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Review Article

A Review of COVID-19-associated Fungal Infections

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A B S T R A C T

Acute respiratory coronavirus 2, the causative agent of the 2019 coronavirus disease (COVID-19), has been among the most important pathogens driving the healthcare delivery system in the past few years. Immunosuppressive drugs are used to treat this disease, and perhaps the nature of this disease has increased opportunistic infections in these patients. This study aims to investigate the number of fungal infections in patients with COVID-19. For this reason, keywords such as: "COVID-19", "*Aspergillus*", "fungi", "*Candida*", "Cryptococcus," "*Pneumocystis,*" and "*Mucorales*" were searched. According to the investigation that was carried out, *Aspergillus*, *Cryptococcus*, *Pneumocystis*, *Mucorales*, and *Candida* were among the fungi that were investigated in patients with COVID-19. Lung damage, immunosuppression, need for oxygen therapy, steroid therapy, and hospitalization in intensive care units were known predisposing factors for fungal infections in these patients.

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Introduction

In December 2019, a third outbreak of coronavirus, known as "coronavirus disease 2019 (COVID-19)", was reported in China, which causes severe respiratory disease [1, 2]. COVID-19 is a highly contagious disease with millions of associated deaths worldwide [3]. Patients with respiratory viral diseases are at increased risk of secondary infections by bacterial, parasitic, fungal, or other viral agents, which can lead to a worse prognosis [3]. In the context of COVID-19, Acute respiratory coronavirus 2 (SARS-CoV-2) infection may precede a previous microbial infection or have a co-infection or superinfection [4]. A study reported that approximately one-fifth of people with COVID-19 had an associated primary or secondary infection. In the mentioned study, co-infection was reported in 19% of patients with COVID-19, and superinfection was reported in 24% of patients, and an analysis supported a correlation between the presence of an associated COVID-19 infection and a poor prognosis, including increased mortality [5]. Studies in the United States (USA) and Europe also reported an increased risk of mortality and severe disease among early hospitalized patients with SARS-CoV-2 and bacterial co-infection [6, 7]. *Pseudomonas aeruginosa*, *Mycoplasma pneumonia*, and *Haemophilus influenza* are among the most common bacteria that cause infection in patients with COVID-19. Respiratory syncytial virus and influenza A are among the most common viruses that cause infection in patients with COVID-19 [8]. It is also reported that some fungal agents have caused infection in patients with COVID-19 [8, 9]. The nature of the corona disease and some of the drugs used may cause an increase in fungal infections in people suffering from this viral disease [10]. However, the actual incidence, related risk factors, best diagnostic strategies, prevention, and treatment of fungal infections associated with COVID-19 continue to evolve despite numerous observational studies and recent consensus guidelines [11, 12]. So, in this study, we review current literature regarding the type, characteristics, incidence, and diagnosis of fungal infections associated with COVID-19.

Overview of SARS-CoV-2

COVID-19 results from SARS-CoV-2 infection, first isolated from patients exposed at a seafood market in Wuhan City, Hubei Province, China [13]. The coronavirus particle is usually round or multi-shaped with a diameter of 120 to 160 nm and includes a triple spike (S) protein for virus attachment and membrane fusion during infection. There are four main subgroups of coronaviruses, including α, β, γ, and δ [14]. SARS-CoV-2 is a β coronavirus [15]. The sources of SARS-CoV-2 are infected animals and humans [14]. Bats are considered the most likely primary hosts of SARS-CoV-2, while pangolins may be intermediate hosts. Respiratory droplets and contact transmission are the main routes of person-to-person transmission of SARS-CoV-2. Other potential routes include fecal-oral and

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aerosol transmission, which have not been confirmed yet. Older people (over 50 years) account for 53.6% of cases, and children (under 10 years) account for only 0.9% of reported cases [14]. Patients with underlying conditions such as diabetes, high blood pressure, cardiovascular disease, pre-existing respiratory infections, and cancer are more likely to develop more severe forms of COVID-19 [14, 16]. People of all ages, including infants and pregnant women, are susceptible to infection. Most patients have mild to moderate symptoms [14]. Fever, fatigue, dry cough, sore throat, pharyngalgia, nausea, vomiting, headache, and myalgia are the most common symptoms [17]. The complications of COVID-19 include acute respiratory distress syndrome (ARDS), respiratory failure, liver damage, acute myocardial damage, acute kidney damage, septic shock, and even multiple organ failure [18]. Complete definitive diagnosis requires SARS-CoV-2 isolation, viral genome sequencing, or viral nucleic acid testing by polymerase chain reaction (PCR) in a sample collected from the upper respiratory tract (nasopharyngeal and oropharyngeal swabs) and, if possible, from the lower respiratory tract (sputum, tracheal aspiration, and bronchoalveolar lavage) [19]. Symptoms, epidemiological history, and chest computerized tomography are also effective in diagnosis [20].

An overview of fungi

Fungi that can cause infection are eukaryotic, heterotrophic, non-chlorophyll-free microorganisms, including yeasts, molds, and dimorphic fungi [21, 22]. Fungi can be unicellular or highly complex multicellular organisms that reproduce by producing sexual and asexual spores [23, 24]. Many of these fungi exist in our environment, such as wood, air, plant material, soil and water, and some exist as natural flora in the body [22, 25, 26-29]. Fungi can cause several health problems, such as allergies, poisoning, and fungal infections [22, 30-34]. Of the millions of known fungal species, only a few can naturally infect humans. Some life-saving treatments now may interfere with the normal functioning of the immune system and predispose patients to fungal infections. Humans naturally resist most invasive fungal infections due to their highly complex innate and adaptive immune systems [35]. However, some fungi can cause disease in healthy people [36]. Only fungi that can resist the human immune system and grow at 37 degrees Celsius or higher can cause invasive fungal disease in healthy people [35]. However, most fungal infections occur in people experiencing serious diseases such as cancer, autoimmunity, trauma, solid organ transplants, hematopoietic stem cells, and complex surgeries [34]. In addition to the diseases mentioned above, COVID-19 has also recently caused an increase in the incidence of fungal diseases [37], which will be further explained.

Opportunistic fungal infections associated with COVID‑19

Studies have looked at the role of several fungi in COVID‑19, which we discuss below (Table 1).

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Table 1. Characteristics of some fungi associated with COVID-19

Fungal genus	Characteristics	Related species
Aspergillus	Hyaline and septated mycelia, flask-shaped or cylindrical phialides either in a single or double series on the surface of a vesicle at the apex of a conidiophore.	*A. flavus, A. fumigates, A. nidulans, A. niger, A. acolumnaris, A. brunneus, A. collinsii, A. depauperatus,* …
Candida	Diploid, gram-positive, unicellular or multicellular, yeast, hyphae or pseudohyphae, formation of biofilms, phenotype switching	*C. albicans, C. glabrata, C. tropicalis, C.parapsilosis, C. krusei, C. lusitaniae*
Cryptococcus	Globose to elongate yeast, polysaccharide capsule, cream-colored and mucoid colonies, non-myceliated, non-fermenting.	*C. neoformans, C. gattii*
Pneumocystis	Yeast-like fungus, the spherical, oval, cup-shaped, thick-walled cyst, 6 to 8 µm in diameter, contains up to eight intracystic pleomorphic sporozoites. The extra-cystic trophozoite is thin-walled and varies in size from 2 to 6 µm, antigenic differences in various strains.	*Pneumocystis jirovecii*
Mucorales	Rapidly growing mycelium, unseptate or irregularly septate, multi-spored sporangia	*Rhizopus, Mucor, Lichtheimia, Rhizomucor*

Aspergillus genus

The genus *Aspergillus* is one of the most common filamentous fungi of the order Eurotiales, whose species are found in air, soil, vegetation, and indoor environments [38, 39]. This genus was introduced in 1729 and has more than one thousand species recorded in the database [40]. Some *Aspergillus* species benefit humans due to their ability to produce antibiotics, enzymes, organic acids, and other bioactive metabolites [41]. However, some species are harmful to humans due to causing disease and health problems [42]. *Aspergillus fumigates*, *Aspergillus flavus*, *Aspergillus terreus*, *Aspergillus niger*, and *Aspergillus nidulans* are the most common species of this fungus that can cause disease [43]. The most common diseases caused by *Aspergillus* species include invasive. Aspergillosis, allergic bronchopulmonary aspergillosis, and chronic pulmonary aspergillosis [44]. Invasive aspergillosis is often identified in severely immunosuppressed individuals, particularly those associated with hematologic malignancies and transplantation. Invasive aspergillosis is characterized by hyphal invasion through bronchial or lower airway tissues, with potential vascular invasion and prominent radiographic findings reflecting bleeding and necrosis. Recently, coronavirus-associated pulmonary aspergillosis (CAPA) has been identified through rapid reports, mainly from European centers. Pulmonary aspergillosis syndromes complicating severe viral infections are distinct from classic invasive aspergillosis,

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often diagnosed in neutropenic and other immunocompromised individuals. In this disease, epithelial damage, inflammation, systemic immunosuppression, and underlying lung disease occur, so strategies are urgently needed to improve its diagnosis, prevention, and treatment [45]. The occurrence of CAPA in patients with COVID-19 has been reported between 3.8% and 30% [45-49]. The use of systemic or inhaled steroids to manage inflammation in patients with COVID-19 has been cited as the most common cause of CAPA [45].

Candida genus

Candida species are fungi that grow as yeasts and are considered "imperfect" due to their unknown sex cycle [50]. The *Candida* genus was first recovered in 1844 from the sputum of a tuberculosis patient [51]. Many species of yeast belonging to the *Candida* genus are commensal members of the microbial flora of human skin and mucous membranes such as the oral cavity, intestine, genital and urinary tracts [52, 53]. *Candida albicans (C. albicans)*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, C. krusei, *C. stellatoidae*, *C. guilliermondii*, *C. auris*, *C. lusitaniae*, *C. famata*, and *C. dubliniensis*are the most common *Candida* species isolated from clinical cases [51]. Under certain predisposing conditions, they can disseminate throughout the host and initiate various diseases, such as chronic disseminated candidiasis, vaginitis, meningitis, endocarditis, and endophthalmitis. The incidence of *Candida* infections has increased worldwide, and the mortality rate in specific patient populations has exceeded 70% [54]. Despite the increase in non-*Candida albicans* species, *C. albicans* is still the most common cause of candidiasis, especially candidemia [55]. Immune deficiency, mucosa damage, antibiotic use, and cancer are risk factors for candidiasis [51]. Another risk factor recently introduced for candidiasis is COVID-19 [56]. During the COVID-19 pandemic, multiple cases of clinically significant candidiasis were reported [57, 58]. In India, a study reported *Candida* species as the third most common pathogen (4.1%) of secondary bloodstream infections in patients with Covid-19 [57]. Another study in central India reported a 24.3% incidence of secondary infections due to *Candida* species [58]. In Korea, *C. albicans* was noted as one of the common pathogens among patients with Covid-19 [59].

Risk factors such as lung injury, immune-suppression, monoclonal antibodies, steroid therapy, and oxygen therapy predispose patients with COVID-19 to fungal infections. COVID-19 patients have disorders in the immune response, including decreased CD80 monocyte upregulation, impaired release of interleukin (IL)-1,6, and tumor necrosis factor (TNF), which may increase the infection by *C. albicans* [60]. In addition, the SARS-CoV-2 virus causes an increase in the growth of *Candida* species by disrupting the production of an oral fungal growth inhibitor called salivary histatin-5 [61]. Dysbiosis of the lung and gut microbiota, characterized by a shift to *Candida* colonization and a decrease in fungal diversity, is associated with the development of acute respiratory distress syndrome in patients with COVID-19 [62-64]. Some

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studies showed that the mortality rate of COVID-19 patients with candidemia was significantly higher than that of non-COVID-19 patients with candidemia. Hospitalization in intensive care units (ICUs) is another risk factor for candidiasis in patients with COVID-19. Factors such as the use of mechanical ventilators, steroids, central venous catheters, immunosuppressants, and older age increase candidiasis in patients hospitalized in ICUs [60].

***Cryptococcus* genus**

Cryptococcus is a unique environmental fungus isolated from peach juice samples. Of the various cryptococcal species, only *C. neoformans* and *C. gattii* commonly cause disease. *Cryptococcus* can enter the body through the lungs and cause pulmonary disease, but due to its neurotropic nature, the central nervous system is the main target organ. The polysaccharide capsule of *Cryptococcus* is the main pathogenic agent of this fungus [65]. Clinically, the high prevalence of cryptococcosis is commonly seen in immunocompromised patients, particularly those lacking adaptive T-cell responses, such as human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS) patients [66]. Several cases of cryptococcosis associated with COVID-19 have been reported [11, 67-69]. Among the reported cases, all patients were over 55 and had an underlying disease. Cryptococcosis was isolated from blood culture, cerebrospinal fluid, or bronchoalveolar lavage and treated with flucytosine and amphotericin. All patients died except one [11].

Pneumocystis

Pneumocystis is an opportunistic pathogen that causes no apparent disease in an immunocompetent host yet can cause potentially fatal pneumonia in an immunocompromised host. The organism was first identified in the early 1900s but did not gain attention as an important human pathogen until after World War II when outbreaks of *Pneumocystis* pneumonia occurred in European orphanages [70]. *Pneumocystis* pneumonia is a severe lung infection, mainly in immunocompromised patients [71]. Several cases of *pneumocystis jirovecii* associated with COVID-19 have been reported. In general, the disease occurred in older people (mean age 78 years), and there was an underlying immunodeficiency disease such as HIV, malignancy, or chronic steroid use [72, 73]. Patients are usually diagnosed by PCR of respiratory samples from 2 to 21 days after the initial presentation of COVID-19. A prospective study testing some patients with severe COVID-19 over one month found that seventeen percent had positive respiratory samples for *Pneumocystis* [73]. However, it has been speculated that contamination or colonization rather than actual infection may contribute to the high prevalence [11]. Treatment of *Pneumocystis* in COVID-19 uses trimethoprim-sulfamethoxazole and steroids, with reported mortality ranging from 42% to 100% [72, 73].

Mucorales species

Mucorales are a group of commercial and medical molds classified in the subphylum Mucoromycotina. Reports limit the order of

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Mucorales to 55 genera and 260 species [74]. Twenty-five species of these fungi cause infection in humans [75]. The most common genera that cause mucormycosis are *Rhizopus*, *Mucor*, *Lichtheimia*, and *Rhizomucor* [74, 76]. Mucormycosis can present as a cutaneous, gastrointestinal, rhinocerebral, pulmonary, or disseminated infection, depending on the infecting species involved and the route of infection [76]. Therefore, infections can result from inhalation of spores into the nares, oropharynx, or lungs, ingesting contaminated food or water, or skin inoculation [77]. All mucoral species that cause mucormycosis in humans must be able to grow at 37 °C [74]. Weakness of the immune system, diabetes, ketoacidosis, hematological malignancies, organ transplants, chemotherapy recipients, and trauma are among the risk factors of mucormycosis [77, 78]. The management of COVID-19 has become more challenging with the increasing prevalence of COVID-19-associated mucormycosis (CAM) [79]. During the Covid-19 pandemic, fungal diseases have increased and are causing concern [80]. CAM is an emerging threat that requires more attention in COVID-19 patients, even recovered patients, because it presents a poor prognosis and requires timely diagnosis and treatment [81]. CAM may occur due to immune dysregulation caused by COVID-19 or related treatments with corticosteroids and immunomodulatory drugs that disrupt host defense mechanisms against molds [82]. Supplemental oxygen through a home oxygen concentrator may also increase the risk of mucormycosis infections due to unsanitary conditions [83]. Repeated testing of nasopharyngeal swabs by causing microtrauma to the nasal mucosa and nasopharynx may also be a risk factor for mucormycosis [79]. Long-term stay in the intensive care unit and lung and brain involvement with mucorales can also increase the risk of mortality [84].

Discussion

Treatment of the novel COVID-19 remains a complex challenge, particularly among patients with severe disease. Immunosuppressants effectively control cytokine storm syndrome in severe cases of COVID-19. However, immunosuppressive agents have increased the risk of opportunistic infections. Fungal infections are among the most important opportunistic infections that increase mortality in these patients [85]. *Aspergillus* is one of the mold fungi that can cause infection in patients with COVID-19 [86]. The levels of pro-inflammatory cytokines such as IL-2, soluble receptor IL-2 and IL-6, TNF-α, and IL-10 of patients with severe COVID-19 are higher than those with moderate disease, but CD4, CD8, and IFN-γ are lower [87]. This immune dysregulation and/or lung damage caused by the immunopathology of COVID-19 may facilitate *Aspergillus* infection. Several studies have reported the prevalence of *Aspergillus* infection in patients with COVID-19 [88-90]. These studies are limited by the lack of tissue-proven diagnoses [86]. Notably, invasive pulmonary aspergillosis is often associated with tissue necrosis due to fungal angioinvasion and thrombosis, and COVID-19

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is associated with a hypercoagulable microthrombi [86]. Antiphospholipid antibodies have been suggested as a potential cause of hypercoagulability associated with COVID-19 [91]. Fungal superinfections are challenging to distinguish from severe COVID-19 based on clinical or imaging findings, and a high index of suspicion is needed to diagnose aspergillosis. If aspergillosis is a complication of COVID-19 in a significant number of critically ill hospitalized patients, failure to recognize or diagnose the disease is likely to result in excess mortality [86]. *Candida* species are other microorganisms that can cause infections in patients with COVID-19. Mortality from invasive candidiasis is thought to be 19-40% [92]. Neutrophils and monocytes/macrophages, important defense cells against candidiasis, are not affected by SARS-CoV-2, suggesting that they are probably not responsible for COVID-19-associated candidiasis [93]. Although a previous study in Iran showed a relatively low level of oral candidiasis among patients with COVID-19, this study included all patients who presented with COVID-19 but not patients with ARDS, which may have led to an underestimation of oral candidiasis in the context of COVID-19 [94]. *Cryptococcus* is another fungus mentioned in COVID-19, considering that Cryptococci patients have a high mortality risk [95, 96]. Due to the low number of reports, it is unclear whether COVID-19 creates a specific setting for cryptococcal infection [11]. However, clinicians must maintain a high index of suspicion for cryptococcosis in patients with severe COVID-19 suspected of having meningitis [11]. It is worth noting that cases of pneumonia caused by *P. jirovecii* have been reported in COVID-19 patients, although most patients suffer from AIDS. A possible bias in diagnosing *P. jirovecii* pneumonia is related to the clinical features shared with COVID-19, which underestimates possible cases and makes it difficult to predict risk factors [97]. Mucorals gained importance during the second wave of the COVID-19 pandemic, which increased mortality and morbidity. Management of COVID-19 disease has become more challenging with the increasing prevalence of mucormycosis associated with COVID-19 [79]. It should also be mentioned that there is a report of its higher prevalence in rural areas than in urban areas, possibly due to a lack of proper treatment [98]. Physical factors, such as frequent nasopharyngeal swab testing for COVID-19, may be an independent factor associated with a higher risk of mucormycosis associated with COVID-19 [79].

Conclusion

The recent SARS-CoV-2 pandemic further highlighted the importance of fungal infections in increasing morbidity, even in previously immune-competent populations. To reduce the morbidity and mortality caused by opportunistic fungi and improve the infection outcome, public awareness of the association of fungal co-infection is necessary to avoid delays in diagnosis and treatment. There are particular challenges related to the diagnosis of

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secondary infections in COVID-19. It is high time to develop a standard method for diagnosing these infections. It seems that among fungi, the role of *Aspergillus* and *Candida* species has been mentioned more in COVID-19. Standard prophylactic strategies in high-risk COVID-19 patients, such as patients receiving immunosuppressive therapy, patients with underlying medical conditions, patients admitted to the intensive care unit, and those receiving invasive mechanical ventilation, may reduce fungal infections in these people.

Ethical Considerations

All ethical considerations were followed in compiling this work.

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Conflicts of interest

We declare no conflict of interest.

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Authors' Contributions

A.K and M.T.S both performed sample collection, data curation, data analysis and wrote the manuscript draft, edited and approved the final manuscript.

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