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The overlapping of COVID-19 with Mucormycosis: A systemic review

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ABSTRACT. The COVID-19 pandemic is a global health concern that is causing new problems worldwide. The pandemic's expansion is causing new overlaps with other illnesses, such as a spike in mucormycosis cases, particularly in India around May 2020. Physicians worldwide have been perplexed by the continuous pandemic and its shifting method of action, as well as symptoms that coincide with those of other infectious illnesses, making differential diagnosis difficult. The researchers sought to see if there was any crossover between mucormycosis and COVID-19. Diabetes is considered a risk factor for COVID-19 and mucormycosis on its own. The accessible electronic literature, current medical databases, and created evidence-based on specialized recommendations were used to address the granular details of individuals with mucormycosis and COVID-19 reported worldwide. We studied patient characteristics, associated comorbidities, diabetes, immunodeficiency syndrome, site of mucormycosis, steroid use, and outcome in individuals with COVID-19. According to our findings, diabetes, corticosteroid usage, environmental conditions, hypoxia and hypertension were the most often seen risk factors. Excessive usage of broad-spectrum antibiotics was also seen in some situations. The death rate is significant despite medical and surgical therapy. The best way to avoid infection is to use a comprehensive approach to improving the settings that prevent COVID-19-associated mucormycosis (CAM) from developing. In individuals with COVID-19, all efforts should be taken to maintain appropriate glucose levels and only use corticosteroids sparingly.

Keywords: acute diabetes; corticosteroids; COVID-19-associated mucormycosis; immunodeficiency syndrome; risk factor

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INTRODUCTION

COVID-19 is produced by the "SARS-CoV-2 virus" and has been connected to various fungal and bacterial infections. India faced considerable challenges during the COVID-19's second phase, which began in early 2021. Daily, the number of critically ill patients infected has risen considerably (Kubin *et al*., 2021; Bhowmick, 2021). Mucormycosis, an invasive fungal infection, has become more common among COVID-19 patients, worsening the condition. The incidence of fungal co-infection was greater in severely sick corona patients, reaching up to 30%, according to the clinical symptoms of COVID-19 patients (Sonng *et al*., 2020). Recently, multiple cases of mucormycosis have been reported in COVID-19 patients globally. An unholy trinity of diabetes, rampant use of corticosteroid in a background of COVID-19 appears to increase mucormycosis (Awadhesh *et al*., 2020). A favourable environment appears to be the primary source of fungal development, including hypoxia, diabetes, steroid-induced hyperglycemia, and impaired immune system. When paired with other patients, frequent risk factors prolonged hospitalization (Apicella, 2020; NHM-HP, 2021). In addition, instances of immunocompromised individuals with acute respiratory distress syndrome exacerbated by fungal infection and, as a result, a greater COVID-19 infection rate have been documented (Bhatt *et al*., 2021). Mucormycetes, a kind of mould that may be found in moist environments such as soil or compost, cause the black fungus. Fungal spores invade the respiratory system and assault the sinuses and lungs. It is not contagious and cannot be passed from one person to another (Patel *et al*., 2020; Ravani *et al*., 2021). These fungi are not dangerous, but they can damage those who have weak immune systems. The COVID-19 patients are susceptible not only because the virus affects the immune system but because the therapeutic regimen (e.g., steroids) that used for severe cases can suppress the immune response (CDC Guideline, 2021; Ahmad *et al*., 2021).

COVID-19 patients in critical care units who are getting oxygen treatment may contact humidifiers in the ward, increasing their moisture exposure and making them more susceptible to fungal infection (DGHS Guideline, 2021). The objectives of this systematic review were to characterize mucormycosis associated with COVID-19, analyze risk factors that result in overlaps between mucormycosis and COVID-19, and develop evidence-based guidelines to aid in infection prevention early detection, and treatment based on illness severity and rational drug use.

MATERIALS AND METHODS

A complete literature search using the terms COVID-19, mucormycosis, risk factors, diabetes, and corticosteroids was undertaken in PubMed and Google Scholar. Additionally, the details of reported cases of mucormycosis in COVID-19 patients were analyzed. The evaluation considers research and studies on this subject published in specialized scientific journals and recommendations. The literature that was excluded are the ones that did not give accurate scientific explanations because they are not specialized in this field. This section discusses the fundamental reasons for the co-occurrence of COVID-19 and mucormycosis, the consequences of co-occurrence, environmental variables, host risk factors, and therapeutic recommendations. Following that, patient characteristics, associated co-morbidities, site of mucormycosis, steroid use, and outcome were studied in COVID-19 patients.

RESULTS AND DISCUSSION

All the selected data and information were checked for their relation to the following most essential topics. A total of 52 published papers in English language out of 79 were selected to write this review article.

Leading causes of Mucormycosis during COVID-19. Mucormycosis is an infection that is not communicable and is caused by saprophytic Mucorales fungi such as *Rhizopus, Lichtheimia, Mucor*, and *Rhizomucor*. The first three species account for three-quarters of all cases (Sharma *et al*., 2021). It is an opportunistic infection that can affect the lungs, skin, stomach, rhino-cerebral areas, and central nervous system, each with its own set of symptoms. Infectious spores in the environment can enter the human body and develop into angioinvasive hyphae through inhaling, ingesting, or injecting directly through wounds (Placik *et al*., 2020; Maini *et al*., 2021). Mucormycosis is extremely rare in individuals but may occur in those with risk factors such as uncontrolled diabetes, organ transplantation, immunosuppression, or corticosteroid use (Karimi *et al*., 2021). COVID-19 is well recognized for suppressing the host's immune system.

A typical situation of triple immune suppression is the scientific backdrop of diabetes and steroid use, which increase severe hyperglycemia and acidosis and impaired phagocytic function. When steroids are utilized as a primary component of a treatment program for individuals with severe COVID-19 illness, the situation worsens (WHO, 2021). This medication works by lowering patients' immune responses, leaving them more susceptible to secondary infections like mucormycosis, especially if they have been on steroids for a long time. Steroids can also be used to raise and lower blood glucose levels by creating insulin resistance, which reduces the effect of insulin (Zhang *et al*., 2020). Mucormycetes are also more prone to develop in those who have uncontrolled diabetes. Although India is renowned as the world's diabetes capital, most Indian patients' diabetes care is still inadequate. Numerous other variables, such as filthy water used in humidifiers, industrial oxygen, unsterilized medical equipment, and prolonged use of the same masks, can cause mucormycosis and contribute to the overlap with COVID-19 (Mehta & Pandey, 2020). Vitamin C, vitamin D, and zinc have all been used in the COVID-19 therapy regimen to boost immunity while also renewing or boosting mucormycosis. On the other hand, zinc is recognized to be necessary for fungal growth and development, as well as having a protective effect against fungal pathogenicity (Hira *et al*., 2021).

What effect does mucormycosis have on COVID-19 patients? Mucormycosis, an invasive fungal infection that has become increasingly widespread in COVID-19 patients, is a more dangerous

scenario. The most frequently encountered type is rhino-orbital-cerebral. Around three-quarters also had diabetes and were treated with corticosteroids for COVID19 (Bhardwaj, 2021; Bhattacharyya *et al*., 2021). It is possible that the process is connected to immunological and inflammatory responses. Diabetes, when combined with COVID19-induced systemic immunological alterations, impairs immunity and increases the risk of secondary infections. Mucormycosis associated with COVID-19 is thought to be caused by three immunological and inflammatory processes (Fig.1): significant lymphopenia, which results in a dramatic decrease in the availability of T lymphocytes ("CD4+ and CD8+"), thereby opening the door for opportunistic fungal infections; elevated pro-inflammatory markers in patients with severe illness; and COVID-19's apparent damage to pulmonary tissues, which aids invasive fungi, particularly those that are resistant (Bhatt *et al*., 2021; Sarkar *et al*., 2021; Yanghong *et al*., 2021). Excessive interleukin-6 ("IL-6") release & macrophage activation produce hyperferritinemia, which is caused by the availability of free iron inside cells. Endothelitis is caused by damage to the endothelium and inflammation. Furthermore, the virus's hepcidin-mimetic activity permits ferritin synthesis even when the inflammatory response is suppressed (Jose *et al*., 2021). Elevated ferritin levels aid fungal growth, and thermo-tolerant fungi thrive at higher body temperatures. Increased ferritin levels support fungal growth, and increased body temperature is ideal for thermo-tolerant fungi (Simple *et al*., 2021). COVID-19-induced immunosuppression increases the risk of opportunistic infection, affects the endothelium and alveolus, facilitates fungal invasion, and boosts glucose levels due to the acute diabetes-like condition caused by pancreatic injury. Immunosuppression, downregulation of angiotensin-converting enzyme2 expression in various physiological organs, and engineering a microenvironment system in COVID-19 that increases the likelihood of co-infection are all intriguing hypotheses (Pandiar *et al*., 2021). Increased glucose and iron levels, caused by diabetic ketoacidosis (DKA) or aggravated by dexamethasone use, facilitate or increase fungal penetration. Increased glucose and iron levels caused by DKA or aggravated by dexamethasone use aid fungal penetration even more. Fungal entry is facilitated by increased glucose and iron levels caused by DKA or induced by dexamethasone usage (Hariprasath *et al*., 2021). Increased glucose and iron content caused by DKA or driven by dexamethasone use also enhances fungal entry. Additionally, upregulation of the 78-kDa glucose-regulated protein (GRP78), a heat shock protein, in COVID-19 patients (5 times that of controls) due to elevated glucose and iron content caused by DKA or dexamethasone use facilitates fungal invasion. Mucorale's pathogenicity and virulence have also increased (Chandra & Rawal., 2021).

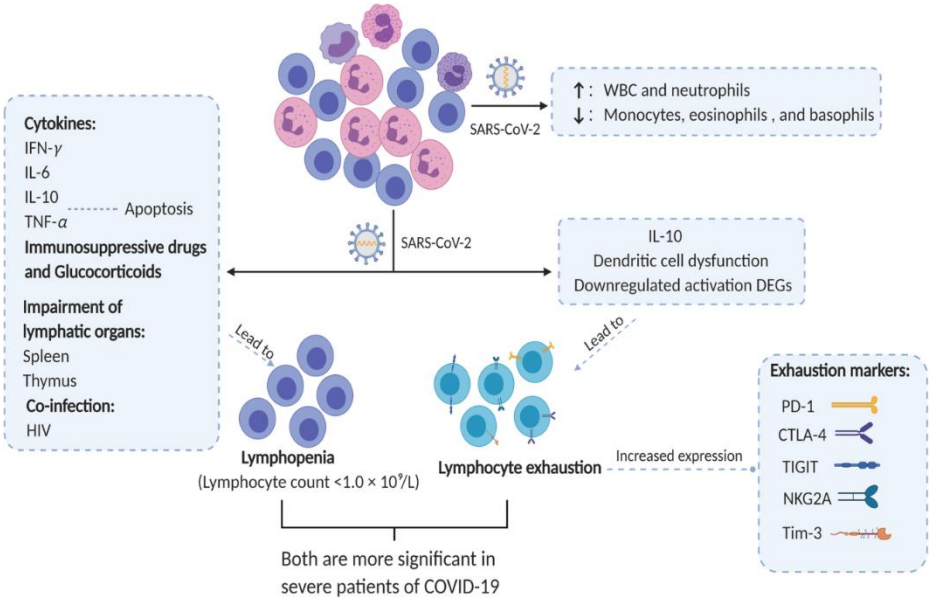

Fig.1. Immune responses of lymphocytes to SARS-CoV-2 infection. Lymphopenia and lymphocyte exhaustion are two important characteristics of SARS-CoV-2 infection, which are aggravated in severe patients of COVID-19 compared to milder cases (according to Yanghong *et al*., 2021)

Implications of overlapping between Mucormycosis and COVID-19. Mucormycosis, a severe and rare fungus, has recently been found in COVID-19 patients worldwide. The most common symptoms in COVID-19-associated mucormycosis patients were face pain, proptosis, visual acuity, and vision loss. Individuals who had both medical and surgical therapy had a 64.96 per cent probability of survival, whereas overall mortality among infected individuals was 38.32% (Salman *et al*., 2021). According to various studies, the infection can cause a loss of taste and smell as 1st and sole symptom. (Gautier & Ravussin, 2020). The COVID-19 virus suppresses the immune system of the host. Furthermore, increasing hyperglycemia and acidity are associated with diabetes and steroid use, both related to immune suppression (Ceriello, 2020). In the context of multilayer immune suppression, zinc supplementation might have provided a source of fuel for fungal proliferation. Unsanitary conditions, a lack of living standards, and poverty, all of which have been aggravated by COVID-19 lockdowns, may have contributed to the fungus epidemic (Awal *et al*., 2021). Zinc supplements have been widely recommended as an antiviral agent in the broader sense since the COVID pandemic started in 2020. In the lack of a definite anti-COVID medicine, zinc, along with other vitamins known as "immunity boosters," is commonly utilized as a part of a therapeutic or preventive regimen. On the other hand, zinc deficiency has been scientifically demonstrated to impede microbial development in tissues, while zinc is a crucial nutrient for fungal growth. Zinc shortage causes biological stress in fungal cells and inhibits fungal growth by inhibiting zinc-binding proteins' function (Oyagbemi *et al*., 2021). COVID-19 has been demonstrated to influence other physiological systems, including the eye and the described symptoms (High *et al*., 2021). The virus can harm the eye in various ways, causing a variety of visual symptoms. (Bertoli *et al*., 2020). *Mucormycosis* is a dangerous and sometimes deadly infection caused by mucormycetes, an uncommon yet opportunistic fungi. Risk factors include haematological and non-haematological malignancies, organ transplantation, chronic neutropenia, immunosuppressive and corticosteroid use, iron overload, and hemochromatosis (Karimi-Galougahi *et al.*, 2021). The increased use of steroids, industrial oxygen, unsterile medical equipment, frequent intubation, a weakened immune system, and pre-existing diseases such as diabetes may all increase. As a result, taking action to address the current surge in mucormycosis patients is crucial. As a result, rising Zinc use across all COVID patients might have contributed to the rise in COVID-19 infections. Hyperglycemia was the most critical risk factor for mucormycosis in COVID-19 patients, accounting for 83.3 per cent of cases. Cancer was responsible for 3.0% of the cases (Vuorio & Kovanen, 2021).

Environmental factors are increasing mucormycosis cases in patients with COVID-19. Environmental variables such as humid climates, tropical-subtropical, and hot weather in various places and nations may promote fungal growth and make disease prevalence more likely. Because fungal development has been connected to high temperatures and humidity, researchers believe that the environment and climate have a role. As a result, the concurrent increase in overlapping COVID-19 and mucormycosis cases in different countries could be attributed to climate similarities (Johnson *et al.*, 2021). Periodic fluctuations in mucormycosis have been noticed in meteorological conditions, which is interesting. The existence of several Mucorales species in Indian soil, such as Apophysomyces, may bolster this theory. Healthcare related *Apophysomyces* infection was noted in 29.2% patients in india (Umabala *et al.*, 2020). The use of cow dung for medicinal purposes is questionable since animal excrement might be a source of illness (Moona & Islam, 2021). Moulds of the Mucorales order, which may be found in the soil, on plant surfaces, rotting fruits and vegetables, and animal dung, cause mucormycosis. *Mucor* moulds cannot infect people because they cannot grow at body temperature (Sarrda *et al*., 2021). Thermotolerant species, such as those identified from COVID-19associated mucormycosis patients in India, can induce opportunistic infection, which can be fatal. If the fungus takes hold, the spores germinate and generate hyphae, which enter blood vessels and surrounding tissue, obstructing blood flow and causing tissue death. Immunological weaknesses, such as diabetes, are well-known for creating immune abnormalities that allow fungal infections to grow while predisposing individuals to severe COVID-19. (World Health Organization, Key Facts,

2021). Furthermore, to prevent discovery during early infection, the COVID-19 adopts several novel techniques that further weaken the immune system. Aside from host-related factors, prior information on mucormycosis-related outbreaks was reviewed to see if any interactions might have contributed to the current pandemic's increased patient numbers. (Bostanci & Ozates, 2020). The following are the relevant associations that were shortlisted: Air handling systems and ventilation ducts that have been contaminated, negative-pressure isolation chambers, water leakage (wall dampness leading to accumulation of fungus), hospital construction; dust and humidity, and infection of nebulizer devices by fungus. However, practitioners prescribed excessive doses of steroids for prolonged periods, significantly exceeding WHO guidelines, impairing patients' immune systems, increasing blood sugar levels, and increasing susceptibility to fungal infection, both in patients with and without underlying diabetes problems. As scientists attempt to determine what causes this disease, it is becoming clear that due to the fungi's opportunistic nature (Revannavar & Samaga, 2021). *Mucor* moulds seized the opportunity when host defenses were depleted and a pandemic consumed the world. COVID-19-associated mucormycosis has uncovered several medical issues, most notably in treating fungal infections such as mucormycosis. It is partly due to the similarities between fungus and human cells complicating designing antifungal medications that are not toxic to the host. Mucormycosis is becoming more frequently associated with and reported COVID-19.

Host risk factors. During COVID19, some countries reported exceptionally high rates of self-medication and home medications among infected and uninfected people, possibly indicating a significant risk of incorrect dosing (Casalini *et al*., 2021). Effective use of steroids was detected in India during the COVID-19 lockdown period, which appears to be the most significant amount ever at the world level. Steroids primarily work by interacting with glucocorticoids receptors or impairing macrophage and neutrophil activity. which lowers the immune system by preventing macrophages from producing inflammatory cytokines like tumour necrosis factors (Choudhary *et al*., 2021). Opportunistic infections like mucormycosis have arisen as a new health risk in COVID-19 patients. Because opportunistic infections can exacerbate COVID-19 symptoms, it is crucial to understand the risk factors to be avoided, identified, and treated as soon as possible. This situation might be caused by a virus, fungus, the environment, or the host. Extended hospital stays, reduced host immune system function due to viral infection, and high glucocorticoids in COVID-19 patient therapy are the primary factors for mucormycosis in COVID-19 patients. Patients with COVID-19 can avoid invasive fungal infections by training health workers and identifying the association between paranasal sinus mucormycosis of various types of the severe acute respiratory syndrome as the aetiology of COVID-19 (Taghinejad, 2021). Extremely high COVID-19 cases connected to mucormycosis were recorded through the acute rise of COVID-19 infections in India in 2021; this is much more than projected based on current data on the condition's prevalence and risk factors and as an unusual combination of many risk factors for this disease (Shivakumar *et al.,* 2021). Mucormycosis has a high background incidence in India due to a high prevalence of risk factors such as untreated or poorly managed diabetes. The risk is increased by COVID-19-induced immunological suppression caused by steroid therapy. The importance of exposure to the environment is debatable. Systemic concerns, such as a lack of healthcare access during a pandemic can result in delayed diagnosis and ineffective treatment, which can have negative consequences (Narayanan *et al*., 2021).

The treatment and recommendations. Over a million individuals have already died due to COVID-19 over the world. Supportive care is critical in the treatment of COVID-19. The only drugs shown to treat COVID-19 patients are glucocorticoids, which have been shown to reduce mortality in hypoxemic COVID-19 patients (Hariprasath *et al.,* 2021). The use of corticosteroid therapy suppresses the function of immune cells such as macrophages, neutrophils, platelets and T cells. So, glucocorticoid-induced immune defects and altered receptor expression may enhance the pathogenesis of CAM. On the other hand, glucocorticoids can increase the chance of infection in the future. With the number of cases of mucormycosis steadily rising throughout the world, it is vital to act now to help limit the spread of the disease. Mucormycosis is caused by uncontrolled diabetes,

long-term steroid usage, protracted critical care unit hospitalizations, post-transplant patients, and voriconazole users. As a result, these patients must exercise caution and awareness by following the letter's COVID-19 and mucormycosis public health standards and recommendations. The following are some of the most significant preventative measures: when visiting construction sites, use masks when managing dirt, moss, or manure, wear shoes, long trousers, long shirts, and hand gloves, keeping personal hygiene by scrubbing when bathing is said to be one of the most effective ways to avoid the spread of mucormycosis infection, and overuse of zinc throughout the COVID19 pandemic raised zinc levels in the body, which might explain the spike in mucormycosis cases and COVID-19 overlap.

CONCLUSION

In conclusion, mucormycosis appears to be exacerbated by diabetes and high corticosteroid use in COVID19. In COVID19 patients, all attempts should be taken to maintain appropriate glucose levels, with only limited use of corticosteroids. Immunocompromised individuals, diabetics, those on steroids, and those with co-morbidities such as cancer or organ transplants are more prone to contract COVID-19. There are significant indicators that mucormycosis is becoming more common, connected to the rising trend in diabetes mellitus. On the other hand, Mucormycosis is closely linked to diabetes and immune system diseases. Participants in COVID-19 who have mucormycosis risk factors may be able to reduce their corticosteroid use, which might help them prevent infection. Overuse of antibiotics and antifungal drugs during the COVID-19 pandemic may result in future antibiotic and antifungal medication resistance. Furthermore, prescription-based practices must be followed to the letter, and self-medication must be closely monitored and prevented.

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