Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The role of SARS-CoV-2 immunosuppression and the therapy used to manage COVID-19 disease in the emergence of opportunistic fungal infections: A review

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ABSTRACT

Since December 2019 SARS-CoV-2 infections have affected millions of people worldwide. Along with the increasing number of COVID-19 patients, the number of cases of opportunistic fungal infections among the COVID-19 patients is also increasing. There have been reports of the cases of aspergillosis and candidiasis in the COVID-19 patients. The COVID-19 patients have also been affected by rare fungal infections such as histoplasmosis, pneumocystosis, mucormycosis and cryptococcosis. These fungal infections are prolonging the stay of COVID-19 patients in hospital. In this study several published case reports, case series, prospective and retrospective studies were investigated to explore and report the updated information regarding candidiasis, crytptococcosis, aspergillosis, mucormycosis, histoplasmosis, and pneumocystosis infections in COVID-19 patients. In this review, the risk factors of these co-infections in COVID-19 patients have been reported. There have been reports that the comorbidities and the treatment with corticoids, monoclonal antibodies, use of mechanical ventilation, and use of antibiotics during COVID-19 management are associated with the emergence of fungal infections in the COVID-19 patients. Hence, this review analyses the role of these therapies and comorbidities in the emergence of these fungal infections among COVID-19 patients. This review will help to comprehend if these fungal infections are the result of the co-morbidities, and treatment protocol followed to manage COVID-19 patients or directly due to the SARS-CoV-2 infection. The analysis of all these factors will help to understand their role in fungal infections among COVID-19 patients which can be valuable to the scientific community.

Contents

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Introduction

The first case of COVID-19 was reported in Wuhan, China in December 2019 (Spiteri et al., 2019). Since then; it has spread worldwide and taken the form of a pandemic. As of 6th June 2022, approximately 529,410,287 people have been infected and 6,296,771 people have succumbed to COVID-19 (WHO, WHO Coronavirus (COVID-19) Dashboard, 2021). The SARS-CoV-2 infection causes fever; dry cough, dyspnea, diarrhoea, headache, muscle pain and malaise in mild and moderate cases (Hassan et al., 2020). About 5 % of the patients affected by COVID-19 become critically ill suffering from severe pneumonia and acute respiratory distress syndrome thus requiring admission to the intensive care unit and mechanical ventilation (Murthy et al., 2020). Along with the SARS-CoV-2 infections; the COVID-19 patients are being co-infected with various other pathogens. There have been reports of viral bacterial and fungal co-infections among COVID-19 patients (Lai et al., 2020). There have been increasing reports of candidiasis; aspergillosis and mucormycosis in the COVID-19 patients (Hughes et al., 2020; Lahmer et al., 2021; Mehta and Pandey, 2020). These fungal co-infections affect the course of COVID-19 disease. Studies show that these infections are prolonging the stay of COVID-19 patients in hospitals and also increase the mortality rate (Lahmer et al., 2021; Koehler et al., 2020). Also; during the earlier viral pandemic caused by H1N1 and SARS-CoV-1 there was an increase in fungal infections (Patti et al., 2020).

This review of literature aims to explore and report the updated information regarding candidiasis, cryptococcosis, aspergillosis, mucormycosis, histoplasmosis, and pneumocystosis infections in COVID-19 patients. In this review, the risk factors of these co-infections in COVID-19 patients have been reported. Apart from the co-morbidities, the treatment with corticoids, antibiotics, monoclonal antibodies, and the use of mechanical ventilation during COVID-19 management could also cause fungal infections in the COVID-19 patients. The use of inexpensive glucocorticoids and anti-inflammatory therapies can also make the COVID-19 patients predisposed to secondary fungal infections (Garg et al., 2021; Kimmig et al., 2020). The use of antibiotics during the treatment of COVID-19 will overwhelm the normal microflora, which will allow the establishment of pathogenic fungi (Gandra et al., 2021). Chakraborti *et al* have reported that long-term mechanical ventilation is related to pulmonary and urinary fungal infections (Chakraborti et al., 2018). Hence, we also aimed to review if the treatment with corticoids, monoclonal antibodies, use of mechanical ventilation, and use of antibiotics during COVID-19 treatment along with other co-morbidities were associated with various fungal in COVID-19 patients. The effects of these co-infections on the course of COVID-19 such as prolonged stay in ICU have also been discussed. The review also provides information regarding co-morbidities of the patients who were diagnosed with SARS-CoV-2 and later on were infected with pathogenic fungi. This will help to comprehend if the fungal infections were the result of the co-morbidities, treatment protocol followed to manage COVID-19 patients or directly due to the SARS-CoV-2 infection. The information about the duration after which the fungal infections were diagnosed after the confirmation of SARS-CoV-2 infection has also been provided. The analysis of all these factors will help to understand their role in fungal infections among COVID-19 patients which can be valuable to the scientific community. The antifungal therapy used for the treatment of these infections has also been summarized which can be beneficial to the health practitioners.

Risk factors of fungal infections in COVID-19 patients

Most of the fungal infections are caused by the fungi of exogenous origin. However, the fungi found endogenously inside the host or mycobiome which comprises a very small proportion of the total microbiota have been complice in the onset of different diseases (Huffnagle and Noverr, 2013). The fungal microbiome can act as a reservoir for pathogenic fungi where they exist without causing diseases for a long time as a commensal but whenever the host is immunocompromised or under antibiotic treatment, they bloom to cause harmful diseases. Candida species are the most common colonizers of the mucosal surfaces, 30–70 % of healthy adults carry them, and under favourable conditions such as during antibiotic treatment and immunosuppression, they can cause candidemia and mycoses. Similarly, *Pneumocystis* and *Cryptococcus neoformans* can also exist as commensal in the lung but cause life-threatening infections during immunosuppression (Huffnagle and Noverr, 2013).

COVID-19 patients with comorbidities such as diabetes, hypertension, malignancy, multiple uses of antibiotics, chronic obstructive pulmonary diseases (COPD), Hepatitis B infection, chronic kidney diseases, renal failure, cerebrovascular diseases and cardiovascular diseases are at high risk of having poor clinical outcomes (Guan et al., 2020; Villanueva-Lozano et al., 2021). Furthermore, the critically ill COVID-19 patients have low levels of $CD4^+$ and $CD8^+$ T cells and monocytes, thus making them immunocompromised (Monneret et al., 2020; Tavakolpour et al., 2020; Yang et al., 2020). The comorbidities along with the compromised immunity of COVID-19 patients can make them more susceptible to fungal infections. COVID-19 causes hyper-ferritinemic syndrome where there is an increase in ferritin levels which eventually causes excess release of free iron and iron overload (John et al., 2021). The excessive release of free iron along with iron overload is some of the major risk factors of mucormycosis (John et al., 2021). Prolonged stays of COVID-19 patients at the hospital, mechanical ventilation and admission to intensive care units can also increase the risk of fungal infections in the COVID-19 patients (Song et al., 2020). The use of inexpensive glucocorticoids and anti-inflammatory therapies can also make the COVID-19 patients predisposed to secondary fungal infections (Garg et al., 2021; Kimmig et al., 2020). The use of corticosteroids in COVID-19 patients makes them predisposed to fungal infections such as mucormycosis by subduing the immune system and elevating the level of blood glucose (Gandra et al., 2021). The use of immunosuppressive drugs in COVID-19 patients with organ transplants can also make the patients prone to fungal infections (Khatri et al., 2021). Apart from immune dysregulation and the aforementioned risk factors, lack of oral hygiene can also increase the chances of candidiasis in the oral parts such as the tongue, gingiva and palate of the COVID-19 patients (Iranmanesh et al., 2020). Moreover. the viral infections also cause immunosuppression and damage to the pulmonary epithelium which can facilitate the fungal infection (Koehler et al., 2020). Ichai *et al* have hypothesized that the use of negative pressure in the ICU which is used to protect the staff from SARS-CoV-2 infections can also make the COVID-19 patients prone to opportunistic *Aspergillus* species infections (Ichai et al., 2020). Improper disinfection and cleaning can also contribute to the cases of nosocomial fungal infections in COVID-19 patients (Bhatt et al., 2021). Furthermore, the use of antibiotics during the course of treatment of COVID-19 will overwhelm the normal microflora, which will allow the establishment of pathogenic fungi (Gandra et al., 2021). Moreover, the hypoxia induced by SARS-CoV2 infections can also further deteriorate the tissues affected by angioinvasion in cases of mucormycosis (Gandra et al., 2021).

Cryptococcosis, histoplasmosis and pneumocystosis following SARS-CoV-2 infections

Cryptococcus species are a major cause of highly fatal cryptococcal meningitis which mostly affects immunocompromised patients and has a high mortality rate of 21 % in general patients (Brizendine et al., 2013; Iyer et al., 2021). Almost 95 % of the infections are caused by the pathogenic yeast *Cryptococcus neoformans* (serotype A) while the remaining infections are due to *C. neoformans* (serotype B) or *Cryp-*

tococcus gatti (Maziarz and Perfect, 2016). Generally, impaired immunity, HIV infection, cancer, solid organ transplant and use of steroid therapy make the patients more susceptible to *Cryptococcus* species infections (Henao-Martínez et al., 2016). Histoplasmosis is caused by *Histoplasma capsulatum* and it is endemic in Latin America and the United States of America (Bertolini et al., 2020). Similarly, pneumocystosis is caused by *Pneumocystosis jirovecii*. Both pneumocystosis and histoplasmosis affect immunocompromised individuals with low CD4 cell counts such as HIV patients, individuals with malignancies and organ transplants (Hochhegger et al., 2021). Studies have reported that severe COVID-19 patients have low CD4 cell counts (Chen et al., 2020; Jiang et al., 2020). Moreover, some reports show that SARS-CoV-2 infections cause lymphopenia which makes the patients more susceptible to pneumocystosis and other secondary fungal infections (Blaize et al., 2020). These studies suggest that the severe SARS-CoV-2 infection predisposes the patients to histoplasmosis due to the lack of CD4 cells which are vital for maintaining a robust immune response. As SARS-CoV2 infections are also reported to affect the immune status of the patients and corticosteroids as well as other immunomodulatory drugs are routinely being used by clinicians to manage the COVID-19 patients, it is more likely that COVID-19 patients will become more prone to these fungal infections. PUBMED, Scopus, Web of Science, and Google Scholar databases were searched using the keywords ("Cryptococcus" OR "Cryptococcosis" OR "Cryptococcal meningitis"), ("Pneumocystis" OR "Pneumocystosis" OR "*Pneumocystis jirovecii*"), ("Histoplasma", "Histoplasmosis" OR "*Histoplasma capsulatum*") and ("SARS-CoV-2" OR "COVID-19") AND ("SARS-CoV-2" and "COVID-19") without date until June 10th 2021, to find relevant studies.

Altogether five case reports were identified where COVID-19 patients were also suffering from Cryptococcosis. One case report was excluded, as in that case, the patient did not acquire Cryptococcus infection after SARS-COV-2 infection (Chiappe Gonzalez et al., 2020). The patient has already been infected with *C. neoformans* and the patient acquired the SARS-CoV-2 infection after his stay at the hospital (Chiappe Gonzalez et al., 2020). In the other four cases, the patients acquired the *C. neoformans* infection after they tested positive for SARS-CoV-2. Similar to the results by Henao-Martinez *et al*, most of the cases were male (3/4) (Henao-Martínez et al., 2016). All the patients were above 60 years old and are more likely to have impaired immunity (Saltzman and Peterson, 1987). Hence, they have more chances of getting affected by SARS-CoV-2 and fungal infections such as cryptococcosis. All of the patients were under corticosteroid therapy and one patient received tocilizumab which may have made the patients more susceptible to *Cryptococcus* species infection by subduing the immune system. Furthermore, all the patients were under mechanical ventilation and two of the patients also received antibiotics during COVID-19 treatment. Three of the patients were presented with comorbidities that may also have aided in the SARS-CoV-2 infection which could have eventually led to the secondary fungal infection. *C. neoformans* can also exist as commensal in the lung and cause life-threatening infections during immunosuppression (Huffnagle and Noverr, 2013). There was a report of pulmonary *C. neoformans* infection in a patient following SARS-CoV-2 infection (Cafardi et al., 2021). This case suggests that there is a likelihood of activation of latent *C. neoformans* infections in patients due to the overwhelming effect of SARS-CoV-2 and the corticoids on the patient's immune system. There are also chances that the patients were infected with hospital-borne or environmental *C. neoformans* which in due course overwhelmed the patients due to co-morbidities, SARS-CoV-2 infection and use of steroids. As, there is limited number of reports and due to the involvement of plethora of factors, it is very difficult to establish the role of SARS-CoV-2 and the therapy used in its management to these secondary infections. Overall, three out of the four patients died. However, it is difficult to affirm the cause of deaths due to the *Cryptococcus* infections. The details of the patients reported in these case reports are represented in Table 1.

Altogether seven case reports were identified where COVID-19 patients were also suffering from Histoplasmosis. Three of the case reports were from Brazil, two from Argentina and 1 from the USA. In four of the case reports including 3 patients suffering from AIDS, histoplasmosis was already detected before the diagnosis of COVID-19 patients (Bertolini et al., 2020; Basso et al., 2021; Messina et al., 2020; Stasiak et al., 2021). In the remaining three cases histoplasmosis was confirmed after the patients underwent treatment for COVID-19 (Table 1) (Cafardi et al., 2021; de Macedo et al., 2021). Two of the cases were adults (20 and 32 years) and had no co-morbidity. The third patient in which histoplasmosis was confirmed after the confirmation of COVID-19 was old (62 years) and diabetic. In this old and diabetic patient, the impaired immunity could have also aided in the secondary *Histoplasma* infection. One of the patients came in contact with the potential environmental source of *Histoplasma capsulatum* after recovering from SARS-CoV-2 infection (de Macedo et al., 2021). This case report suggests that the pulmonary damage due to SAR-CoV-2 infection could have facilitated the *Histoplasma* infection after the possible inhalation of *Histoplasma* conidia from the environment by the patient. The case of the other two patients suggests that the treatment of COVID-19 patients with corticosteroids or monoclonal antibodies could have reactivated the latent *Histoplasma* or made the patients more prone to infection from environmental or nosocomial sources. As, there are only three cases of Histoplasmosis in patients after SARS-CoV-2 infections, the hypotheses that the SARS-CoV-2 infection and the therapy used to manage COVID-19 are associated with *Histoplasma* infection cannot be corroborated. As of now, it is impossible to conclude whether there is coincidental, causal or contributory relation between the effect of SARS-CoV-2 on patients' immunity and treatment protocol with the cases of histoplasmosis. However, the clinicians should consider in mind the possibility of *H. capsulatum* infections in COVID-19 patients during or even after the treatment of COVID-19, especially in USA and South American countries. All the patients whose cases are reviewed in this study that had histoplasmosis infections following SARS-CoV-2 infection survived (Table 1).

Altogether 12 case reports were identified where COVID-19 patients were also diagnosed with *Pneumocystis jirovecii* infections. In two case reports identified in this study, there were concurrent SARS-CoV-2 and *P. jirovecii* infections in HIV patients (Coleman et al., 2020; Bhat et al., 2020). In another case report where a patient was admitted to the hospital due to COVID-19 complications was also found to be HIV positive, later this patient also tested positive for *P. jirovecii* infection (Mang et al., 2020). As, these patients were HIV positive, a major risk factor of pneumocystosis, it cannot be concluded that the *P. jirovecii* infections were a result of SARS-CoV-2 infection or the consequence of the therapy used to manage the COVID-19 patients. Similarly, in another case report also an 83 years old female patient with leucocytosis and lymphocytopenia was diagnosed with concurrent SAR-CoV-2 and *P. jirovecii* infections (Menon et al., 2020). In one case report, a 46 years old woman with Raynaud's syndrome was admitted to the hospital due to pneumonia-like symptoms and was later diagnosed simultaneously with HIV, SARS-CoV-2 and *P. jirovecii* (Larzábal et al., 2020). In another case, a 52 years old male with several co-morbidities ischemic heart disease, chronic alcohol liver disease, hypertension, and hepatic steatosis died within 17 h after admission to the hospital and the necropsy revealed the simultaneous co-infection of SARS-CoV-2 and *P. jirovecii* (Jeican et al., 2021). In two of the case reports the patients (n = 3) were present with respiratory symptoms and suspected as COVID-19 patients (Choy and Wong, 2020; Kelly et al., 2020). However, later they tested positive for HIV and *P. jirovecii* was also detected which implied that the respiratory symptoms were due to pneumocytosis. Similar cases were also reported in Denmark where patients with suspected COVID-19 disease

Table 1
Reported cases of cryptococcosis, histoplasmosis and pneumocystosis following SARS-CoV-2 infections along with the information regarding the co-morbidities and therapy used to manage the COVID-19 patients.

Case/Country	Age	Gender	Co-morbidities	Use of antibiotics during COVID-19 management	Use of immune-modulatory drugs during COVID-19 management	Mechanical ventilation during COVID-19 management	Days after which infection was confirmed following a positive RT-PCR result	Antifungal treatment	Outcome	Ref
Disseminated/*Cryptococcus neoformans*/USA	75	Male	Cirrhosis of liver, hypertension, kidney transplant recipient	Yes; ceftriaxone and clarithromycin	Yes, Prednisone	Yes	12 days	Fluconazole	Death after 18 days of admission due to septic shock	(Passarelli et al., 2020)
Disseminated/*Cryptococcus neoformans*/Qatar	60	Male	Diabetes, hypertension, ischemic heart disease	NA	Yes, methylprednisolone, hydrocortisone, tocilizumab	Yes	48 days	Flucytosine with Amphotericin B	Death due to sepsis after 10 days of cryptococcemia	(Khatib et al., 2020)
Meningoencephalitis/*Cryptococcus neoformans*/USA	73	Female	None	Yes, azithromycin	Yes, dexamethasone	Yes	12 days	Flucytosine with Amphotericin B	Survived	(Ghanem et al., 2021)
Pulmonary/Cryptococcus neoformans/USA	78	Male	COPD, hypertension	No	Yes; methylprednisolone	Yes	20 days	Amphotericin B changed to isavuconazole due to renal injury	Death after 39 days of hospital admission	(Cafardi et al., 2021)
Histoplasma capsulatum/USA	62	Female	Diabetes	Yes; levofloxacin and azithromycin	Yes, tocilizumab and dexamethasone	NA	26 days	Liposomal amphotericin B which was later changed to isavuconazole	Survived. Discharged after 89 days from hospital.	(Cafardi et al., 2021)
Pulmonary/*Histoplasma capsulatum*/Brazil	20	Male	None	NA	NA	NA	4 months	Itraconazole	Survived	(de Macedo et al., 2021)
Pulmonary/*Histoplasma capsulatum*/Brazil	32	Male	None	NA	Yes; methylprednisolone	NA	NA	Itraconazole	Survived	(de Macedo et al., 2021)
China/*Pneumocystis jirovecii*	72	Female	Rheumatoid arthritis	Yes; cefoperazone	Yes; methylprednisolone, tocilizumab	No	20 days	Caspofungin	Survived	(Cai et al., 2020)
Italy/*Pneumocystis jirovecii*	65	Male	Kidney transplant recipient, diabetes, hypertension	Yes; azithromycin and piperacillin/tazobactam	Yes; methylprednisolone	No	2 days	Trimethoprim-sulfamethoxazole	Death due to respiratory failure and multiple organ dysfunction	(De Francesco et al., 2020)
Italy/*Pneumocystis jirovecii*		Male	No	Yes; ceftaroline	Yes; dexamethasone	Yes	18 days	trimethoprim-sulphamethoxazole	Survived	(Viceconte et al., 2021)
USA/*Pneumocystis jirovecii*	38	Male	HIV	No	Yes; prednisone	Yes	15 days	Trimethoprim-sulfamethoxazole	Death after 22 days of hospitalization due to respiratory failure	(Merchant et al., 2021)

were later diagnosed with *P. jirovecii pneumonia* and HIV (Borchmann and Hansen, 2021). These two case reports that along with COVID-19 clinicians should also be wary about pathogens that mimic COVID-19 such as *P. jirovecii.* Two fatalities were reported, one with HIV infection and another with anti-melanoma differentiation-associated gene 5 juvenile dermatomyositis, who had a simultaneous diagnosis of SARS-CoV-2 and *P. jirovecii* (Broadhurst et al., 2021; Quintana-Ortega et al., 2021). Both these patients died because of respiratory failure and the contribution of these infections to disease severity was unclear (Broadhurst et al., 2021; Quintana-Ortega et al., 2021). The case reports reviewed in this section suggest in patients with HIV infection who present with pneumonia-like symptoms; the clinicians should test for both *P. jirovecii* and SARS-CoV-2 infections as these patients are more prone to these infections because of their weakened immunity. Furthermore, there is a chance of misdiagnosis as both COVID-19 and *P. jirovecii* show similar clinical and radiological features. The simultaneous infections of *P. jirovecii* and SARS-CoV-2 also make it difficult to understand the role of these pathogens in the disease progression in the patients. The case reports discussed above do not support the hypotheses that the pulmonary inflammation/pulmonary damage, immunosuppression caused by SAR-CoV-2 infections and therapy used to manage the COVID-19 patients facilitated the pneumocystosis in COVID-19 patients as these patients were either already infected with *P. jirovecii* or the SARS-COV-2 infection and *P. jirovecii* were diagnosed simultaneously. Furthermore, these patients were also diagnosed with HIV or immunosuppression which are risk factors for *P. jirovecii* infections.

However, in four case reports, *P. jirovecii* was detected after the patients were confirmed of SARS-CoV-2 infection and the treatment for COVID-19 had begun. The details of these case reports are listed in Table 1. The cases of *P. jirovecii* infections were confirmed after 2–20 days of a positive result for SARS-CoV-2 infection. All of the patients were under the steroids for management of COVID-19 and 3 patients were treated with antibiotics during COVID-19 treatment. One of the patients was HIV positive and another was the recipient of a kidney transplant (De Francesco et al., 2020; Merchant et al., 2021). As HIV and solid organ transplant are major risk factors for *P. jirovecii* infections it is difficult to determine whether the *P. jirovecii* infections were result of these co-morbidities or due to the SARS-CoV-2 infection and the therapy used to manage the COVID-19 patients. Based on just four case reports it becomes impossible to confirm if the *P. jirovecii* were the result of SARS-CoV-2 infection or the therapy used to manage the COVID-19 patients.

Treatment of cryptococcosis, histoplasmosis and pneumocytosis in COVID-19 patients

The cases of cryptococcosis in COVID-19 patients reviewed in this study were treated with fluconazole or the combination of Amphotericin B and flucytosine which are also recommended by Centres for Disease Control and Prevention (CDC), USA (CDC, Treatment for C. neoformans Infection, 2021). The COVID-19 patients who were also infected by *Histoplasma capsulatum* received liposomal amphotericin B and itraconazole for the treatment of histoplasmosis which is also recommended by an expert panel of Infectious Diseases Society of America for the management of histoplasmosis (Wheat et al., 2007). For the treatment of pneumocytosis in COVID-19 patients, trimethoprim-sulphamethoxazole was used in the cases analysed in this study. According to CDC, trimethoprim-sulphamethoxazole is the most common form of treatment for pneumocystosis in general patients (CDC, Pneumocystis pneumonia, 2021).

Mucormycosis following SARS-CoV-2 infection

Mucormycosis is mostly caused by fungi belonging to Mucor and Rhizopus species (CDC, Where Mucormycosis Comes From | Mucormycosis | CDC, 2021). Other fungi genera of the order Mucorales such as Rhizomucor, Apophysomyses, Absidia, Cunninghamella and Syncephalastrum can also cause mucormycosis (Prabhu and Patel, 2004). Generally, these fungi are not harmful, but in patients with compromised immunity, they can infect different body parts and become lethal (CDC, Where Mucormycosis Comes From | Mucormycosis | CDC, 2021). The incidence rate of mucormycosis is between 0.005 and 1.7 cases per million population and the fatality rate is 46 % in the general population (Jeong et al., 2019). It is common in transplant recipients and patients with haematological malignancy (Jeong et al., 2019). These infections are very rare and hard to diagnose, and a delay in their diagnosis can significantly increase the 30-day mortality rate (Werthman-Ehrenreich, 2021). During mucormycosis, the spores are inhaled in the airways or seeded on the susceptible epithelial tissues where these spores germinate and undergo angioinvasion by using the general host conditions like iron overload, hyperglycemia, neutropenia and ketoacidosis (Ahmadikia et al., 2021; Petrikkos and Tsioutis, 2018). Then, the mucormycosis causes necrosis, thrombosis and local hemorrhage which eventually gets disseminated to different organs thus increasing the risk of fatality (Ahmadikia et al., 2021; Petrikkos and Tsioutis, 2018). As SARS-CoV-2 infection also affects the patients' immunity, the cases of mucormycosis are expected to increase in the COVID-19 patients similar to the cases of Aspergillosis and Candidiasis. Furthermore, the use of immunomodulatory drugs, broad-spectrum antibiotics and corticosteroids during the treatment of COVID 19 patients also makes them more vulnerable to mucormycosis. Generally, mucormycosis can be rhino-orbital-cerebral, cutaneous, pulmonary, gastro-intestinal, and disseminated (Riley et al., 2016). In COVID-19 patients rhino-orbital-cerebral, rhino-orbital, pulmonary and gastrointestinal mucormycosis have been reported (Mehta and Pandey, 2020; Werthman-Ehrenreich, 2021; Monte Junior et al., 2020; Placik et al., 2020). In a review of 41 cases of COVID-19 associated mucormycosis (CAM) by John *et al*, it was reported that CAM was mostly diagnosed (94 % of patients) with diabetes mellitus (John et al., 2021). A retrospective, interventional study performed by Sen *et al* reported 6 cases of rhino-orbital mucormycosis in COVID-19 patients at two different ophthalmic centers in India (Sen et al., 2021). These patients were male, aged between 46 and 73 years, diabetic, and received systemic corticosteroids for treating COVID-19 (Sen et al., 2021). All the patients who were under liposomal amphotericin B treatment along with posaconazole eventually survived, however, all of them lost their vision (Sen et al., 2021). Ravani *et al* reported 31 cases of mucormycosis in COVID-19 patients (Ravani et al., 2021). All these patients were diabetic, liposomal amphotericin B was used to treat all these patients and mortality was reported in one case (Ravani et al., 2021). However, they did not report the days after which mucormycosis was diagnosed after positive RT-PCR test for SARS-CoV-2, the use of corticosteroids during the treatment of COVID-19 and individual age and sex of the COVID-19 patients with mucormycosis (Ravani et al., 2021). Table 3 provides information about the cases in which mucormycosis was diagnosed following SARS-CoV-2 infection. Apart from the cases mentioned in Table 2 different cases mentioned in various case series and retrospective studies were also included in this study (Sen et al., 2021; Ravani et al., 2021; Bayram et al., 2021; Nehara et al., 2021; Sarkar et al., 2021; Sharma et al., 2021; Moorthy et al., 2021).

PUBMED, Web of Science, Scopus and Google Scholar databases were searched using the keywords such as ("Mucormycosis" OR "Mucor" OR "Black fungus" OR "Mucorales") and ("SARS-CoV-2" OR "COVID-19") without date until June 10, 2021. Altogether 128 cases of mucormycosis were identified in this study. Most of the cases were reported in males (103 out of 128). In 87 cases, age-related information was available. For these cases, the mean age was 59.55 years. The categorization of these cases in different age groups is shown in Table 2. The age group 60–69 had the highest cases of mucormycosis in patients with confirmed SARS-CoV-2 infections. Patients between

Table 2
Classification of the reported cases of mucormycosis following SARS-CoV-2 infections in different age groups.

Age group	Number of cases (in %)
20–29	5 (5.74)
30–39	8 (9.19)
40–49	18 (20.68)
50–59	16 (18.39)
60–69	25 (28.73)
70–79	12 (13.79)
80–89	3 (3.44)

the ages of 40–79 accounted for 81.6 % of the total cases. Rhino-orbital mucormycosis was most common in the patients (n = 114). Cutaneous (n = 1), pulmonary (n = 10), musculoskeletal (n = 1), disseminated (n = 1) and gastrointestinal mucormycosis (n = 1) were also detected. Diabetes was the most common comorbidity among these patients. 107 out of the 128 cases were diabetic (83.59 %). four of the patients had no comorbidities. Other comorbidities included hypertension, obesity, asthma, kidney disease, hypothyroidism, kidney disease, organ transplant reception and cancer. Amphotericin B was the most commonly used antifungal drug to treat mucormycosis infection. Out of all the cases, nine patients did not receive any steroids for the treatment of COVID-19 whereas 96 patients (75 %) received steroids such as dexamethasone, and methylprednisolone. For the rest of the cases, no data related to the use of steroids during COVID-19 treatment was available. Three of the cases had tocilizumab treatment for COVID-19. Out of these three cases, two had the use of both antibody and steroid therapy for treating COVID-19. For 47 cases data related to the days after which mucormycosis was confirmed following a positive RT-PCR result for SARS-CoV-2 was available (Table 4). Mucormycosis was detected in the patients between 3 days to 3 months of SARS-CoV-2 confirmation. The average days after which mucormycosis was confirmed following a positive RT-PCR result for SARS-CoV-2 is 16.95 days. 26 out of the 47 cases (55.31 %) of mucormycosis were detected after 11–20 days of a positive RT-PCR result for SARS-CoV-2. 25 of the cases required mechanical ventilation during COVID-19 treatment whereas 9 patients did not require mechanical ventilation; and for the rest of the cases, no related information about mechanical ventilation during COVID-19 management was available (Table 3). Recently Patel *et al* also reported that the inappropriate use of glucocorticoids and COVID-19 associated hypoxemia were independently associated with COVID-19 associated mucormycosis among patients in India (Patel et al., 2021). Furthermore, the immunosuppression and the increase of blood glucose levels in diabetic COVID-19 patients due to the use of corticosteroids creates ketoacidotic environment which fosters the growth of opportunistic pathogenic fungal infections (Petrikkos and Tsioutis, 2018; Dallalzadeh et al., 2021). Dallalzadeh *et al* also postulated that the SARS-CoV-2 associated immunosuppression and mechanical ventilation can be risk factors for mucormycosis in COVID-19 patients (Dallalzadeh et al., 2021). The cases studied in this review support the hypotheses that the immunosuppression caused by SARS-CoV-2 and the therapy used to control COVID-19 such as the use of glucocorticoids, monoclonal antibodies and mechanical ventilation are likely to be associated with mucormycosis infections in COVID-19 patients.

Treatment of mucormycosis in COVID-19 patients

In the cases reviewed in this study, mostly liposomal amphotericin was used for the treatment of mucormycosis in COVID-19 patients. A COVID-19 patient suffering from mucormycosis was transitioned from liposomal amphotericin to posaconazole due to acute kidney damage (Mekonnen et al., 2021). Similarly, the combination of amphotericin B, micafungin and isavuconazole has also been used to treat mucormycosis in COVID-19 patients (Dallalzadeh et al., 2021). The combination of liposomal amphotericin B with posaconazole has also been used for the treatment of mucormycosis in COVID-19 patients (Khatri et al., 2021). According to the European Confederation of Medical Mycology high dose liposomal amphotericin B is recommended as first-line treatment whereas moderate strength isavuconazole or posaconazole can be used as salvage treatment of mucormycosis in general patients (Cornely et al., 2019).

Infection of Candida species in COVID-19 patients

Candida species are opportunistic pathogens which can cause nosocomial infections in COVID-19 patients and further exacerbate the patient's health condition. The COVID-19 patients are at increased risk of Candida infections due to their poor immunity and other risk factors discussed in the earlier section. PUBMED, Web of Science, Scopus and Google Scholar databases were searched using the keywords such as ("Candidiasis" OR "Candida infection" OR "*Candida albicans*", "non-Candida albicans") and ("SARS-CoV-2" OR "COVID-19") without date until June 10, 2021. In a retrospective cohort study at two hospitals in the United Kingdom, 21.4 % of the respiratory samples collected from COVID-19 patients tested positive for secondary Candida infection (Hughes et al., 2020). The study suggested that these isolates were part of a normal microbiome rather than pulmonary candidiasis. However, in three patients who were admitted to the intensive care unit, there were three incidents of hospital-acquired, central line-associated *Candida albicans* infections (Hughes et al., 2020). Different studies have reported the oral manifestation of Candidiasis in the labial mucosa, buccal mucosa, gingiva, tongue, oropharynx, and palate of the COVID-19 patients (Corchuelo and Ulloa, 2020; Riad et al., 2021). Prevalence of Xerostomia (dry mouth) in the COVID-19 patients along with the inability of the patients to maintain proper oral hygiene could be the possible causes of oral Candidiasis (Riad et al., 2021). Apart from *Candida albicans*, other non-*albicans Candida* species have also been reported to be isolated from COVID-19 patients. Villanueva-Lozano *et al* reported the isolation of *C. auris* from blood and urine of the COVID-19 patients in the intensive care unit (ICU) of COVID-19 facility in Mexico (Villanueva-Lozano et al., 2021). Furthermore, three *C. auris* isolates were obtained from the environmental samples such as bed rails and infusion pumps (Villanueva-Lozano et al., 2021). These COVID-19 patients with *C. auris* co-infections were under mechanical ventilation and also had prolonged stay in ICU, and also had the insertion of urinary catheter and peripherally inserted central line (Villanueva-Lozano et al., 2021). 8 of the 15*C. auris* isolates were resistant to both Amphotericin B and fluconazole and an 83.3 % mortality rate was reported among the patients with Candidemia (Villanueva-Lozano et al., 2021). Similarly, *C. auris* isolates were obtained from deep tracheal aspirates of 7 patients who previously had COVID-19 pneumonia at an ICU unit in Lebanon (Allaw et al., 2021). All these patients with co-infection of *C. auris* were under mechanical ventilation, had prolonged stay at the hospital, were elderly, had central venous and urinary catheters and also had the intake of steroids (Allaw et al., 2021). In Florida, USA also *C. auris* were isolated from the 52 % of 67 COVID-19 patients (Kuehn, 2021). Chowdhary *et al* reported the isolation of *C. auris* from 10 COVID-19 patients in India where 6 out of these 10 patients eventually died; thus suggesting a very high fatality rate of 60 % (Chowdhary et al., 2020). Posteraro *et al* reported the detection of invasive *C. glabrata* infection in a diabetic patient who was also diagnosed with COVID-19 (Posteraro et al., 2020). However, after 13 days of treatment with caspofungin, the fungi developed pan-echinocandin resistance and the patient eventually died of septic shock before he could benefit from treatment with another antifungal therapy (Posteraro et al., 2020). From another COVID-19 patient who had prolonged stay

Table 3
Reported cases of mucormycosis following SARS-CoV-2 infections along with the information regarding the co-morbidities and therapy used to manage the COVID-19 patients.

Case/Country	Age	Gender	Co-morbidities	Use of antibiotics during COVID-19 management	Use of immune-modulatory drugs during COVID-19 management	Mechanical ventilation during COVID-19 management	Days after which mucormycosis was confirmed following a positive RT-PCR result	Antifungal treatment	Outcome	Ref.
Rhino-orbital mucomycosis/India	60	Male	Diabetes	Yes; meropenem and vancomycin	Yes, dexamethasone and methylprednisolone	Yes	10	Amphotericin B	Death after 6 days of admission	(Mehta and Pandey, 2020)
Rhino-orbital mucormycosis/USA	33	Female	Diabetes, asthma, hypertension	Yes; piperacillin-tazobactam and Vancomycin	NA	NA	NA	Amphotericin B	Death after 26 days of admission	(Werthman-Ehrenreich, 2021)
Gastrointestinal Mucormycosis/Brazil	86	Male	Arterial hypertension	Yes, azithromycin and ceftriaxone	Yes, hydrocortisone	Yes	5 days	No	Death after 7 days of admission	(Monte Junior et al., 2020)
Rhino-orbital mucormycosis/USA, Rhizopus, Proven	60	Male	Diabetes, asthma, hypertension, hyperlipidemia	Yes; cefepime and vancomycin	Yes; dexamethasone	Yes	4 days	Liposomal Amphotericin B, posaconazole and caspofungin	Death after 31 days of admission	(Mekonnen et al., 2021)
Rhino-cerebral/USA	41	Male	Diabetes	Yes, cefepime	Yes	No	NA	Liposomal Amphotericin B	Discharged	(Alekseyev et al., 2021)
Pulmonary/USA/ *Rhizopus*	49	Male	None	Yes; ceftriaxone and azithromycin	Yes; dexamethasone	Yes	14 days	Amphotericin B	Death after 21 days of admission	(Placik et al., 2020)
Pulmonary/India/ Probable/*Rhizopus*	55	Male	Diabetes, kidney disease	Yes; meropenem	Yes; dexamethasone	Yes	21 days	Liposomal Amphotericin B	Discharged after 54 days	(Garg et al., 2021)
Pulmonary/Italy/ *Rhizopus*	66	Male	Hypertension	Yes, piperacillin-tazobactam, levofloxacin, meropenem	No	Yes	14 days	Liposomal Amphotericin B	Death after 62 days of admission	(Pasero et al., 2021)
Pulmonary/USA/ Rhizopus	79	Male	Diabetes, hypertension	Yes; ceftriaxone and azithromycin	Yes; dexamethasone	Yes	29 days	Liposomal Amphotericin B	Discharged after 36 days to acute care facility	(Johnson et al., 2021)
Disseminated mucormycosis/UK	22	Male	Obesity, hypothyroidism	Yes; azithromycin	Yes	NA	After 20 days in autopsy	NA	Death after 20 days of admission	(Krishna et al., 2021)
Rhino-orbital-cerebral mucormycosis/Iran	40	Female	None	Yes; vancomycin and meropenem	Yes; dexamethasone	Yes	8 days	IV Amphotericin B	Death after 3 months of admission due to cerebral infection	(Veisi et al., 2022)
Rhino-orbital mucormycosis/Iran	54	Male	Diabetes	Yes, Levofloxacin	Yes; dexamethasone	Yes	8 days	IV Amphotericin B	Survived	(Veisi et al., 2022)
Rhino-orbital/India/ *Rhizopus oryzaae*	38	Male	None	No	Yes; dexamethasone and methylprednisolone	No	18 days	Amphotericin B	Survived	(Maini et al., 2021)
Rhino-orbital/Mexico/ *Absidia*	24	Female	Obesity, Diabetes	Yes; imipenem/linezolid	NA	Yes	NA	Amphotericin	Death due to septic shock	(Waizel-Haiat et al., 2021)
Cutaneous/USA/ Rhizopus microspores	68	Male	Heart transplant recipient, diabetes, hypertension, chronic kidney disease	Yes; vancomycin and meropenem	NA	NA	3 months	Liposomal Amphotericin B, posaconazole	Death after 175 days due to septic shock	(Khatri et al., 2021)
Rhino-orbital/India	47	Male	Renal transplant recipient, diabetes	NA	Yes, Tacrolimus, steroids. But for treating COVID-19 no steroids were used.	NA	14 days	Liposomal amphotericin B	Death after 51 days of admission	(Meshram et al., 2021)
Pulmonary/India	25	Male	Renal transplant recipient, diabetes	NA	Yes, Tacrolimus, steroids, mycophenolic acid. But for treating COVID-19 no steroids were used.	NA	10 days	Liposomal amphotericin B	Death after 49 days of admission	(Meshram et al., 2021)
Rhino-orbital-cerebral/ USA	36	Male	Diabetes	No	Yes	No	NA	intravenous amphotericin, isavuconazole,	Death due to extension of infection to the cranial cavity after 4 days of	(Dallalzadeh et al., 2021)

(*continued on next page*)

Table 3 (*continued*)

Case/Country	Age	Gender	Co-morbidities	Use of antibiotics during COVID-19 management	Use of immune-modulatory drugs during COVID-19 management	Mechanical ventilation during COVID-19 management	Days after which mucormycosis was confirmed following a positive RT-PCR result	Antifungal treatment	Outcome	Ref.
								and micafungin	hospital admission.	
Rhino-orbital-cerebral/ USA	48	Male	Diabetes	NA	Yes, dexamethasone	NA	6 days	Amphotericin B and isavuconazole	Death due to extension of infection to the cranial cavity	(Dallalzadeh et al., 2021)
Rhino-orbital/Iran	61	Female	No	No	Yes	No	21 days	Amphotericin B	NA	(Karimi-Galougahi et al., 2019)
Rhino-orbital/India	66	Male	Diabetes	NA	Yes	NA	12 days	Amphotericin B	Survived after orbital exenteration	(Rao et al., 2021)
Pulmonary/USA/ *Rhizopus azygosporus*	56	Male	Renal disease	No	Yes; methylprednisolone and tocilizumab	No	19 days	Liposomal Amphotericin B	Dead after 17 days in hospital due to cardiac arrest.	(Kanwar et al., 2021)
Pulmonary/Austria/ *Rhizopus microspores*	53	Male	Acute myeloid leukaemia	Yes, piperacillin/tazobactam	Yes; prednisolone and tocilizumab	Yes	After 24 days in autopsy	No	Dead after 24 days	(Zurl et al., 2021)
Rhino-orbital/Spain/ *Rhizopus oryzae*	62	Male	Diabetes, recipient of kidney transplant	Yes, ceftriaxone and azithromycin	Yes, dexamethasone	Yes	17 days	Liposomal Amphotericin B, posaconazole	Survived	(Arana et al., (2021))
Musculoskeletal/Spain/ Lichtheimia ramose	48	Male	Kidney disease, recipient of kidney transplant	Yes, azithromycin	Yes, tocilizumab	No	21 days	Liposomal Amphotericin B and isavuconazole	Survived	(Arana et al., n/a (2021))
Pulmonary/France/ Rhizopus microspores	55	Male	Follicular lymphoma	NA	Yes	Yes	15 days	Liposomal Amphotericin B	Dead after 0 days in hospital	(Bellanger et al., 2021)
Rhino-orbital/Iran/ Rhizopus oryzae	50	Female	Diabetes, hypertension	NA	Yes, dexamethasone	No	26 days	Liposomal Amphotericin B	Survived	(Tabarsi et al., 2021)
Pulmonary/India	72	Male	Hypothyroid, hypertension, diabetes	Yes, imipenem	Yes, methylprednisolone	No	NA	Liposomal Amphotericin B and posaconazole	Survived	(Chennamchetty et al., 2021).
Chile	62	Male	None	Yes	Yes	Yes	12 days	None	Survived	(Rabagliati et al., 2021)
Chile	55	Male	Diabetes, hypertension	Yes	Yes	Yes	5 days	Liposomal Amphotericin B	Death	(Rabagliati et al., 2021)
USA/Pulmonary	44	Female	Diabetes	Yes, cefepime and vancomycin	Yes, methylprednisolone	No	13 days	Liposomal Amphotericin B	Death after 17 days of admission	(Khan et al., 2020)
Rhino-orbital/Egypt	65	Female	Diabetes	NA	NA	NA	14 days	Amphotericin B	Survived	(Ashour et al., 2021)
Rhino-orbital/Egypt	67	Male	Chronic Kidney disease	NA	NA	NA	14 days	Amphotericin B	Death after 28 days of admission	(Ashour et al., 2021)
Rhino-orbital/Egypt	42	Male	Diabetes	NA	NA	NA	NA	Amphotericin B	Survived	(Ashour et al., 2021)
Rhino-orbital/Egypt	63	Female	Diabetes	NA	NA	NA	NA	Amphotericin B	Survived	(Ashour et al., 2021)
Rhino-orbital/Egypt	41	Female	Diabetes	NA	NA	NA	14 days	Amphotericin B	Survived	(Ashour et al., 2021)
Rhino-orbital/Egypt	42	Male	Diabetes, Chronic Kidney disease, hypertension	NA	NA	Yes	16 days	Amphotericin B	Death after 31 days of admission	(Ashour et al., 2021)
Rhino-orbital/Egypt	50	Male	Diabetes	NA	NA	NA	14 days	NA	Death after 31 days of admission	(Ashour et al., 2021)

Table 4
Days after which mucormycosis was confirmed following a positive RT-PCR result for SARS-CoV-2.

Days	Number of cases (in %)
0–10	11 (23.40)
11–20	26 (55.31)
21–30	8 (17.02)
31 +	2 (4.25)

at hospital in Oman also *C. glabrata* was isolated (Al-Hatmi et al., 2021). Also from the same intensive care unit, *C. tropicalis* along with *C. albicans* was isolated from the blood culture of a patient with COVID pneumonia (Al-Hatmi et al., 2021). In a study in Iran, apart from *C. albicans* and *C. glabrata*, other fungi such as *C. krusei, C. parapsilosis, C. tropicalis and C. dublinienesis* were isolated were isolated from the COVID-19 patients who also suffered from lymphopaenia (Salehi et al., 2020). These studies show that the *C. albicans* is the most common cause of Candidemia and there is an upsurge in the cases of non-albicans Candida species among the COVID-19 patients. The studies also show that the co-infection with the Candida species can worsen the disease course of COVID-19 and cause increase in the mortality.

Treatment of the Candida infections in COVID-19 patients

For the treatment of oral Candidiasis, various antifungal protocols have been used. Topical applications of nystatin and miconazole have been used for the successful treatment of oral Candidiasis in COVID-19 patients (Corchuelo and Ulloa, 2020; Riad et al., 2021). Intravenous administration of fluconazole has also been used in combination with oral/topical administration of nystatin or miconazole (Riad et al., 2021; Amorim dos Santos et al., 2020). Along with the antifungal drugs, Chlorhexidine gluconate (0.12 to 2 %) and hydrogen peroxide (1 %) were also prescribed to the COVID-19 patients suffering from oral Canididasis (Corchuelo and Ulloa, 2020; Riad et al., 2021; Amorim dos Santos et al., 2020). For the treatment of COVID-19 patients co-infected with *C. auris* echinocandins such as anidulafungin and caspofungin were used at an ICU in Lebanon (Allaw et al., 2021). Similarly, for the treatment of Candidemia, the combination of voriconazole and caspofungin; and a combination of amphotericin B and caspofungin has also been used (Al-Hatmi et al., 2021).

Infection of Aspergillus species in COVID-19 patients

Aspergillus species can cause invasive pulmonary aspergillosis, aspergilloma (fungal ball), allergic bronchopulmonary aspergillosis and tracheobronchial aspergillosis in general patients (Patti et al., 2020). Globally the cases of COVID-19 associated pulmonary aspergillosis (CAPD) have increased and it is associated with the exacerbation of the course of COVID-19 disease and also increasing mortality (Koehler et al., 2020). PUBMED, Web of Science, Scopus and Google Scholar databases were searched using the keywords such as ("Aspergillosis" OR "Aspergilloma" OR "*Aspergillus*") and ("SARS-CoV-2" OR "COVID-19") without date until June 10, 2021. Most of the cases of CAPD are caused by *Aspergillus fumigatus* followed by *Aspergillus flavus* (Lai and Yu, 2021). Along with these *Aspergillus* species, other species such as *A. lentulus, A. niger, A. nidulans* and *A. citrinoterreus* have also been reported (Bartoletti et al., 20212021; Falces-Romero et al., 2020; Machado et al., 2021). In the study by Machado *et al* in Spain, CAPD was diagnosed in 0.3 % of the 2723 COVID-19 patients which accounted for 3.3 % of the 239 COVID-19 patients in the ICU (Machado et al., 2021). Arkel *et al* reported a high incidence rate of Aspergillosis (19.4 %) among 31 ICU patients (van Arkel et al., 2020). However, in a study in China, CAPA was diagnosed in 7.75 of the COVID-19 patients which accounted for 30.7 % of the ICU patients (Wang et al., 2020). In a recent review by Chong and Neu, the overall incidence rate of CAPD in COVID-19 patients was reported as 13 %, with a range from 2.5 to 35 % (Chong and Neu, 2021). The treatment of the COVID-19 patients with corticosteroids such as dexamethasone and monoclonal antibodies such as tocilizumab which can affect the patients' immune system has contributed to the increase in the cases of CAPA (Salmanton-García et al., 2021). Furthermore, viral pneumonia elevates the risk of *Aspergillus* infections because of the damage caused to the airway epithelium and alveolar endothelium which can aid the *Aspergillus* invasion (Koehler et al., 2020; Herold et al., 2015). SARS-CoV-2 has also shown the ability to damage the integrity of human airway epithelial cell culture which suggests that the COVID-19 patients are at increased risk of pulmonary Aspergillosis (Zhu et al., 2020). The SARS-CoV-2 infection also causes loss of cilia in the airway epithelia (Zhu et al., 2020; Hao et al., 2020). These cilia play an important role in trapping and then transporting microbes such as Aspergillus out of the airway. Hence, the loss of cilia in the airway epithelia due to SARS-CoV-2 makes the COVID-19 more susceptible to co-infection from pulmonary Aspergillosis. In a report by Salmanton-Garcia, most of the cases (81.7 %) Aspergillosis were diagnosed within 10 days after the positive RT-PCR test for COVID-19 (Salmanton-García et al., 2021). Another study reported that Aspergillosis was diagnosed after a median of 15 days of mechanical ventilation (Machado et al., 2021). Chong and Neu reported the diagnosis of CAPA between 8 and 16 days from the onset of illness and 4–15 days from the ICU admission (Chong and Neu, 2021). Apart from invasive pulmonary aspergillosis, there have also been reports of fungal balls, and aspergilloma, in a COVID-19 patient (Patti et al., 2020). Fungal rhinosinusitis (inflammation of sinuses due to fungal infection) has also been reported in a COVID-19 patient in India which was caused by dual infection of *Aspergillus fumigatus* and Rhizopus (Sebastian et al., 2021). The patient who developed fungal sinusitis was under corticosteroid treatment and developed the fungal infection after 10–15 days of onset of COVID-19 illness (Sebastian et al., 2021).

Lahmer *et al* reported that the COVID-19 associated pulmonary aspergillosis (CAPA) is associated with the increased mortality rate (Lahmer et al., 2021). Their study showed that in the patients with CAPA the ICU mortality rate was 36 % in comparison to the COVID-19 patients without CAPA (9.5 % mortality rate) (Lahmer et al., 2021). Koehler *et al* also reported a similar outcome in their study where 44 % 30 days mortality rate was observed in CAPA patients in comparison to those without CAPA (19 % mortality rate) (Koehler et al., 2020). In a review of literature done by Machado *et al,* a mortality rate of 56.3 % was reported (Machado et al., 2021). Similarly, another study reported a very high CAPA mortality rate of 48.4 %, ranging between 22.2 % and 100 % mortality rate (Chong and Neu, 2021).

Treatment of aspergillosis in COVID-19 patients

Voriconazole is preferred for the treatment of patients with invasive Aspergillosis because of the fewer adverse effects and better results in patients in comparison to Amphotericin B (Herbrecht et al., 2002). The consensus guidance issued by the European Confederation for Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) recommend intravenous administration of either voriconazole or isavuconazole for the treatment of COVID-19 associated pulmonary aspergillosis (Koehler et al., 2020). The ECMM/ISHAM group also recommends the use of liposomal Amphotericin B (3 mg/kg/day) if resistance to azoles is observed (Koehler et al., 2020). Salmanton-Garcia *et al* reported that the treatment of CAPD with voriconazole was associated with reduced death (Salmanton-García et al., 2021). For the treatment of fungal sinusitis voriconazole and liposomal Amphotericin B have been used and for

treating fungal balls intravenous voriconazole has been used (Patti et al., 2020; Sebastian et al., 2021).

Conclusion

The studies discussed here show the increase in the cases of fungal infections among the COVID-19 patients. However, due to the limited number of cases/studies particularly among the COVID-19 patients with pneumocytosis, cryptococcosis or histoplasmosis, it becomes impossible to conclude if the fungal infections are due to SARS-CoV-2 infection, other co-morbidities or the therapy used to manage the COVID-19 patients. In the cases of mucormycosis, the studies reviewed here suggest that comorbidities such as diabetes along with the use of steroid therapy and monoclonal antibodies are likely to be associated with the increase of cases of mucormycosis among the COVID-19 patients. In the cases of aspergillosis and candidiasis in COVID-19 patients, also the co-morbidities and the therapy used to manage the COVID-19 play an important role. However, it is difficult to determine if the cases of these fungal infections and COVID-19 are causal, coincidental, or contributory. These studies suggest that the amalgamation of the effect of the SARS-CoV-2 on host immunity, co-morbidities, immunocompromised conditions along with the treatment regimen followed to manage the COVID-19 patients affect the immune system to create optimum conditions for various pathogenic fungal infections. The studies reviewed here also imply that these fungal infections are associated with the prolonged stay of the COVID-19 patients in the hospital. Further studies are required among both the healthy patients and patients with co-morbidities to establish or dismiss the role of SARS-CoV-2 infections and its treatment protocol in the increasing cases of secondary fungal infections, worldwide.

CRediT authorship contribution statement

Nahid Akhtar: Conceptualization. **Atif Khurshid Wani:** Conceptualization. **Surya Kant Tripathi:** Conceptualization. **Ajit Prakash:** Conceptualization. **M. Amin-ul Mannan:** Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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