



A Comprehensive Study of the Global COVID-19 Pandemic and Fungal Co-Infections: A Review

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-19), which has resulted in high death tolls around the world and a significant health burden. The purpose of this study is to bring attention to the early diagnosis and treatment of fungal diseases in coronavirus disease 2019 (COVID-19) patients.

Materials and Methods: We searched peer-reviewed articles, reviews, surveillance reports, and clinical studies published from January 2020 to December 2023 using databases including PubMed, Scopus, and Web of Science.

Results: Severely ill COVID-19 patients are at high risk for life-threatening fungal co-infections. The most prevalent is pulmonary aspergillosis, affecting up to a third of ICU patients, largely driven by corticosteroid use. Candidiasis is also common with prolonged ICU stays. Diagnosis is challenging, and treatment requires specific antifungals.

Conclusion: Fungal co-infections increase COVID-19 mortality. Manage with early diagnosis, targeted antifungals, and risk factor control. Global focus on awareness, diagnostics, and antifungal stewardship is crucial.

Keywords: COVID-19; Sars-cov-2; Fungal co-infection; Aspergillosis; Mucormycosis; Candidiasis.

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Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan, China, in December 2019 and rapidly evolved into a global health crisis by March 2020 [1]. The disease's progression, particularly in severe cases, involves extensive viral replication, cytokine storms, and inflammatory responses that can damage pulmonary tissue and impair host immunity [2,3]. These immunological disruptions increase the risk of secondary infections, including bacterial, viral, and particularly fungal co-infections. Fungal co-infections have emerged as a serious complication in patients with COVID-19, particularly those admitted to intensive care units or receiving immunosuppressive therapy [4]. Risk factors for invasive fungal infections (IFIs) include pre-existing conditions such as diabetes and structural lung disease, as well as acquired factors like leukopenia, immune dysregulation, prolonged corticosteroid therapy, immunomodulators, and broad-spectrum antibiotics [5]. Moreover, SARS-CoV-2 infection itself can induce immune dysfunction that independently predisposes patients to fungal invasion [6].

The most commonly reported COVID-19-associated fungal infections (CAFIs) include invasive pulmonary aspergillosis, candidiasis, and mucormycosis. Less frequently observed infections include fusariosis, cryptococcosis, *Pneumocystis pneumonia*, coccidioidomycosis, paracoccidioidomycosis, and histoplasmosis [7]. Early detection of these co-infections is challenging but crucial, as delayed diagnosis can lead to poor outcomes. Diagnosis typically relies on a combination of clinical assessment and laboratory testing, such as direct microscopy, histopathological examination, fungal cultures, galactomannan assay, polymerase chain reaction (PCR)-based methods, and the 1,3- β -D-glucan test [8]. In this review, we provide a comprehensive overview of the epidemiology, risk factors, diagnostic approaches, and treatment strategies for major fungal co-infections associated with COVID-19, aiming to aid early recognition and optimize clinical management.

Materials and Methods

This narrative review was conducted to synthesize and critically evaluate the available literature on fungal co-infections in the context of COVID-19 globally. We searched peer-reviewed articles, reviews, surveillance reports, and clinical studies published from January 2020 to December 2023 using databases includ-

ing PubMed, Scopus, and Web of Science. The search terms included combinations of keywords such as "COVID-19," "SARS-CoV-2," "fungal infection," "Aspergillus," "Candida," "Mucormycosis," and "Co-infection." Boolean operators and MeSH terms were utilized where applicable. Inclusion criteria comprised studies that: (1) reported on fungal co-infections in COVID-19 patients, (2) were published in English, and (3) involved human subjects. Exclusion criteria included studies focused solely on bacterial or viral co-infections, those lacking clinical or microbiological evidence of fungal involvement, and non-peer-reviewed preprints unless they provided substantial and unique insights. The selection process followed a two-stage screening: first by title and abstract, then full-text review. Data extraction was carried out manually and included geographic origin, fungal species identified, diagnostic criteria used, treatment regimens, and patient outcomes. Quality assessment of included studies was based on relevance, methodological rigor, and completeness of reporting, although no formal scoring system was applied due to the diversity of study designs. This review adheres to guidelines for narrative reviews, ensuring transparent reporting and comprehensive coverage of the literature.

Results

COVID-19-associated pulmonary aspergillosis (CAPA):

CAPA is a secondary opportunistic infection primarily affecting patients with COVID-19-induced acute respiratory failure [9]. In critically ill patients, aspergillosis has been reported in up to one-third of the cases [10]. Risk factors for CAPA include older age, need for respiratory support, immune modulation (e.g., corticosteroids and IL-6 antagonists), disease severity, and diabetes mellitus, which is particularly relevant in ICU settings [11] (Table 1). Major contributors to mortality in CAPA include acute respiratory distress syndrome (ARDS), inappropriate glucocorticoid use, and delayed or missed diagnosis [12].

Laboratory findings such as neutrophilic leukocytosis, lymphopenia, thrombocytopenia, and hyperferritinemia have been linked to CAPA pathogenesis, offering new targets for the cellular therapies [12]. Corticosteroids and immunomodulators, particularly dexamethasone, may increase CAPA risk due to immunosuppression and T cell exhaustion [13,14]. The role of interleukin-6 inhibitors remains controversial, with conflicting evidence regarding their risk profile [9,15]. CAPA is associated with higher mortality rates than those without CAPA [16]. Differentiating CAPA from COVID-19 pneumonitis is challenging based on

clinical and radiographic findings alone. Moreover, distinguishing between infection and colonization using mycological data is often not feasible [17]. Diagnostic tools such as Galactomannan (GM) testing, PCR, and cultures of bronchoalveolar lavage fluid (BALF) and tracheal aspirates are commonly used [12,18] (Table 2). However, bronchoscopy may pose a risk of viral aerosolization [6]. An international panel has proposed a diagnostic classification scheme, possible, probable, and proven CAPA, based on radiological findings, GM levels and mycological tests [19]. For example, pulmonary infiltrates plus positive non-directed BALF culture or GM may indicate possible CAPA, while the inclusion of positive BALF culture, serum GM, or (1-3)- β -D-glucan elevates the diagnosis to probable CAPA [20]. Proven CAPA requires histopathological confirmation of fungal invasion [19].

Treatment options include mold-active antifungals like Voriconazole and Isavuconazole, recommended as first-line agents. Liposomal amphotericin B is considered in azole-resistant cases [19] (Table 3). However, no randomized controlled trials have defined the optimal CAPA treatment [21]. COVID-19-associated mucormycosis (CAM): Mucormycosis, caused by fungi in the order Mucorales, emerged as a significant complication during the COVID-19 pandemic, especially in immunocompromised individuals [22]. India accounted for 70% of global CAM cases during the pandemic second wave [23]. Prolonged neutropenia, hypoxia, hyperglycemia, acidosis, cytokine storms, altered immune response, organ transplantation, acquired immunodeficiency syndrome (AIDS), hematological malignancies, increased ferritins and decreased phagocytic activity of white blood cells, administration of systemic steroids/immunosuppressive drugs and broad-spectrum antibiotics, and prolonged hospitalization with or without mechanical ventilation are immunocompromised conditions that predispose Mucormycosis [24,25]. *Rhizopus* spp. is the most prominent genus involved, though other genera such as *Apophysomyces*, *Cunninghamella* and *Lichtheimia* also cause CAM [26]. Mucormycosis may affect various organs, depending on the patient's underlying condition. Rhino-orbital-cerebral mucormycosis (ROCM) is the most common in diabetics, while pulmonary mucormycosis is seen in patients with neutropenia, hematological malignancies and organ transplantation. Also, malnutrition increases the risk of gastrointestinal mucormycosis [24]. The high use of corticosteroids during COVID-19, combined with diabetes and immunosuppression, has contributed to the surge in CAM cases,

especially in India [24] (Table 1). ROCM diagnosis follows a tiered classification: possible (clinical symptoms in at-risk patients), probable (with imaging findings), and proven (confirmed via microscopy, culture, or histopathology) [27]. Treatment requires aggressive and early intervention. Lipid-based amphotericin B is the first-line drug, followed by oral posaconazole or isavuconazole (Table 3). Surgical debridement is often necessary [28–30]. Combination antifungal therapy lacks strong evidence and is generally not recommended [31]. Glycemic control has been shown to improve outcomes [32]. Preventive strategies include cautious steroid and tocilizumab use, metabolic management, and reducing exposure to infectious sources [27].

COVID-19-associated candidiasis (CAC):

CAC has emerged as a notable complication during the COVID-19 pandemic. *Candida* spp., typically part of the normal human flora, can become pathogenic in immunocompromised hosts [33]. Risk factors for CAC include prolonged ICU stays, immunosuppressive therapy, broad-spectrum antibiotics, and deficiencies in iron or zinc [34] (Table 1). Prompt diagnosis and treatment are essential to reduce mortality [35]. Candidiasis is diagnosed using physical symptoms, blood cultures, β -D-glucan (BDG), mannan antigen, PCR, and the T2 *Candida* panel, the latter being particularly useful due to blood cultures' limited sensitivity [36,37] (Table 2). Antifungal therapy selection depends on disease severity and patient comorbidities. Echinocandins are the first-line treatment for invasive candidiasis in COVID-19 cases, while fluconazole, liposomal amphotericin B, voriconazole, osaconazole, and isavuconazole are secondary options [38,39] (Table 3).

Other fungal co-infections:

Fusarium spp., especially *F. solani* and *F. oxysporum*, are emerging causes of keratitis and invasive fusariosis, particularly in immunocompromised patients [40]. Fusariosis has a high mortality rate, especially in steroid-treated COVID-19 patients with compromised immunity [41] (Table 1). Treatment is challenging due to antifungal resistance; available options include amphotericin B, voriconazole, and Posaconazole [18,42] (Table 3). *Pneumocystis jirovecii*, a human-specific pathogen, causes pneumocystis jirovecii pneumonia (PJP), which may co-occur with COVID-19 [43]. Risk factors include immunosuppressive therapy and lymphocytopenia (Table 1). Diagnosis of *P. jirovecii* infection relies on clinical worsening, immunosuppression, lymphocytopenia, elevated serum (1,3)- β -D-glucan level, radiology, lactate dehydrogenase level, positive

PCR and response to treatment [44-46] (Table 2). First-line therapy remains trimethoprim-sulfamethoxazole, with alternatives available for those intolerant to standard treatment [47] (Table 3). The estimated prevalence of major fungal co-infections associated with COVID-19 varies, with aspergillosis and mucormycosis being the most frequently reported, followed by

candidiasis, pneumocystis pneumonia, and fusariosis. These estimates are visually summarized in Figure 1, which provides a comparative overview based on published data [10,23,33,40].

Table 1. Risk factors for major COVID-19-associated fungal infections.

Fungal Infection	Key Risk Factors
CAPA	Corticosteroid use, mechanical ventilation, IL-6 inhibitors, diabetes, ARDS
CAM	Uncontrolled diabetes, corticosteroid overuse, hypoxia, prolonged ICU stay
CAC	Broad-spectrum antibiotics, TPN, central venous catheters, and long ICU stay
PJP	Lymphocytopenia, immunosuppressants, HIV/AIDS
Fusariosis	Hematological malignancies, corticosteroids, and ICU admission

Table 2. Diagnostic modalities for fungal co-infections.

Fungal Infection	Diagnostic Tests
CAPA	BALF culture, serum GM, PCR, CT chest
CAM	Microscopy, histopathology, nasal endoscopy, MRI/CT
CAC	Blood culture, β -D-glucan, T2 Candida panel, PCR
PJP	β -D-glucan, PCR, chest imaging
Fusariosis	Biopsy, histopathology, culture, PCR

Table 3. Recommended antifungal treatments.

Infection	First-Line Treatment	Diagnostic Tests
CAPA	Voriconazole, Isavuconazole	Liposomal Amphotericin B
CAM	Liposomal Amphotericin B	Posaconazole, Isavuconazole
CAC	Echinocandins	Fluconazole, Amphotericin B
PJP	TMP-SMX	Atovaquone, Pentamidine
Fusariosis	Amphotericin B	Voriconazole, Posaconazole

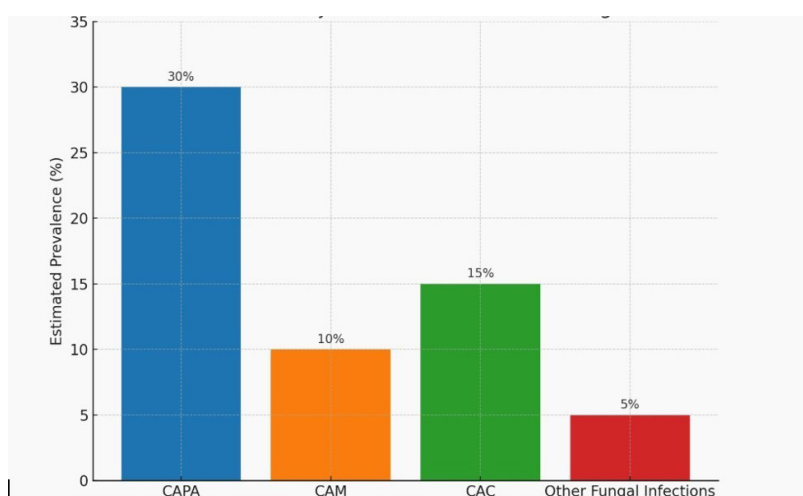


Figure 1. Estimated prevalence of major COVID-19-associated fungal co-infections.

Discussion

The emergence of fungal co-infections in the context of COVID-19 has significantly complicated clinical outcomes, especially in critically ill and immunocompromised patients [9–12,22–24,33–35,40–41]. This study demonstrates the diversity and complexity of fungal pathogens—primarily *Aspergillus* spp., *Mucorales*, *Candida* spp., and other opportunistic fungi such as *Fusarium* and *Pneumocystis jirovecii*—in the setting of SARS-CoV-2 infection. These pathogens exploit both the host's immunosuppressed state and the intensive therapeutic interventions often employed in severe COVID-19 cases [6,9,13,24,27,44]. The high incidence of CAPA among ICU patients, compounded by the use of corticosteroids and IL-6 inhibitors, emphasizes the importance of careful risk-benefit assessment in immunomodulatory therapy [10,11,13–15]. Despite the availability of diagnostic tools such as GM and PCR, distinguishing invasive disease from colonization remains difficult, often leading to delayed or inappropriate treatment and increased mortality [12,16–18]. The lack of consensus on diagnostic criteria and standardized treatment protocols underlines the need for further research and guideline development [19–21].

CAM, especially rhino-orbital-cerebral mucormycosis, has emerged as a geographically skewed epidemic, most notably in India [23–25]. The interaction between uncontrolled diabetes, steroid use, and environmental exposure underscores the multifactorial etiology of CAM [24–26]. Timely diagnosis and early surgical intervention combined with antifungal therapy are essential to improving survival. However, resource limitations and diagnostic delays in many settings have hindered optimal outcomes [27–30,32]. CAC, particularly involving *Candida Auris*, raises additional concerns due to high antifungal resistance and nosocomial transmission [33,34]. Invasive candidiasis continues to pose diagnostic and therapeutic challenges, necessitating the integration of molecular and antigen-based diagnostics alongside conventional blood cultures [35–37]. Empirical use of echinocandins remains critical in high-risk patients, though resistance surveillance is necessary [38,39]. Other fungal co-infections, while less common, are increasingly reported and require heightened awareness among clinicians. Fusariosis and PJP, for example, demand early suspicion and targeted diagnostics, especially in patients with profound immunosuppression [40–47]. Their emergence reflects the broader impact of COVID-19 on host-pathogen dynamics and health care practices. Overall, fungal co-infections represent a significant but

often under-recognized contributor to morbidity and mortality in COVID-19. Strengthening infection surveillance systems, promoting rational use of immunosuppressive drugs, optimizing glycemic and metabolic control, and expanding access to rapid diagnostics and antifungal agents are all critical strategies [27,32,48]. Multidisciplinary collaboration, continuous education, and robust public health initiatives will be key to mitigating the impact of fungal co-infections during current and future pandemics.

Conclusion

Fungal co-infections in COVID-19 significantly increase patient morbidity and mortality. Early identification, appropriate antifungal therapy, and control of underlying risk factors are key to improving outcomes. Global efforts must focus on awareness, diagnostic access, and antifungal stewardship.

Conflict of Interest

There is no conflict of interest to declare.

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