Predisposing factors of important invasive fungal coinfections in COVID-19 patients: a review article

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Abstract

Severe acute respiratory syndrome coronavirus-2 has caused a devastating pandemic lasting for more than a year. To date, 47 million individuals have been infected and 1.2 million individuals have died worldwide. Some of the most important coinfections in patients with coronavirus disease 2019 (COVID-19) are opportunistic invasive fungal infections (OIFIs), which are sometimes not rapidly diagnosed and are often diagnosed after death. Aspergillosis and candidiasis are the most prevalent OIFIs in patients with COVID-19. Mycormycosis, cryptococcosis, and other fungal diseases have also been documented more rarely. This review aimed to summarize factors affecting COVID-19 transmission, prevalence, morbidity, and mortality in Iran as well as to review common OIFIs in patients with COVID-19. Immunological factors, underlying diseases, and social, cultural, and environmental factors can affect COVID-19 transmission. There is a need to improve diagnostic and therapeutic criteria for OIFIs and to optimize management procedures so that patients with OIFIs can receive treatment as rapidly as possible. Screening of patients with confirmed COVID-19 for OIFIs at the treating physician's discretion could enable early OIFI diagnosis, treatment, and mortality reduction.

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Introduction

Coronaviruses

Coronaviruses are a large group of RNA viruses that can cause infections in humans, birds, bats, snakes, mice, and other animals. The seven human coronaviruses identified to date are 229E, OC43, NL63, HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus, and SARS-CoV-2. The lattermost three coronaviruses are highly pathogenic and human infections have high case fatality rates. The disease caused by SARS-CoV-2 infection is called coronavirus disease 2019 (COVID-19). Lower and upper respiratory infection with this virus can be asymptomatic or produce mild symptoms. However, in some patients infection results in acute respiratory distress syndromes (ARDS) requiring critical care and mechanical ventilation.[1–4] SARS-CoV-2 is an enveloped RNA betacoronavirus that was first identified in Wuhan by the Chinese Center for Disease Control and Prevention.[5,6]

Symptoms of COVID-19

In a study of 99 Chinese patients with COVID-19, the most common symptoms were fever (83%), cough (82%), shortness of breath (31%), muscle ache (11%), confusion (9%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (25), diarrhea (2%), and nausea and vomiting (1%). The majority (89%) of patients had more than one symptom and 15% simultaneously experienced fever, cough, and shortness of breath.[7] Most patients experienced at least one of fatigue, muscular weakness, sleep difficulties, anxiety, depression, and cognitive impairment following recovery.[8] Approximately 11% of patients required acute medical care.[9] Loss of sense of smell and taste may also occur (Figure 1).

SARS-CoV-2 transmission routes

SARS-CoV-2 can spread from an infected individual to others 2 days (range: 1–3 days) before the onset of symptoms (presymptomatic stage). Infected individuals who later develop symptoms are defined as being presymptomatic. Asymptomatic transmission occurs more often than symptomatic transmission.[10–12] Asymptomatic individuals play an important role in the spread of the virus. Direct transmission of the virus occurs through expulsion of small respiratory droplets from the nose or mouth of an
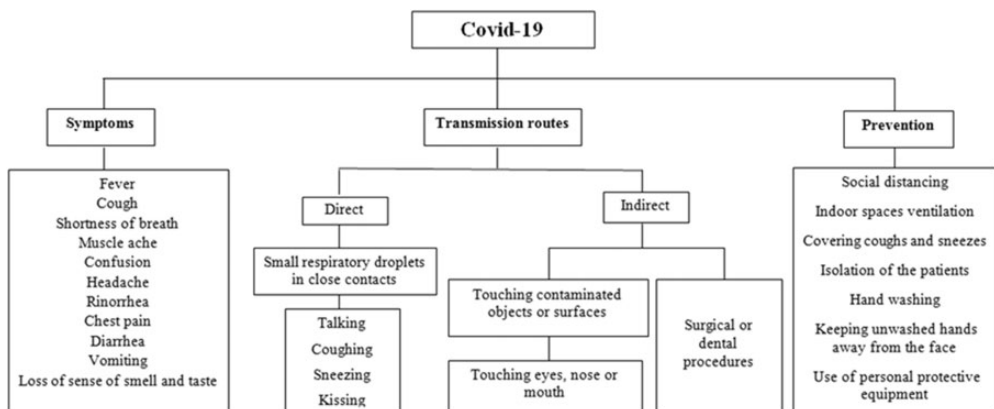

Figure 1. Overview of the symptoms, transmission routes, and prevention of COVID-19.

infected individual while talking, coughing, or sneezing. These droplets can land on objects and surfaces surrounding the infected individual. Indirect transmission occurs by touching contaminated objects or surfaces and then touching the eyes, nose, or mouth. SARS-CoV-2 has been detected in the eyes, nasopharynx, saliva, alveolar lavage fluid, blood, semen, intestine, and feces.[9,13] It should be noted that although live virus has been isolated from saliva and stool, and viral RNA has been detected in sperm and blood, there has been no confirmed report of transmission of the virus through feces, blood, or sexual contact.[14] The number of people infected on average by a single infected individual varies (Figure 1).

COVID-19 status in Iran

Since the outbreak of the COVID-19 pandemic in December 2019 in Wuhan, more than 110 million individuals have been infected and more than 2.45 million have died (mortality rate 2.21%). The first official report of a SARS-CoV-2 outbreak in Iran was on 19 February 2020. Although patients with COVID-19 symptoms were referred to medical centers before this date, cases were not identified because of unfamiliarity with the disease. By 25 May 2020, 133,521 confirmed COVID-19 cases and 7359 deaths (mortality rate 5.52%) had occurred in Iran.[15] Since the beginning of the outbreak, the highest number of daily deaths occurred on 3 November 2020 (440 deaths). According to the official news in Iran, on 3 November 2020 the number of cases had reached 628,780 with 35,738 deaths. At the time of writing this article (19 February 2021), the number of cases had reached 1,558,159 with 59,341 deaths (mortality rate 3.81%), and the number of new cases and deaths per 24 hours had exceeded 8017 and 77, respectively (daily mortality rate 0.96%). These data suggest a decrease in mortality following the initial period of the pandemic (from 5.52% to 3.81%). The fatality rate has varied by location and over time (e.g., mortality of 0.2% in Germany versus 7.7% in Italy). Elderly patients are at increased risk of mortality.[3]

According to the latest census, the population of Iran is more than 80 million people. Public health education, social distancing, restriction of intra- and inter-city traffic, restriction of non-essential working hours, virtual training of students, and contact management are among the policies implemented to prevent the spread of COVID-19 in Iran. More than 5000 patients with COVID-19 (about 1% of cases) were hospitalized in critical condition. However, the true number of cases is probably higher than the reported number because many patients are asymptomatic and some patients do not present at medical centers for various reasons. Because of the lack of screening tests in medical centers, many carriers of the virus are not identified. Close contact with infected individuals as well as failure to comply with hygiene practices are pivotal factors promoting further spread of the virus in Iran.

Prevention strategies for COVID-19

Social distancing, ventilation of indoor space, covering the mouth when coughing or sneezing, case isolation, hand washing, avoiding touching the face, and use of personal protective equipment are essential to reduce the risk of transmission.[9] Analysis of increases and decreases in morbidity and mortality show that these rates are strongly dependent on social and health behaviors (Figure 1).

Immunity to SARS-CoV-2 and predisposing risk factors for COVID-19

COVID-19 causes damage to the pulmonary epithelium and elicits inflammatory

reactions, both of which are predisposing risk factors for opportunistic invasive fungal infections (OIFIs).[16] The virus invades epithelial cells and type II pneumocytes following binding of the SARS-CoV-2 spike protein to angiotensin-converting enzyme 2.[13,16,17]

CD4+ T-cells play pivotal roles in regulating immune responses and stimulation of Immune cells, especially CD8+ T-cells. CD4+ T-cells facilitate virus-specific antibody production via T-dependent activation of B cells. CD8$^+$ T-cells exert their effects mainly through two mechanisms: cytolytic activities against target cells and secretion of cytokines and chemokines such as interferon γ (IFN-γ), tumor necrosis factor alpha (TNF-α), and interleukin-2 (IL-2).[6]

CD8+ T-cell dysfunction, combined with an increase in levels of epithelial cytokines, affects the functions of dendritic cells and macrophages.[18] Most patients with COVID-19 have mild symptoms, but some may experience ARDS following a cytokine storm.[19] Patients with severe COVID-19 have higher levels of pro-inflammatory cytokines such as IL-2, soluble IL-2 receptor, IL-6, TNF-α, decreased levels of anti-inflammatory cytokine levels such as IL-10, fewer CD4+ and CD8+ T-cells, and weaker IFN-γ production by CD4+ cells.[4]

COVID-19 patients may experience immunosuppression characterized by a decrease in natural killer cells, CD3$^+$ T cells, CD4$^+$ T cells, and CD8$^+$ T-cells. Decreases in CD8+ T-cells are more serious than decreases in CD4+ T cells, and therefore the CD4/CD8 ratio is significantly increased in these patients.[20] Critically ill patients, especially those admitted to intensive care units (ICUs), requiring mechanical ventilation, or with longer hospital stays up to 50 days, are more likely to develop OIFIs. Hence, it is important to remember that COVID-19 patients can develop OIFIs during the middle and latter stages of the disease, especially those with severe COVID-19.[21] Routine checks of CD4+ and CD8+ T-cell counts, similar to those performed for patients with human immunodeficiency virus infection, may be helpful for routine care of patients with COVID-19.

Increased production of IL-1 and IL-6 has been reported in patients with severe COVID-19. Similar changes have been observed following infections by *Aspergillus fumigatus*. Therefore, at least in some patients with COVID-19, changes in levels of these cytokines may be associated with OIFIs.[16] Up-regulation of IL-10 can further inhibit macrophage activity.[22]

Other factors such as administration of immunosuppressive agents, corticosteroids, and broad-spectrum antibiotics, ICU admission, intubation/mechanical ventilation, and surgery are associated with OIFIs.[23,24] Factors predisposing to fungal diseases are commonly observed in symptomatic patients with COVID-19 such as leukopenia (9%–25%), lymphopenia (35%–63%) and T-cell dysfunction[4] (Figure 2).

OIFIs

Filamentous fungi and yeasts are increasingly recognized as major clinical pathogens causing opportunistic infections in critically ill patients. Assessing the risk factors for hospital-acquired OIFIs, determining environmental factors associated with disease, and understanding changes in medical practices and the epidemiology of fungal diseases are all effective strategies for the prevention and treatment of OIFIs.[23] OIFIs are a significant cause of morbidity and mortality, particularly in immunocompromised patients.[22,25] Fungal co-infections have an unclear impact on the morbidity and mortality of COVID-19. In addition from *Aspergillus* infections, other fungal infections may occur more easily because
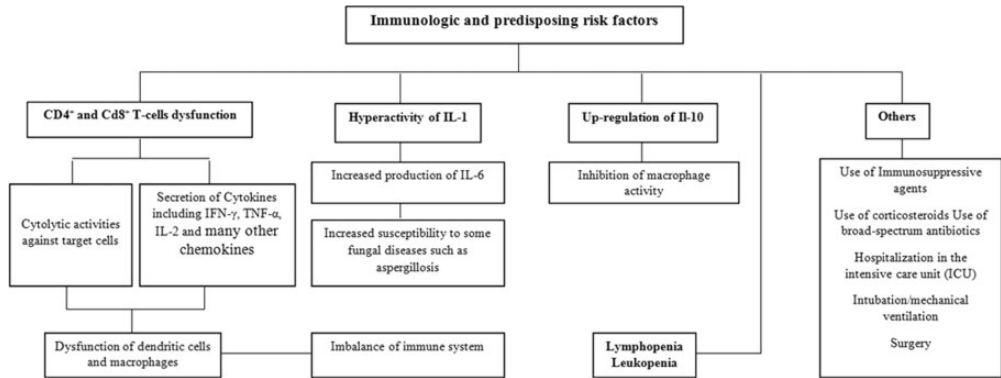
Figure 2. Immunological and predisposing risk factors for fungal co-infections in patients with COVID-19.

of immune dysregulation and the critical condition of these patients.[18] In France, OIFIs were associated with a high risk of mortality in patients with COVID-19 and comorbidities (mortality from 9.2% to 40% depending on the fungal pathogen).[24]

The main fungal pathogens responsible for fungal co-infections in patients with severe COVID-19 are *Aspergillus* and *Candida* species. Other infrequent opportunistic pathogenic fungi causing lung infections should also be considered, such as *Mucor* and *Cryptococcus* species.[21] In recent years, the incidence of fungal infections has reached alarming levels.[23] Co-infections by bacteria or fungi may be frequent complications of COVID-19. Independent reports from Chinese hospitals showed that 27 (96.4%) of 28 patients with fatal COVID-19 and 11 (16%) of 68 COVID-19 patients who survived had secondary infections.[26] A review article concluded that 8% of hospitalized patients with COVID-19 had secondary bacterial or fungal infections.[27] In a retrospective study, 257 patients with laboratory-confirmed COVID-19 were tested for respiratory pathogens; 242 (94.2%) patients were co-infected with one or more pathogens. The proportions of viral, fungal, and bacterial–fungal co-infections were the highest among patients with severe COVID-19. Sixty-nine of 257 patients had fungal co-infections; *Aspergillus* species (60 patients, 23.3%) were the most frequently identified pathogens followed by *Mucor* species (six patients, 2.5%), *Candida* species (two patients, 0.8%), and *Cryptococcus* species (one patient, 0.4%). Most co-infections occurred within 1 to 4 days of COVID-19 onset.[28] In a screening study, the prevalence of aspergillosis and yeast infections among patients with COVID-19 admitted to ICUs was 14.1% and 12.6%, respectively. The mortality rates were 53% and 31% among patients with and without OIFIs, respectively. Mortality rates were reduced by the use of antifungal therapies.[29] Up to 40% of patients with COVID-19 are hospitalized with ARDS and are therefore susceptible to opportunistic bacterial and fungal infections.[16] Patients with severe COVID-19 and immunodeficiency are more prone to develop OIFIs.[21] Evaluation of fungal infections in patients with COVID-19 and underlying disease is difficult and therefore careful examination and recording of patient characteristics is required.

Aspergillosis in patients with COVID-19

Members of the genus *Aspergillus*, especially *A. fumigatus*, are ubiquitous environmental pathogens in that are responsible

for a wide range of human fungal infections including invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, fungal asthma, and *Aspergillus* bronchitis. These infections can be fatal in immunocompromised individuals.[16] Serious viral pulmonary infections are associated with increased risks of fungal superinfections, including IPA in immunocompromised patients.[31] Respiratory viruses damage the airway epithelium as well as disrupt normal ciliary clearance, causing leukopenia and lymphopenia and resulting in transient defects in cellular immunity that may provide an opportunity for *Aspergillus* species to invade tissues.[4] Since the emergence of COVID-19, there have been warning signs regarding the impacts of secondary OIFIs in various parts of the world. Isolation of *Aspergillus flavus* from the respiratory tract of 1 of 99 patients in the first described group of patients with COVID-19 and *Aspergillus* species from 3.8% of critically ill patients in the second group was reported in Wuhan.[31] Although *Aspergillus* species can be isolated from septum and tracheal specimens in patients with COVID-19 and IPA, the fungus may also colonize the oropharyngeal area.[32] A recent study reported 38 cases of *Aspergillus* co-infection among patients with severe COVID-19 leading to ARDS. The authors stated that additional cases may not be diagnosed because of a lack of knowledge regarding clinical signs and limited access to diagnostic screening.[3] Accurate estimation of the prevalence of IPA among patients with COVID-19 admitted to ICUs is not possible; however, reported cases are expected to represent a subset of the true rate.[32]

A fatal case of probable IPA in a patient with acute myeloid leukemia patient infected with SARS-CoV-2 who developed ARDS was reported in Iran.[30] By June 2020, the prevalence of IPA among patients with COVID-19 admitted to ICUs in the Netherlands, France, and Germany was 19.4%, 33%, and 26%, respectively.[31,32] Reports from China indicate that fungal co-infections, including aspergillosis, occur in at least 10% of patients hospitalized with ARDs in ICUs.[34] The first case of azole-resistant COVID-19-associated invasive pulmonary aspergillosis (CAPA) was reported by Meijer et al. (2020) in an immunocompetent patient receiving ICU support with no previous history of azole therapy.[33] A strong association has been observed between multiple positive *Aspergillus* tests and use of high-dose systemic corticosteroids.[29] Because of the increase in reported cases of IPA in patients with COVID-19, physicians should pay special attention to the signs of this fungal co-infection.

Candidiasis and other rare invasive yeast infections in patients with COVID-19

Prolonged ICU stays, central venous catheters, and broad-spectrum antibiotic use are among the most important causes of invasive yeast infections in patients with COVID-19.[36] Studies have shown high prevalence of *Candida* infections among patients with COVID-19, so *Candida* species should be considered as potential pathogens in these patients.[34] *Candida* species reside on the mucosal surfaces of the skin as well as the respiratory, digestive, and urinary tracts. Members of the genus *Candida* are the most frequently recovered pathogens in ICUs, affecting between 6% and 10% of patients.[35] *Candida albicans* is the predominant species and is detected in 17% of patients hospitalized in ICUs. *C. albicans* infection is associated with significant morbidity and mortality. Infections by other species of the genus *Candida* are becoming more common, especially among neutropenic patients and patients receiving azole therapy.[23] The estimated mortality of invasive candidiasis is 19% to 40% but this can be

even higher (up to 70%) among ICU patients.[35] In a study from Iran, 65 *Candida* isolates were gathered from 53 patients with COVID-19 and oropharyngeal candidiasis. *C. albicans* (70.7%) was the most common pathogen detected, followed by *C. glabrata* (10.7%), *C. dubliniensis* (9.2%), *C. parapsilosis* (4.6%), *C. tropicalis* (3%), and *Pichia kudriavzevii* (also known as *C krusei*, 1.5%).[36] In a study from India, 15 critically ill patients with COVID-19 admitted to ICUs developed candidemia. *C. auris* was responsible for two-thirds of these infections, six of which were fatal (60%).[37] Another study found that most yeast infections in patients with COVID-19 (93.8%) were caused by members of the genus *Candida*. A case of fungemia caused by *Rhodotorula* was also reported.[38] Two male patients with COVID-19 and *Saccharomyces cerevisiae* bloodstream infection were reported; the patients were 76 and 73 years old. Both patients had arterial hypertension and one had diabetes. Both patients required ICU support for severe COVID-19 following *Saccharomyces* co-infection.[18]

Mucormycosis in patients with COVID-19

The *Mucorales* are important opportunistic fungal pathogens that can cause mucormycosis in immunocompromised patients. Dissemination of disease can often occur as a result of delayed diagnosis, and therefore rapid and accurate diagnosis is essential.[37] Weakened host defense is a major risk factor for pulmonary mucormycosis.[39] The incidence rate of mucormycosis is between 0.005 and 1.7 cases per million individuals and the fatality rate is about 46%. Infection is characterized by infarction and necrosis of host tissues. Mucormycosis is thought to be a secondary infection in susceptible hosts that results from inhalation of spores into the paranasal sinuses.[39,40] Diagnosis of mucormycosis is difficult but early diagnosis and treatment

are essential. In high-risk individuals, mucormycosis should be suspected if there is unilateral facial pain or swelling, orbital swelling, or proptosis.[40] Although the incidence of IPA in patients with COVID-19 is increasing, reported cases of mucormycosis are rare. Greg et al. (2021) reported a case of mucormycosis in a 55-year-old man with COVID-19. The patient had diabetes and end-stage kidney disease.[41] Khatri et al. (2021) reported a case of pulmonary and systemic mucormycosis in a patient with COVID-19 who had recently received a heart transplant. Approximately 3 months after diagnosis of COVID-19, he was diagnosed with cutaneous mucormycosis.[41] A case of mucormycosis was reported in a 60 year-old man with COVID-19 who was admitted to hospital with a 3-day of history severe breathlessness, pyrexia, tachypnea, and generalized malaise.[43] A case of pulmonary mucormycosis also occurred in a 52-year-old man. These reports highlight the difficulties in diagnosing mucormycosis and the importance of performing histological tests to enable early diagnosis and treatment of the disease.[39]

Cryptococcosis

Cryptococcosis is an invasive fungal infection caused by *Cryptococcus neoformans*, which is found worldwide. Disease typically occurs in immunocompromised patients. A case of cryptococcosis was reported in a 61-year-old male patient with a history of prostate cancer during an outbreak of COVID-19; the patient died following respiratory failure.[44] Zhu et al. (2020) also reported a case of *C. neoformans* in a patient with COVID-19.[28]

Diagnosis of OIFIs in patients with COVID-19

Bacterial, fungal, and viral secondary infections or co-infections affect COVID-19

mortality. Rapid and accurate diagnosis plays a crucial role in treatment outcome.[16] Invasive fungal diseases affect various organs and tissues, but the lungs are the most common site of involvement. Diagnosis remains a major challenge because of atypical clinical features and ambiguous laboratory test results. These factors directly affect treatment and prognosis. Diagnosis of OIFIs in critically ill patients is difficult because radiological changes are usually non-specific.[31] Diagnosis is mainly based on three methods. First, clinical examination can be used to inform diagnosis, including assessment of fever, cough, dyspnea, chest pain, and hemoptysis; however, these characteristics are only present in some patients. Second, diagnosis can be made based on radiologic imaging results including denseness, cavitation, air crescent signs, or halo signs; however, only a few patients have typical features and some even show negative results. Third, definitive diagnosis of the causative agent can be made using mycological methods.[45] *Aspergillus* and *Candida* infections in patients with COVID-19 patients require early detection using comprehensive diagnostic investigations.[21] In addition to mycological methods such as direct microscopic examination and culture of samples, serological and molecular methods can also be used to diagnose invasive fungal infections.

Optimization of diagnostic tools and patient management is essential to enable rapid diagnosis and early treatment of fungal diseases.[24] Patients with COVID-19 and progressive features should be screened for CAPA. Screening for CAPA involves a combination of chest imaging, an *Aspergillus* antigen tests on bronchoalveolar lavage fluid, serum tests of galactomannan, ELISA or lateral-flow tests, or *Aspergillus* PCR.[31] Recommended diagnostic tests for confirming candidiasis include the *Candida albicans* germ-tube antibody test, $(1,3)$-β-D-glucan assays, PCR-based assays targeting the rDNA internal transcribed spacer (ITS), and new methods such as T2 magnetic resonance and matrix-assisted laser desorption/ionization mass spectrometry. Recommended diagnostic tests for confirming cryptococcosis include cryptococcal antigen tests, latex agglutination tests, enzyme-linked immunoassays, lateral-flow immunoassays, panfungal PCR, DNA sequencing, multiplex PCR, isothermal amplification, probe-based microarrays, and high resolution melting analysis; target genes include the IGS1-CAP5- ITS as well as 18S, ITS, 28S, or rDNA.[21] The use of advanced mycological tests is recommended for screening ICU patients with severe respiratory illness or deterioration of respiratory function 1 week after diagnosis of COVID-19.[29]

Conclusion

The rising number of confirmed COVID-19 and cases and deaths has increased the challenges associated with prevention, control, and management of the disease. More epidemiological research is needed to identify and describe transmission routes and the clinical spectrum of disease features. Early diagnosis and management of OIFIs including aspergillosis, candidiasis, cryptococcosis, and mucormycosis should be considered. Use of efficient molecular methods is recommended to diagnose fungal infections associated with ARDS in hospitals receiving patients with COVID-19.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

All data collection and manuscript writing were performed by both authors.

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