



## **Post-COVID- 19 Mucormycosis: A Review**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background and Aims:** After being affected by a severe second wave of COVID-19 with numerous cases and deaths, India is now facing new challenges due to the disease. One of these is the feared complication of rhino-orbital mucormycosis in post-infectious individuals. Case reports and research studies on this association are on the rise. Our goal is to conduct a comprehensive literature review to evaluate the distinctiveness of individuals with mucormycosis and COVID-19.

**Methods:** A literature search was done on the following databases: PubMed, Google Scholar, and Cochrane Library using the following keywords like COVID 19, Mucormycosis, Mucor, Novel coronavirus, and SARS CoV-2, a systematic.

**Results:** Studies have shown that history of diabetes mellitus and steroid treatments were the common possible factors for the increased post-covid-19 mucormycosis. Hyperglycemia secondary to uncontrolled hyperglycemic states like DM and immunosuppression secondary to covid-19 infection, steroid use form a vicious cycle causing mucormycosis.

**Conclusion:** Increased incidence of mucormycosis in India post-COVID infection appears to be due to a triad of diabetes, irrational steroid use, and COVID-19 itself. To decrease the frequency of deadly mucormycosis in patients with COVID-19, all attempts should be made to preserve optimal sugar levels in the body, and the use of corticosteroids should be restricted and should be given as per recommended by ICMR.

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**Keywords:** COVID-19; Mucormycosis; Novel coronavirus; mucor; diabetes mellitus; SARS CoV-2.

## 1. INTRODUCTION

India is one of the nations which were poorly affected by the subsequent wave of the COVID-19 pandemic. Apart from the burden of disease & deaths, post-covid-19 complications were particularly concerned. The reason for opportunistic bacterial and fungal infections is related to co-morbidities (like diabetes, chronic obstructive lung disease) and immune-compromised states (corticosteroid therapy, ventilation, intensive unit stay). One among these opportunistic infections with a high fatality rate is Mucormycosis.

Mucormycosis is one of the most severe forms of Zygomycosis because of the Mucorales species of Zygomycota. It is a possibly fatal illness that affects predominantly immunocompromised people, especially diabetes, leukemia, and lymphoma [1,2].

In contrast to the global rate of 0.005-1.7 per million populations, the rate of mucormycosis in southeast Asian countries like India is 0.14 per 1000, about 80 times more than that of countries like America [3]. Though the fatality rate is 46% worldwide, it can rise to 80 %due to elements like intracranial or orbital involvement irreparable immune suppression. In immunosuppressed people, a strong feeling for this illness must be reflected. Tissue necrosis, a defining feature of mucormycosis, is frequently a delayed symptom [4,5].

In the situation of the COVID-19 epidemic, where corticosteroids are frequently administered, these findings need to be reconsidered. Mucormycosis event information/series in persons with COVID-19 has increased dramatically, particularly in India. Many instances have also been recorded from other regions of the world. These findings are ground-breaking and have enormous public health implications, owing to the high mortality rate associated with mucormycosis. Mucormycosis intracranial involvement, in particular, raises the mortality proportion has elevation up to 90% [6]. Furthermore, the velocity with which mucormycosis spreads is an unusual occurrence, & even a 12-hour interval in diagnosis can be deadly, which is why 50 percent of cases of mucormycosis have historically been detected only in post-mortem autopsy series [7]. As a result, we conducted an organized review of published case

information/series of mucormycosis in COVID-19 patients to establish historical correlations with co-morbidities, associations with COVID-19 drugs and general patient features with prognosis.

## 2. MATERIALS AND METHODS

### 2.1 Aims and Objectives

This article aims to provide an overview of research findings on mucormycosis in post-covid-19 patients and identify the etiology of mucormycosis in these patients.

### 2.2 Methods

A systematic literature search was held on the following database:

PubMed, Google Scholar, and Cochrane Library using keywords like COVID 19, Mucormycosis, Mucor, Black fungus, Noval coronavirus, and SARS CoV-2.

### 2.3 Selection of Article

From all the articles that were relevant to the topic of review. All of the instances of mucormycosis (both established and assumed) in patients with COVID-19 that have been reported thus far have been retrieved. Each patient's characteristics were recorded and evaluated for various endpoints and results. Two writers double-checked the data's validity.

## 3. RESULTS

Mucormycosis is an angioinvasive fungus that develops on moist surfaces, dead and rotting vegetable materials, and is generally found in the environment. The name "black fungus" is incorrectly used for mucormycosis since "black fungus" refers to a distinct group called dematiaceous fungi. Immunocompromised hosts, uncontrolled hyperglycemic states like DM, particularly diabetic ketoacidosis, glucocorticoids, Haematological neoplasia, hematopoietic stem cell transplantation, iron-chelating treatments, trauma/burns, Autoimmune deficiency syndrome, iron-chelating treatments, and so on are all risk factors for mucormycosis [8].

A literature review has shown that there is no single reason behind the development of

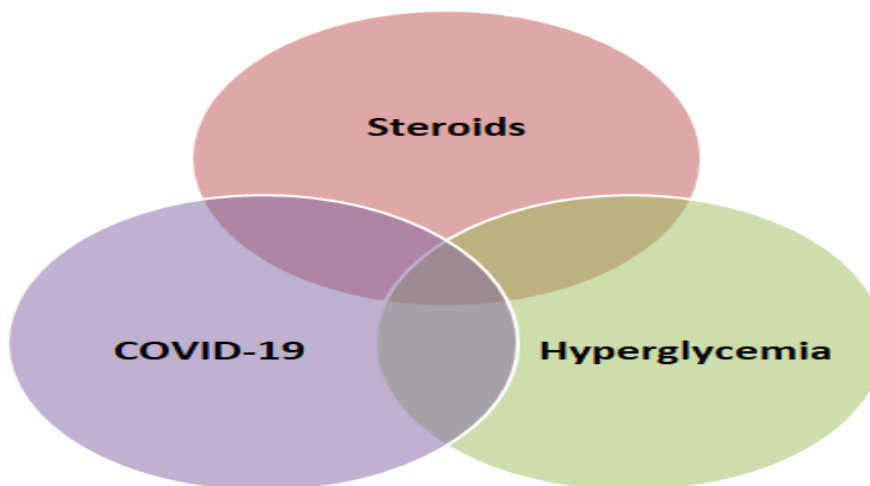
mucormycosis post-COVID in the Indian context; instead, it is due to a multitude of factors- some modifiable and some non-modifiable. Uncontrolled diabetes mellitus is a common co-occurrence in these patients, particularly ours. There may be technical lapses due to overcrowding in hospitals like lack of monitoring of blood sugar levels in COVID patients, as the primary concern remains saving the life. Use/prescription of dexamethasone above the recommended dose of 6.0 mg/day, duration of 5-10 days, is another crucial risk factor for this complication. It can be due to the over-the-counter use of steroids by mild-moderate/asymptomatic patients due to fear of severe illness and hospitalization. Irrational use of steroids by treating doctors either as a life-saving measure or to regulate the oxygen saturation when clinics experience scarcity of oxygen are other factors. In warm and humid climatic conditions like those prevailing in India, fungal/mucor spores are more likely in the air.

The condition is most commonly found during the COVID-19 healing phase, suggesting several variables contribute to fungal colonization. Individuals with COVID-19 had extensive endothelium damage, according to autopsy investigations, when related to people who died from H1N1 influenza. Mucormycosis begins with endothelial adherence and penetration. The endothelium receptor glucose-regulated protein and Mucorales receptor protein homologs are induced by hyperglycemia, creating ideal circumstances for adherence to mucormycosis and penetration [9,10,11]. Insulin resistance

promoted by interleukin-6 affects the phosphorylation of the insulin receptor substrate-1 and insulin receptor, usually high in people with severe COVID-19. Glucocorticoids, lopinavir, ritonavir, and redeliver, used to cure COVID-19, can disturb glycemic mechanisms and predispose to mucormycosis. Mucorales use free iron levels in the serum as an etiological factor hence individuals with diabetic ketoacidosis have a higher chance of mounting Covid-19 related mucormycosis.

Ignorance of patients about mucormycosis symptoms like pain and wrongly believing it to be a part of persisting COVID-19 symptoms lead to the delay in identification and treatment. Such patients reached the hospital when the disease was severe enough, and the prognosis was poor after 1-3 weeks of the onset of symptoms. The nose and sinuses were the most common organs affected by mucormycosis (88.9%), tailed by rhino-orbital (56.7%), and Rhino-orbital-cerebral Mucormycosis type (22.2 %). The rise of the Rhino-Orbital-Cerebral Mucormycosis type is specific to COVID-19 in the Indian context.

Evidence is given that a malfunctioning immune system caused by SARS-COV-2 and injudicious use of corticosteroids may be primarily responsible for uncontrolled diabetes in individuals. Diabetes mellitus seems to induce a brutal cycle of hyperglycemia and immunosuppression when coupled with the SARS COV 2 Virus and steroid treatment, which often causes chronic fungal establishment like mucormycosis [6,7,8].



**Fig. 1. Triad of risk factors responsible for post-COVID mucormycosis**

Clinical presentation varies depending upon the site of involvement by the fungus in the body. The commonest ones are Rhino-orbital-cerebral mucormycosis and pulmonary mucormycosis forms. Originated on medical and radiological findings and the disease's progression, diagnosis can be decided. Though tissue necrosis and thrombosis are the hallmarks of the disease, they are relatively rare phenomena. The early signs and symptoms include unilateral facial or eye pain, numbness, blurred vision, cranial nerve palsies, swelling of eyelids, ocular motility changes, headache, ophthalmoplegia, acute loss of vision, blackish lesions/discharge from nasal bridge or mouth [12,13].

Diagnosis of pulmonary type is more challenging as clinical features and imaging results are non-specific and overlap with pulmonary aspergillosis. Fever unresponsive to antibiotics and dry cough can suggest the underlying disease. Reverse halo sign in CT is more frequently seen in pulmonary mucormycosis than aspergillosis.

The illness is worsened by an incorrect or mistaken diagnosis and the use of antibiotics and steroid medications. Although challenging, it is critical to identify Mucormycosis from other bacterial illnesses, including aspergillosis. There is no circulating antigen detection test for mucormycosis, equivalent to antigen detection for invasive aspergillosis.

A biopsy is required for diagnosing mucormycosis as an antigen detection test is not available. Direct microscopy of hyphae in samples is critical since it is quick and highly indicative of the illness [14].

In the instance of COVID-19 ASSOCIATED MUCORMYCOSIS, we discovered that surgical debridement in most cases as a supplement to antifungal medication was linked to a greater survival rate. Before the infection migrating to different parts of the body, especially the brain, debridement surgery is required. As a result, prompt removal is critical in cultivating patient outcomes in COVID-19 ASSOCIATED MUCORMYCOSIS; nevertheless, surgery in a patient infected with SARS-CoV-2 can be difficult & necessitates extra measures & the use of barrier draping methods by operating surgeons [15,16,17]. Mucormycosis has a bleak prognosis due to the nature of this opportunistic angioinvasive fungal infection that affects immunodeficient people with uncontrolled

hyperglycemic states like DM, which is a mutual threat aspect in most occurrences well as the time it takes for patients to reach emergency rooms. Studies have shown that history of diabetes mellitus and steroid treatments were the common possible factors for the increase of post-covid-19 mucormycosis. Hyperglycemia secondary to uncontrolled hyperglycemic states like DM and immunosuppression secondary to a covid-19 infection, steroid use form a vicious cycle causing mucormycosis.

#### 4. DISCUSSION

The novel SARS-CoV-2 virus, which roots Covid-19 infection, is sometimes reawakened wide variety of symptoms, from mild to severe pulmonary illness [18]. Literature review has shown that there is no single reason behind development of mucormycosis post-COVID in Indian context rather it is due to a multitude of factors- some modifiable and some non-modifiable. Uncontrolled diabetes mellitus is a common co-occurrence in these patients particularly in a country like ours. There may be technical lapses due to overcrowding in hospitals like lack of monitoring of blood sugar levels in COVID patients as the primary concern remains saving the life. Although mucormycosis is enormously difficult to find in healthy people, it is caused by a number of immunocompromised conditions. This includes unrestrained diabetes with or without Diabetic Ketoacidosis, cancers, corticosteroid therapy, immunosuppressive and prolonged neutropenia, iron overload or hemochromatosis, deferoxamine or desferrioxamine therapy, transplantation of organ, burn injury, Autoimmune deficiency syndrome, and intravenous drug abusers, malnutrition & open wound following trauma [1]. Mucormycosis can affect the nose, sinuses, orbit, central nervous system, kidney, lungs (pulmonary), gastrointestinal tract, heart, skin, jaw bones, joints, and mediastinum (aggressive form), although RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS is the most frequent variant encountered in clinical practice across the world. It's worth noting that the phrase "rhino-orbital-cerebral illness" encompasses the full spectrum, from restricted Sino-nasal disease (Sino-nasal tissue attack) to rhino-orbital-cerebral sickness (CNS involvement). Due to the underlying disease, the region of participation may vary. For example, RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS is commonly associated with uncontrolled DM and DKA, lung association is frequently seen in patients with transplantation of

organ, neutropenia, bone marrow, & hematological neoplasm & Gastro intestinal tract involvement is further common in malnourished people. The presence of a dark eschar in the nose orifice or above the hard palate is common, but it is not suggestive of disease. Tissue infraction, acute neutrophilic infiltrate, vasculitis with thrombosis, hemorrhage, and mycotic blood vessel infiltrate are all histological characteristics [19,20,21].

The condition is most commonly found during the COVID-19 healing phase, suggesting that a number of variables contribute to fungal colonisation. Nonetheless, a number of factors seems to be involved in the development of mucormycosis in people with COVID-19 who are given corticosteroids. Some of these factors are as follow:

Mucormycosis occurs frequently in people who has less phagocytes or have decreased phagocytic function. Hyperglycemia causes phagocyte malfunction, poor chemotaxis, and inefficient intracellular killing by oxidative and non-oxidative processes, as observed in individuals with unrestrained hyperglycemic state like DM [9].

Insulin resistance promoted by interleukin-6 affecting the phosphorylation of the insulin receptor substrate-1 and insulin receptor, which is usually high in people with severe COVID-19 [10].

Glucocorticoids, lopinavir, ritonavir, and remdesivir, which are used to cure COVID-19, can disturb glycemic mechanism and predispose to mucormycosis [11].

Free iron levels in the serum are used by mucorales as etiological factor, hence individuals with diabetic ketoacidosis have a higher chance of mounting Covid-19 related mucormycosis [22-27].

COVID-19 causes lymphopenia, endothelial injury, thrombosis, endothelitis, and a decrease in CD4+ and CD8+ T-cell levels, putting the patient at threat for secondary or opportunistic fungal infection. The presence of Diabetes, whether with or without Diabetic Ketoacidosis, increases the chance of developing mucormycosis, & Diabetes is frequently linked to higher COVID-19 severity.

The possible prevention of covid-19 associated mucormycosis are:

1. To use corticosteroids within the recommended dose and to limit duration for which it is used.
2. Avoiding the use of iron and zinc for the supplements of covid -19 management
3. Voriconazole should not be used as an antifungal prophylactic.
4. Maintain the blood sugar levels of diabetic patients and to monitor high risk patients.
5. Use of broad-spectrum antibiotics should be avoided until absolutely necessary.
6. Maintenance of personal hygiene in post covid-19 patients.
7. Decontamination of the hospital environment should be done properly.

When to suspect mucormycosis in patients with covid-19 especially those who are immunocompromised or suffering from diabetes:

1. Toothache, loosening of teeth and jaw pain.
2. Unilateral facial pain and lack of sensation.
3. Blackish discoloration of palate.
4. Sinusitis along with dark or bloody discharge and native pain.
5. Blurred vision with pain
6. Chest discomfort, pleural effusion, deterioration of lung symptoms.

Management of such patients include following:

1. Controlling hyperglycemia and DKA.
2. Stopping immunomodulating medications.
3. Reducing steroids with intend to cease rapidly.
4. No antifungal prophylaxis required.
5. Antifungal therapy with Amphotericin B infusion for 4-6 weeks.
6. Surgical Debridement (extensive) to remove all the dead tissue.
7. Monitoring the patient for disease progression.

The current systematic review contains the most comprehensive data on COVID-19 ASSOCIATED MUCORMYCOSIS accessible to date. We discovered examples that we would have lost if we had limited our exploration to site like PubMed using the detailed literature hunt in the Google Scholar databank. Furthermore, to the finest of our data, this is the only methodical assessment of COVID-19 ASSOCIATED

MUCORMYCOSIS that has followed the PRISMA declaration. Nonetheless, we sincerely admit our review's limits. First, without a denominator, it was impossible to assess the occurrence of COVID-19 ASSOCIATED MUCORMYCOSIS in COVID-19 patients. Further, we were unable to identify the risk variables that might forecast the progress of COVID-19 ASSOCIATED MUCORMYCOSIS in COVID-19 patients due to the lack of a control group (i.e. COVID-19 without COVID-19 ASSOCIATED MUCORMYCOSIS). Third, because to a lack of sufficient controls, we were unable to determine attributable death rate of COVID-19 ASSOCIATED MUCORMYCOSIS yet again. Fourth, since data on the dose and period of glucocorticoid medication, as well as glycemic control measures (blood glucose, HbA1c), were rarely recorded, they were excluded from the systematic review.

## 5. CONCLUSION

Increased mucormycosis in India appears to be the result of an unholy trinity of diabetes (high genetic incidence), excessive corticosteroid usage (increases blood glucose and leads to immunocompromised fungal infection), and COVID-19 (cytokine storm, lymphopenia, endothelial damage). To decrease the incidence of deadly mucormycosis, all determinations should be taken to keep optimum hyperglycemia, and only cautious proof-based use of corticosteroids in patients with COVID-19 is suggested.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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