Narrative review of the relationship between COVID-19 and PJP: does it represent coinfection or colonization?

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Abstract

Background Pneumocystis jirovecii (P. jirovecii) is increasingly identified on lower respiratory tract specimens of COVID-19 patients. Our narrative review aims to determine whether the diagnosis of pneumocystis jirovecii pneumonia (PJP) in COVID-19 patients represents coinfection or colonization based on the evidence available in the literature. We also discuss the decision to treat COVID-19 patients with coinfection by PJP.

Methods A literature search was performed through the Pubmed and Web of Science databases from inception to March 10, 2021.

Results We identified 12 COVID-19 patients suspected to have PJP coinfection. All patients were critically ill and required mechanical ventilation. Many were immunosuppressed from HIV or long-term corticosteroids and other immunosuppressive agents. In both the HIV and non-HIV groups, severe lymphocytopenia was encountered with absolute lymphocyte and CD4+T cell count less than 900 and 200 cells/mm, respectively. The time to PJP diagnosis from the initial presentation was 7.8 (range 2–21) days. Serum lactate dehydrogenase and beta-D-glucan were elevated in those coinfected with PJP. All patients were treated with anti-PJP therapy, predominantly sulfamethoxazole-trimethoprim with corticosteroids. The overall mortality rate was 41.6%, and comparable for both HIV and non-HIV groups.

Conclusion As the current evidence is restricted to case reports, the true incidence, risk factors, and prognosis of COVID-19 patients with PJP coinfections cannot be accurately determined. Comorbidities of poorly controlled HIV with lymphocytopenia and multiple immunosuppressive therapies are likely predisposing factors for PJP coinfection.

Keywords Severe acute respiratory syndrome coronavirus 2 · SARS-CoV-2 · Coronavirus disease 2019 · COVID-19 · Pneumocystis jirovecii pneumonia · Pneumocystis carinii pneumonia · PJP · PCP

Introduction

Since it was first recognized in December 2019, coronavirus disease 2019 (COVID-19) has led to the ongoing pandemic. While clinical care is highly focused on the diagnosis and management of COVID-19, there is emerging evidence that COVID-19 patients are at risk of developing concurrent pulmonary infections by bacterial and fungal microorganisms [1–3]. Moreover, during the pandemic, opportunistic infections such as tuberculosis and Pneumocystis jirovecii pneumonia (PJP) have been increasingly described in COVID-19 patients, especially those with human immunodeficiency virus (HIV) [1, 4]. The difficulty in diagnosing PJP in patients with COVID-19 pneumonia is due to the many overlapping clinical, radiological, and laboratory abnormalities shared between these two often indistinguishable entities [5, 6]. PJP generally follows a more subacute course than COVID-19, particularly when considering milder form, with clinical manifestation of dry cough, dyspnea, and hypoxia [7–9]. PJP symptoms can last for several weeks before a diagnosis is made compared to COVID-19, with a median time to diagnosis of 7–9 days from illness onset [10, 11]. The typical radiological features for COVID-19 seen on CT imaging are diffuse, bilateral, peripheral-predominant multifocal lung infiltrates consisting of ground-glass opacities (GGO); however, these findings can be seen
in non-COVID-19-related pneumonia from viral, bacterial, and fungal etiologies [5, 6]. The purpose of our narrative review is to determine whether PJP diagnosis in COVID-19 patients represents actual infection or colonization based on the evidence available in the literature.

Methods

We performed a literature search through the Pubmed and Web of Science databases from inception to March 10, 2021, using the search term in Medical Subjects Headings (MeSH) and title/abstract: (“coronavirus disease 2019” OR “COVID-19” OR “COVID-19” OR “COVID19” OR “novel coronavirus” OR “2019 novel coronavirus” OR “2019-nCoV” OR “2019-nCoV” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS-CoV” OR “SARS-CoV-2”) AND (“Pneumocystis jirovecii” pneumonia OR “Pneumocystis carinii” pneumonia OR “Pneumocystis pneumonia” OR “Pneumocystis jirovecii” OR “Pneumocystis carinii” OR “pneumocystis” OR “PJP” OR “PCP”). No date restrictions were applied. We included studies: (1) involving hospitalized COVID-19 patients with PJP coinfections; (2) involving observational studies, case series, and case reports; and (3) with the diagnosis of COVID-19 infections made via RT-PCR from a nasopharyngeal or oropharyngeal swab or bronchoalveolar lavage (BAL). We excluded: (1) other systematic reviews, literature reviews, editorials, and opinion articles, but references were screened for relevant articles; (2) studies discussing other infectious outbreaks; (3) studies on animals or in vitro studies; and (4) studies published in languages other than English were excluded if no translated version of the manuscript was available. We defined PJP coinfection in COVID-19 patients as those with Pneumocystis jirovecii (P. jirovecii) identification from lower respiratory tract (LRT) specimen such as sputum, endotracheal aspirate (ETA), and BAL by methods of positive microscopic staining (MS), immunofluorescence microscopy (IFM), or polymerase chain reaction (PCR) result and treated with anti-PJP therapy. LRT specimen can be obtained before or after the PCR result and treated with anti-PJP, antimicrobials, and anti-COVID-19 therapies received.

Results

Clinical characteristics and lymphocyte count

Twelve case reports describing PJP coinfection in COVID-19 patients were identified (Fig. 1). The mean age of patients was 49.9 ± 20.8 years (Table 1). Out of the 12 patients included with COVID-19 and PJP coinfection, 58.3% (7/12) had positive HIV status, and 41.7% (5/12) had negative HIV status. All patients in the HIV group were male, but only 40% (2/5) were male in the non-HIV group. The common radiological features described on chest imaging suggestive of PJP in one-half of cases were GGO predominantly in the upper lobes of the lung, multiple lung cysts, and pneumothoraces. All COVID-19 patients were critically ill and required ICU admission during their respective hospitalization. For the highest level of respiratory support, 75% (9/12) of patients required IMV, and the remainder required NIMV and HFNC (Table 2).

91.7% (11/12) of COVID-19 patients were immunocompromised at baseline from either a positive HIV status or long-term exposure to immunosuppressants such as high-dose corticosteroids, leflunomide, tacrolimus, mycophenolate mofetil (MMF), fludarabine, cyclophosphamide, and rituximab in the non-HIV group. These immunosuppressive therapies were for comorbidities of renal transplant, chronic lymphocytic leukemia (CLL), and connective tissue disease of rheumatoid arthritis (RA) and dermatomyositis. The overall ALC during PJP diagnosis was 520 cells/mm³ (496 cells/mm³ for the non-HIV group and 544 cells/mm³ for HIV group), and the overall nadir CD4+ T cell counts were 96 cells/mm³ (163 cells/mm³ for the non-HIV group and 77 cells/mm³ for HIV group).

Diagnosis, outcome, and treatment

The time to presentation from illness onset and time to PJP diagnosis from the initial presentation was highly variable, with a mean of 15.0 (range 1–28) days and 7.8 (range 2–21) days, respectively. COVID-19 patients with HIV had a delay in presentation from illness onset (mean 16.8 days vs. 13.2 days) than the non-HIV group (Table 2). No difference
Table 1  Clinical characteristics of 12 COVID-19 patients with PJP coinfection

| Author                  | Month, Year | Country       | Age (Y) | Gender | HIV status | ALC (count cells/mm³) | Lowest CD4+T cell counts (cells/mm³) | Long-term corticosteroids (Dose) | Other immunosuppressants | Radiology PJP features                      |
|-------------------------|-------------|---------------|---------|--------|------------|----------------------|--------------------------------------|----------------------------------|-------------------------------|---------------------------------------------|
| Cai et al.[13]          | June, 2020  | China         | 72      | Female | Negative   | 340                  | NR                                   | Methylprednisolone (4–40 mg)      | Leflunomide for RA             | Worsening BUL infiltrates            |
| De Francesco et al. [73]| September, 2020 | Italy        | 65      | Male   | Negative   | 738                  | 35                                   | Methylprednisolone (NR)           | Tacrolimus and MMF for renal transplant | NR                           |
| Menon et al.[74]        | July, 2020  | USA           | 83      | Female | Negative   | 1094                 | 291                                  | Budesonide (3 mg)                 | NR                           | Multiple BUL cysts                  |
| Mouren et al.[49]       | February, 2021 | France       | 65      | Male   | Negative   | 200                  | NR                                   | NR                               | Fludarabine, CTX, RTX for CLL     | NR                           |
| Quintana-Ortega et al.[75]| January, 2021 | Spain       | 11      | Female | Negative   | 110                  | NR                                   | Prednisone (1 mg/kg)              | Tacrolimus, MMF for dermatomyositis | Right PTX                      |
| Bhat et al.[76]         | July, 2020  | USA           | 25      | Male   | Positive   | NR                   | 32                                   | NR                               | NR                           | Right PTX                      |
| Blanco et al.[12]       | April, 2020 | Spain         | 31      | Male   | Positive   | 900                  | 13                                   | NR                               | NR                           | NR                           |
| Broadhurst et al.[77]   | February, 2021 | South Africa | 54      | Male   | Positive   | 690                  | 26                                   | NR                               | NR                           | NR                           |
| Coleman et al.[78]      | July, 2020  | UK            | 55      | Male   | Positive   | NR                   | 422                                  | NR                               | NR                           | Subpleural and paramediastinal cystic changes, BUL GGO |
| Kelly et al.[79]        | November, 2020 | UK          | 50–60 s | Male   | Positive   | 140                  | 28                                   | NR                               | NR                           | Worsening BUL infiltrates, Right PTX |
| Mang et al.[80]         | July, 2020  | Germany       | 52      | Male   | Positive   | 590                  | 12                                   | NR                               | NR                           | NR                           |
| Rubiano et al.[81]      | January, 2021 | USA         | 36      | Male   | Positive   | 400                  | 8                                    | NR                               | NR                           | NR                           |

ALC absolute lymphocyte count, BUL bilateral upper lobes, CLL chronic lymphocytic leukemia, CTX cyclophosphamide, HIV human immunodeficiency virus, GGO ground-glass opacities, MMF mycophenolate mofetil, NR not reported, PTX pneumothorax, RA rheumatoid arthritis, RTX rituximab, Y year
| Author                          | Highest ventilator support | Outcome | Symptoms onset to admission (D) | Admission to diagnosis (D) | LRT Specimen Source | Serum LDH (IU/L) | Serum BDG (pg/mL) | Respiratory microorganisms coinfection | Anti-PJP therapy | COVID-19 therapy | Antimicrobial therapy |
|--------------------------------|-----------------------------|---------|--------------------------------|---------------------------|----------------------|-----------------|-----------------|---------------------------------|-----------------|----------------|----------------------|
| Cai et al.[13]                 | IMV                         | Survived | 1                              | 19                        | BAL PCR              | NR              | NR              | Aspergillus fumigatus              | Unspecified     | Lopinavir-ritonavir, methylprednisolone, tocilizumab | Cefoperazone-sulbactam, caspofungin |
| De Francesco et al.[73]        | IMV                         | Dead    | 2                              | 2                         | Sputum PCR           | 380             | NR              | Aspergillus fumigatus, *Chlamydia pneumoniae* | SMX-TMP, methylprednisolone, dexamethasone | Dexamethasone, tocilizumab, darunavir-ritonavir, hydroxychloroquine | Azithromycin, piperacillin-tazobactam, voriconazole |
| Menon et al. [74]              | IMV                         | Survived | 14                             | 3                         | ETA PCR              | 348             | 305             | NR                             | SMX-TMP         | NR             | Azithromycin, amoxicillin-clavulanate |
| Mouren et al. [49]             | NR                          | Survived | 21                             | NR                        | BAL MS/PCR           | NR              | NR              | SMX-TMP                         | NR             | NR             | NR |
| Quintana-Ortega et al. [75]    | IMV                         | Dead    | 28                             | NR                        | BAL MS               | NR              | NR              | Enterococcus faecium bacteraemia | SMX-TMP, methylprednisolone, dexamethasone | Hydroxychloroquine, remdesivir, tocilizumab, methylprednisolone, dexamethasone, | NR |
| Bhat et al.[76]                | IMV                         | Survived | NR                             | 4                         | BAL PCR              | NR              | NR              | SMX-TMP, prednisone              | Remdesivir, prednisone | Hydroxychloroquine, interferon beta, corticosteroids | Azithromycin, cefaroline-fosamil |
| Blanco et al. [12]             | NIMV                        | Survived | 7                              | NR                        | Unspecified          | 1149            | NR              | SMX-TMP, corticosteroids         | SR, prednisone  | Hydroxychloroquine, interferon beta, corticosteroids | Meropenem, fluconazole |
| Broadhurst et al.[77]          | IMV                         | Dead    | 21                             | 2                         | Sputum IFM           | NR              | 500             | Acinetobacter baumannii bacteraemia | SMX-TMP, dexamethasone | Dexamethasone | Meropenem, fluconazole |
| Coleman et al. [78]            | HFNC                        | Survived | 7                              | NR                        | Sputum PCR           | NR              | NR              | SMX-TMP, prednisolone            | SMX-TMP, prednisolone | Prednisolone | NR |
| Kelly et al.[79]               | IMV                         | Dead    | 28                             | 4                         | BAL IFM              | NR              | NR              | SMX-TMP, prednisolone            | SMX-TMP, prednisolone | Prednisolone | Unspecified |

*Table 2* Diagnosis, outcome, and treatment of 12 COVID-19 patients with PJP coinfection
was observed in the duration of PJP diagnosis from presentation (mean 7.6 days vs. 8.0 days) in the HIV and non-HIV groups. The diagnosis of PJP coinfection was made by the LRT specimen source of BAL in 58.3% (7/12) and sputum in 25% (3/12) of COVID-19 patients (Table 2). In most cases, PCR [58.3% (7/12)] was used to detect P. jirovecii, followed by MS and IFM [25% (3/12)], respectively. Only one case report by Blanco et al. did not describe the source of the LRT specimen [12]. Serum LDH was measured in 41.7% (5/12) of COVID-19 patients, with elevated mean levels of 636 IU/L. Serum BDG levels were only elevated in 25.0% (3/12) of COVID-19 patients, with a mean of 435 IU/L. 41.6% (5/12) of patients with PJP and COVID-19 co-infection had other bacterial or fungal microorganisms identified from LRT specimens that suggested additional bacterial or fungal coinfections. The microorganisms isolated were Chlamydia pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter dijkshoorniae, and Aspergillus fumigatus. 25.0% (3/12) patients had underlying bacteremia from Acinetobacter baumannii and Enterococcus faecium.

The overall mortality rate was 41.6% (5/12), involving 40% (2/5) in the non-HIV group and 42.9% (3/7) in the HIV group (Table 2). 57.1% (4/7) of patients with suspected bacterial or fungal coinfections died during hospitalization. Most patients (91.6% (11/12)) with COVID-19 and PJP coinfections received anti-PJP therapy of sulfamethoxazole-trimethoprim (SMX-TMP) together with corticosteroids. Cai et al. was the only case report that did not describe the type of anti-PJP therapy administered [13]. 83.3% (10/12) of case reports described a variety of COVID-19 therapies given, which includes anti-viral (e.g., lopinavir-ritonavir, darunavir-ritonavir, and remdesivir), immunomodulators (e.g., corticosteroids, hydroxychloroquine, interferon beta, and tocilizumab), and convalescent plasma. 66.7% (8/12) of patients received antimicrobial therapy of antibiotics and/or antifungals during hospitalization.

**Discussion**

We identified 12 COVID-19 patients to have coinfections by PJP in which more than one-half of patients had a positive HIV status. Common radiological features suggestive of PJP were GGO predominantly in the upper lobes of the lung, multiple lung cysts, and pneumothoraces. All patients were critically ill and required IMV. Many patients were immunosuppressed from HIV or long-term corticosteroids and other immunosuppressive agents. In both the HIV and non-HIV group, severe lymphocytopenia (<1000 cells/mm³) was encountered with ALC, and CD4+ T cell count was less than 900 and 200 cells/mm³, respectively. The time to presentation from illness onset was 15.0 (range 1–28)
days, and the time to PJP diagnosis from the initial presentation was 7.8 (range 2–21) days. Patients with HIV had a delay in presentation from illness onset than the non-HIV group. PJP diagnosis was made by LRT specimen source of BAL in more than one-half of patients, and either ETA or sputum in the remaining patients. PCR was frequently used to examine the LRT specimen for *P. jirovecii* over MS and IFM. Although serum LDH and BDG were elevated during PJP diagnosis, less than 50% of COVID-19 patients had serum LDH and BDG examined. All patients were treated with anti-PJP therapy, predominantly SMX-TMP with corticosteroids. The majority of patients received COVID-19 therapies of anti-viral, immunomodulators, and convalescent plasma. Nevertheless, the overall mortality rate was 41.6% and appeared similar for both HIV and non-HIV groups. 58.3% of patients were suspected to be coinfected by other bacterial and fungal microorganisms, in which more than half of these patients died during hospitalization despite antimicrobial therapies.

In contrast, concurrent PJP infection has not been reported in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In a 2019 study, up to 7% of critically ill influenza A patients had positive *P. jirovecii* in their BAL PCR. However, the authors did not comprehensively delineate whether those patients had actual infection versus colonization [14]. Several cases have been reported in the literature involving both immunocompetent and immunocompromised HIV-negative status influenza A patients with confirmed PJP demonstrating an absolute lymphocyte count and CD4+ T cell count less than 600 cells/mm$^3$ and 200 cells/mm$^3$, respectively [15–17]. Influenza A is known to deplete both the innate alveolar immunity involving dendritic cells, macrophages, and monocytes together with T and B cells as a result of influenza A-induced cell apoptosis and migration of these cells from the circulation to the infected respiratory tract as a consequence of infection [18–21]. Lymphocytopenia seen in up to 69% of influenza A patients typically recover after 1–3 weeks from illness onset or even after the fever subsides [22, 23].

**Factors favoring PJP coinfection**

Lung infiltrates of GGOs predominantly in the bilateral upper lobes are useful distinguishing radiological features for PJP [5, 24]. However, when PJP is superimposed on
COVID-19 pneumonia, these findings are indistinguishable between the two entities, mainly when lung infiltrates are diffuse. The involvement of lung typically more diffuse in those without HIV than those with HIV (86% vs. 44%; \( P = 0.02 \)), which further complicates the diagnosis of PJP coinfection in advanced COVID-19 pneumonia [9, 25–28]. Cavitation, pleural effusions, and lymphadenopathies are rarely seen in COVID-19 pneumonia and PJP; however, these radiological findings may support a diagnosis of superimposed bacterial and fungal pneumonia [5, 6]. PJP coinfection should be part of the differential diagnosis when multiple lung cysts are observed, possibly with spontaneous pneumothorax in the setting of immunocompromised status [6, 28]. These cysts, typically diffuse, bilateral, and thin-walled, are seen in up to 56% of PJP patients and may resolve with PJP treatment. However, the frequency of cystic lesions can be less than 10% in patients without concurrent HIV infection [28, 29]. The occurrence of pneumothorax is similar for PJP patients, regardless of HIV-positivity status [5, 6, 28, 30]. Compared to COVID-19 pneumonia, pneumothorax is a rare radiological finding and observed in less than 5% of cases [27, 31].

In the absence of classical risk factors of HIV, PJP coinfection is increasingly identified in COVID-19 patients with lymphocytopenia and multiple immunosuppressants. Lymphocytopenia, observed in up to 83% of hospitalized COVID-19 patients, is one of the many etiologies predisposing to concurrent PJP infections, a pathogen commonly seen in patients with defects in T cell immunity [8]. The innate and adaptive immune system is activated during COVID-19 infection, causing the release of cytokines to trigger the recruitment of macrophages, monocytes, and both T and B cells from the circulation towards the inflamed tissues [32, 33]. As a result of the proinflammatory cytokines’ release and COVID-19-induced lymphocyte apoptosis, the immunosuppression stage follows, characterized by sustained lymphocytopenia that occurs within a week from COVID-19 illness onset before returning to normal levels, two weeks later [34, 35]. An ALC less than 1700 cells/mm\(^3\) had 84% sensitivity and 55% specificity for predicting a CD4 + T cell count of less than 200 cell/mm\(^3\).[36] Unlike ALC, CD4 + T cell count is rarely measured in COVID-19 patients unless a strong suspicion exists for concurrent HIV infection or a severely immunocompromised state. Patients diagnosed with PJP had CD4 + T cell count of less than 100 cell/mm\(^3\) in 78.7% of cases, followed by 16.2% and 5.1% when CD4 + T cell count was 100–200 cell/mm\(^3\), and 200 cell/mm\(^3\) and above, respectively [37]. However, this datum was extracted from an observational study involving HIV-patients. Therefore, strong suspicion should exist for PJP coinfection in those with severe lymphocytopenia, regardless of HIV status. Second, COVID-19-induced alveolar macrophage dysfunction is likely responsible for \( P. jirovecii \) evading phagocytosis by the alveolar macrophage, primary host defense while dysregulating surfactant production [38–40]. Surfactant is essential to facilitate attachment of \( P. jirovecii \) to the macrophages for phagocytosis and inhibit replication that explains why \( P. jirovecii \) favors the upper lobe of the lungs containing the least amount of surfactant required to maintain lung compliance.

Corticosteroids have anti-inflammatory and immunomodulatory properties by inhibiting cytokines, decreasing leukocyte migration, and triggering lymphocytes apoptosis, specifically T cells [33, 35]. Therefore, corticosteroids help prevent and treat cytokine storm and ARDS in COVID-19 patients. A prolonged course (4 weeks <) of corticosteroid with a median daily dose equivalent to 30 mg of prednisone is often associated with PJP infection [41, 42]. However, patients receiving does as low as 15 mg or have baseline lymphocytopenia (HR 10.7; 95% CI 1.8–63.8; \( P = 0.01 \)) are also at increased risk [41]. CLL patients are already immunocompromised due to the exhaustion of CD4 + T cell and immunoglobulins production, an essential component of adaptive immunity towards the advanced stage of the disease. The addition of other immunosuppressants such as fludarabine and rituximab will induce a profound CD4 + T cell lymphocytopenia and hypogammaglobulinemia predisposing to opportunistic infections such as PJP [43]. Tocilizumab, an IL-6 inhibitor biologic, is commonly used in COVID-19 and RA patients, with reported PJP events of 0.28 per 100 patient-years [44, 45]. MMF and tacrolimus have been shown to deplete lymphocytes, specifically T cells and complement levels, increasing the risk of opportunistic infection such as PJP when used in conjunction with corticosteroids [46, 47].

Despite a huge variation in timing from illness onset to presentation in our study population, HIV-positive patients had a delay in clinical presentation from illness onset than those without HIV (Table 2). This is frequently seen in many HIV patients with PJP coinfection, in which the HIV group had a longer duration of illness (18 days vs. 10 days; \( P < 0.05 \)) than the non-HIV group [30]. BAL cell differentials are often non-specific in patients with COVID-19 pneumonia; however, BAL cell counts that are predominant lymphocytosis (13% <) with flow cytometry showing high levels of CD8 + T cells (30% <) and cell viability (80% <) but low CD4 + T cells (50% >) and CD4 + /CD8 + T cell ratio (2.5 >) are suggestive of PJP coinfection [48]. Mouren et al. was the only case report reporting BAL findings in COVID-19 patients with PJP coinfection, demonstrating a total white cell count of 468 × 10\(^3\) cells/mm\(^3\) and 38% lymphocytes [49]. Nevertheless, the significance of low levels of PJP detected by PCR and BAL cell count differentials need to be interpreted in conjunction with clinical context.
Factors favoring colonization

Our study results demonstrated that all patients in the HIV group were male, but only 40% were males in the non-HIV group (Table 1). Furthermore, the mortality rate was similar for both HIV and non-HIV groups (Table 2). This is inconsistent with the findings from several observational studies demonstrating that COVID-19 patients without HIV are predominantly males and have a higher fatality rate than COVID-19 patients with HIV. In 2008, an observational study comparing 72 PJP patients revealed that the non-HIV group were males (80.4% vs. 40.7%; \( P < 0.05 \)), had a higher severity of illness (38% vs 27%; \( P < 0.05 \)), and greater ICU-mortality (48% vs. 17%; \( P < 0.05 \)) [30]. In 2020, a large observational study involving 3938 PJP patients demonstrated that a greater proportion of non-HIV patients were males (79.85 vs. 48.5%; \( P < 0.01 \)), more likely symptomatic (38.2% vs. 30.3%; \( P < 0.01 \)), and had a higher mortality (6.6% vs. 4.2%; \( P < 0.01 \)) than those with HIV [50]. The difference in host inflammatory immune response rather than virulence of the \( P. jirovecii \) explains the acute illness, severe hypoxia, and rapid decline in respiratory status in non-HIV patients [28, 29].

Given the evidence of proinflammatory cytokines, innate and adaptive immune factors playing a significant role in promoting severe COVID-19, the immunosuppressive characteristics of HIV can lead to better outcomes in COVID-19 patients with PJP coinfections [32, 33]. Critically ill COVID-19 patients will generally have CD4+ T cell response heavily skewed towards T helper cell type 2 (TH2) activation. TH2 is known to secrete interleukin-6, a cytokine predominantly responsible for COVID-19-induced immune dysregulation, but is suppressed in those with HIV [51, 52]. Therefore, the findings above could suggest colonization instead of actual infection. An observational study by Alanio et al. reported that in 108 non-HIV COVID-19 patients requiring IMV, the detection of \( P. jirovecii \) by PCR obtained by routine bronchoscopy with BAL was 9.3% [53]. More than one-half of these patients had low serum BDG and were not treated for PJP, where outcomes, including mortality, did not differ, suggesting possible colonization.

Decision on treatment

The gold-standard staining or immunofluorescence microscopy to detect \( P. jirovecii \) in LRT specimens, frequently obtained from BAL, are used to confirm PJP [9]. Like many patients without HIV, the diagnosis of PJP becomes challenging, in whom the burden of PJP is generally lower and limits the sensitivity of microscopy [9]. Given the high sensitivity of \( P. jirovecii \) PCR in detecting low fungal loads, even in non-HIV patients, the distinction between actual infection and colonization is a common problem [54, 55]. PCR has 87.2% sensitivity and 92.2% specificity; 51.5% positive predictive value and 98.7% negative predictive value for diagnosing PJP [56]. Therefore, a negative PCR can exclude PJP and allows cessation of therapy. Studies have suggested using quantitative \( P. jirovecii \) PCR and serum BDG to distinguish between actual infection and colonization [57, 58]. Specifically, a quantitative BAL PCR greater than \( 1.6 \times 10^3 \) DNA copies/μL and BDG cut-off level of 100 pg/mL can distinguish between \( P. jirovecii \) infection and colonization with close to 100% sensitivity, regardless of HIV status [57]. In combination, the high sensitivity of PJP PCR from BAL and serum BDG may even prevent the need for IFM. It has even been proposed that in symptomatic non-HIV patients with positive serum BDG and PCR but negative sputum or BAL microscopy, clinical suspicion should remain high for PJP [9]. Nevertheless, these resources were lacking in many studies included (Table 2).

In critically ill COVID-19 patients who are unable to tolerate diagnostic bronchoscopy, compatible clinical and radiological features with elevated serum biomarkers levels of LDH and BDG may be the only useful tools to warrant an empirical trial of anti-PJP therapy such as sulfamethoxazole-trimethoprim (SMX-TMP) [59]. BDG levels are typically low, less than the cut-off of 80 pg/mL in COVID-19 infection, as the COVID-19 virus lacks the polysaccharide cell walls present in certain fungal and bacteria microorganisms [60, 61]. In 2011, a meta-analysis demonstrated that serum BDG had 94.8% sensitivity and 86.3% specificity for the diagnosis of PJP in the setting of compatible clinical manifestations and risk factors [62]. LDH levels are commonly elevated in both COVID-19 and PJP patients, making it a sensitive but not specific biomarker to distinguish between the two entities [8, 63]. However, serum LDH has been shown higher among non-survivors than survivors for both COVID-19 (mean 521 IU/L vs. 253 IU/L; \( P < 0.01 \)) and PJP (mean 447 IU/L vs. 340 IU/L; \( P < 0.05 \)) [63, 64]. An observational study suggested that serum LDH level greater than 450 IU/L has close to 100% sensitivity in diagnosing PJP in the context of compatible clinical symptoms in non-COVID-19 patients [63].

When clinical suspicion for PJP is high, treatment can be initiated even before making a definitive diagnosis because \( P. jirovecii \) persists in respiratory specimens for up to 3 weeks after adequate treatment is initiated [65]. Clinical improvement with anti-PJP therapy can be expected around 4–8 days [9, 55]. Serum BDG, despite being a reliable, adjunct diagnostic marker, may indicate favorable treatment response with decreasing levels but does not always reflect the severity and prognosis in PJP patients [66–68]. With anti-PJP therapy, serum BDG will generally reduce by a median of 17 (IQR 0–82) pg/mL over a week and may occasionally increase in levels for a few weeks before declining, and does not reflect treatment failure [66, 67].
Limitations

The major limitation of our narrative review is the literature on PJP coinfection in COVID-19 patients is limited to 12 case reports. Therefore, the true incidence, risk factors, and prognosis of COVID-19 patients with concurrent PJP infections cannot be precisely determined. The difficulties in confirming the diagnosis of PJP are due to the concerns of viral transmission between COVID-19 patients and healthcare workers, and worsening hemodynamic status in a severely hypoxic COVID-19 patient while performing aerosolized generating procedures such as bronchoscopy to obtain LRT specimen of sufficient quality. Therefore, bronchoscopy is often discouraged unless an alternate diagnosis provided by BAL would significantly impact clinical management [69]. However, recent observational studies have demonstrated the low risk for viral transmission to healthcare workers when adhering to WHO guidelines on airborne precautions for aerosol-generating procedures [70–72]. Other important diagnostic and prognostic markers for PJP, such as serum BDG and the ratio of partial pressure of arterial oxygen to fractional inspired oxygen (paO2/FiO2), were not consistently evaluated. The overall mortality rate could have been affected by other microorganisms causing secondary pulmonary infections or sepsis among the 58.3% of patients included in our study, in which more than half of these patients died during hospitalization despite antimicrobial therapies. However, it is even possible that these bacterial and fungal microorganisms identified could be colonizers similar to *P. jirovecii*.

Conclusion

There is huge variability in timing from illness onset to presentation, and presentation to PJP diagnosis in COVID-19 patients, regardless of HIV status. It remains unclear if COVID-19 patients with *P. jirovecii* identified on LRT specimens represent actual infection versus colonization due to the similarities in clinical presentation. Comorbidities of poorly controlled HIV with lymphocytopenia and multiple immunosuppressive therapies are likely predisposing factors for PJP coinfection. As PJP coinfection is under-recognized and under-reported, causing the lack of diagnostic testing, the true incidence and outcomes of COVID-19 patients with PJP coinfection remain uncertain. Incorporating HIV screening of all patients admitted for COVID-19 into institutional protocols is a sensible approach to reducing diagnostic uncertainty and anchoring biases due to significant overlap in clinical presentation. It essential to maintain a broad differential diagnosis and prudent to consider additional diagnostic testing for *P. jirovecii* in COVID-19 patients, mainly when there is a lack of clinical improvement in respiratory status, radiological features of lung cysts and possibly with pneumothorax, and laboratory findings of elevated serum LDH and BDG, even in the absence of classical risk factors such as HIV. As the current evidence in the literature is restricted to case reports, the incidence, risk factors, and prognosis of COVID-19 patients with PJP coinfections cannot be accurately determined. A large, well-designed study is needed to differentiate between PJP coinfections and colonization, possibly with the development of sensitive diagnostic criteria due to the similarities in clinical presentation.

Author contributions All authors had access to the data and were involved in writing the manuscript.

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