

Covid-19 and Fungal Co-Infection: A Literature Review with Special Reference to India

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Abstract: Covid-19 pandemic and fungal co-infections have overwhelmed the healthcare facilities of many countries, including India. Development of secondary bacterial and fungal infections are well-known complications of viral pneumonia. In this pandemic situation, tracking the recent developments and disease epidemiology is of utmost importance to develop a better strategy to combat the disease. In the present study, a literature review was carried out to understand the status of fungal co-infections in Covid-19 patients. The study observed a high incidence of aspergillosis and candidiasis fungal infections in several European and American countries. While, in India, there was a surge in mucormycosis cases among Covid-19 patients. The use of vaccines and strict adherence to medical guidelines seems to be the only strategy to defeat Covid-19 pandemic and secondary infections.

Keywords: Covid-19; Fungal co-infection; Aspergillosis; Mucormycosis; Candidiasis.

Introduction

December 31st of 2019, is still fresh in our memory when a mysterious case of pneumonia was detected in Wuhan city of China. In January 2020, the causative agent was identified as a new coronavirus (2019-nCoV), and the disease was officially named Covid-19 [1]. The name was selected based on letters from the words; "co" for corona, "vi" for virus, "d" for disease, and "19" because the outbreak began in the year 2019. Globally, as of 3:24 pm CEST, 29 May 2021, there have been 169,118,995 confirmed cases of Covid-19, including 3,519,175 deaths [2]. Today, Covid-19 pandemic has spread to more than 200 countries worldwide. Fever, dry cough, and tiredness are the most common symptoms of Covid-19, including aches and pains, sore throat, diarrhoea, conjunctivitis, headache, and loss of taste or smell less-common symptoms. While in serious conditions, patients may feel difficulty breathing or shortness of breath, chest pain or pressure, or loss of speech or movement (https://www.who.int/health-topics/coronavirus#tab=tab_3). As per available reports, about 5% of patients with Covid-19 require intensive care unit (ICU) management [3]. Though Covid-19 has been with humans for more than one year now, there are no medicines to combat the pandemic. Nevertheless, the development of vaccines against Covid-19 by countries around the

world brings hope to the citizens. As per the WHO update, May 26th of 2021, a total of 1,546,316,352 vaccine doses have been administered globally.

At the time when the world is struggling with the first wave of the Covid-19 pandemic, the emergence of new variants (strains) of the SARS-CoV-2 virus with higher infectivity and transmissibility has made the fight challenging and more complicated. Several new strains of virus have been reported from different parts of the world. In September 2020, a new SARS-CoV-2 variant, called B.1.1.7 was first identified in Greater London in England [4]. On December 18, national authorities in South Africa announced another variant of SARS-CoV-2, called SAB.1.351. Similarly, other new strains such as P2, B.1.427/B.1.429, B.1.256, and B.1.617 were reported from Brazil, California, New York, and India, respectively. In March 2021, US Government formed a SARS-CoV-2 Interagency Group to look after the emergence of new covid variants. It classified the virus stains into three main classes; variant of interest, variant of concern, and variant of high consequences [5]. At the same time, available literature revealed the rise of bacterial or fungal secondary infections to Covid-19 patients, especially in patients with weak immune system and other co-morbidity such as diabetes and hypertension. Available publications suggest contrasting differences in the mortality rate of Covid-19 patients with and without fungal co-infections [6, 7]. In the present study, a critical review was carried out to understand the morbidity and mortality of Covid-19 patients co-infected with different fungal species.

Research Methodology

To review the incidence of fungal co-infections among Covid-19 patients, a literature survey was carried out using Google Scholar and PubMed databases from 25th to May 30th 2021. The main keywords and phrases used were 'Covid-19 and fungal infections, Covid-19 and aspergillosis, Invasive pulmonary aspergillosis and Covid-19, mucormycosis, Covid-19 and mucormycosis, Covid-19 and mucormycosis in India, Covid-19 and candidiasis, epidemiology of fungal infection during Covid-19, pulmonary mucormycosis, cutaneous mucormycosis.

Covid-19 and Fungal Co-Infection

Fungal (and bacterial) secondary infection to viral pneumonia is not an uncommon medical complication. Such cases have been reported during SARS (2003) and H1N1 (2009) pandemics [8, 9]. Several studies have reported fungal co-infection in Covid-19 patients. Coronavirus-associated pulmonary aspergillosis (CAPA) is one of the major fungal co-infections widely seen among patients with weak immune system. In a retrospective study from Jiangsu Province of China, Zhu and colleague [10] observed fungal and bacterial co-infection in 242 (94.2%) Covid-19 patients. However, the study showed no death in all the cases. Chen et al. [11] revealed 5% (5/99) positive cases of fungal infection, including one case of *Aspergillus flavus*, *Candida glabrata* and three cases of *C. albicans* among the Covid-19 patients in Wuhan Jinyintan Hospital of China. Yang et al. [12] also reported an almost similar (5.8%) rate of fungal co-infection in 52 critically ill patients, including *A. flavus*, *A. fumigatus*, and *C. albicans*. In a similar study, co-infections of three *Candida* spp. - *C. albicans*, *C. glabrata*, and *C. tropicalis* were reported from five Covid-19 patients in Ghana [13]. Equally, *A. fumigatus* was identified as the major fungus among 186 Covid-19 patients co-infected with pulmonary aspergillosis [14]. In another study, CAPA was diagnosed in 30 patients (27.7% of total) after a median of 4 days of ICU admission and 14 (11-22) days from Covid-19 symptom onset.

The CAPA cases reported in several publications from different parts of the world are provided as Supplementary T1. Available information showed a high mortality rate of Covid-19 patients with secondary fungal infections. Out of 148 CAPA cases shown in Table 1 from 22 publications, the mortality rate was about 50%. Similarly, a study from three Hospitals in Bologna, Italy, reported a high death rate of 44% in CAPA cases than patients without CAPA (19%) [15].

In China, among the 221 ICU admitted Covid-19 patients, fungal co-infection was diagnosed in seven patients. However, no data was presented about the causative agent of the co-infection [16]. In a similar study from Spain, Bardi et al. [17] observed that 40.7% (of 140) Covid-19 patients developed fungal and bacterial co-infection during ICU stay. Generally, secondary co-infections were observed at a median of 9 days of ICU admission. At an academic hospital in Santiago, Chile, 16 cases of mucor mold infection were seen among 164 Covid-19 patients, and the mortality was 32% [18]. Recent publications reported that at least 10% of co-infection during Covid-19 in patients hospitalized in ICU were *Aspergillus* infections [11]. In a review paper, Mohamed et al. [19] reported 38 Covid-19 patients from Europe co-infected with CAPA, where 13 patients died. *A. fumigatus* was reported as the major causative agent of fungal co-infection. Al-Hatmi et al. [13] reported five Covid-19 associated Candidiasis from Oman who had central venous catheter at the onset of the disease and received antibiotic therapy.

Candidiasis is another important disease caused by *Candida* spp. of fungus. Supplementary T2 showed the prevalence of Candidiasis among Covid-19 patients from different parts of the world. Three patients died after 7-14 days of ICU admission, and *C. albicans* and *C. galabrata* were detected from the patient's blood culture. In Florida, six patients were found *C. auris* positive out of 35 Covid-19 patients with secondary infections. At the same time, eight patients lost their lives within 30 days of diagnosis out of 67 Covid-19 patients. However, whether *C. auris* contributed to the death was unknown [20]. In a nationwide study, White et al. [21] reported 26.7% fungal co-infection (14.1% aspergillosis, 12.6% yeast infections) among 135 Covid-19 patients from the United Kingdom. The overall mortality rate was 38%, 53% and 31% in patients with and without secondary fungal infections. They also opined the use of corticosteroids and history of chronic respiratory disease as the major risk factors for aspergillosis. Similarly, Antinori et al. [22] reported three cases of candidemia out of 43 Covid-19 patients infected with *C. albicans*, *C. tropicalis*, and *C. parapsilosis*, respectively. All the candidemia patients survived by Parenteral nutrition and Tocilizumab treatment. In Iran, 53 Covid-19 patients were reported to be co-infected with Oropharyngeal Candidiasis. After about five days of antifungal therapy with fluconazole, nystatin and caspofungin, all the patients recovered from the disease and survived [23]. In Lebanon, the first report of Candidiasis with *C. auris* infection was reported among 14 Covid-19 patients, five of whom succumbed to death due to hypoxia and septic shock [24]. Figure 1 showed the mortality of Covid-19 patients with secondary fungal infections.

Covid-19 and Fungal Co-Infection in India

India has seen a surge in secondary fungal infections among Covid-19 patients. The second wave of Covid-19 accompanied by fungal co-infection, called 'mucormycosis (MCR)', popularly known as Black fungus, has challenged the healthcare infrastructure of India. MCR is a life-threatening fungal co-infection caused by molds belonging to the subphylum Mucoromycotina in the order Mucorales [25]. MCR causes blackening or discoloration over the nose, blurred or double vision, chest pain, breathing difficulties, and coughing blood. Like aspergillosis, MCR also caused a high mortality rate

in Covid-19 patients. MCR has also been reported from several other parts of the world (Supplementary T3). According to the Government resources, India has recorded 11,717 cases of MCR patients till May 25 2021, with Gujarat, Maharashtra, Andhra Pradesh, Madhya Pradesh, and Telangana together account for over 65% of the total cases.

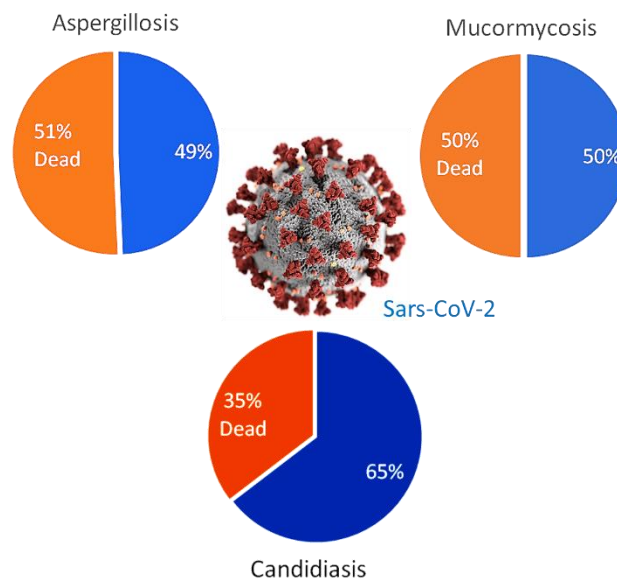


Figure 1: Covid-19 with secondary fungal infections and percentage of death.

In a multi-centric study by clinicians of three different specialties in Bangalore, India—ENT, maxillofacial surgery and ophthalmology 18 Covid-19 patients were reported with aggressive maxillofacial rhino-cerebro-orbital fungal co-infection [26]. The study also revealed that corticosteroid and uncontrolled diabetes mellitus is the underlying risk factor of the six patients who lost their lives during the treatment. In a recent survey, Khurana et al. [27] reported MCR co-infection in 151 Covid-19 patients (out of 1179) in AIIMS hospital, Delhi, where the death rate was found to be 33% (of co-infected cases) with a median hospital stay of 12 days. *Candida* fungal spp. was observed in the urine culture of the patients.

Along with many other clinical manifestations, Nehara et al. [28] also observed rhino-orbital MCR in five Covid-19 patients from Rajasthan, and *Rhizopus* spp. was found to be the causative agent. A retrospective study of secondary infections from June to August from 10 ICMR hospitals revealed the development of secondary bacterial or fungal infections among 3.6% of 17534 Covid-19 patients. The mortality rate was 56.7% in secondary co-infected patients against the overall mortality of 10.6%. The study also reported 16 cases of *Aspergillus* infection in the respiratory specimen of the patients. In a systemic survey of MCR prevalence, Singh et al. [30] reported 82 Covid-associated MCR cases with diabetes and corticosteroid treatment as the major risk factors. Rhinocerebral MCR was reported in 88.9% of the patients, while rhino-orbital MCR was observed in 56.7%. The mortality rate was found to be 30.7%. Sen et al. [31] reported rhino-orbito-cerebral MCR in six patients who received corticosteroids during Covid-19 treatment. The rhino-orbital mucormycosis symptom appeared about 30–42 days following Covid-19 diagnosis.

Similarly, Sarkar et al. [32] reported ten cases of orbital mucormycosis in Covid-19 patients with diabetes co-morbidity. Within one month of the diagnosis, four patients expired. Five patients had satisfactory systemic results but with irreversible vision loss in them. In contrast, one patient had a favorable outcome. Similarly, *Candida* sp. fungal infection was reported in 15 ICU admitted Covid-

19 patients in Delhi, of which eight patients died [33]. In a recent study, Revannavar et al. [34] observed one Covid-19 patient with mucormycosis with left-sided facial pain, complete ptosis and fever as clinical presentation. After one week of conventional amphotericin B and antibiotics treatment, the patient showed significant recovery and improvement. Until this paper's writing, there was little information about the aspergillosis cases in India except for few media reports.

Clinical Presentation of Fungal Co-Infection

Symptoms of some fungal co-infection are similar to Covid-19, including fever, cough, and shortness of breath. Many studies reported bacterial and fungal infections mainly in severe Covid-19 patients, such as those in ICU. Patients hospitalized in ICU for Covid-19 share risk factors and underlying diseases reported for fungal infection, particularly chronic respiratory disorders, corticosteroid therapy, intubation/mechanical ventilation, cytokine storm, etc. [35]. The most common fungal infections in patients with Covid-19 include aspergillosis, candidiasis, or mucormycosis [34, 35].

Aspergillosis

Aspergillosis is an infection, allergic reaction, or fungal growth caused by the *Aspergillus* fungus. The illnesses usually affect the respiratory system, but their signs and severity vary greatly (<https://www.healthline.com>). Aspergillosis or invasive aspergillosis often occurs in people who already have other medical conditions, making it difficult to differentiate the symptoms of aspergillosis. Cough (sometimes with blood), chest pain, shortness of breath, and fever are the common symptoms. The infection starts with the inhalation of *Aspergillus* spores (conidia), followed by deposition in bronchioles or alveolar spaces. Individuals with strong immunity can evade the conidia infection. In contrast, weaker immunity fails to neutralize it, leading to the germination of fungus in the lung [36]. Available reports suggest the development of aspergillosis in patients with severe immunodeficiency [37]. In invasive pulmonary aspergillosis, invasion of pulmonary vasculature causes tissue hypoxia, which is enhanced by secreted fungal metabolites that downregulate angiogenesis. However, aspergillosis may infect organs other than the lungs, such as sinuses, gastrointestinal tracts, or skin [38]. Besides the diffuse alveolar damage with severe inflammatory exudation, Covid-19 patients may require intensive care unit in critically ill patients. More extended hospital stays or mechanical ventilation patients were more likely to develop fungal co-infections [12].

Candidiasis

Candidiasis is another fungal infection caused by a yeast (a type of fungus) so called *Candida*. Yeast species such as *Candida albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* are the most predominant fungal species residing on several mucosal surfaces, skin and the respiratory, digestive, and urinary tracts [39]. In most cases, candidiasis is harmless, but it can cause serious infections that range from superficial skin infections to life-threatening systemic diseases under certain circumstances. Sporadic incidence of candidiasis has been reported from different parts of the world. The most common symptoms of invasive candidiasis are fever and chills that do not improve after antibiotic treatment. Other symptoms can develop if the infection spreads to other parts of the body, such as the heart, brain, eyes, bones, or joints. *Candida* usually lives on the skin and inside the body, mouth, throat, gut, and vagina, without causing any problems. However, it can cause infections if it grows out of control [40]. As a mechanism of pathogenesis, fungal cells adhere to the

cell surface by expressing some adhesive molecules. These secretory molecules finally mediate the fungal cells to enter inside the host cells to endocytosis. Inside the host cells, fungal infections start by activating secondary mechanisms [41]. However, the details of the mode of action are not fully understood.

Mucormycosis

Mucormycosis (MCR), commonly known as 'black fungus' is a rare fungal disease caused by exposure to mucor mould, commonly found in soil, air and even in the nose and mucus of humans. *Rhizopus oryzae* is the most common causative agent and detected in ~70% of mucormycosis cases [42]. Like aspergillosis, mucormycosis infection can occur if someone inhales fungal spores and the immune system fails to clear them [43]. Diabetes ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ transplantation, neutropenia, trauma and burns, malignant hematologic disorders, and deferoxamine therapy acts as a risk factor for mucormycosis [44]. The fungal infections affecting different body parts show other symptoms. Likewise, the MCR of sinuses and brain is called rhinocerebral MCR, pulmonary MCR for lung, cutaneous MCR for skin, and gastrointestinal MCR. The primary symptoms of rhinocerebral MCR include one-sided facial swelling, headache, fever, nasal or sinus congestion, or black lesions on the nasal bridge or upper inside of mouth that quickly become more severe. Like Covid-19, fever, cough, chest pain, and shortness of breath are the major symptoms of pulmonary MCR. Similarly, blisters or ulcers, blackening of the infected area, pain, warmth, excessive redness, or swelling around the wound are the known symptoms of skin MCR. Symptoms of gastrointestinal MCR include abdominal pain, nausea and vomiting, and gastrointestinal bleeding. It was observed that Covid-19 patients under corticosteroid therapy carry a risk of rhino-orbital and rhino-orbitocerebral mucormycosis, especially when the patients have another risk factor like diabetes mellitus or hypertension or both.

Conclusion

This work was done by the importance of dealing with the Covid-19 pandemic in combination with the fungal co-infections. The fungus can grow to a wide range of environments; soil, water, dead or decaying matters or sometimes on living bodies. The emergence of fungal co-infection has severely affected the healthcare infrastructure and treatment strategy of Covid-19. Medical practitioners have prescribed several broad-spectrum antimicrobial drugs. Despite the best efforts, the mortality rate of patients with fungal co-infection is higher than Covid-19 patients. There is little information that establishes a relationship between Covid-19 and fungal infection. Co-morbidities such as diabetes, hypertension or weak immunity seems to increase fungal susceptibility in Covid-19 patients. In India, Covid-19 associated fungal infection is rising, though sporadic in other parts of the world. Available information suggests improper use of steroids as one of the many reasons for post-covid fungal infection. Medical fraternity also believes whether using cocktails of drugs during Covid-19 treatment has anything to do with mucormycosis in India? A thorough scientific study is the need of the hour to go into the bottom of the fungal co-infection during the Covid-19 pandemic.

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Supporting Information

Any further supporting information will be provided upon sending a direct request to the corresponding author: A. Swargiary (*Email: ananbuzoo101@gmail.com*).

Disclosure Statement

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