature of the clinical findings, this radiology finding appears to be an essential clue for confirming a diagnosis of PCP, even in asymptomatic high-risk patients. Numerous studies reported less common radiographic findings such as consolidation, pleural effusion, and lung nodules. Combining co-infection and PCP might be necessary to interpret the various image findings. The diagnostic accuracy of radiology in PCP remains unclear, and further studies are required.

PCP is challenging to diagnose. Asymptomatic lung colonization can occur in people with normal immune systems who may unknowingly become reservoirs (asymptomatic carriers) for the spread of pneumocystis to immunocompromised individuals.[77] A few articles have discussed the relevance of sputum colonization vs. bronchoalveolar lavage sampling and the sensitivities between PCR and microscopy staining.

There were several limitations in this study. First, high heterogeneity was observed in almost all of the analyses performed due to the observational nature of the studies and their differing purposes. Although random effects were considered in data analysis, selection bias was possible. Second, the detection of pathogens is different from the diagnosis of infection. No uniform criteria were included in studies to differentiate between detecting pathogens and diagnosing disease, especially in the prevalence of CMV infection. Thirdly, all of the clinical features of PCP in patients without HIV infection were conducted in a single-arm meta-analysis. There was no comparison between PCP and community-acquired pneumonia or other types of pneumonia. Fourth, a limited number of studies discussed the clinical features of PCP in terms of different comorbidities; therefore, it was impossible to perform a subgroup analysis of clinical features according to comorbidity.

## Conclusions

PCP is a life-threatening disease in immune-compromised patients. Men are more susceptible than women, and there is an association with comorbidities. Dyspnea, fever, and cough were nonspecific clinical findings in PCP, and GGO was observed in most patients.

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## Author Contributions

M.I. contributed to the study search, quality check, data extraction, and drafting. As principal investigators, H.K. and S.T. worked on the study search, quality check, data extraction, and analysis. T.H., Y.I., K.W., and N.S. worked on the interpretation of data and the revision process. All the authors have approved the final version of the manuscript for publication.

## Data Availability Statement

The datasets used in the current study are available from the corresponding author upon reasonable request.

## Ethical Statement

Not applicable.

## Conflicts of Interest

The authors declare that no conflicts of interest exist.

## Supplemental Information

Supplemental information for this article can be found online at https://sup.jclinque.com/api/articles/39/download-suppl.

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