The urge for early detection and effective therapy against COVID-19 fungal co-infection: A retrospective study

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Abstract
A conspicuous feature of COVID-19 is that the disease has become a pandemic in less than three months. Suppression of immune system, particularly reduction in CD4+T cells and CD8+T cells has led to co-infection by other microbial pathogens. Among them, fungal co-infections are rarely identified and often ignored. Fungal co-infection has also been reported in MERS, SARS-CoV-1 and other viral infections as influenza. But from the reports of COVID-19, most cases of the fungal infections were observed to be fatal. This raises a serious concern on fungal pathogens causing co-infection in COVID-19. The fungal pathogens causing co-infections were found to be Aspergillus sp., Candida sp., Saccharomyces cerevisiae, Pneumocystis jirovecii, Histoplasma capsulatum, Cryptococcus sp., Coccidioides sp. and Mucormycetes. The unidentified and untreated infection leads to death of the patient. Researchers all over the world are facing several difficulties in identifying and diagnosing fungal co-infections, as early detection and proper treatment can increase the chances of patient survival. The current review summarizes the occurrence of fungal co-infection among COVID-19 patients. The immunological imbalance, diagnosing methods and detailed explanation on fungal pathogens and combination therapy are discussed.

1. Introduction
In December 2019, the coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China. It quickly spread across mainland China, posing a global challenge. Despite the global containment and promising preventive steps like quarantine efforts and isolation measures, the infection rate of cases about the disease’s epidemiological and clinical characteristics has skyrocketed with no approved antiviral drugs available commercially to prevent or treat serious COVID-19 patients (Zhu et al., 2020). Several collective clinical symptoms of the infection have been documented, including dry cough, corryza, myalgia, sore throat, fatigue and dyspnea. However, reports of unusual symptoms and signs have also been observed. In severe cases, malfunctioning of respiratory organs develops, leading to acute respiratory distress syndrome (ARDS), which is characterised by multiorgan failure that affects kidney and cardiac function, as well as death (Li et al., 2020). The causative pathogen, extreme acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) has infected 15,36,32,236 people worldwide and killed 32,15,270 people as of May 4, 2021 (www.cdc.gov).

A conspicuous feature is that COVID-19 has become pandemic in less than three months. The key risk factors for severity and mortality in COVID-19 are older age, diabetes, hypertension, cardiovascular disease and chronic obstructive pulmonary disease. Modern medicine has aided in the prompt detection of SARS-CoV-2, formerly known as the 2019 novel coronavirus and also the discovery of new therapies for SARS-CoV-2, such as lopinavir/ritonavir, chloroquine/hydroxychloroquine, and Remdesivir (Zhang et al., 2020). However, many problems remain unsolved, including a viable strategy for preventing disease dissemination, the collection of suitable clinical samples, the transmission path, viral dynamics, and successful drug therapies. The risk of co-infection with other microbial pathogens resulted in uncertainty of the patients survival. This, however, should be a major concern for clinicians dealing with COVID-19 (Wu et al., 2020).

Researchers all over the world have been facing several difficulties in identifying and diagnosing fungal co-infections. Hence, early detection and effective antifungal therapies to treat fungal infections have acquired a lot of attention in the fight against these important (but often ignored) diseases on a global scale. Furthermore, the treatment of fungal infection costs thousands of dollars per year in both the public and private sectors, which has a significant effect on the economy of healthcare systems around the world (Peng et al., 2021). On analysing all the evidences, the current review focuses on a summary and severity of fungal infections identified in COVID-19 positive patients till now with an emphasis on combination therapy in these patients.

1.1 Co-infection in influenza, SARS and Middle East respiratory syndrome (MERS)
Since co-infections are a common and serious complication of influenza, and it is difficult to rule out the presence of co-infection in a patient with community-acquired pneumonia (CAP) who tests positive for influenza, the American thoracic society (ATS) and the infectious diseases society of america (IDSA) recently released CAP guidelines that recommended initial antimicrobial treatment for adults with CAP who test positive for influenza. Co-infection of bacterial/fungal pathogens has been observed in MERS and SARS-CoV-1 infections, according to previous reports on serious coronavirus
infections (Metlay et al., 2019). In a retrospective analysis, 28% of reports mentioned co-infection in SARS-CoV-2, 6% among MERS, and 17% among other coronaviruses. It is well understood that bacterial and fungal co-infections exacerbate viral respiratory infections (influenza), and the SARS outbreak was marked by a high rate of nosocomial transmission of drug-resistant microorganisms (Rawson et al., 2020). These findings elaborated the co-infection of bacterial/fungal pathogens with coronaviruses and other respiratory pathogens (Yap et al., 2004).

1.2 Co-infection in COVID-19

Until now, the care guidelines for possible co-infections in COVID-19 positive patients have been based on the initial guidelines for treating co-infections in patients with serious flu. However, because the clinical entities capable of causing co-infections are expected to be the same for both extreme acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections (Schauwvlieghe et al., 2018), this is an observational assumption. All patients from a Wuhan hospital received empirical antimicrobial treatment, while 93% received antiviral therapy, according to an early analysis on COVID-19 infections in China (Huang et al., 2020). According to another report from the Wuhan experience, antiviral, antifungal and antibacterial agents were given to 76%, 15% and 71% of COVID-19 patients, respectively (Chen et al., 2020). Since the majority of COVID-19 patients in hospitals are receiving intensive medical treatment, such as intubation or mechanical ventilation, they are at risk of contracting hospital infections. Broad-spectrum antibiotics were administered in 75% of COVID-19 infected patients admitted to intensive care units (ICU) in accordance with this statement. According to the overall meta-analysis, 50% of COVID-19 infections had co-infection, and 8% had co-infection during hospitalisation (Cox et al., 2020).

In COVID-19 patients with predisposing factors, the frequency of opportunistic fungal infections is significantly higher (e.g., diabetes, mechanical ventilation and cytokine storm). However, owing to the COVID-19 patients’ complex medical conditions and the improper collection of clinical specimens, the vast majority of fungal infections in this community of patients are misidentified. The presence of fungal co-infection in COVID-19 patients has been shown to have a significant impact on hospitalisation time, disease duration, and mortality (Hughes et al., 2020). In support of this assertion, the researchers have seen an increase in evidence of secondary invasive fungal infections, which result in poor patient outcomes and, as a result, high mortality rates. As a result, this vital fact necessitates a rush to concentrate on various aspects of this emerging disease. Several studies with Aspergillus sp. co-infection with COVID-19 were published, similar to previous findings that showed an association between influenza and invasive pulmonary aspergillosis (Huang et al., 2019).

1.3 Necessity for diagnosis of fungal co-infection and techniques

Some fungal diseases have symptoms that are similar to COVID-19, such as fever, cough, and shortness of breath. Critically ill patients, especially those admitted to the intensive care unit (ICU) who needed mechanical ventilation, or those who had longer hospital stays, even up to 50 days, were more likely to develop fungal co-infections (Yang et al., 2020). These fungal co-infections are becoming more common, and they have been linked to serious illness and death. It is important to be aware of the risk of fungal co-infection in order to minimise diagnostic and treatment delays and help avoid serious illness and death from these infections. As a result, it is important to remember that COVID-19 patients, especially those who are seriously ill, may develop new fungal infections in the middle and later stages of the disease. To determine whether a person has a fungal co-infection with COVID-19, laboratory testing is needed (Gangneux et al., 2020). Histopathology, microscopic observation, and culturing are the traditional methods of diagnosis. These methods can pose unpredictable biosafety risks because the related specimens cannot be inactivated; hence, advanced methods such as molecular identification and serological tests must be used instead (Wang et al., 2020). The identification of blood samples using molecular analysis (qPCR technique) was found to be effective. Serological assays for fungal antigens, such as (1,3)-b-D-glucan (G), galactomannan (GM), and mannan (Mn) tests are often used to diagnose fungal infection (Salehi et al., 2020). If, the result of preliminary findings are positive, a confirmation step is performed with blood biomarkers, such as serum galactomannan and/or serum beta-D-glucan and/or cryptococcal antigenemia for fungal pathogens. The specificity of the G test in invasive Candida and Aspergillus infection is 70%-80%, and the specificity of serum GM detection ranges from 70% to 80%. Mannan detection has a specificity of 93%. The specificity of combined mannan antigen and antibody detection can be increased to 83% to 86% (Ahmad and Khan, 2012).

1.4 Immunosuppression paves way for fungal co-infection

The angiotensin-converting enzyme 2 receptor, which is highly expressed on alveolar epithelial cells as well as heart, kidney and intestinal cells, allows SARS-CoV-2 to reach target cells. In the response to viral infections, a variety of innate immune cells (neutrophils and monocytes) and adaptive immune cells (particularly CD4+ T cells and CD8+ T cells) are involved and COVID-19 is no exception. SARS-CoV-2 has been shown to strongly activate the immune system, causing a “cytokine storm” of abnormal cytokine output, particularly in severe cases. Indeed, people with extreme COVID-19 had higher levels of pro-inflammatory cytokines and chemokines in their blood, as well as less T cells in their peripheral blood, possibly due to lymphocyte aggregation at the infection site (Mehta et al., 2020). This heightened immune response can destroy infected cells, but it can also worsen the disease and cause lung damage. It is worth noting that, in addition to respiratory symptoms, thrombosis and pulmonary embolism have been found in extreme COVID-19 patients. More research is required to identify the molecular players in SARS-CoV-2 pathogenesis, which could lead to the discovery of main targets for reducing or inhibiting the cytokine storm (Yuki et al., 2020).

Candida species and Pseudomonas aeruginosa can colonise mucous membranes and skin in healthy people, and antifungal and antibacterial defences are aided by both innate and adaptive immune cells. The main cellular players are neutrophils, macrophages, dendritic cells, and T- and B-lymphocytes. The first line of protection is the innate immune cells, and the release of inflammatory cytokines and chemokines causes neutrophils to be recruited from the peripheral blood (Jiang, 2016). Dendritic cells play a crucial role in triggering the adaptive immune response. CD4+ T helper cells are important adaptive immune cells, with Th17 being the most significant subtype. These cells primarily work at the lung mucosal barrier, producing/releasing interleukin-17 (IL-17), which aids in the
organisation of B and T cells into bronchus-associated lymphoid tissue, which is involved in secondary immune responses, as well as the release of antifungal b-defensins. Suppression of the immune system occurs among COVID-19 patients due to the decline in CD4 T and CD8 T cells. Patients with IL-17 synthesis or signalling deficiencies tend to be more vulnerable to fungal pathogens. As a result, the incidence and survivability are also reduced (Netea et al., 2015).

In the past, scientists believed that aspergillosis only affected people who had extremely compromised immune systems. However, aspergillosis is becoming more common in patients who do not have a compromised immune system but have serious viral respiratory infections, such as influenza (Lamothe and Calandra, 2018). The activation of antiviral immunity in infected patients host tissue (the lungs are the most commonly affected organs in COVID-19 positive patients) can provide a favourable environment for the establishment, growth, and development of various microorganisms. In persons with active infection induced by the human immunodeficiency virus (HIV), extreme flu, and COVID-19, for example, a significant rise in fungal infections (e.g., candidiasis, aspergillosis, cryptococcosis, pneumocystosis, histoplasmosis) has been identified (Huang et al., 2020).

1.5 Fungal infections associated with COVID-19

1.5.1 Aspergillosis

COVID-19 progression, like extreme flu, causes acute respiratory distress syndrome (ARDS), which puts patients at risk for secondary pulmonary aspergillosis. *Aspergillus* sp., a filamentous fungus found all over the world, causes this infection. Since *Aspergillus* spores are commonly found in the atmosphere, they can easily penetrate the airway system and, as a result, invade human lung tissue and/or paranasal sinuses via inhalation. *Aspergillus* induces a broad variety of infections with a wide range of clinical symptoms, from localised to disseminated disease (Kosmidis and Denning, 2015). Invasive aspergillosis, for example, often affects highly immunocompromised patients as a result of organ transplantation, cancer treatment (due to chemotherapy and/or radiotherapy), neutropenia, and long-term corticosteroid treatment. Furthermore, allergic aspergillosis (e.g., allergic bronchopulmonary aspergillosis, or ABPA) has been linked to asthma exacerbation and bronchitis in people with hyperactive immune systems, as well as cystic fibrosis patients. Even, if detected early and treated with antifungal medication, invasive aspergillosis caused by *Aspergillus* species (e.g., *Aspergillus fumigatus, Aspergillus niger, Aspergillus flavus, Aspergillus terreus*) has a mortality rate of 30 to 95% (Brown et al., 2012).

In people with serious COVID-19, scientists are still investigating aspergillosis. Patients with severe COVID-19 are more likely to develop CAPA (COVID-19 related pulmonary aspergillosis). Since patients may have non-specific symptoms and testing usually involves a specimen from deep inside the lungs, it may be difficult to diagnose. Long-term illness may often turn fatal. Even, if patients with extreme COVID-19 who have deteriorating respiratory function or sepsis do not have classical risk factors for aspergillosis, clinicians should consider the likelihood of aspergillosis. CAPA is diagnosed by taking samples from a patient’s lower respiratory tract and testing them for *Aspergillus* sp. galactomannan antigen and fungal culture (Wang et al., 2020).

CAPA has been recorded in several recent studies. According to some Chinese reports, COVID-19 patients have a high rate of aspergillosis (Arastehfar et al., 2020). In a retrospective analysis from a Wuhan ICU, *Aspergillus flavus* and *Aspergillus fumigatus* were isolated from respiratory tract secretions in two out of every seven (28.6%) patients with hospital-acquired pneumonia (Yang et al., 2020). In another retrospective study of 85 fatal cases of COVID-19 performed in two Wuhan hospitals, fungal cultures obtained from sputum obtained from 9 patients were confirmed positive in 33.3% of cases, with 8 (9.4%), 3 (3.5%), and 2 (2.4%) patients receiving voriconazole, fluconazole, and caspofungin, respectively (Du et al., 2020). However, fungal infections were poorly described in all of the Chinese reports, making it difficult to draw any conclusions. Table 1 shows the detailed case reports of patients coinfected with aspergillosis and severity based on recovery status.

1.5.2 Candidiasis

As a consequence of compromised immune system functions, fungal infections caused by yeasts may also occur in patients with ARDS, like COVID-19. Invasive candidiasis is a serious healthcare-associated fungal infection that causes high mortality rates. It is caused by a variety of opportunistic *Candida* species, the most common of which is *Candida albicans* and *Candida tropicalis*. Patients admitted to the hospital for COVID-19 are at risk for healthcare-associated infections (HAIs), such as candidemia, or *Candida*-related bloodstream infections. In patients with extreme COVID-19, fungal infections resistant to antifungal treatment have also been reported. In patients with serious COVID-19 fungal co-infections, early detection and surveillance for *Candida* infections and antifungal resistant infections (e.g., *Candida auris*, azole-resistant *Aspergillus*) are critical to reducing death from COVID-19 (Pappas et al., 2018).

During COVID-19 pandemic in New York City, USA, *Candida* sp. was one of the most commonly detected fungi in the bloodstream of patients using central venous catheters. The majority of *Candida* species recovered from COVID-19 patients, according to recent reports, came from the oropharynx. Oropharyngeal candidiasis is a localised mucous membrane infection characterised by oral epithelial cell invasion and destruction (Nori et al., 2021). During the first COVID-19 pandemic, *Candida* spp. and other yeasts were isolated from the respiratory tract in 21.4% of positive cases of co-infection in two hospitals in the United Kingdom (21.4%) (Hughes et al., 2020).

A retrospective research in Italy looked at the respiratory specimens of COVID-19 patients in the intensive care unit. The results revealed that nearly 52% of the specimens tested positive for bacteria and fungi (*Candida albicans* and *Candida glabrata*) (Intra et al., 2020). Furthermore, the authors of an Iranian study found that *Candida albicans* was the most common, followed by *Candida glabrata* (10.7%), *Candida dubliniensis* (9.2%), *Candida parapsilosis sensu stricto* (4.6%), *Candida tropicalis* (3%), and *Pichia kudriavzevii* (C. krusei, 1.5%) (Salchi et al., 2020). Table 2 shows the prevalence of candidiasis among COVID-19 cases, as well as the severity of the infection based on the patients’ recovery status.
### Table 1: COVID-19 cases co-infected with Aspergillosis

<table>
<thead>
<tr>
<th>Study</th>
<th>City/country</th>
<th>No. of patients</th>
<th>Fungal co-pathogen</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koehler et al., 2020</td>
<td>Cologne, Germany</td>
<td>5/19</td>
<td>Aspergillus fumigatus</td>
<td>2 alive; 3 died</td>
</tr>
<tr>
<td>Lamoth et al., 2020</td>
<td>Lausanne, Switzerland</td>
<td>3/80</td>
<td>Aspergillus fumigatus</td>
<td>2 alive; 1 died</td>
</tr>
<tr>
<td>Meijer et al., 2020</td>
<td>Nijmegen, The Netherlands</td>
<td>1</td>
<td>Aspergillus fumigatus</td>
<td>Died</td>
</tr>
<tr>
<td>García Clemente et al., 2021</td>
<td>Oviedo, Spain</td>
<td>2</td>
<td>Aspergillus fumigatus and Aspergillus nidulans</td>
<td>2 alive</td>
</tr>
<tr>
<td>Nasri et al., 2020</td>
<td>Isfahan, Iran</td>
<td>1</td>
<td>Aspergillosis</td>
<td>Died</td>
</tr>
<tr>
<td>Trovato et al., 2021</td>
<td>Catania, Italy</td>
<td>1</td>
<td>Aspergillus niger</td>
<td>Died</td>
</tr>
<tr>
<td>Santana et al., 2020</td>
<td>Mansus, Brazil</td>
<td>1</td>
<td>Aspergillus penicilliodes</td>
<td>Died</td>
</tr>
<tr>
<td>Nasir et al., 2020</td>
<td>Karachi, Pakistan</td>
<td>9/23</td>
<td>Aspergillosis</td>
<td>4 alive; 5 died</td>
</tr>
<tr>
<td>Alanio et al., 2020</td>
<td>Paris, France</td>
<td>2</td>
<td>A. fumigatus</td>
<td>2 died</td>
</tr>
<tr>
<td>Prattes et al., 2021</td>
<td>Graz, Austria</td>
<td>1</td>
<td>A. fumigatus</td>
<td>Died</td>
</tr>
<tr>
<td>Lescure et al., 2020</td>
<td>Paris, France</td>
<td>1</td>
<td>A. flavus</td>
<td>Died</td>
</tr>
<tr>
<td>Rutsaert et al., 2020</td>
<td>Antwerp, Belgium</td>
<td>6</td>
<td>A. fumigatus</td>
<td>3 death; 3 alive</td>
</tr>
<tr>
<td>Van Arkel et al., 2020</td>
<td>Breda, Netherlands</td>
<td>6</td>
<td>A. fumigatus</td>
<td>2 alive; 4 died</td>
</tr>
<tr>
<td>Antinori et al., 2020</td>
<td>Milan, Italy</td>
<td>1</td>
<td>A. fumigatus</td>
<td>Died</td>
</tr>
<tr>
<td>Lahner et al., 2020</td>
<td>Munich, Germany</td>
<td>2</td>
<td>A. fumigatus</td>
<td>2 died</td>
</tr>
</tbody>
</table>

Source: Pubmed and web of knowledge (case reports published till April, 2021).

### Table 2: COVID-19 cases co-infected with Candidiasis

<table>
<thead>
<tr>
<th>Study</th>
<th>City/country</th>
<th>No. of patients</th>
<th>Fungal co-pathogen</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seitz et al., 2020</td>
<td>Vienna, Austria</td>
<td>1</td>
<td>Candida glabrata</td>
<td>Died</td>
</tr>
<tr>
<td>Agrifoglio et al., 2020</td>
<td>Madrid, Spain</td>
<td>21/139</td>
<td>Candidiasis</td>
<td>12 alive; 9 died</td>
</tr>
<tr>
<td>Posteraro et al., 2020</td>
<td>Rome, Italy</td>
<td>1</td>
<td>Candida glabrata</td>
<td>Died</td>
</tr>
<tr>
<td>Sari et al., 2021</td>
<td>Jakarta, Indonesia</td>
<td>1</td>
<td>Candida tropicalis</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Source: Pubmed and web of knowledge (case reports published till April, 2021).

### Table 3: COVID-19 cases co-infected with Saccharomyces infection

<table>
<thead>
<tr>
<th>Study</th>
<th>City/country</th>
<th>No. of patients</th>
<th>Fungal co-pathogen</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventoulis et al., 2020</td>
<td>Ptolemaida, Greece</td>
<td>2</td>
<td>Saccharomyces cerevisiae</td>
<td>2 alive; 0 died</td>
</tr>
<tr>
<td>Amorim dos Santos et al., 2020</td>
<td>Brasilia, Brazil</td>
<td>1</td>
<td>Saccharomyces cerevisiae</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Source: Pubmed and web of knowledge (case reports published till April, 2021).

1.5.3 Saccharomyces infection

One of the fungal pathogens found to co-infect is *Saccharomyces cerevisiae*. However, there are only a few reports on Saccharomyces co-infection, and the severity was found to be mild. Anidulafungin and fluconazole were the most common antifungal drugs used. The organism was discovered to be a poor pathogen, and no deaths have yet been recorded (Nori et al., 2021). Table 3 shows the prevalence of Saccharomyces infection among COVID-19 cases, as well as the severity of the infection based on the patients' recovery status.

1.5.4 Pneumocystis

Pneumocystis pneumonia, one of the most common opportunistic fungal infections associated with acquired immunodeficiency syndrome (AIDS) patients, has long been linked to other immunodeficiencies (White et al., 2018). Pneumocystis pneumonia is caused by a fungal pathogen *Pneumocystis jirovecii*. COVID-19 and *Pneumocystis pneumonia* have similar clinical characteristics, but this fungal infection is often misdiagnosed. In a case reported by Mang et al., 2020, *Pneumocystis pneumonia* was diagnosed in a German patient after a chest tomography, revealed slight reticular changes. The presence of *Pneumocystis jirovecii* in the bronchoalveolar lavage fluid was verified, and the patient was given intravenous trimethoprim-sulfamethoxazole (20 mg/kg/day of trimethoprim) and 50 mg of prednisone (a corticoid drug) daily to prevent adverse immune reactions. Table 4 shows the prevalence of Pneumocystis among COVID-19 cases, as well as the severity of the infection based on the patients recovery status.
Table 4: COVID-19 cases co-infected with Pneumocystis

<table>
<thead>
<tr>
<th>Study</th>
<th>City/country</th>
<th>No. of patients</th>
<th>Fungal co-pathogen</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta and Pandey, 2020</td>
<td>Mumbai, India</td>
<td>1</td>
<td>Mucormycosis</td>
<td>Died</td>
</tr>
<tr>
<td>Basso et al., 2021</td>
<td>Rio Grande, Brazil</td>
<td>1</td>
<td>Histoplasma capsulatum</td>
<td>Alive</td>
</tr>
<tr>
<td>Shah et al., 2020</td>
<td>CA, USA</td>
<td>1</td>
<td>Cryptococcus neoformans</td>
<td>Died</td>
</tr>
<tr>
<td>Khatri et al., 2021</td>
<td>NY, USA</td>
<td>1</td>
<td>Coccidiomycosis</td>
<td>Died</td>
</tr>
<tr>
<td>Waizel-Haiai et al., 2021</td>
<td>Mexico City, Mexico</td>
<td>1</td>
<td>Mucormycosis</td>
<td>Died</td>
</tr>
</tbody>
</table>

Source: Pubmed and web of knowledge (case reports published till April, 2021).

Table 5: COVID-19 cases co-infected with other fungal pathogens

<table>
<thead>
<tr>
<th>Study</th>
<th>City/country</th>
<th>No. of patients</th>
<th>Fungal co-pathogen</th>
<th>Patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menon et al., 2020</td>
<td>Massachusetts, United states</td>
<td>1</td>
<td>Pneumocystis jirovecii</td>
<td>Alive</td>
</tr>
<tr>
<td>Jeican et al., 2021</td>
<td>Cluj-Napoca, Romania</td>
<td>1</td>
<td>Pneumocystis jirovecii</td>
<td>Died</td>
</tr>
<tr>
<td>De Francesco et al., 2020</td>
<td>Brescia, Italy</td>
<td>1</td>
<td>Pneumocystis jirovecii</td>
<td>Died</td>
</tr>
</tbody>
</table>

Source: Pubmed and web of knowledge (case reports published till April, 2021).

1.5.5 Other fungal co-infection

Symptoms of fungal pneumonias can resemble COVID-19. Fever, cough, and shortness of breath are symptoms of other fungal infections, such as Valley fever (Coccidioidomyces), histoplasmosis, and blastomycosis, which are related to COVID-19 and bacterial pneumonias. These fungi can only be found in soil. People are affected by inhaling fungi that are found in the air. If COVID-19 testing is negative, clinicians may accept fungal pneumonias as a potential cause of respiratory illness. It is worth noting that these fungal infections may happen at the same time as COVID-19 (Bertolini et al., 2020; Shah et al., 2020).

Fungal infections like Cryptococcosis and Mucormycosis were also discovered. In a retrospective analysis, 94.2% of COVID-19 patients were co-infected with one or more respiratory microbial pathogens. Six cases of *Mucor* (2.5%) and two cases of *Cryptococcus* (0.8%) were found in COVID-19 infected patients, in addition to the common cases of Aspergillus and Candida species. Fungal infection was found in 29.5% of all co-infected cases in that study (Zhu et al., 2020). Table 5 shows the prevalence of other fungal infection among COVID-19 cases, as well as the severity of the infection based on the patients recovery status.

1.6 Combination therapy with antifungal antibiotics and its complications

The initial recommendations for the treatment of possible co-infections in the ATS/IDSA CAP treatment guidelines were made for influenza. Since SARS-CoV-2 infections may have a common clinical entity of co-infection, this recommendation has been used in the treatment of COVID-19 infections and has been documented in previous studies on SARS-CoV-2 infections in China. Beyond the difficulties of treating critically ill patients with a single dangerous infection, such as COVID-19 (for which there are currently no effective drugs), treating critically ill patients with two potentially fatal infections is much more difficult. This situation is exacerbated in the COVID-19 infection scenario, if the co-infection is caused by fungi, since the antifungal arsenal is severely reduced, resulting in dangerous drug interactions, high toxicity, and serious and severe side effects, such as kidney or liver injury.

COVID-19 reports show that a serious viral infection can damage multiple organs on its own (e.g., liver, kidney, and heart). When multiple infections were present, such safety issues were even more troublesome. In particular, when COVID-19 patients are combined with fungal infections, particularly those caused by multidrug-resistant strains, the situation can become more complicated. Several evolving fungal pathogens have been found to have novel resistance patterns, making available antifungal drugs ineffective in treating these infections, resulting in a classic therapeutic failure (Silva et al., 2019). Antifungal resistance can develop after prolonged clinical exposure to previously active new triazoles (such as posaconazole, voriconazole, and isavuconazole) or echinocandins (such as caspofungin, anidulafungin, and micafungin), resulting in therapy failures. This phenomenon has been reported in the literature and can occur in patients who have been taking antifungal medications for a long time. Therefore, combination therapy with antifungal agents could reduce the severity and prevents from mortality (Chowdhary et al., 2017; Perlin, 2015).

Another factor to consider is the possibility of drug-drug reactions during treatment. For COVID-19 therapy, a variety of medications are currently being studied or used empirically. Many studies highlight the drugs tocilizumab, an interleukin (IL)-6 receptor blocker, and glucocorticoids, which are widely used to inhibit intense and dangerous inflammatory processes. Over-suppression of the immune system, on the other hand, has been shown to favour the emergence of opportunistic fungal infections. In this sense, some reports indicate that tocilizumab should be used with caution in COVID-19 patients because the disease can be exacerbated by it, resulting in complicated pneumonia cases or candidemia episodes. Similarly, other immunomodulatory drugs in development for COVID-19, such as anakinra (recombinant IL-1Ra) and janus kinase (JAK) inhibitors, can predispose patients to pulmonary aspergillosis (Antinori et al., 2020a; Morena et al., 2020).

Antifungal therapeutic failure can be traced back to improper specimen sampling, a scarcity of standard equipment for microbiological analyses, a lack of early identification of fungal elements in contaminated tissue, and a lack of specialist practitioners to accurately
diagnose the fungal agent (many clinicians disregard fungal infections). Regrettably, this practical picture could have a significant effect on the rising number of COVID-19 positive patients who succumb to fungal infections. In ICU patients with serious COVID-19 associated pneumonia, efforts should be made to investigate cases as quickly as possible to maintain or rule out a diagnosis of invasive fungal infections. Patients with pre-existing risk factors, especially those with organ transplant (SOT) recipients, should be given special consideration. Furthermore, since most mycological parameters lack precision but are critical in the diagnosis of fungal superinfections in the ICU, they should be multiplied and carefully examined to avoid overdiagnosis and antifungal therapy overuse (Arastehfar et al., 2020; Cox et al., 2020).

2. Conclusion
Most importantly, when secondary fungal infections are suspected, effective antifungal therapy should be started as soon as possible. Continuous monitoring of COVID-19 patients at described risk factors should be performed for early detection and development of fungal co-infections. Since there are only a few groups of systemic antifungal agents, the global emergence of antifungal resistance in fungal pathogens has made treatment more difficult. As most of the fungal co-infections reported are lethal, the continuous monitoring and effective antifungal therapy could save lives of several patients.

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Conflict of interest
The author declares that there are no conflicts of interest relevant to this article.

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