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Review Article

# Occurrence of mucormycosis in association with Covid - 19 pandemic

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ABSTRACT

Mucormycosis is a severe and potentially fatal fungal infection caused by opportunistic fungi belonging to the class *Zygomycetes*. *Coronavirus* 2019 (COVID-19) is a severe worldwide disease. One of the problems faced by Covid-19 patients is concurrent infection with microbial agents such as life-threatening fungal infections. Studies show that people with diabetes who have recovered from COVID-19 are more likely to develop mucormycosis. In addition, patients with COVID-19 are at increased risk of acute heart damage, arrhythmias, thromboembolic complication, and secondary infection. However, the exact reasons and mechanisms of increasing this deadly infection need to be investigated to understand the pathogenicity and discover reasonable ways of prevention and treatment. Studies show that increasing overuse of steroids, antibiotics, and zinc as an act of self-medication during the Covid-19 epidemy may increase intestinal microbiota dysbiosis, thereby suppressing the system—immunity in the group at risk of this fungus. Ocular and cerebral mucormycosis is the most common form of the disease, with a mortality rate of over 49%, especially in patients with pulmonary or diffuse or cerebral mucormycosis. In addition, a significant proportion of survivors of the disease showed symptoms such as 46% vision loss. This article addresses potential mechanisms, host-related factors, pathogenicity, and innate and acquired immune system responses that may help understand the mystery of the sudden, severe, and fatal increase in mucormycosis infections due to Covid-19. Early detection of such conditions with the above-mentioned consequences is vital for optimal treatment and better results.

## 1. Introduction

The world is facing a devastating epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Systemic corticosteroid therapy can reduce mortality in people with the most severe disease episodes. However, in combination with immunological and other clinical factors, this treatment can predispose patients to secondary fungal disease. Although COVID-19-associated pulmonary aspergillosis has been of high interest in the literature on

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COVID-19 secondary infections. There are other systemic fungal infections, including candidiasis, fusariosis, and mucormycosis, that are probably underreported in association with COVID-19 are less probably reported. Risk factors that predispose patients to mucormycosis include uncontrolled diabetes, neutropenia, blood malignancies, organ transplants, trauma and burns, and immunosuppressants such as corticosteroids (Hoenigl et al., 2022). In addition diabetes is a significant comorbidity that complicates the management of COVID-19. Although dexamethasone is helpful in some groups of COVID-19 patients admitted to the hospital, it can increase the risk of invasive fungal infections. Hyperglycemia occurs in people with undiagnosed or uncontrolled diabetes but can also be caused by corticosteroids. Patients with diabetes and hyperglycemia often have an inflammatory condition that causes persistent uptake and local activation of immune cells, including macrophages and neutrophils, which secrete proinflammatory cytokines and produce persistent inflammation. In these patients, activating antiviral immunity to SARS-CoV2 may potentiate this inflammatory phenotype, contributing to secondary infections (Chan et al., 2021). The diagnosis of COVID-19-associated mucormycosis is challenging because the clinical and radiological features of pulmonary and disseminated mucormycosis are nonspecific and may overlap with findings thought to be associated with COVID-19, leading to no or late diagnosis. Mucormycosis associated with COVID-19 can also be confused with other invasive fungal diseases that invade vessels, particularly with pulmonary aspergillosis associated with COVID-19, which is the predominant disease form of acute respiratory distress syndrome associated with COVID-19.

The presence of a reverse air crescent, mainly in the peripheral areas of the lung, has been suggested as a predictor of pulmonary mucormycosis in immunocompromised patients that helps initiate preventive antifungal therapy. However, it is less specific in patients with COVID-19, although it has also been described as a potential radiological feature of COVID-19. Although cavities in the lungs may be more common for fungal diseases in COVID-19 than the reverse halo, lesions are more common in COVID-19-associated pulmonary aspergillosis and COVID-19-associated pulmonary mucormycosis. In the absence of serum antigenic biomarkers and the lack of access to molecular tests in low-income countries, the diagnosis of mucormycosis related to Covid-19 is also challenging (Islam et al., 2022). Despite a limited number of reports of Covid-19-associated mucormycosis, there are still few studies that compare the disease in different parts of the world. The purpose of this review is to describe the epidemiology of risk factors, pathogenicity, and treatment of mucormycosis, Covid 19, and the outcome of COVID-19-associated mucormycosis based on influencing immune system factors.

## 2. *Mucur* molds

*Mucur* molds are of Mucorales memberes. Eleven genera and 27 species in Mucorales are associated with human infections. *Rhizopus arrhizus* is the most common causative agent of mucormycosis worldwide, followed by *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, *Mucor*, and *Cunninghamella*. From a morphological aspect of view, they appear with no transverse walls and are widely found in soil, on plant surfaces, decaying fruits, vegetables, and animal manures. Most mucous molds cannot grow in the human body because their temperature is not suitable for their growth (Kumar et al., 2021).

### *2.1. Mucormycosis and clinical signs*

Mucormycosis is a severe and potentially fatal fungal infection caused by a *zygote* class's rare but opportunistic fungal pathogen. People become infected mainly by inhaling sporangia, eating contaminated food, or harmful injections into the skin. If the fungus succeeds in causing disease in humans, its spores block blood flow by creating invasive hyphae in the arteries and surrounding tissues, and by spreading in the body, they cause widespread tissue death. Recently, mucormycosis, also known as black fungus, has increased mortality in patients with Covid 19 with invasive mucormycosis.The causative agents of mucormycosis are present throughout the year in the environment, and a strong seasonal pattern of infection is observed (Vaezi et al. 2021), Most diseases are common in the early stages of the hot, dry summer, and

most cases are reported at the end of the season. During this period, there is a high temperature, relative humidity, and minimal rainfall. The same was true of the prevalence of mucormycosis in India, especially in the second wave of the Covid-19 epidemic. Therefore, the seasonal trend in mucormycosis can be related to the prevailing climatic conditions.

*2.2. Clinical forms*

Mucormycosis includes the following:

**A.** Rhinocerebral mucormycosis, which is associated with sinus and brain involvement, is more common in people with diabetes and those who have had a kidney transplant (checkenbach et al., 2021). Symptoms include unilateral swelling of the face, pain, headache, fever, blindness, and Black spots as necrotic tissue. If invasive interventions such as antifungal treatments and debridement of dead tissue that make the patient look bad are not performed, mucormycosis will quickly kill the patient. People with weakened immune systems are prone to mucormycosis.

**B.** Pulmonary form is the most common type of mucormycosis in people with cancer and those with organ transplants or bone marrow transplants are susceptible to this form.

C. The gastrointestinal form is more prevalent among premature and low birth weight infants, who became susceptible to this infection under surgery, broad-spectrum antibiotics, or drugs that weaken the immune system (Tinmouth et al., 2001).

**D.** The skin form is observed in people with leukemia, uncontrolled diabetes, transplant patients, people with AIDS, and those taking intravenous drugs after burns, or skin damage.

The 1950 Smith and Krishner criteria are considered the gold standard for the clinical diagnosis of mucormycosis, including blackening and necrosis of the nasal septum that is easily confused with dried blood. Nasal discharge with blood and facial pain, soft swelling around the orbital or the nose with discoloration and stiffness, eyelid ptosis, eyeball proptosis, ophthalmoplegia, and cranial nerve palsy are seen in this disease (Kumar et al., 2021).

*2.2.1. Pathogenicity of risk factors*

The main risk factors include corticosteroids, neutropenia and uncontrolled diabetic ketoacidosis, bone marrow or organ transplants, burns, and other traumatic injuries that cause cracks in the skin. It has also been observed that people with underlying diseases such as neutropenia, iron deficiency due to deferoxamine mesylate treatment in kidney disease, kidney failure, malnutrition, cirrhosis of the liver, and conditions such as AIDS and lymphoma that are related to the immune system, are prone to this disease. In addition, tuberculosis has been reported as a risk factor for mucormycosis (Werthman-Ehrenreich et al., 2021). Studies show that people who defect in phagocytic cells or have a poor phagocytic function are at higher risk of developing mucormycosis. For example, patients with severe neutropenia are at risk of mucormycosis. In contrast, AIDS patients do not appear to be at increased risk for mucormycosis. These findings indicate that neutrophils are critical for inhibiting fungal spore proliferation. In addition, mononuclear phagocytes and polymorphonuclears in immunocompromised hosts destroy mucorals by producing oxidative metabolites and cationic peptides and defensins (Morales-Franco et al., 2021).

*2.2.2. Epidemiology of mucormycosis*

Changes in the epidemiology of mucormycosis have been observed in recent years with increasing prevalence, new causative agents, and susceptible populations. This rise is perceived globally but is very high in Asia. Although diabetes is the most critical risk factor in Asia, tuberculosis and chronic kidney failure are also known as new risk groups. Cerebral nasal mucormycosis is more common in patients with diabetes, while pulmonary mucormycosis is more common in patients with hematologic malignancies and transplant recipients (Sharma et al., 2022). Renal mucormycosis has also been reported in immunocompromised patients from China and India alone. The causative agents of mucormycosis vary in different geographical locations. Although *Rhizopus oryzae* is the most common isolated species worldwide. *Apophysomyces variabilis* is prevalent in Asia and *Leichthemia* species in Europe. New agents, *Rhizopus homothallicus*, *Mucor irregularis*, and *Thamnostylum lucknowense*, have been reported from Asia. Mucormycosis is rare, and its

prevalence depends on the geographical location. The disease is about 80 times more common in India. This is the third serious fungal infection after aspergillosis and candidiasis to which people become contaminated. Health officials in various Indian states reported a deadly outbreak of black fungus, and an increase in cases of mucormycosis prompted the Indian government to declare an epidemic. Reports of black fungus in early May 2021 indicated that the patients included those who had recently recovered and had weakened immune systems or those with underlying diseases such as diabetes. Mucorales are heat-resistant fungi found everywhere in nature and are widely found in decaying organic matter. People can become infected by inhaling the spores of these fungi through air humidifiers or water in oxygen tanks in hospitals or homes. In the black fungus epidemic in India, there were reports of a very high incidence of 7250 cases in May 2021. The epidemic has focused on Maharashtra and Gujarat. The epidemiology of mucormycosis in different risk groups depends on the analysis of the clinical pattern of the disease, its geographical location, and the identification of other species of mucoracles. although the prevalence of mucormycosis is increasing worldwide and in Asia, this increase belongs in India and China among patients with uncontrolled diabetes, a study of 851 cases of mucormycosis from January 2000 to 2017 showed a higher incidence of the disease in Europe than in Asia (34% in Europe and 31% in Asia North or South America (28%), Africa (3%), Australia, and New Zealand (3%). The article associates contradictions in infected patients' data with wrong reports from Asian countries in that period of time. in fact, an increasing number of cases have been reported in India.

Eleven genera and 27 species have been identified in the category of mucolores that cause mucormycosis determined by macroscopic, microscopic methods, and molecular techniques. Species of the genera *Rhizopus*, *Lichtheimia*, and *Mucor* are the most common causative agents, and *Rhizopus arrhizus* is the most common agent. A meta-analysis of mucormycosis cases showed that *Rhizopus* species are often the cause of *Rhinocerebral Mucormycosis*. A variety of species distribution was observed between different geographical areas. Infections caused by *Lichtheimia* species are common in Europe and relatively rare in other regions. Apophysomyces variabilis is the second most common cause of mucormycosis in India. In India, approximately 60% of cases of mucormycosis are caused by *Apophysomyces* species. In addition to *Apophysomyces variabilis* infections caused by *Rhizopus Microsporus* and *Rhizopus homothallicus* are rising in India. A case of fatal lung infection caused by *Rhizopus homothallicus* has been reported in France. Infections caused by unusual mucoral species by *Cokeromyces recurvatus*, *Syncephalastrum*, and *Saksenaea* are rarely reported. A detailed ecological study in India finds the presence of many different species of Mucorales, such as *Apophysomyces variabilis* and *Rhizopus homothallicus*, in Indian soils. According to studies, the exact burden of mucormycosis is not known; it is rare in developed countries. The disease is common in developing countries, but laboratory facilities are not optimal in the region, as risk groups and interventions are different in developing and developed countries. In developing countries, the prevalence of diabetes is alarmingly high, which may increase the incidence of mucormycosis. In developed countries, increased mucormycosis is associated with severe immune system suppression in malignancies of blood and transplant recipients. Changes in the epidemiology of mucormycosis have been noted in recent years with the emergence of new risk factors. chronic kidney failure and staying in an intensive care unit are new risk factors for the disease, after tuberculosis, especially in developing countries. New species are emerging, including *Rhizopus homothallicus*, *Thamnostylum lucknowense*, and *Mucor irregularis* (Skiada et al., 2020). Understanding the global epidemiology of the disease requires population-based studies of people at particular risk (e.g., diabetes, transplant recipients).

### *2.2.3. Prevention and treatment*

Preventive measures include using masks in dusty areas, avoiding direct contact with damaged and decaying, and fungal buildings, and protecting feet and hands skin in cases exposed to soil or manure, such as gardening or specific particular tasks outdoors. In high-risk groups, such as those with a transplant, antifungal drugs may be prescribed as a preventative measure. If the disease is

suspected, amphotericin B is first given slowly intravenously, then every day for 14 days.

Treatment with amphotericin sometimes lasts longer. In 2015, the FDA approved isavuconazole as a treatment for mucormycosis. Posaconazole is also an alternative treatment. Other treatments include the removal of the fungal ball through surgery. The disease must be carefully monitored for symptoms of re-emergence. Surgery can be very severe, and removal of infected brain tissue may be needed if the fungus has invaded the nasal cavity and brain. Removing the palate, nasal cavity, or eye structures can prevent spreading to other areas. Sometimes more than one operation is required. Hyperbaric oxygen has been used as adjunctive therapy because oxygen pressure further increases the neutrophil's ability to kill the fungus. The effectiveness of this treatment is unclear (Hage et al., 2022).

## 3. Covid-19 virus

### *3.1. Virology*

The causative agent of coronavirus 19 is a new coronavirus belonging to the genus Beta-coronaviruses of the coronaviridae family. Human beta-coronaviruses (SARS-Corona, Mers-Corona, SARS-Corona-2) are very similar, but there are differences between genetic and phenotypic structures that contribute to their pathogenicity (Hu et al., 2020). The virus also enters the target cell by binding to angiotensin 2 (ACE2) receptors, abundant in the respiratory and gastrointestinal tracts Some coronaviruses also contain hemagglutinin-esterase protein. Coronaviruses are a large family of positive single-stranded RNA viruses, including genera α, β, γ, and δ, with varying degrees of pathogenicity and immunogenicity. Most CoVs only cause self-limiting respiratory infections. In contrast, SARS-CoV, SARS-CoV-2, and MERS-CoV belong to the genus β-CoV and may cause acute respiratory distress syndrome (ARDS) and extrapulmonary manifestations of diarrhea, shock, severe renal and hepatic impairment, and Multiple organ dysfunction syndromes (MODS). The genomic structure of SARS-CoV-2 provides important information about the pathogenicity and related pathogens. The entire SARS-CoV-2 genome has been sequenced and contained 29,903 nucleotides. SARS-CoV-2 is genetically like SARS-CoV and bat-like SARS viruses found 82% nucleotide similarity between SARS-CoV-2 genome and human SARS-CoV genome. The genetic analysis further confirmed that SARS-CoV-2 is 79% homologous to SARS-CoV and 50% homologous to MERS-CoV20. Structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, play an essential role in the pathogenesis of viruses, as well as the accumulation and structure of virions. Glycoprotein S has a powerful effect on the virulence phenotype of the virus. S protein is the primary protein that mediates the binding of SARS-CoV-2 to the ACE2 receptor of host cells and induces membrane fusion, which plays an important role in the entry of the virus into the cell.

### *3.2. Covid disease, transmission methods, clinical signs, and epidemiology:*

Covid 19 virus, which was initiated in China in December 2019 and is currently affecting many countries worldwide, including Iran, has been officially declared a pandemic by the World Health Organization (Zhang et al., 2020). The disease can range from a simple infection to acute respiratory failure syndrome. In the Covid-19 virus, factors such as cytokine storm. Genetic predisposition, hemoglobin chain disorder and blood type determines how and to what extent this new virus is damaging the human respiratory (Zietz et al., 2020). Covid virus 19 has a wide range of clinical symptoms divided into two types, respiratory and non-respiratory. The disease with respiratory signs, such as dry cough, fever, shortness of breath, and sore throat symptoms is more common. The non-respiratory form accounted for 11% of cases in the form of gastrointestinal symptoms. In addition, skin manifestations were also observed in the covid-19 disease, and studies attributed the cause of skin manifestations to blood supply disorders. Another non-respiratory form is the neural form. The virus enters the central nervous system through various channels such as blood, lymph, and nerves, causing neurological symptoms caused by hypoxia and inflammation caused by the cytokine storm. In Iran, cough and fever symptoms are more common in the elderly. Lack of oxygen and inflammatory reactions and side effects of treatment for viral damage to heart tissue, while the virus has not been isolated from the heart cells, have also led

to cardiac symptoms. Ocular manifestation is another clinical sign of Covid-19. Also, in laboratory tests, the titer of the virus antigen in the throat sample is critical. The highest prevalence of Covid 19 disease is reported in the fifth decade of life and in males. The disease has been observed at a younger age. However, children with severe forms of the disease are less common (Castillo-López et al., 2020). The disease course is between 5 to 14 days, and even in some articles, 24 days. In Covid 19 disease, one of the essential factors in the spread of the disease is the presence of asymptomatic patients. Screening tests in optimal conditions can identify 50 to 95% of asymptomatic cases. In this disease, three stages are defined based on severity, consisting of three phases: mild, moderate, and severe, sometimes called mild, intense, and critical. In the mild phase, it is controlled by supportive therapies without the need for hospitalization. In the moderate phase, drugs and support, and hospitalization is needed. In the severe phase of clinical symptoms, clinical signs are indicative of acute respiratory failure syndrome. The patient needs artificial respiration and hospitalization in the ICU. Transmission of the virus through coughing, sneezing, or talking to a symptomatic patient can occur within one to two meters, although asymptomatic patients can also play a role. Other means of transmission are aerosols in the inhaled air, in which the virus adheres to the particles in the air and can be contagious over long distances and even last up to three hours. Some also believe that aerosol transmission is possible only at a very close distance from the patient. Otherwise, the virus is too heavy to remain in the air for hours. Another way of transmission is direct contact with the patient through handshake and hugging that infected particles in the hands enter the body through mucous surfaces (mouth, nose, eyes, etc) (Ehsanifar et al., 2021). The duration of the Covid-19 virus persistence on the skin surface is 9 hours (flu approximately 7 hours) and it disappears within 15 seconds after topical use of 80% alcohol. The virus lasts for more than nine days on lifeless surfaces in low temperatures and humidity. The real role of the transmission is from unknown levels. Public places for smoking, changing rooms, bathrooms, common rooms, areas where many people move around, and cafeterias are among the most polluted places (Rollenskeet al., 2021).

### *3.3. Covid 19 pathogenicity and risk factors*

The flu is an acute and highly contagious viral infection. Reproduction of the virus in the upper respiratory tract occurs in the trachea of most patients. The disease is benign but may be associated with (a) primary influenza viral pneumonia, (b) Secondary bacterial pneumonia, and (c) Combined flu from viral pneumonia and bacterial pneumonia. During the several epidemic years of 1918, 1947, and 1968, the virus emerged as a common mutant between humans and animals, most likely derived from animals (pigs, birds). Covid-19 is a different virus that often causes a flu-like illness. RNA COVID-19 in coronavirus is thought to be a mutated form of the virus similar to that obtained from bats the earliest cases of novel coronavirus (2019-nCoV)-infected pneumonia (NCIP) occurred in Wuhan, Hubei Province, China and were linked demographically to Huanan Seafood Wholesale Market. Five years prior to this pandemic, another group identified a severe acute respiratory syndrome (SARS)-like a virus, SHC014-CoV circulating in Chinese horseshoe bat populations as a potential risk for SARS-CoV human outbreak. Studies show that the genomes of these two viruses are very similar to the entire genome of the bat coronavirus, which is based on the presence of the same angiotensin-converting enzyme (ACE2) receptor that enters the cell (Bahadori et al., 2021).

### *3.4. Pathogenesis of Covid 19*

The pathogenesis of the new coronavirus (COVID-19) has not yet been fully elucidated. Clinical and experimental findings from studies examining COVID-19 have shown that the immune system's inflammatory responses play an essential role in the critical infection of acute coronary syndrome 2 (SARS-CoV-2). Severe covid-19 is characterized by limb dysfunction, hypercytokinemia, and lymphopenia. It is hypothesized that direct cytopathological harm of the host cells and an irregular immune response induced by SARS-CoV-2 may be the primary underlying mechanisms for COVID-19 infection (Gates et al., 2020).

*3.5. Treatment and prevention*

In most cases and mild forms of the disease, treatment is maintenance-based and based on symptom control and patient isolation. Anti-inflammatory drugs, anti-malarial drugs, and anti-viral drugs have been tested, and the evaluation of their definitive effectiveness has been postponed to future studies. Methods such as plasma therapy and treatment with Mesenchymal cells are also being studied (Hafeez, 2020). Sometimes complementary medicine, especially Chinese medicine and Iranian medicine has presented theories and strategies for the prevention and treatment of Covid 19. For example, according to traditional Iranian medicine, an important factor in developing this disease is instinctual heart weakness and lung and heart weakness. With this view, substances that strengthen instinctual heat and lung and heart, such as honey and saffron, may be effective in preventing the disease or treating the early stages. Medicinal plants such as jujube, chamomile, floss, and sorrel, as well as consumption of peppermint, almonds, raisins, grape juice, apple paste, quince paste, aromas such as rose and reduction in the volume of food, especially pastries, yogurt, buttermilk, the use of soups, and foods containing rice, barley, coriander, spinach, fenugreek, squash, chickpeas, have been suggested as other solutions of traditional Iranian medicine. There are studies on the effect and mechanism of medicinal plants on specific viruses. For example, oranges, blackberries, and chamomile have anti-coronavirus-family effects in laboratory environments. The active ingredients of some plants, such as licorice, have been effective against the SARS virus in laboratories and may have the potential to affect Covid-19. Recent studies have suggested herbs such as oranges and garlic because of their inhibitory effect on ACE enzyme 2 in Covid-19. A study in Iran found a relationship between blood magnesium deficiency and arterial blood oxygen saturation in patients with an acquired lung infection. However, supplements should not be overused. According to some studies, higher than normal blood magnesium levels, same as magnesium deficiency, have increased mortality in patients with an acquired lung infection. In a study using 450 FDA-approved chemicals, ACE2-spike interactions were blocked. Three drugs were selected, including an antifungal drug and two antiretroviral drugs (anidulafungin, lopinavir, and indinavir) that showed a high affinity for ACE2 receptors. The activity of the selected compounds was finally tested using Vero and HEK-ACE2 cells in laboratory conditions. Overall, anidulafungin and lopinavir are the most effective drugs that have been tested against ACE2-S receptor antagonists. Based on the studies, it was suggested that anidulafungin is a potential new drug that targets ACE2, which warrants further research in the treatment. COVID-19 requires (Abubakar, 2021).

## 4. Relationship between mucormycosis and Covid 19

Coronavirus 2019 (COVID-19), caused by Coronavirus Acute Respiratory Syndrome (SARS-CoV-2), has been linked to a wide range of opportunistic fungal and bacterial infections. Aspergillus and Candida have been identified as significant pathogens involved in co-infection with COVID-19. Several cases of mucormycosis in people with COVID-19 have been reported increasingly worldwide, especially in India (Mahajan, 2022).

*4.1. COVID-19-associated mucormycosis*

As it has been shown in Table 1, COVID-19 has been associated with many fungal infections (Table 1). Fungal infections in COVID-19 are caused by lymphopenia and changes in the immune system. The change in the number of granulocytes and monocytes caused by the Covid-19 virus leads to lung tissue damage and makes it susceptible to fungal infections. Studies have shown that changes in iron metabolism occur in COVID-19 infection. Diabetic ketoacidosis may cause ferritin synthesis and increased intracellular iron concentrations. An autopsy performed on COVID-19 patients showed vascular endothelial damage and the formation of new blood vessels (Girelli, 2021). COVID-19 infection can damage pancreatic lymphocytes and beta cells directly and cause lymphocytopenia, thrombocytopenia, and an insulin-like state.

Steroids suppress the immune system by inhibiting the transcription of cytokine genes, especially IL1 and 6, and by isolating CD4 + lymphocytes (Conti et al., 2020).

**Table 1**. Association of COVID-19 and fungal infections

| Country | Number of cases | species | Clinical presentation | Site of infection | outcome | References |
|---|---|---|---|---|---|---|
| Brazil | 1 | NA | Gastrointestinal | Gastrointestinal | Died | Sarkar S et al. 2021 |
| Egypt | 8 | Aspergillosis | Pulmonary | Respiratory system, orbital cavities, ethmoidal and maxillary sinuses, nasal cavity, nasopharynx, carotid artery, hard palate, skin | Alive (n = 5) Died (n = 3) | Ashour MM et al. 2021 |
| Egypt | 36 | Mucor and Aspergillus species | Rhinoorbital–cerebral, sinoorbital | Facial painfacial numbness, ophthalmoplegia, and visual loss | Died (n = 13) Alive (n = 23) | El-Kholy NA et al. 2021 |
| France | 1 | Rhizopus microsporus | Pulmonary | Lung | Died | Sargin F et al. 2021 |
| India | 10 | Rhizopus spp. | Rhino-orbit cerebral | Nasal sinus, Orbit CNS | Died (n = 4), Alive (n = 6) | Moorthy A et al. 2021 |
| India | 1 | Rhizopus oryzae | Nasal sinus, orbit | Sino-orbital | Alive | Karimi-Galougahi M et al. 2021 |
| India | 1 | Rhizopus microsporus | Pulmonary | Lung | Alive | Maini A et al. 2021 |
| Iran | 1 | NA | Rhino-orbital | Variable | Died | Pakdel F et al. 2021 |
| Iran | 2 | NA | Rhino-orbitocerebral | Nasal sinus, Orbit, CNS | Died (n = 1), Alive (n = 1) | Zurl C et al. 2021 |
| Iran | 1 | NA | Rhino-orbital | Nasal sinus, Orbit | Alive | Waizel-Haiat S et al. 2021 |
| Italy | 1 | Rhizopus spp. | Pulmonary | Nasal sinus lung | Died | Pasero D et al. 2020 |
| Spain | 1 | *Rizopus oryzae* | Rhinosinusal | Nasal sinus, Orbit | Alive | Arana, C et al. 2021 |
| Spain | 1 | Lichtheimia ramosa | Musculoskeletal | Lower right limb | Alive | Arana, C et al. 2021 |
| Spain | 2 | NA | Abdominal, musculoskeletal | Abdominal and facial pain | Died (n = 1), Alive (n = 1) | Baskar HC et al. 2021 |
| Turkey | 11 | NA | Rhino-orbital. Rhino-orbito – cerebral | Nasal sinus, Orbit CNS | Died (n = 7), Alive (n = 4) | Bayram N et al. 2021 |
| Mexico | 1 | NA | Rhino-orbital | Nasal sinus, Orbit | Died | Rao R et al. 2021 |
| UK | 1 | NA | Pulmonary | Lung | Autopsy report | Maini A et al. 2021 |
| UK | 1 | Aspergillosis | Pulmonary, heart, hilar nodes, brain, pharynx, nasal mucosa, trachea | Acute anterior cerebral artery, Pneumonitis | Died | Krishna V et al. 2021 |
| USA | 1 | Rhizopus arrhizus | Pulmonary | Lung | Alive | Monte Junior ESD et al. 2020 |
| USA | 2 | Rhizopus microsporus | Cutaneous | Skin | Died | Sen M et al. 2021 |
| USA | 1 | Rhizopus species | Rhino-orbital - cerebral | Nasal sinus, CNS | Died | Kanwar A et al. 2021 |
| USA | 1 | NA | Rhino-orbital | Nasal sinus, Orbit | Alive | Khatri A et al. 2021 |
| USA | 1 | Rhizopus spp. | rhino-orbital | Nasal sinus, Orbit | Died | Mekonnen, Z.K et al. 2021 |

NA= not available

India ranks second after China regarding the number of people living with diabetes. In a systematic review of CAM (COVID-19-associated mucormycosis) reported cases, it was concluded that before 13 May 2021, 80% of the reported cases of CAM patients had diabetes, and 14.9% of them had acute diabetic ketoacidosis in addition to diabetes. Diabetic ketoacidosis is when high levels of blood acids called ketones are produced in the body. As a result, patients with diabetic ketoacidosis develop immune suppression. Neutrophils, the phagocytic cells that makeup forty to seventy percent of white blood cells in humans are the first cells to respond to inflammation and are essential for the innate immune response. Immunosuppressants such as diabetes not only allow fungi to grow by creating an immune imbalance but also make the patient vulnerable to severe COVID-19; In addition, SARS-CoV-2 in the early stages of infection offers strategies to escape the immune system, which further weakens the immune system (Mahajan et al., 2022). In response to an invading pathogen, a properly functioning immune system initiates two major cellular responses. In this regard, type 1 interferons are produced, which alert other immune cells that an active infection has occurred, and the immune system then prepares the cells to repel the virus that is trying to spread. Immunity relies on the transcription factor (NF-κB). Due to its chemotaxis properties, it induces secreted proteins and recruits innate and adaptive immune cells, including T cells, B cells, monocytes, and neutrophils, and natural killer cells, to neutralize infection.

Immune responses to SARS-CoV-2 are unique in that they induce NF-κB while blocking INF-1, allowing SARS-CoV-2 to replicate uninhibited and without cell contact. Significant amounts of immune cells and cytokines and infiltration of neutrophils are produced, which is one of the essential pathological findings in SARS-CoV-2 infections with a proinflammatory nature. When these cells accumulate, they cause inflammation and eventually create a "cytokine storm" associated with severe COVID-19. (Allegra et al., 2020).

Finally, direct damage to the epithelial cells of the respiratory tract and blockage of INF-1 pathways increases susceptibility to fungal invasion. Corticosteroids such as dexamethasone may be prescribed to control inflammation, corticosteroid use is a risk factor for mucormycosis, and high blood sugar is a known side effect. If there is an underlying disease of diabetes, the risk increases greatly. It seems that the main reason for facilitating the proliferation of spores entering the mucosa in people with covid-19 is reduced oxygen (hypoxia), increased glucose (diabetes, emerging hyperglycemia), acidic environment (metabolic acidosis, diabetic ketoacidosis (DKA), level High iron (high ferritin) and reduced phagositic activity of white blood cells due to immunosuppression (due to SARS-CoV-2, use of corticosteroids, or underlying diseases) along with several common risk factors such as prolonged hospitalization in The hospital is with or without mechanical air conditioning. The use of hyperbaric oxygen is an adjunct treatment for mucosal infections. Increasing demand for the use of industrial oxygen in place of medical oxygen for oxygen cylinders in the management of COVID-19 is suggested as one of the causes of mucormycosis. Industrial oxygen is completely different from medical oxygen, and the quality and health of the oxygen may be at risk. The water used to hydrate the oxygen may be the source of fungal spores that are inhaled into the lungs. The use of hyperbaric oxygen is an adjunctive treatment for mucosal infections (Islam et al., 2022). Long-term use of corticosteroids has often been associated with several opportunistic fungal infections, including aspergillosis and mucormycosis. Recently, even short-term use of corticosteroids has been reported to be associated with mucormycosis, especially in diabetic individuals. While the widespread use of corticosteroids continues, these findings should be reconsidered in the context of the COVID-19 epidemic. There has been a significant increase in reports of mucormycosis in people with Covid-19, particularly from India. Increasing cases have also been reported from other parts of the world (Jose et al., 2021). These findings are unprecedented and of great public health importance, as the mortality rate of mucormycosis is very high, especially since intracranial involvement of mucormycosis increases mortality by 90%. In addition, the speed at mucormycosis spread in the body is extraordinary, and even 12 hour’s delay in

diagnosis can be fatal. Extensive studies on the development of mucormycosis in people with covid-19 and its relationship to covid-19 drugs and general characteristics of patients, as well as disease mechanisms on why mucormycosis may be associated with covid-19, are needed. Hyperglycemia at the time of referral (due to pre-existing diabetes or hyperglycemia with new-onset or newly started diabetes or diabetic ketoacidosis [DKA]) alone is the most important risk factor observed in most cases (83.3%) of mucormycosis in people with COVID-19, followed by cancer (3.0%). There was a history of corticosteroid use in the treatment of Covid-19 in 76.3% of cases, followed by RamedSivir (20.6%) and Tocilizumab (4.1%). Since there is no study comparing patients with mucormycosis in non-diabetic individuals who suffered from covid-19 and did not receive anti-inflammatory drugs (NSAIDs) to covid-19 patients who have received steroid-treated and suffering from mucormycosis, it is difficult to establish a causation relationship between Covid 19 and mucormycosis in this disease.

Factors that accelerate the development of mucormycosis in people with COVID-19 in relation to corticosteroids:

**A)** The presence of DM with or without DKA increases the risk of mucormycosis, and DM is often associated with an increase in the severity of COVID-19.

**B)** Uncontrolled hyperglycemia and the presence of DKA are often seen due to corticosteroid use. Low pH due to acidosis is a suitable environment for mucous spores to germinate. In addition, the use of steroids reduces the phagocytic activity of the first and second-line defense mechanisms and impairs the migration of bronchoalveolar macrophages and the fusion of phagolysosomes. All of this makes a diabetic patient very susceptible to mucormycosis.

**C)** COVID-19 often causes endothelial damage, thrombosis, lymphopenia, and decreased CD4 + and CD8 + T cell levels, ultimately predisposing to secondary or opportunistic fungal infections.

**D**) Free available iron is an ideal source for mucormycosis. Hyperglycemia causes the glycosylation of transferrin and ferritin and increases free iron by reducing iron binding to ferritin. In addition, the increase in cytokines in patients with Covid-19, especially interleukin-6, increases free iron by increasing ferritin levels due to increased synthesis and decreased iron transfer. Simultaneous acidosis increases free iron by the same mechanism and reduces the ability of transferrin to form iron chelates.

**E)** High glucose, low pH, free iron, and ketones increase mucor growth in the presence of decreased WBC phagocytic activity. In addition, the expression of glucose-regulating protein 78 (GRP-78) in endothelial cells and homologous protein increases the coverage of fungal ligand spores (CotH) and allows vascular invasion, blood diffusion, and tissue necrosis (Ibrahim et al., 2012).

In the initial care of the disease, it is important to pay attention to the warning signs and symptoms of mucormycosis. For the management of mucormycosis, suspected cases of mucormycosis due to nasal obstruction or sinusitis should be considered. In addition to blood glucose monitoring in patients with covid-19 and diabetes, steroid therapy should be considered in post-covid-19 patients. It is recommended to start mucormycosis treatment at the right time without unnecessary delay. One of the treatments for mucormycosis is amphotericin B, which targets fungal and human cell membrane sterols and lipids. Ergosterol, a compound found in fungal cell membranes, is more sensitive to this antifungal than cholesterol. However, the administration of amphotericin B is limited due to the toxicity associated with its intravenous administration. Toxicity associated with intravenous injection of amphotericin B is associated with the production of proinflammatory cytokines. In addition, concomitant use of corticosteroids and amphotericin B can affect CAM therapy by causing metabolic disturbances such as hypokalemia (Hoenigl et al., 2022).

## Conclusion

Increased reported cases of mucormycosis appear to be due to factors such as diabetes (due to a high genetic prevalence), overuse of corticosteroids (increased blood glucose, and opportunistic fungal infections), and COVID-19 (cytokine storm, lymphopenia, injury) and the use of contaminated oxygen. All efforts should be made to maintain optimal blood sugar, and only evidence-based use of corticosteroids in patients with COVID-19 is recommended to

reduce the burden of fatal mucormycosis. Various cases are not understood in relation to the triple threat that has emerged from this pandemic, but in the future, controlling blood glucose levels and finding out about the patient's underlying diseases before using corticosteroids to treat the patient will be of great importance.

**Refereces**


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