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The underlying factors of occurrence of Mucormycosis in post-COVID-19 patients – A meta-analysis of case histories

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ABSTRACT

Mucormycosis is a life-threatening fungal infection caused by fungi of the order Mucorales. It usually affects people with weakened immune systems, such as those with uncontrolled diabetes, acquired immunodeficiency syndrome, iatrogenic immunosuppression, and hematological malignancies, as well as individuals who have had organ transplants. The type of mucormycosis a person suffers from is often determined by their underlying conditions. The most common types are rhino-cerebral mucormycosis, pulmonary mucormycosis, cutaneous mucormycosis, cerebral mucormycosis, gastrointestinal mucormycosis, and disseminated mucormycosis. The incidence of mucormycosis has been increasing over the years, with an overall mortality rate of 54%. Recent cases have shown a correlation between COVID-19 and mucormycosis. Using anti-inflammatory drugs to combat the cytokine storm associated with COVID-19 can weaken the immune system, making individuals more susceptible to opportunistic fungal infections like mucormycosis. Underlying health conditions further exacerbate the condition. This study reviewing 198 cases of mucormycosis and conducting a meta-analysis found that post-COVID-19 patients most commonly developed rhino-orbital-cerebral mucormycosis, followed by pulmonary and gastrointestinal mucormycosis. The study also identified diabetes as the most common underlying factor contributing to the development of mucormycosis in post-COVID-19 patients, followed by hypertension and obesity. The study also examined the influence of age, affected organs, and

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the use of certain drugs on the development of mucormycosis. Age was found to be a significant factor in the infection. This meta-analysis is one of the first to compare post-COVID mucormycosis cases with those from the pre-COVID era. The hope is that this study and analysis will help identify the determinants of mucormycosis in post-COVID patients and aid the scientific community in finding a solution to this problem.

1 Introduction

Black fungus, also known as dematiaceous fungus, refers to fungi that produce dark melanoid pigments on the cell walls of vegetative cells and conidia, giving them a distinctive blackish-grey hue in their colonies (Chowdhary et al. 2014). There are numerous black fungi in the environment, many of which are pathogenic to humans and animals (de Hoog et al. 2000). While some species, such as *Auricularia auricula* and *Pestalotiopsis* sp. have been studied for their nutritional benefits (Yao et al. 2019; dos Santos et al. 2020), others like *Trichophyton schoenleinii* and *Microsporum audouinii* are known to cause diseases and infections in humans (Matsumoto et al. 1994; Revankar 2012). These fungi are commonly found in soil and are widespread, with some associated with a few specific diagnoses and others occupying specialized ecological and geographical niches. They have increasingly been recognized as significant pathogens in both immunocompromised and healthy individuals. The treatment for these uncommon and occasionally refractory illnesses is not standardized, necessitating further research for better understanding. Between 2019 and 2021, the term "black fungus" gained sudden prominence after the COVID-19 pandemic. This term refers to a rare but serious infection known as Mucormycosis, caused by fungal spores of the class Mucormycetes (Petrikkos et al. 2012). These organisms are commonly found in the environment and seldom cause illness in healthy individuals. The most likely transmission routes in susceptible individuals are inhalation of spores or direct inoculation into the skin or mucosa during interventional procedures or trauma (Petrikkos et al. 2003).

2 Mucormycosis

2.1 Types of Mucormycosis

Mucormycosis can manifest in various types, and the clinical symptoms of infections are influenced by the site of the organisms' infection and the method of transmission. Pulmonary mucormycosis has a fatality rate of 40-70% (Khan et al. 2020; Muthu et al. 2021). The infection begins when fungal spores are inhaled into the body. The individual's immune system determines the severity and progression of the infection. The infection is more common in immunocompromised individuals with transplants and hematological malignancies. The most common fungal species associated with pulmonary mucormycosis are *Rhizopus* spp., *Mucor*, and *Rhizomucor* species (Novais et al. 2020). Gastrointestinal mucormycosis is exceptionally rare, accounting for approximately 2 to 11% of all cases (dos Santos et al. 2023). The stomach and intestine are the most commonly affected organs, and in some cases, the infection can spread to other parts of the digestive system. Infections are typically moderate, but in rare cases, they can be severe. The intestinal infection begins when spores are ingested with food or other substances and then pass through the gastrointestinal tract (Clemente-Gutiérrez et al. 2019). Cutaneous mucormycosis can manifest as a localized infection or progress to affect deeper tissues and potentially spread to other body parts. This infection is caused by the pathogen entering the body through skin injuries or wounds from surgery, natural disasters, or contact with soil and other contaminated sources. The infection can rapidly progress from the skin's surface to the subcutaneous layer, fascia, and bone. *Apophysomyces* and *Saksenaea*, widespread soil saprophytes, are the most prevalent species associated with Cutaneous mucormycosis. Cutaneous mucormycosis infections can be categorized into two main types: primary and secondary. Primary infections occur when the organism is present on the skin and directly invades through breaches in the skin barrier, such as wounds, burns, surgical sites, or areas of trauma. Secondary infections occur when the organism spreads to the skin from another site of infection, often through the bloodstream. The most affected regions in cutaneous mucormycosis are the legs and arms, with uncommon incidences in the scalp, face, back, thorax, breast, neck, and genitals (Zuglian et al. 2019). Disseminated mucormycosis is the rarest form and mainly occurs in neutropenic individuals with hematologic malignancies or post-transplant recipients. Despite its rarity, it has a high fatality rate of roughly 90% due to the invasive nature of the infection (Alqarihi et al. 2023). The tendency to invade endothelial cells within the vascular system contributes to the high rate of dissemination associated with mucormycosis. Infections can spread to various organs, such as the lung, pancreas, brain, and spleen, causing moderate to severe infections in some or all of these areas. Extremely immunocompromised individuals who have received deferoxamine, a medication that binds iron and aluminium, are at risk of developing the disease (Araf et al. 2022). The disseminated mucormycosis symptoms and presentations are often unclear, leading to delayed diagnosis and further infection. Direct inoculation of the fungus is the most common route of transmission, which can lead to cutaneous, subcutaneous, muscular, and skeletal tissue infections (Alqhamdi et al. 2019).

Rhino cerebral mucormycosis is a rare disease caused by a filamentous fungus of the order Mucorales. This fungus affects the

paranasal sinuses, nose, and brain. When the fungus develops rapidly and aggressively, it may become chronic. The most common form of mucormycosis is rhino cerebral mucormycosis, and the incidence of infections varies depending on the presence of certain high-risk groups. The infection starts in the nasal cavity and then spreads to the nearby paranasal sinuses. The fungus then adheres to the surface of the sinus and begins multiplying due to the moist environment, promoting its proliferation and invasion. In the early stage of the infection, a fungus ball grows in the maxillary sinus with no evidence of bone degradation (Aggarwal et al. 2022). Depending on the length of the infection, the host's immunity, and the severity of the infection, the condition may worsen. Several virulence factors drive the disease's progression. It starts with blood vessel invasion and destruction of endothelial cells, leading to ischemia and tissue necrosis. The invasion of the sphenopalatine and internal maxillary arteries results in the invasion of the brain and orbits of the brain. Diabetic individuals with diabetic ketoacidosis and hyperglycemia are more likely to develop rhino cerebral mucormycosis (Dong et al. 2022). The generic symptoms of the illness make it difficult to diagnose the infection early. Common symptoms include one-sided pain behind the eyes and fatigue. Other symptoms encompass face discomfort, numbness, nasal discharge, sinusitis, convulsions, altered mental state, and gait issues (Martínez-Herrera et al. 2021).

2.2 Affected groups

Studies have revealed that specific groups of individuals are more vulnerable to mucormycosis. Hyperglycemia creates an optimal environment for fungal growth. *Mucor* and *Rhizopus* species possess an active ketone reductase system, enabling them to thrive in an acidic pH and glucose-rich environment (Ibrahim et al. 2012). Furthermore, hyperglycemia fosters fungal proliferation and impacts neutrophil chemotaxis, leading to frequent occurrences in patients with diabetic ketoacidosis. *Rhizopus* species thrive in iron-rich environments and are commonly found in patients undergoing deferoxamine therapy (an iron-chelating agent) (Pathak et al. 2018). Mucorales also rely on iron for growth, leading to phagocytic activities and dissemination into the vasculature (Thomas et al. 2020). Studies have also demonstrated that individuals with leukemia, particularly those who have undergone hematologic bone marrow transplants, are prone to various types of mucormycosis. Immune deficiencies associated with hematological malignancies may heighten susceptibility to opportunistic fungi, as neutrophils play a crucial role in the protective host response (Cheong et al. 2017). Long-term use of glucocorticoids and corticosteroids also significantly contributes to mucormycosis development. Corticosteroids are often prescribed for the treatment of various disorders, including severe allergies or skin conditions, asthma, arthritis, or autoimmune diseases such as Systemic Lupus Erythematosus (SLE) (Arnold et al. 1988; Durcan and Petri 2016; Daley-Yates et al. 2021; Reynolds et al. 2024). Furthermore, abnormal levels of iron and aluminum play a substantial role in mucormycosis development, particularly in patients undergoing dialysis or iron-chelating therapy (Reyes et al. 2008).

2.3 Pathology

2.3.1 Route of Infection

Mucormycetes, also known as black fungi, are spores of molds that typically thrive in organic matter such as soil or compost. These spores can enter the human body through inhalation, ingestion, or direct inoculation via skin wounds. Inhalation of spores is the primary route of infection, causing severe conditions like rhinocerebral and pulmonary mucormycosis in immunocompromised individuals (Prakash and Chakrabarti 2019). Ingestion of spores can lead to gastrointestinal mucormycosis, especially in neonates and malnourished individuals (Roden et al. 2005). Direct inoculation through traumatic injuries or burns can result in cutaneous mucormycosis, commonly observed in disaster settings (Pilmis et al. 2018).

2.3.2 Colonization

Mucormycetes are commonly found but typically do not cause significant issues because our immune system is equipped to defend against such infections. Iron is essential for the growth and development of mucormycetes, and the fungus has developed various strategies to obtain it from the host (Ibrahim et al. 2012). A higher concentration of iron provided by the host's serum increases the likelihood of fungal proliferation. Unbound free iron can be toxic and create an unguarded platform for infecting pathogens. It triggers harmful reactive oxygen species, causing damage to cellular components. Simultaneously, pathogens exploit free iron for growth and proliferation. Excess unbound iron overwhelms the body's defense mechanisms, facilitating pathogen colonization and infection. This highlights the crucial role of iron balance in maintaining health and preventing disease. To counter this, humans have a defense mechanism that involves binding iron to proteins such as transferrin, ferrin, and lactoferrin. Mucorales cannot thrive in iron-low serum unless it is externally added (Ibrahim et al. 2012). Mucorales utilize various strategies to acquire iron from the host. One method involves using xenosiderophores, such as deferoxamine, which strips iron from transferrin proteins and transports it intracellularly after converting it into a soluble form. Another mechanism involves the utilization of high-affinity iron permease, including ferrous reductase, multicopper oxidase, and ferrous permease, to actively convert ferric to soluble ferrous iron and facilitate its uptake. Additionally, Mucorales use heme-oxygenase to sequester iron from heme proteins found in the host's blood, further enhancing their ability to acquire this essential nutrient (Ibrahim et al. 2012).

During the COVID-19 pandemic, mucormycetes have been labelled as "opportunistic black fungus" because they exploit the situation where the immune system is weakened by the use of corticosteroids administered to COVID patients to address the exaggerated release of cytokines mediated by angiotensin-converting enzyme 2 (ACE2). This leads to vascular inflammation, shock, and ultimately results in multi-organ failure and death (Singh et al. 2020).

2.3.3 Immunopathology of COVID-19

Infection with the SARS-CoV-2 virus compromises the integrity of the respiratory passages, providing a pathway for the invasive Mucorales (Zhang et al. 2023). The overexpression of GRP78 in COVID-19 may facilitate Mucorales hyphal invasion and spore germination (Alqarihi et al. 2020). COVID-19 disrupts macrophage function by directly infecting them, making them prone to hyperglycemia and generating neutrophil extracellular traps, which affects innate defenses against Mucorales. Thrombocytopenia, a decline in natural killer (NK) cells, and infected dendritic cells are all linked to the COVID-19 virus, leading to a reduced immune response to Mucorales. Cytokines generated during COVID-19 induce leucocyte oxidative damage, disrupt mitochondria, and lead to a build-up of reactive oxygen species. Additionally, COVID-19 infection results in hyperferritinemia, which inhibiting the hematological growth of B- and T-lymphocytes (Dave et al. 2022).

2.3.4 Treatment

The FDA has only approved three antifungal drugs for treating mucormycosis: amphotericin B, posaconazole, and isavuconazole lipid formulations. Surgical debridement is also performed if needed. However, the mortality rate for mucormycosis remains over 50% when only antifungal drugs are used for treatment (Gebremariam et al. 2019). Surgical removal of necrotic tissue is the primary therapy for mucormycosis (Sipsas et al. 2018). Patients with pulmonary mucormycosis show significant improvement after surgical intervention combined with antifungal drugs compared to treatments relying solely on antifungal drugs. In some cases, localized surgery may be sufficient. Magnetic Resonance Imaging (MRI) is used for rhino-orbital-cerebral mucormycosis to determine the extent and exact location of the necessary surgical intervention. Surgical intervention is crucial in these cases (Sipsas et al. 2018).

Additionally, adjunctive therapy plays a crucial role in treatment, aiming to reactivate the suppressed immune system (Sipsas et al. 2018). Patients often succumb to the disease due to poor recovery of bone marrow function. One approach is to reverse neutropenia in hematologic patients by incorporating hematopoietic growth factors into the host's system or by white cell transfusion (Whitsett 1995). In HIV/AIDS patients, immunity restoration can be achieved through antiretroviral therapy. Aggressive hyperglycemia in individuals with uncontrolled diabetes should be addressed and can be treated with sodium bicarbonate to block the invasion of endothelial cells by the fungus, restoring host iron chelation and neutrophil function. Another effective strategy to inhibit the growth of fungal infection is through iron chelation, reducing iron availability in the host's blood. Deferasirox was tested on mice, and the survival rate increased. Neutrophil functionality can be enhanced by increasing oxygen pressure with hyperbaric oxygen (HBO), mediating the improvement of neutrophil functionality and wound healing. This is particularly helpful for diabetic patients with sinusitis or cutaneous mucormycosis (Sipsas et al. 2018).

Certain protocols were issued by the European Confederation of Medical Mycology (ECMM) and mycoses Study Group Education and Research Consortium in 2019 (Bhatt et al. 2021). According to these protocols, immediate surgical intervention is advised whenever possible in cases of fungal infection. The primary approach to managing these infections involves using antifungal drugs, with a combination of liposomal *amphotericin B*, *isavuconazole*, and *posaconazole* being the preferred initial treatment. In cases where patients have undergone graft transplants and are experiencing graft vs host reactions, *prophylaxis* involving *posaconazole* may be recommended (Bhatt et al. 2021). For CAPA (SARS-CoV-2) associated pulmonary *aspergillosis*, the recommended drugs are classified into two main categories: allergic *aspergillosis* and invasive aspergillosis (Bhatt et al. 2021). The most common strain responsible for this type of Black fungal infection is *Aspergillus fumigatus*, which commonly affects immunosuppressed individuals, patients who have undergone hematopoietic transplantation, or those receiving corticosteroid treatment for COVID-19-related lung injury.

Allergic *aspergillosis* is typically treated with *triazoles* (such as *itraconazole*, *voriconazole*, *posaconazole*, and *isavuconazole*) in combination with *corticosteroids*. As for invasive *aspergillosis* observed in post-COVID-19 patients, treatment may involve *voriconazole*, lipid *amphotericin* B formulations, *posaconazole*, *isavuconazole*, *itraconazole*, and *echinocandins* (*micafungin* or *caspofungin*). Triazoles can also be administered but require close Therapeutic Drug Monitoring (TDM) to monitor for potential side effects in patients due to *azole* (Bhatt et al. 2021). For *Cryptococcus neoformans* variant infections in immunosuppressed patients post-COVID-19, the recommended treatment protocol includes *trimethoprim*, sulfamethoxazole, and TDM, as outlined by Hoagland et al. (1961). Severe lung infections or central nervous system infections may require the use of *Amphotericin* B in combination with *flucytosine*, as recommended by the CDC (Center for Disease Control and Prevention). Following this, *flucytosine* alone is administered until the patient fully recovers (Bhatt et al. 2021).

In cases of *Candida auris* infections, which are responsible for hospital outbreaks and commonly observed in COVID-19 patients, treatment typically involves *echinocandins* (*caspofungin*, *micafungin*, *anidulafungin*), *azoles* (*fluconazole*, *voriconazole*, *itraconazole*), and *Amphotericin* B, including its liposomal formulations. Identifying *C. auris* poses a challenge due to its multidrug resistance (Bhatt et al., 2021). Salvage options include *Deferasirox* and *Posaconazole* (Spellberg et al., 2009). *Deferasirox* should not be administered for more than 4 weeks due to a substantial increase in toxicity, while *posaconazole* can be administered for longer durations.

In a study by Gebremariam et al. (2019), a new approach to combat mucormycosis was demonstrated. The study revealed that mucormycosis targets human umbilical vein endothelial cells (HUVEC) by using the fungal cell surface protein cot-H3, which specifically binds to another protein on the surface of HUVEC called glucose-regulated protein-78 (GRP-78). When the levels of glucose, iron, and ketone bodies in the bloodstream are higher than normal, the expression of GRP-78 and Cot-H3 is increased, enabling fungal cells to gain access to endothelial cells through endocytosis. This discovery suggests that selectively silencing Cot-H3 expression can halt fungal infection, as Cot-H3 is highly conserved within the order Mucorales and is a promising target for therapeutic interventions. Additionally, the study found that polyclonal antibodies synthesized against two peptides forming the GRP-78 binding region on Cot-H3 effectively prevented invasive and hematogenous dissemination of the fungus.

Another study by Watkins et al. (2018) demonstrated that inhibiting the epidermal growth factor receptor (EGFR) signaling could be a potential strategy against mucormycosis. Through RNA-seq analysis, the researchers investigated the host transcriptional response to *Rhizopus delemar*, a fungal strain, and found that the EGFR pathway was activated by *mucorale* species, facilitating invasion of host cells. Using Gefitinib, an FDA-approved drug, the study showed that it could prevent invasion by modulating gene expression related to EGFR signaling. This research was conducted using human alveolar epithelial cells and *R. delemar*. The study illustrated that EGFR plays a central role in the uptake of *mucorale* and subsequent lung cell damage. By blocking EGFR signaling using Gefitinib and the monoclonal antibody Cetuximab, the research team prevented the fungus from gaining control over the host's body.

2.3.5 Challenges in the treatment of mucormycosis

Despite advancements in fungal infection management strategies, the overall mortality rate remains at 90% in cases of disseminated mucormycosis (Boutin and Luong 2024; Katragkou et al. 2014). Different strains show varying responses to different drugs. Further, *R. oryzae* was found resistant to *posaconazole* in vitro, while *Mucor circinelloids* were susceptible to *posaconazole*. When the *R. oryzae* strain was sequenced, it was revealed that it had genetically adapted to survive in unfavorable environments with antifungal agents. As a result, *itraconazole* and *posaconazole* need to be administered in higher doses for their efficacy, which exceeds the safely achievable drug concentration. Recurring infections by *R. oryzae* in *voriconazole*-administered patients suggest its lack of activity. Similarly, when prescribed liposomal amphotericin B, it is administered at the maximum tolerated dose with a risk of nephrotoxicity (Katragkou et al., 2014).

2.4 Disease burden and demographic characteristics of mucormycosis

According to epidemiological studies, mucormycosis's frequency and characteristics may vary among countries (Prakash and Chakrabarti 2019; Skiada et al. 2020). However, most European countries experienced lower incidences, and after this, haematological malignancies and transplantation emerged as primary risk factors. In contrast to this, India exhibited the highest estimated incidence of mucormycosis, and uncontrolled diabetes is reported as the predominant risk factor. A French study that employed data extraction codes from the French hospital information system and the International Classification of Diseases (ICD) to classify diseases was the primary source of the current countrywide population-based incidence statistics (Sacconi et al. 2018). From 1997 to 2006, there was a rising trend in the incidence of mucormycosis. The incidence rate in France was frequently utilized as a benchmark for evaluating the burden of mucormycosis in other nations (Corzo-León et al. 2015; Pegorie et al. 2017; Sabino et al. 2017). To determine the public health measures and the diagnostic and therapeutic needs of the population, a thorough evaluation of the disease burden and the identification of the group at risk must be performed. However, large-scale epidemiological studies on mucormycosis are still rare in Asia and are mostly restricted to reviews of single- or multicenter studies conducted in India (Prakash and Chakrabarti 2021). Taiwan's National Health Insurance Research Database (NHIRD) can be used as a population-based database for extensive healthcare research (Hsieh et al. 2019). Studies using NHIRD showed an increase in the number of people with diabetes and immunocompromised people over time. A significant rise in the incidence of invasive pulmonary *aspergillosis* from 2002 to 2011 was also observed based on these data (Sheen et al. 2019; Sun et al. 2016). The incidence of mucormycosis was not quantified. Therefore, using *aspergillosis* as a comparator, this study sought to outline the temporal trend of disease burden and demographic characteristics of mucormycosis in Taiwan from 2006 to 2017 based on the NHIRD

3 Previous Case History

The first recorded case of mucormycosis was documented by Furbinger from Germany in 1876 after a cancer patient passed away and scans revealed hemorrhagic infarct of fungal hyphae and

sporangia in the right lung (Skiada et al. 2020). Subsequently, in 1885, Arnold Paltauf reported the first case of disseminated mucormycosis, which he named "mucosismucorina." His illustrations depicted structures resembling rhizoids and sporangiospores, identifying the causative organism as *Lichtheimia corymbifera* (Skiada et al. 2020). Since then, the incidence of mucorales fungal infections has risen, making it the second most common disease-causing mold after *Aspergillus*. Initially deemed incurable, the first documented recovery occurred in the United States in 1955, when a young girl with diabetes was successfully treated with *amphotericin* B (Skiada et al. 2020).

The understanding and findings of mucormycosis advanced when, in 1957-1958, two cases led to the prescription of various antibiotics due to uncertainty regarding the cause of the disease, including *penicillin* and *chloramphenicol* (Hoagland et al. 1961). Once it became evident that the fungus was the underlying cause of the malignancy and was aggressively progressing, the antibiotics were discontinued, and *nystatin* and potassium iodide were administered instead. Similarly, in 1960, *amphotericin* B was used to combat the infection, coupled with surgical intervention to excise the necrotic tissue (Hoagland et al. 1961). A literature review revealed that between 1970 and 1993, 203 cases of mucormycosis were documented (Hendrickson et al. 1999).

In a study discussing the treatment of rhinocerebral mucormycosis with hyperbaric oxygen therapy, Couch et al. (1988) highlighted the main forms of mucormycosis, including pulmonary, rhinocerebral, and intestinal. They noted that individuals at high risk of infection included those with weakened immune systems, diabetes, burns, and those undergoing corticosteroid therapy. The overall mortality rate associated with rhinocerebral mucormycosis was 70% until the 1960s, before the availability of *amphotericin* B and radical surgical debridement. Following the introduction of these treatments, the mortality rate decreased to approximately 40%. The study suggested that hyperbaric oxygen therapy showed potential in treating fungal infections, although the specific mechanism for controlling the infection was not fully understood then. Additionally, the exact duration and dosage of *amphotericin* B required for eradicating the fungus were not yet established (Couch et al. 1988).

In a separate review of cases of rhino-orbito-cerebral mucormycosis, Hendrickson et al. (1999) noted that the fungus could infect individuals of any age or occupation, including seemingly healthy individuals. They also highlighted that individuals with leukemia and lymphomas were particularly susceptible to fungal infection. Other underlying conditions that could potentially lead to mucormycosis included renal disease transplantation, malnutrition, and patients undergoing deferoxamine treatment. It was identified that *deferoxamine* led to alterations in transferrin levels, which enabled the fungus to thrive more easily while decreasing cellular immunity. The study provided general treatment guidelines for rhinocerebral mucormycosis, clearly outlining the dosage of *amphotericin* B and introducing newer formulations, such as liposomal encapsulated and lipid complex *amphotericin* B, which had fewer side effects. The study also indicated that the mode of action of hyperbaric oxygen therapy was being further understood (Hendrickson et al. 1999).

A review by Roden et al. (2005) found that mucormycosis can also target a broader and more diverse population, unlike other fungal infections that mainly affect immunocompromised patients. The review documented that over 50% of the cases were observed in individuals with either diabetes mellitus or no underlying conditions. Additionally, the study noted that while most fungal infections spread from other organs to the skin, mucormycosis exhibited the opposite pattern in cutaneous mucormycosis. The highest percentage of disseminated infection was found in patients taking *deferoxamine* as part of their treatment, indicating iron's importance in the infection's virulence. Some researchers suggested that *estrogen* may be behind the observed higher susceptibility of males to the infection compared to females, but this remains unexplained. Roden et al. (2005) reported a mortality rate of over 54% due to mucormycosis infection. Bitar et al. (2009) studied mucormycosis cases in France from 1997 to 2006, revealing an increase from 0.7 cases per million in 1997 to 1.2 cases per million in 2006. The number of cases was particularly high in patients with hematological malignancies and those who had undergone bone marrow transplants. The study also found a higher incidence of the infection in diabetic patients.

After compiling data from various sources, Danion et al. (2015) reported that the species causing infection varies depending on the geographic area. For example, in North America, most cases were caused by *Rhizopus* spp., followed by *Mucor* spp., *Rhizomucor* spp., and *Lichtheimia* spp. In France, *Rhizopus arrhizus* was the most common, followed by *Leichtheima* and *Rhizopus* microspores, while in India, *Rhizopus arrhizus* and *Apophysomyces elegans* were the most commonly isolated species.

4 Black Fungus Infections in Post-Covid-19 Patients in India: A brief Case Study

As of July 15, 2021, there have been 45,432 reported cases of mucormycosis or black fungus in India, resulting in more than 4,300 deaths. 84.4% of the black fungus patients had previously COVID-19. Among these cases, rhino cerebral mucormycosis is the most common (77.6%), followed by cutaneous (4.3%) and pulmonary (3%) (Dutta 2021; “Mucormycosis: India Records More than 4,300 ‘Black Fungus’ Deaths,” 2021). This "opportunistic black fungus" infects COVID-19 patients by taking advantage of weakened immune systems caused by factors such as

diabetes, cancer, or the prolonged use of medications like steroids. These reports led to a review of 198 case histories related to mucormycosis from literature databases. A meta-analysis was also conducted to identify the determining factors of the black fungus infection, which will be discussed in the upcoming sections.

5 Data Analysis

5.1 Methods of Data Acquisition

Search engines like PUBMED (https://pubmed.ncbi.nlm.nih.gov) and Elsevier (https://www.elsevier.com) have been used to retrieve data using keywords such as "Mucormycosis" or "Black Fungus" in conjunction with "COVID-19" (Table 1) and "Mucormycosis" and "Cases" (Table 2). Each report was thoroughly examined to confirm the presence of both COVID-19 and mucormycosis. Furthermore, we considered cases reported from 1944 to 2021 during our analysis. A mathematical analysis explored the correlation between different co-factors, potentially linking COVID-19 and mucormycosis. Frequency was calculated using Microsoft Excel, where Frequency % = (n/N)×100, with "n" being the total number of observations in each category and "N" being the total number of categorical observations across all categories. A total of 16 entries were documented for Table 1, and 198 entries were accounted for Table 2.

5.2 Information Collected

Data from the database were initially screened using titles and abstracts, followed by full-text reviews. Information was extracted from articles, tables, and graphs, including the year of publication, patient demographics, underlying conditions, infection sites, and prevalence of mucormycosis types. Clinical manifestations were categorized based on affected body locations and infection severity at diagnosis, as determined by histopathological and radiological findings. The data analysis primarily focused on correlating underlying diseases and medications with the occurrence of mucormycosis, although limited information was available on prior medication history. The study also investigated the majorly affected organs and types of mucormycosis.

6 Results and Discussion

A study of post-COVID-19 mucormycosis cases discovered that most cases were rhino-orbito-cerebral mucormycosis (69%), followed by pulmonary mucormycosis (25%). This may be due to the prevalence of diabetes among the patients, which commonly leads to rhino-orbital-cerebral mucormycosis. The study also aimed to establish a correlation between underlying diseases and all types of mucormycosis. It was observed that the most common underlying disease was diabetes (56%), followed by hypertension (50%). In diabetic individuals, the altered immunogenic response to infections creates a favorable environment for fungal proliferation (Figure 1). Diabetes ketoacidosis mucormycosis is generally caused by *Rhizopus oryzae*, which thrives in the patient's ketone bodies. The study revealed that the most vulnerable age group to mucormycosis was 60-69 years (31%), followed by 40-49 years (25%). Higher age groups are more vulnerable due to immunological changes and the administration of immunosuppressive antibiotics (Figure 1). The study also examined the influence of drugs administered for underlying diseases and found that insulin was the most commonly administered drug (50%). It was observed that underlying conditions such as diabetes and hypertension had a greater involvement in certain types of mucormycosis. However, the total number of post-COVID-19 mucormycosis cases studied was only 16, so a meta-analysis was performed using a larger dataset (198 studies) to understand the underlying factors better.

Upon analyzing Table 2, the data revealed that most cases were associated with specific types of mucormycosis. Rhino-orbito-cerebral mucormycosis accounted for 42.42% of the cases, followed by pulmonary mucormycosis (17.68%) and cutaneous mucormycosis (13.13%) (Figure 2A). It is important to note that several other types of mucormycosis, such as renal, intestinal, orbital, ENT, orbito-facial, and hepatic, were also documented. These additional types were grouped under the main five categories of mucormycosis to simplify data analysis and to facilitate the generation of general conclusions. The symptoms of rhino-orbito-cerebral mucormycosis included fever, eye discomfort, facial swelling, and headache. Pulmonary mucormycosis presented with symptoms such as fever, fatigue, cough, and chills, while cutaneous mucormycosis manifested as lesions and ulcerations in the affected area.

It was observed that the most common underlying condition preceding mucormycosis was diabetes (31%), followed by leukemia (20%) (Figure 2B). Leukemia, especially in combination with neutropenia (> 500 neutrophils per mm^3 for more than 10 days), prolonged use of broad-spectrum antibiotics for over 96 hours, extensive chemotherapy, and prolonged use of corticosteroids, was found to be a significant contributing factor to mucormycosis (Bhatt et al. 2011).

Analysis of affected body parts before the diagnosis of mucormycosis revealed that the most affected body part was the bone marrow (17%), followed by the pancreas (15%) and the kidneys (12%) (Figure 2C). This could be attributed to therapeutic strategies such as bone marrow transplantations in leukemia patients, as well as the increased vulnerability of diabetic patients, leading to a higher risk for kidney and pancreas complications. The use of various drugs for the underlying conditions was also examined. While this data was often unavailable (45%), it was noted that *prednisone* (11%), *insulin* (7%), and chemotherapy (6%) were the most commonly used drugs before the diagnosis of mucormycosis

Table 1 Correlation of post-COVID-19 Mucormycosis patients with underlying diseases

No of death	Age	Gender	Type of Mucormycosis	Any disease before COVID + Mucormycosis	Drug administration for that disease (Generic name)	Class of drug	Drug administration for COVID	Class of Drug administered for COVID	Organs infected pre-Mucormycosis	Probable infected organs	Infected regions during Mucormycosis	Complications faced	Reference
1	60	M	Rhino-orbital	Diabetis Mellitus	N/A	Antihypoglycemic Medication	Meropenem , oral oseltamivir , Methylprednisolone, Dexamethasone	Carbapenem antibiotic, Antiviral neuraminidase inhibitor, Corticosteroid, Glucocorticoid	N/A	Kidney	Lungs, Brain, Eyes,	Breathlessness, Pyrexia, Tachypnea, Malaise	Mehta and Pandey 2020
1	22	M	Pulmonary	Obesity, Hypothyroidism	N/A	N/A	N/A	N/A	N/A		Lungs	N/A	Hanley et al. 2020
1	49	M	Pulmonary	None	None	None	Remdesivir, Tocilizumab, Dexamethasone	Nucleoside analog, IL-6 receptor inhibitor	N/A		Lungs	Fever, cough, and shortness of breath	Placik et al. 2020
1	86	M	Gastrointestinal	Arterial hypertension	N/A	N/A	Ceftriaxone, Azithromycin, Oseltamivir, Hydrocortisone	Cephalosporin antibiotic, Macrolide antibiotic, Antiviral neuraminidase inhibitor, Glucocorticoid	N/A	Heart	Lungs, Intestine	Acute diarrhea, Cough, dyspnea, fever	Monte Junior et al. 2020
1	66	M	Pulmonary	Arterial hypertension	N/A	ACE-inhibitors	Hydroxychloroquine and lopinavir-ritonavir	Anti-rheumatic drug, HIV-1 protease inhibitor,	N/A	Heart	Lungs	Rapid deterioration of oxygenation	Pasero et al. 2020
1	24	F	Rhino-orbital	Obesity	N/A	Data not provided	Not Administred	Not administered	N/A		Nose, Lungs	Pain in left midface region, left lid swelling, Maxillary hypoesthesia	Waizel-Haiat et al. 2021
1	55	M	Pulmonary	Diabetes mellitus, Hypertensio, and Ischemic cardiomyopathy	N/A	Oral hypoglycemic drugs	Dexamethasone, remdesivir	Glucocorticoid, nucleosideanalog	N/A	Heart, Kidney	Lungs	Fever, Dry cough, and Progressive breathlessness	Garg et al. 2021

No of death	Age	Gender	Type of Mucormycosis	Any disease before COVID + Mucormycosis	Drug administration for that disease (Generic name)	Class of drug	Drug administration for COVID	Class of Drug administered for COVID	Organs infected pre-Mucormycosis	Probable infected organs	Infected regions during Mucormycosis	Complications faced	Reference
0	46	M	Rhino-orbital-cerebral	Diabetes Mellitus	N/A	Insulin	Not Administred	Not Adminitstered	N/A	Kidney	Eyes	Pain, Redness, Periocular swelling, Progressive drooping of eyelids, Limitation of ocular movements, Painful loss of vision	Sen et al. 2021
0	60	M	Rhino-orbital-cerebral	Diabetes Mellitus, hypertension	N/A	Insulin	Methylprednisolone, Oral prednisolone	Corticosteroid	N/A	Kidney, Heart	Eyes	Pain, Redness, Periocular swelling, Progressive, Drooping of Eyelids, Limitation of ocular movements, Painful loss of vision	Sen et al. 2021
0	73	M	Rhino-orbital-cerebral	Diabetes Mellitus, hypertension, Coronary artery disease	N/A	Insulin	Methylprednisolone, Oral prednisolone	Corticosteroid	N/A	Kidney, Heart	Eyes	Pain, Redness, Periocular swelling, Progressive, drooping of eyelids, Limitation of ocular movements, Painful loss of vision	Sen et al. 2021
0	72	M	Rhino-orbital-cerebral	Diabetes Mellitus	N/A	Insulin	Methylprednisolone, Oral prednisolone	Corticosteroid	N/A	Kidney	Eyes	Pain, Redness, Periocular swelling, progressive, Drooping of eyelids, Limitation of ocular movements, Painful loss of vision	Sen et al. 2021

No of death	Age	Gender	Type of Mucormycosis	Any disease before COVID + Mucormycosis	Drug administration for that disease (Generic name)	Class of drug	Drug administration for COVID	Class of Drug administered for COVID	Organs infected pre-Mucormycosis	Probable infected organs	Infected regions during Mucormycosis	Complications faced	Reference
0	62	M	Rhino-orbital-cerebral	Diabetes Mellitus, hypertension	N/A	Insulin	Methylprednisolone, Oral prednisolone	Corticosteroid	N/A	Kidney, Heart	Eyes	Pain, Redness, Periocular swelling, progressive, Drooping of eyelids, Limitation of ocular movements, Painful loss of vision, Headache	Sen et al. 2021
0	47	M	Rhino-orbital-cerebral	Diabetes Mellitus, Coronary artery disease	N/A	Insulin	Methylprednisolone, Oral prednisolone	Corticosteroid	N/A	Heart, Kidney	Eyes	Pain, Redness, Periocular swelling, Progressive, drooping of eyelids, Limitation of ocular movements, Painful loss of vision	Sen et al. 2021
0	41	M	Rhinocerebral	Diabetes mellitus	N/A	Insulin	Hydroxychloroquine	Anti-rheumatic drug	N/A	Kidney	Nose	Deep aching pain in nose and throat	Alekseyev et al. 2021
1	60	M	Rhino-orbital	Diabetes, Asthma, Hypertension, Hyperlipidemia	N/A	Insulin	Remdesivir	Nucleoside analog	N/A	Lungs, Kidney, Heart	Nose	Dyspnea and hypoxia	Mekonnen et al., 2021
1	33	F	Rhino-orbital-cerebral	Hypertension and asthma	N/A	N/A	N/A	N/A	N/A	Heart, Lungs	Brain, Lungs	Vomiting, cough, and shortness of breath	Werthma-Ehrenreich 2021

Various post-COVID-19 cases of Mucormycosis had been taken into account. A total of 17 entries, from the year 2020 to 2021, had been used to perform data analysis. Susceptibility of the disease due to age, most frequent type of mucormycosis and the most common underlying medical comorbidities were studied. Medication and class of drugs taken for the underlying disease as well as COVID-19 were documented.

Table 2 Correlation of Mucormycosis patients with underlying diseases

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1944	U.S	1	0	1	Rhino cerebral	N/A	N/A	N/A	Immovable left arm and leg, Right pupil larger than right with inflammation, Purulent discharge	Eyes, Lungs, Brain	Lecompte and Meissner 1947
1951	U.S	1	0	1	Rhino cerebral	N/A	N/A	N/A	Vitreous humor filled with dust like opacities of rhomboid, Refractile body, Pale gray, Elevated area in lower temporal region	Eyes	Chikley et al. 2019
1953	Georgia	1	0	1	Rhino cerebral	Diabetic mellitus	Protamine-zinc insulin		Spinal cord was grey, Pooled, Turbid with flattened convolution	Brain , Meningitis	Bauer et al. 1955
1954	England	2	2	0	Rhino cerebral	Diabetic	Insulin		Loss of vision, Loss of sensation in the eye, Ulcer in the roof of mouth	Brain	Baker 1957
1954					Rhino cerebral	Diabetic acidosis	N/A		Left eye swelling, Left ethmoid sinusitis	Brain	Baker 1957
1954	U.S	1	0	1	Rhino cerebral	Diabetic	N/A		Retrobulbar space white granular material enveloped the eye muscle, Extended to posterior aspect of the globe	Brain, Eyes	Bauer et al. 1955
1955	U.S	2	2	0	Rhino Orbital	N/A	N/A	N/A	Corneal ulcer, Pain in left eye	Left eye	Barsky 1959
1955					Rhino Orbital	Chronic simple glaucoma	Pilocarpine	Left eye	Severe pain in left eye	Left eye	Barsky 1959
1956	England	1	0	1	Rhino cerebral	Portal hypertension	Portacaval shunt operation	Liver	Fever, Orbital pain	Brain	Baker 1957
1957	Georgia	1	1	0	Rhino cerebral	Diabetic,pancreatitis	Streptomycin	Pancreas	Pain in right malar area, Swelling and redness in right side of the face with decreased sensation	Right eye	Hoagland et al. 1961
1957	U.S	1	1	0	Rhino cerebral	N/A	N/A	N/A	Proptosis of right eye	Eyes,Brain	Faillo et al. 1959
1957	U.K	4	4	0	Rhino Orbital	N/A	N/A	N/A	Pain, Injection, Irritation, Lacrimation, Loss of visual activity of right eye	Right eye	Anderson et al. 1959
1957					Rhino Orbital	Both eye burn	Steroids	Eyes	Swelling, Pain in operated area	Eyes	Anderson et al. 1959
1957					Rhino Orbital	N/A	N/A	N/A	Injection , Decrease in vision, Pain in right eye	Right eye	Anderson et al. 1959

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1957					Rhino Orbital	Conjunctivitis and Corneal ulceration	Sodium sulfacetamide	Eyes	N/A	Eyes	Anderson et al. 1959
1957	U.S	2	2	0	Rhino Orbital	Corneal abscess of left eye	Erythromycin, Procaine penicillin G, Neohydreltasol	Left eye	Perforated cornea	Left eye	Barsky 1959
1957					Rhino Orbital	Diabetic mellitus	N/A	N/A	Pain, Inflammation, Cormeal ulcer in left eye, Blindness	Left eye	Barsky 1959
1958	U.S	4	0	4	Pulmonary	Leukemia, Steroid induced Diabetic	prednisone (meticorten) and 6-mercaptopurine	Bone marrow	Cushingoid features, Fever	Heart, Lungs	Hutter 1959
1958	U.S				Pulmonary	Leukemia	6-chloropurine	Bone marrow	Weakness, Fatigue	Lungs, Spleen	Hutter 1959
1958	U.S				Disseminated	Lymphosarcoma, Metabolic acidosis	X-ray and meticorten	Bone marrow	Respiratory difficulty	Lungs, Vocal cord, Heart, Esophagus , Stomach and small intestine	Hutter 1959
1958	U.S				Disseminated	Acute leukemia, Hepatosplenomegaly, Steroid induced Diabetic	6-Mercaptopurine	Bone marrow	Vesicular eruption on face, Neck, Right arm, Thigh	Brain, Lungs, Stomach, Small intestine	Hutter 1959
1958	U.K	1	1	0	Rhino Orbital	N/A	N/A	N/A	Itching , Burning, Inflammation of left eye	Left eye	Anderson et al. 1959
1958	U.S	2	2	0	Rhino Orbital	N/A	N/A	N/A	Corneal ulcer, Pain in left eye	Eyes	Barsky 1959
1958	U.S				Rhino Orbital	Chronic corneal ulcer	N/A	Eyes	N/A	Eyes	Barsky 1959

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1959	Canada	1	0	1	Rhino cerebral	N/A	N/A	N/A	Fever, Vomiting, Diarrhoea, Left cheek pain, Anorexia	Liver, Spleen, Eyes, Brain	Dolman and Herd 1959
1959	U.S	1	0	1	Rhino cerebral	Diabetic mellitus, Pneumonia, Right renal necrotizing papillitis	Insulin, right kidney removal	Kidney, Lungs	Pain in left upper jaw, Numbness, Swelling in left cheek	Eyes, Nose, Brain	Dwyer and Changus 1958
1959	U.S	1	0	1	Dissemi nated	Diabetic mellitus	N/A	N/A	Dehydration, Shock, Coma	Brain, Lungs, Genital tract, Kidney	Long and Weiss 1959
1961	U.S	2	0	2	Dissemi nated	Extensive third degree burn with 64% burn	Novocain, Chloramphenicol, Penicillin	Skin	Occasional fever	Face, Nasal cavity, Brain,Menin ges, Kidney, Stomach	Rabin et al. 1961
1961					Dissemi nated	Extensive third degree burn with 45% burn	Penicillin, Chlortetracycline, Streptomycin, oxytetracyclin	Skin	Fever	Face, Nasal cavity, Kidney, Heart	Rabin et al. 1961
1962	U.S	1	1	0	Dissemi nated	Diabetic mellitus	Tolbutamide	N/A	Severe frontal headache, Chills, Fever, Sore throat, Weakness	Eyes, Brain, Face	Prockop and Silva-Hutner 1967
1965	U.S	1	0	1	Gastroin testinal	N/A	N/A	N/A	Abdominal pain, Swelling, Chills, Hot sweats	Diaphragm, Abdomen, Lungs	Calle and Klatsky, 1966
1966	U.S	2	2	0	Rhino cerebral	Diabetic mellitus	Tolbutamide	N/A	Cough with yellow sputum, Lethargy, Difficulty in breathing	Brain , Eyes, Lungs	Battock et al. 1968
1966	U.S			0	Rhino cerebral	Diabetic mellitus	Insulin	N/A	Frontal headache, Stiff neck, Protrusion of left eye, Progressive double vision	Left eye, Left side of mouth	Battock et al. 1968

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1966	U.S	1	1	0	Cutaneous	Leukemia	Chemotherapy with Prednisolone, Vincristine, L-asparaginase, Cytosine arabinoside	N/A	Erythema in right arm	Lungs, Right arm	Wirth et al. 1997
1967	U.S	1	0	1	Rhino cerebral	Diabetic mellitus	N/A	N/A	Sore throat, Bifrontal headache, Poluuria, Excessive thirst, Lethargy	Right eye, Brain	Price et al. 1971
1968	U.S	3	0	3	Rhino cerebral	Anaemia and uremia	N/A	N/A	Double vision	Brain, Nose, Eyes, Cheek	Price et al. 1971
1968	U.S				Rhino cerebral	Diabetic mellitus, Diabetic retinopathy, Hypertension	Tolbutamide	N/A	Protrusion, Numbness, Painless swelling	Nose , Eyes	Price et al. 1971
1968	U.S				Rhino cerebral	Diabetic mellitus, Nephropathy , Recurrent bacterial infection	NPH insulin	N/A	Afebrile, Unresponsive	Brain, Meninges	Price et al. 1971
1970	U.S	1	1	0	Other	Progressive renal failure	Hemograft renal transplant, Azathioprine, Prednisone, Antilymphocytic globulin	Kidney	Purulent nasopharyngeal discharge, Dysosmia	Nose	Stevens et al. 1972
1970	U.S	1	1	0	Pulmonary	Acute lymphocytic leukemia	Prednisone, chlorambucil	Lymph node	Short of breath, Cough, Fever	Lung	Medoff and Kobayashi 1972
1970	U.S	1	0	1	Rhino Orbital	N/A	N/A	Eyes, Brain	Diarrhoea, Vomiting, Fever, Draining ears	Eyes, Face	Hale 1971

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1972	U.S	1	0	1	Pulmonary	Diabetic,renal failure requiring peritoneal dialysis	Cephalothin, Chloramphenicol, Gentamicin, Isoniazid, Rifampin	Lungs	N/A	Lungs	Murray 1975
1972	England	1	0	1	Rhino cerebral	None	None	None	Frontal headache in right side, Decreasing vision in right eye, Swelling in right periorbital area	Eyes	Lowe and Hudson, 1975
1973	U.S	1	0	1	Pulmonary	Acute promyelocytic leukemia	Daunorubicin	Bone marrow	N/A	Lungs	Murray 1975
1973	U.S	2	2	0	Rhino Orbital	Diabetic	N/A	N/A	Decreased vision in right eye followed by total loss of perception	Left eye, Brain	Bullock et al. 1974
1973	U.S				Rhino Orbital	Alcohol withdrawal seizure	N/A	N/A	Chemosis, Blepharoptosis in right eye	Right eye, Brain	Bullock et al. 1974
1975	U.S	1	1	0	Cutaneous	Chronic myelogenous leukemia,Diabetic mellitus	Busulfan	Spleen	Pain in right deltoid area	Right arm	Jain et al. 1978
1976	U.S	1	0	1	Pulmonary	Knee problem	Bilateral knee surgery , Cephalothin sodium prophylaxis	N/A	Fever, Chills, Cough with yellow blood tinged sputum	Lung	Record and Ginder 1976
1977	South Africa	1	1	0	Gastrointestinal	Steven-johnson syndrome	N/A	Skin	Vomiting, Epigastric pain, Loss of weight, Constipation	Stomach	Schulman et al. 1979
1977		30	2	28	Gastrointestinal	Diabetic	N/A	N/A	Bloody diarrhoea (13)*	Stomach (19)	Michalak et al. 1980
1977					Gastrointestinal	Diabetic	N/A	N/A	Diarrhoea (7)	Colon (14)	
1977					Gastrointestinal	Leukemia	N/A	N/A	Clinical obstruction (3)	Small bowel (8)	

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1977					Gastroin testinal	Leukemia	N/A	N/A	Perforation (5)	Esophagus (6)	
1977					Gastroin testinal	Typhoid fever	N/A	N/A			
1977					Gastroin testinal	Typhoid fever	N/A	N/A			
1977					Gastroin testinal	Malaria	N/A	N/A			
1979	U.S	1	0	1	Rhino Orbital	Acute stem cell leukemia, Diabetic mellitus	Bone marrow smears, Thioguanine and Cytosine arabinoside	N/A	Small dark gangrenous lesion in right superior gum	Eyes, Brain	Albert et al. 1979
1980	U.S	2	2	0	Cutaneo us	Acute lymphocytic leukemia	Anti-leukemic chemotherapy	bone marrow	Diffusely swollen area in upper right extremity , Lower right extremity, Left lingual area, Left auxillary area	Skin	Ryan et al. 1982
1980					cutaneou s	Acute lymphocytic leukemia	Chemotherapy	bone marrow	Elevated, Dark, Painful lesion with rim of Erythema in inner aspect of right lower leg	Right leg tibia, Skin	Ryan et al. 1982
1981	U.S	1	0	1	Dissemi nated	Refractory anaemia, Dyserythropoie sis	Prednisone, Pyridoxine, Multiple transfusion, Splenectomy	N/A	Fever , Chills, Confusion	Lung, Kidney	Ingram et al. 1989
1982	U.S	1	0	1	Dissemi nated	Hairy-cellleukemia	Prednisone, Chlorambucil	N/A	Fever, Cough with bloody sputum, Hypotension	Lung, Liver, Brain	Ingram et al. 1989
1983	U.S	2	0	2	Dissemi nated	Lymphocytic leukemia, Diabetic mellitus and splenectomy	Vincristine, Prednisone, Chlorambucil	N/A	Fatigue, Shortness of breath	Lungs, Liver, Kidney, Stomach, Lymph nodes	Ingram et al. 1989

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1983	U.S				Disseminated	Polycystic renal disease	Hemodialysis and deferoxamine	Kidney	Headache, Numbness on right side of the body	Brain , Lungs, Kidney	Ingram et al. 1989
1984	U.S	1	1	0	Pulmonary	Diabetic ketoacidosis	N/A	N/A	N/A	Right lung	Christenson et al. 1987
1984	U.S	1	0	1	Disseminated	Uremia	Hemodialysis	Kidney	Hypercalcemia, Jaundice	Lungs, Jejunum, Ileum	Eiser et al. 1987
1984	U.S	1	1	0	Gastrointestinal	Uremia and hypertension	Hemodialysis and bilateral nephrectomy	N/A	Pericarditis	Intestine	Eiser et al. 1987
1985	Israil	1	1	0	Cutaneous	Hypertension	Thiazides	N/A	Unconsciousness	Skin, Lungs	Koren et al. 1986
1986	India	1	0	1	Disseminated	Acute renal disorder	N/A	Kidney	Hiccups, Vomiting , Tarry stools	Lungs, Kidney, Pancreas	Gupta et al. 1987
1986	U.S	1	1	0	Cutaneous	Meningioma	Dexamethasone	Right thigh	Painless, Non-erythematous weeping ulcer in right thigh	Right thigh	Umbert and Su 1989
1986	India	1	1	0	Cutaneous	Tuberculoid granuloma	Streptomycin, isoniazid	N/A	Painful swelling of left foot, Multiple discharging sinuses, Low grade fever	Left foot	Padhye et al. 1988
1986	Australia	1	1	0	Pulmonary	Pneumothoraces in left lung	Surgical pleurodesis	Left lung	Weight loss, Persistent cough , Fatigue	Left lung	Lake et al. 1988
1987	U.S	1	1	0	Cutaneous	Myelogenous leukemia	Intrathecal chemotherapy	Right leg	Hemorrhagic necrotic ulcer in right leg, Area surrounded by edema	Right foot	Umbert and Su 1989
1987	Australia	1	0	1	Disseminated	Acute hepatic failure,encephalopathy,coagulopathy	Charcoal hemoperfusion, orthotopic liver transplantation	Liver	Fever, General deterioration after hepatic transplant	Liver, Heart, Lungs, Brain, Thymus	Nimmo et al. 1988
1988	Italy	1	0	1	Rhino cerebral	Drug addict	N/A	N/A	N/A	Meninges, Brain	Oliveri et al. 1988

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1990	U.S	1	1	0	Rhino cerebral	Cervical squamous cell carcinoma, HIV	Estrogen hormone treatment	Pelvis	Bifrontal headache, Inability to speak clearly	Brain, Lungs, Stomach, Small intestine	Cabot et al. 1990
1991	U.S	1	1	0	Cutaneous	Acute myelocytic leukemia	Chemotherapy with cytarabine, Duanorubicin, Ecotoposide	Bone marrow	Fever, Pleuritic pain, Cough with hemoptoic sputum	Lungs, Right hand	Lopes et al. 1995
1991	Netherlands	1	1	0	Cutaneous	N/A	N/A	N/A	Swelling in lateral right eyebrow that gradually extended	Skin of face	Prevoo et al. 1991
1992	U.S	1	1	0	Pulmonary	Megakaryoblasti cleukemia	Chemotherapy involving duanomycin, Cytosine arabinoside	N/A	Fever, Irritability in behaviour	Left lung	Cohen-Abbo et al. 1993
1992		1	0	1	Pulmonary	Lymphocytic leukemia	Chemotherapy involving mitoxantrone, Cytosine arabinoside	N/A	Intermittent cough, Loose stools , Decreased appetite, Upper abdomen discomfort	Lungs	Cohen-Abbo et al. 1993
1993	Spain	1	1	0	Gastrointest inal	AIDS	Steroids	Immune system	Epigastric pain, Retrosternal discomfort	Stomach, Ileum, Colon	Brullet et al. 1993
1993	U.S	1	1	0	Cutaneous	Aplastic anaemia, Hepatitis A and B, Pneumonia	Antithymocyteglobulin, prednisone, cyclosporin, aminocaproic acid	N/A	Fever, Chills, Bleeding gums, Epistaxis	Thigh	Weitzman et al. 1993
1994	U.S	1	1	0	Cutaneous	Monocytic leukemia	Chemotherapy involving mitoxantrone and diazoquinone	N/A	Lesion in left knee, calf along with palpable lump	Left leg	Fingeroth et al. 1994
1995	U.S	1	0	1	Pulmonary	Bronchial asthma	B2 agonist inhaler	Lungs	Dyspnea, Productive cough	Lungs	Butala et al. 1995
1995	U.S	1	1	0	Pulmonary	Major renal disorder, Diabetic nephropathy	Renal allograft , Prednisone, Solumedrol, Azathioprine	Kidney	Fever, Right foot ulceration	Lungs	Latif et al. 1997
1995	U.S	1	1	0	Other	Diabetic	Clindamycin, Nafcillin	Leg	Necrotic ulcer of proximal right leg, Vomiting, Nausea	N/A	West et al. 1995

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1995	Austria	1	1	0	Gastrointestinal	End stage renal disease	Dialysis, Cyclosporin A , Steroid, Antithymocyte globulin	Kidney	N/A	Stomach	Winkler et al. 1996
1995	U.S	3	2	1	Other	AIDS	Phenobarbital, Nystatin, Aerosolized pentamidine	N/A	Flank pain, Pyuria, Fever	Kidney	Nagy-Agren et al. 1995
1995					Disseminated	AIDS , peptic ulcer disease,anaemia	Trimethoprim Sulfamethoxazole, Fluconazole and Omepraconazole	N/A	Fever, Diarrhoea	kidney, Liver, Spleen, Thyroid, Bone marrow	Nagy-Agren et al. 1995
1995					Disseminated	AIDS, Presumed progressive multifocal leukoencephalopathy	Acyclovir, Dilantin, Aerosolized pentamide	N/A	Recurrent herpes	Small/ Large intestine, Stomach, Blood vessel	Nagy-Agren et al. 1995
1995		1	1	0	Pulmonary	End stage renal disease	Cyclosporin, Azathioprine, Solumedrol	N/A	Soreness of left anterior chest wall, Non-productive cough, Fever	Lungs	Latif et al. 1997
1996	France	1	1	0	Cutaneous	Aplastic anaemia	Antithymocyteglobulin (ATG)	Bone marrow	Febrile neutropenic episode, Fever, Erythema, Tenderness	Heart, Lungs	Leong et al. 1997
1996	China	1	0	1	Pulmonary	Lymphoblastic leukemia	N/A	Bone marrow	N/A	Lungs, Heart	Levy et al. 1996
1996	China	1	0	1	Other	Acute lymphoblastic leukemia	Cytosine arabinoside, Amsacrine	Liver	N/A	Liver, Lungs	Levy et al. 1996
1998	U.S	1	1	0	Rhino cerebral	Diabetic mellitus	Insulin	N/A	Headache, Nasal discharge, Malaise, Lethargy, Fever	Brain	Weprin et al. 1998
1999	Belgium	5	1	4	Pulmonary	Acute lymphoblastic leukemia (ALL)	Vindesine and Methylprednisolone	N/A	Relapse after Bone marrow Transplant	Lung , Oesophagus	Maertens et al. 1999

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
1999					Pulmonary	Chronic myelogenous leukemia (CML)	N/A	N/A	Relapse after Bone marrow Transplant	Lung	Maertens et al. 1999
1999					Pulmonary	Acute Myeloblastic Leukemia with maturation (AML- M2)	N/A	N/A	Relapse after Bone marrow Transplant	Lung	Maertens et al. 1999
1999					Disseminated	Acute Myeloblastic Leukemia with maturation (AML- M2)	N/A	N/A	Relapse after Bone marrow Transplant	Lung	Maertens et al. 1999
1999					Disseminated	Relapsed Acute Myeloblastic Leukemia(AML M5)	N/A	N/A	Relapse after Bone marrow Transplant	Liver, esophagus	Maertens et al. 1999
2000	U.S	1	1	0	Other	Chronic renal insufficiency, Hypercholesterolemia , Diabetic	Kidney , Heart transplant	Kidney and heart	Fever, Chills	Heart, Thorax	Tobon et al. 2003
2002	India	1	1	0	Cutaneous	None	None	None	Fever, boil in upper abdomen	Skin of the abdomen	Kumar et al., 2003
2003	Greece	2	2	0	Rhino cerebral	Diabetic mellitus, Hypertension, Heart failure, Chronic obstructive lung disorder	Gliclazide	N/A	Malodorous discharge from mouth, Necrotic lesion in palatal mucosa	Brain	Kofteridis et al. 2003
2003	Greece				Rhino cerebral	Hypertension, Eye problem, Renal dysfunction	Methylprednisolone	N/A	Left eye infection	Left eye, Brain	Kofteridis et al. 2003
2004	U.S	1	1	0	Pulmonary	Uncontrolled Diabetic	N/A	N/A	Dry, Non-productive cough,Dyspnea, Malaise	Upper lobe of lungs	Reid et al. 2004
2005	India	2	2	0	Cutaneous	N/A	N/A	N/A	Abscess in right leg	Right leg	Shah et al. 2006
2005					Cutaneous	Respiratory distress	Corticosteroid, Broad spectrum antibiotics	N/A	Reddish brown area in perineum	Skin	Shah et al. 2006

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2005	U.S	1	1	0	Rhino cerebral	Diabetic mellitus, Allergic rhinitis, Recurrent sinusitis	N/A	N/A	Right sided facial drooping, Numbness, Diplopia, Right eye ptosis	Eye, Sphenoid sinus	Liang et al. 2006
2006		1	0	1	Rhino cerebral	Cerebral thrombosis, Myocardial infarction, Diabetic mellitus, Hypertension	N/A	N/A	Visual loss of right eye, Pain in right side of the headache	Tongue, Nose, Face, Brain	Yang et al. 2006
2006	Sri-lanka	1	1	0	Rhino cerebral	Malaria	N/A	N/A	Swelling in left side of face	Face, Brain	Jayasuriya et al. 2006
2006	Korea	1	1	0	Gastrointestinal	Acute myeloid leukemia	Idarubicin and cytosine arabinoside	N/A	Diffuse abdominal pain	Stomach	Song et al. 2006
2006	South korea	1	1	0	Rhino Orbital	None	None	None	Right sided facial pain	Paranasal sinus	Park et al. 2006
2006	India	2	2	0	Other	None	None	None	Bilateral flank pain,Fever , Vomiting, White flakes in urine	Kidney	Marak et al. 2010
2006	India				Other	N/A	N/A	N/A	Right flank pain, Fever, Chills and Rigours	Kidney	Marak et al. 2010
2007	Germany	4	3	1	Rhino-orbito-cerebral	Diabetic mellitus	N/A	N/A	Rapid loss of vision, Proptosis bulbi, Ophthalmoplegia	Eyes, Nose	Arndt et al. 2009
2007					Rhino-orbital-cerebral	Hodgkin’s lymphoma	N/A	N/A	Irradiation of the skull	Nose	Arndt et al. 2009
2007					Rhino-orbital-cerebral	Acute Myeloidleukemia (AML)	N/A	N/A	Proptosis bulbi	Eyes, Nose	Arndt et al. 2009
2007	Germany				Rhino-orbital-cerebral	Myelodysplastic syndrome	Cyclosporin A, Anti Myocyte-globuline	N/A	Paranasal sinusitis	Eyes	Arndt et al. 2009
2007	Turkey	2	2	0	Rhino-orbito-cerebral	Idiopathic thrombocytopenic purpura	Antidiabetic medication	N/A	Left facial / periorbital pain, Paraesthesia, Erythema, Visual loss	Brain, Paranasal sinus, Ethmoid sinus	Haliloglu et al. 2008

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2007					Rhino-orbito-cerebral	Diabetic mellitus , Hypertension	N/A	N/A	Headache, Fever, Vomiting, Swelling in upper eyelid	Brain, Paranasal sinus	Haliloglu et al. 2008
2007	Taiwan	1	1	0	Rhino cerebral	Chronic hepatitis, Liver cirrhosis, Diabetic mellitus, Hypertension	N/A	N/A	Pain, Swelling in left side of face	Brain	Lin et al. 2012
2008	North America	1	1	0	Cutaneous	Progressive pulmonary silicosis	Lung transplant , Methylprednisolone	Lungs	Necrosis at site of membrane ventilator placement	Right inguinal region, Thorax	Page et al. 2008
2008	U.S	1	1	0	Gastrointestinal	Hepatitis-C, Hypertension , End-stage renal disease	Hemodialysis	Kidney, Heart	N/A	Colon, Liver	Mezhir et al. 2009
2008	korea	1	1	0	Pulmonary	Renal damage, Pulmonary mucormycosis	Amphotericin B	N/A	Severe nasal obstruction, Facial tenderness	Brain, Lungs	Kim et al. 2013
2008	Australia	1	1	0	Pulmonary	End stage renal failure, Diabetic, Hypertension	Insulin	N/A	Persistent cough	Lungs	Li et al., 2009
2009	Saudi Arabia	1	0	1	Pulmonary	Diabetic mellitus, Aplastic anaemia	Insulin, Tacrolimus	N/A	Fever, Chest pain, Dyspnea	Lungs	Waness et al. 2009
2009	Greece	1	1	0	Disseminated	Acute myeloid leukemia	Cytosine arabinoside,thioguanine and idarubicin	N/A	Febrile, Fever	Liver, Lungs, Brain	Skiada et al. 2009
2009	Israil	1	0	1	Rhino cerebral	Hypertension	Hydrochlorothiazide	N/A	Left palate pain	Brain	Elinav et al. 2009
2010	France	1	1	0	Rhino-orbito-cerebral	AcidoKetotic coma	N/A	N/A	Mucopurulent rhinorrhea, General deterioration of health	Nasal fossa, Right ethmoid, Left anterior ethmoid	Mimouni et al. 2010
2011	Iran	1	0	1	Disseminated	Diabetic mellitus	N/A	N/A	Fever, Polyuria, Polydipsia, Vomiting	Lungs	Mohammadi et al. 2012
2011	Taiwan	1	1	0	other	Hepatitis-B	Tacrolimus, Mycophenolic acid	Liver	Migraine, Swelling , Right sided visual impairment	Eyes, Ethmoid sinus, Paranasal sinus, Sphenoid sinus	Lin et al. 2011

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2011	Italy	1	1	0	Rhino cerebral	Acute lymphoblastic leukemia	Teicoplanin, Imipenem, Caspofungin	N/A	Fever, Painful movement in right eye, Swelling, Palpatation	Right eye, Brain	Gumral et al. 2011
2011	China	1	1	0	Pulmonary	Renal disease and Diabetic mellitus	Renal transplant, Prednisolone, Cyclosporin A, Mycophenolate	N/A	Fever, Dyspnea, Leukocytosis	Lung	Kwan et al. 2013
2012	Japan	2	2	0	Cutaneous	Chronic lymphocytic leukaemia (CLL)	Prednisolone	N/A	Painful purpura/subcutaneous induration (left palm)	Bronchi, Skin	Kawasaki et al., 2012
2012					Cutaneous	Acute myelocytic leukemia (AML)	Prednisolone, Tacrolimus, Mitoxantrone, Etoposide, Cytarabine, Methotrexate	N/A	Lesions head, Nape of neck, Bilateral forearms, Lower limbs	Skin, Lungs	Kawasaki et al., 2012
2012	Malaysia	1	1	0	Rhino-orbito-cerebral	None	None	None	Painful swelling in left eye, Blurring of vision, Diplopia	Eyes, Brain	Shatriah et al. 2012
2012	Taiwan	1	0	1	Disseminated	Acute myeloid leukemia	Blood transfusion	N/A	Fever, Dyspnea, Cough, Loss of appetite	Lungs, Skin	Hsieh et al. 2013
2013	India	1	1	0	Rhino cerebral	Systemic lupus erythematosus (SLE), Anemia	Methylprednisolone, Prednisolone	N/A	Pallor, Swelling face and legs, Hematuria, Oliguria, Diffuse hair loss	Skin	Kumar et al. 2013
2013	China	1	1	0	Cutaneous	Diabetic, Coronary atherosclerosis heart disease, Atrial fibrillation	N/A	N/A	Painful Erythema in forearm	Skin	Li et al. 2013
2013	Iran	1	1	0	Cutaneous	Diabetic	Metformin	N/A	Severe pain, Swelling / bruising in upper extremity, Necrotizing region in hand	Left arm, Forearm	Ahmadinejad et al. 2013
2013	India	1	1	0	Pulmonary	Diabetic mellitus	Insulin	N/A	Tooth ache on left side of face, Swelling, Pain in face	Airways, Eyes, Nose	Singh et al.,2013

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2013	Italy	1	1	0	Rhino cerebral	Diabetic mellitus	Regulatory insulin therapy	N/A	Dental pain, Facial swelling, Ecchymosis in left periorbital region, Decreased visual activity and colour vision	Brain, Eyes, Tongue, Teeth	Di Coste et al. 2013
2014	India	2	2	0	Rhino-orbito-cerebral	Hyperglycemia, Diabetic ketoacidosis, Ketonuria	N/A	N/A	Fever, Abdominal pain, Acidotic breathing, Multiple furuncles over the face	Sinus and Brain	Kumar et al. 2014
2014					Cutaneous	Deep dermal full thickness 60% TBSA burn	Topical antimicrobials, Aseptic antiseptic precautions	Both thighs	Fever, Tachycardia , Tachypnoea	Both thighs	Kumar et al. 2014
2014	U.K	1	1	0	Rhino-orbito-cerebral	Diabetic, Chronic kidney disease , Hypertension, Chronic pancreatitis	N/A	N/A	Left sided facial hyperesthia, Retro-orbital discomfort, Blurred vision, Persistent headache	Left eye, Kidney,Brain	Chow et al. 2014
2014	U.S	1	1	0	Gastrointestinal	B-cell acute lymphoblastic leukemia, Stage 3 rectal cancer	Cetuximab, Capecitabine	N/A	Hemorrhagic shock, Acute hematochezia	Small intestine, Large intestinal, Left leg, Kidney, Ureter	Cloyd et al. 2014
2014	Greece	1	1	0	Rhino cerebral	Diabetic mellitus, Coronary artery disease, Cerebrovascular episodes	Antidiabetic, Hypertensive, Anticoagulant	N/A	Odorous nasal discharge	Brain	Dimaka et al. 2014
2015	Australia	1	1	0	Cutaneous	Diabetic mellitus, Metastatic non-small cell lung cancer	Prednisolone, Chemotherapy	N/A	Erythema, Ulcer, Skin lesion in right lower leg	Right leg	Gardiner et al. 2015
2015	Mexico	1	0	1	Pulmonary	Non-hodgkin T Cell lymphoma	Etoposide,carboplatin,cytarabine	N/A	Fever, Malaise, Persistent cough	Kidney, intestine, abdomen	Rodríguez-Gutiérrez et al. 2015
2016	India	1	1	0	Pulmonary	Diabetic mellitus	N/A	N/A	Fever and cough	Lungs	Biradar et al. 2016

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2016	Spain	1	0	1	Pulmonary	Diabetic mellitus, Siderosis, Renal agenesis	N/A	N/A	Neutropenic fever	Lungs, kidney, thyroid gland	Mouronte-Roibás et al. 2016
2016	North america	1	0	1	Rhino Orbital	Chronic diarrhoea, Recurrent bronchial neuropathy	N/A	N/A	Fever	Ear, face	Kermani et al. 2016
2016	North America	1	1	0	Rhino Orbital	Diabetic	N/A	N/A	Fever, Poorly systematized left inferior lobe infection, Ketoacidosis decomposition	Maxillary sinus, mouth	Kermani et al. 2016
2016	North America	1	1	0	Cutaneous	Arterial hypertension, Diabetic mellitus	N/A	N/A	Pain, Occasional bleeding of lower back	Skin	Rodríguez-Lobato et al. 2017
2017	India	2	0	2	Rhino-orbito-cerebral	Diabetic mellitus	N/A	N/A	Unconsciousness	Brain, Skin	Pathak et al. 2018
2017					Pulmonary	Chronic Persistent asthma, Diabetic mellitus	N/A	N/A	N/A	Lungs	Pathak et al., 2018
2017	Saudi Arabia	1	1	0	Disseminated	Diabetic mellitus	N/A	N/A	Diarrhea, Cough, Weight loss, Shortness of breath	Lungs, stomach	Alqhamdi et al. 2019
2017	Korea	5	4	1	Rhino cerebral	Chronic lymphocytic leukaemia (CLL)	Rituximab, Fludarabine, Cyclophosphamide	N/A	Fever, odontalgia, submandibular swelling	Ectodermal organ (teeth)	Cheong et al. 2017
2017					Rhino cerebral	Acute myeloid leukaemia (AML)	N/A	N/A	Fever, right submandibular swelling	Ectodermal organ (teeth)	Cheong et al. 2017
2017					Rhino cerebral	Acute promyelocytic leukaemia (APL)	N/A	N/A	Neutropenic fever	Ectodermal organ (teeth)	Cheong et al. 2017
2017					Rhino cerebral	Acute myeloid leukaemia (AML)	N/A	N/A	N/A	Ectodermal organ (teeth)	Cheong et al. 2017
2017					Rhino cerebral	Acute myeloid leukaemia (AML)	N/A	N/A	N/A	Ectodermal organ (teeth)	Cheong et al. 2017
2017	China	1	0	1	Gastrointestinal	Rheumatic heart disease, Mitral stenosis	Oral warfarin	N/A	Fever, Difficulty in eating, Abdominal distension, Nausea, Dispnea	Small intestine	Sun et al. 2017

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2017	Pakistan	1	1	0	Other	ALK negative anaplastic large cell lymphoma	N/A	N/A	N/A	Liver	Yasmeen et al. 2017
2017	Mexico	1	0	1	Rhino cerebral	Liver cirrhosis	Prednisone	Liver	Respiratory tract infection, Lethargy , Nose bleed	Nose, Lips, Lungs, Eye, Brain	Avelar Rodriguez et al. 2017
2017	Australia	1	1	0	Pulmonary	End stage renal failure, Diabetic nephropathy	Antithymocyte globulin, Prednisolone, Mycophenolate, Tacrolimus	N/A	Cough, Fever, Hemoptysis	Lungs	Thomas et al. 2018
2017	Iran	1	0	1	Rhino cerebral	Acute lymphoblastic leukemia	Acyclovir, Fluconazole and Ciprofloxacin	Bone marrow	Lethargy, Fever, Chills ,Nasal discharge, Weakness, Difficulty in swallowing	Lungs, Paranasal sinus, Brain	Sharifpour et al. 2018
2018	Korea	1	1	0	Rhino cerebral	Diabetic mellitus, Asthma	N/A	N/A	Nasal obstruction	Brain	Yeo et al. 2018
2018	Greece	1	1	0	Cutaneous	Hypothyroidism	N/A	N/A	Right thigh lesion	Right leg	Gkegkes et al. 2019
2018	Iran	2	2	0	Rhino cerebral	Diabetic, Ischemic heart disease, Neutropenia	Insulin	N/A	Headache, Blurred vision, Pain, Swelling in right eye	Brain	Gholinejad Ghadi et al. 2018
2018					Rhino cerebral	Diabetic mellitus	N/A	N/A	Blurred vision, Headache, Swelling in left posterior maxilla	Brain	Gholinejad Ghadi et al. 2018
2018	U.S	3	3	0	Pulmonary	Hepatitis associated severe aplastic anaemia	Prednisone, Cyclophosphamide, Voriconazole, ATG	N/A	Fever, Pneumonia	Lungs	Elgarten et al. 2018
2018					Pulmonary	Chronic granulomatous disease	Fludarabine, Cyclophosphamide , ATG, Calcineurin inhibitor	N/A	N/A	Lungs	Elgarten et al. 2018
2018					Gastrointestinal	Kidney / Renal disease	Methylprednisolone, Tacrolimus, Mycophenolate mofetil	Kidney, Liver	Abdominal pain, Dark stool	Stomach	Elgarten et al. 2018

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2018	India	1	1	0	Other	N/A	N/A	N/A	Fever, Turbid urine, Diffuse abdominal pain, Vomiting , Swelling of the body	Kidney	Mathew et al. 2019
2019	Taiwan	1	0	1	Pulmonary	Systemic lupus erythematosus (SLE)	Rituximab	N/A	Fever, Chills, Shortness of breath	Lungs	Hung et al. 2015
2019	U.S	1	0	1	Cutaneous	Liver / Renal failure, Hypertension, Macrocystic anaemia	Blood transfusion, Antithymocyte globulin, Phenolic acid, Tacrolimus	Kidney, Liver	Abdominal surgical site became necrotic and oozed out serosanguinous fluid	Surgical site of abdomen	Haque et al. 2019
2019	China	1	1	0	Gastrointestinal	End stage renal disease	Methylprednisolone, Basiliximab, Tacrolimus, Mycophenolate mofetil	Kidney	Chest pain, Dark stool	Stomach	Peng et al. 2019
2019	India	1	1	0	Rhino cerebral	Neonatal sepsis, End stage organ failure	N/A	N/A	Increasing size of head, Downward gaze, Unable to hold neck straight	Brain	Gupta et al. 2019
2019	Pakistan	1	1	0	Rhino cerebral	Diabetic Ketoacidosis	N/A	N/A	Ulcers in oral cavity, Facial swelling along, Oral, Nasal discharge	Brain, Skin	Ali Asghar et al. 2019
2019	India	1	1	0	Disseminated	Diabetic mellitus	N/A	N/A	Fever, Cough with expectoration, Anorexia	Lungs, Skin	Ramesh et al. 2020
2019	Mexico	1	1	0	Pulmonary	Diabetic mellitus, Hypertension	Insulin glargine	N/A	Chest pain	Bronchi, Lungs	O et al. 2019
2019	U.S	1	1	0	Gastrointestinal	Diabetic mellitus	N/A	N/A	Chronic cough, Weight loss, Fever	Stomach, Brain, Lungs	Malek et al. 2019
2019	U.S	1	0	1	Pulmonary	Bipolar disorder, Hyperthyroidism	N/A	N/A	Fever, Fatigue, Non-productive cough, Myalgia	Kidney, Brain, Liver	Huang et al. 2020
2019	U.S	1	1	0	Gastrointestinal	Diabetic mellitus, End-stage renal disease, TB	Dexamethasone, ethambutol,isoniazid,pyridoxine	Brain and lungs	Acute abdominal pain	Stomach	Malek et al. 2019

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2019	Australia	1	1	0	Rhino Orbital	T-cell acute lymphoblastic leukemia	N/A	N/A	Fever, Headache, Nasal congestion, Facial pain	Brain, Eyes, Nose	Lee and Sullivan, 2019
2019	Australia	1	1	0	Rhino Orbital	Diabetic ketoacidosis	N/A	N/A	Febrile, Headache	Brain	Lee and Sullivan, 2019
2019	Australia	1	0	1	Rhino Orbital	Pre-B cell acute lymphoblastic leukemia	chemotherapy and allogeneic bone tranplant	N/A	Nasal pain with bloody discharge, Skin discolouration , Fever, Decreased vision	Brain, Face, Nose	Lee and Sullivan, 2019
2019	Australia	1	0	1	Rhino Orbital	Biphenotypicleukemia	chemotherapy	N/A	Left lower eyelid swelling	Nose, Cheek, Mouth, Brain	Lee and Sullivan, 2019
2019	Australia	1	1	0	Rhino Orbital	High risk pre-B cell acute lymphoblastic leukemia	chemotherapy	N/A	Recurrent headache, Irritability	Brain	Lee and Sullivan, 2019
2019	Australia	1	0	1	Rhino Orbital	Graft vs host disease, B cell acute lymphoblastic leukemia	prednisolone-A,cyclophosphamide,mycophenolate	N/A	Severe headache	Brain, Right arm	Lee and Sullivan, 2019
2020	Australia	1	1	0	Disseminated	Diabetic ketoacidosis, Hypertension, Kidney disease	Ramipril, Amlodipine Insulin aspart, Amitriptyline	Kidney	Central Chest pain, Dyspnea, Pedal edema	Lungs	Thomas et al. 2020
2020	U.S	1	0	1	Pulmonary	N/A	N/A	N/A	Cough, Dyspnea, Respiratory distress	Lungs	Seifert et al. 2020
2020	Iran	5	5	0	Rhino Orbital	N/A	N/A	N/A	Erythema, Edema in left inferomedial canthus	Brain	Amanati et al. 2020
2020					Rhino Orbital	Nasolacrimal duct obstruction	N/A	N/A	Swelling in right inferomedial canthus	Brain	Amanati et al. 2020
2020					Rhino Orbital	N/A	N/A	N/A	Purulent discharge, Eye proptosis	Eye, brain	Amanati et al. 2020
2020					Rhino Orbital	N/A	N/A	N/A	Fever, Edema periorbital area	Brain	Amanati et al. 2020

Year	Place	No of patients affected	No of survival	No of death	Type of Mucormycosis	Any disease before Mucormycosis	Drug administration for that disease /Other Treatment(if any)	Organs infected pre-Mucormycosis	Symptoms prior to diagnosis of mucormycosis	Organs infected during Mucormycosis	Reference
2020					Rhino Orbital	None	None	None	Swelling in periorbital region	Brain	Amanati et al. 2020
2020	U.S	1	1	0	Pulmonary	Diabetic ketoacidosis	N/A	N/A	Fevers, Dyspnea, Rightsubclavicular chest pain	Lungs, Trachea, Bronchi	Elmassry et al. 2020

A collection of 198 cases were accounted for patients having various types of mucormycosis, including Rhino-orbital-cerebral, Pulmonary, Cutaneous, Gastrointestinal, Disseminated and others. The timeline begins from the year 1944 and continues till 2020. The place, type of mucormycosis, status of the patient, underlying diseases and drugs taken due to them, symptoms faced by patient and the organ / region of body affected were documented; N/A: Data not available; *: data in parenthesis represents the number of cases

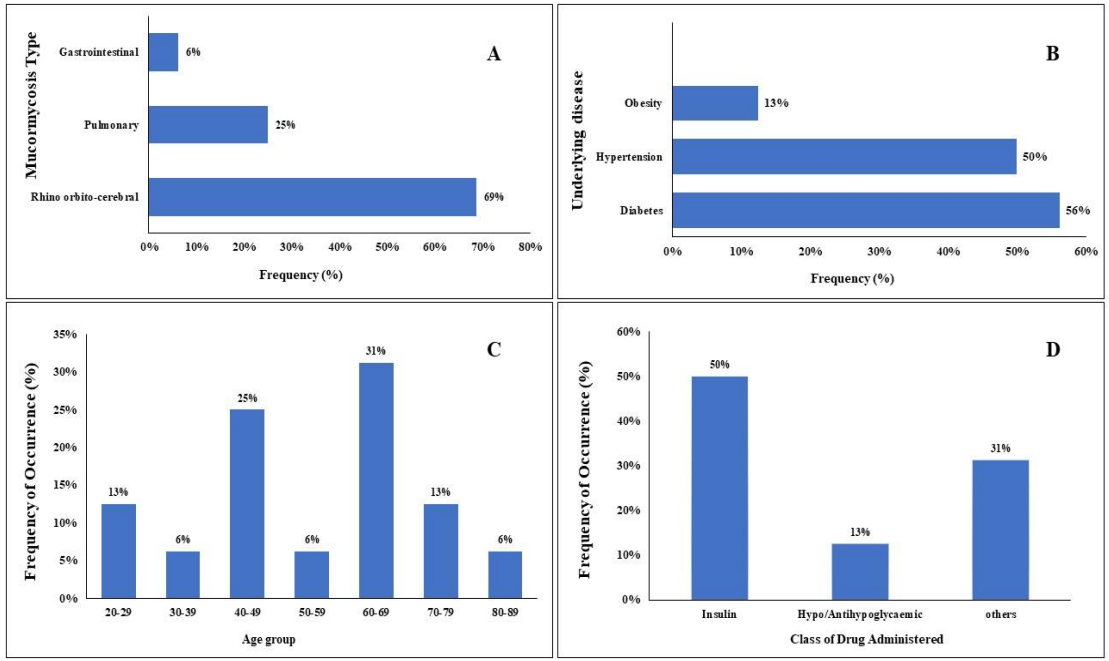

Figure 1 Total number of case histories analysed = 16; (1A) occurrence of mucormycosis in post-COVID-19 patients; (1B) underlying diseases prior to the diagnosis of mucormycosis; (1C) various age groups affected by mucormycosis post COVID-19; (1D) Influence of drugs for underlying diseases on mucormycosis patients.

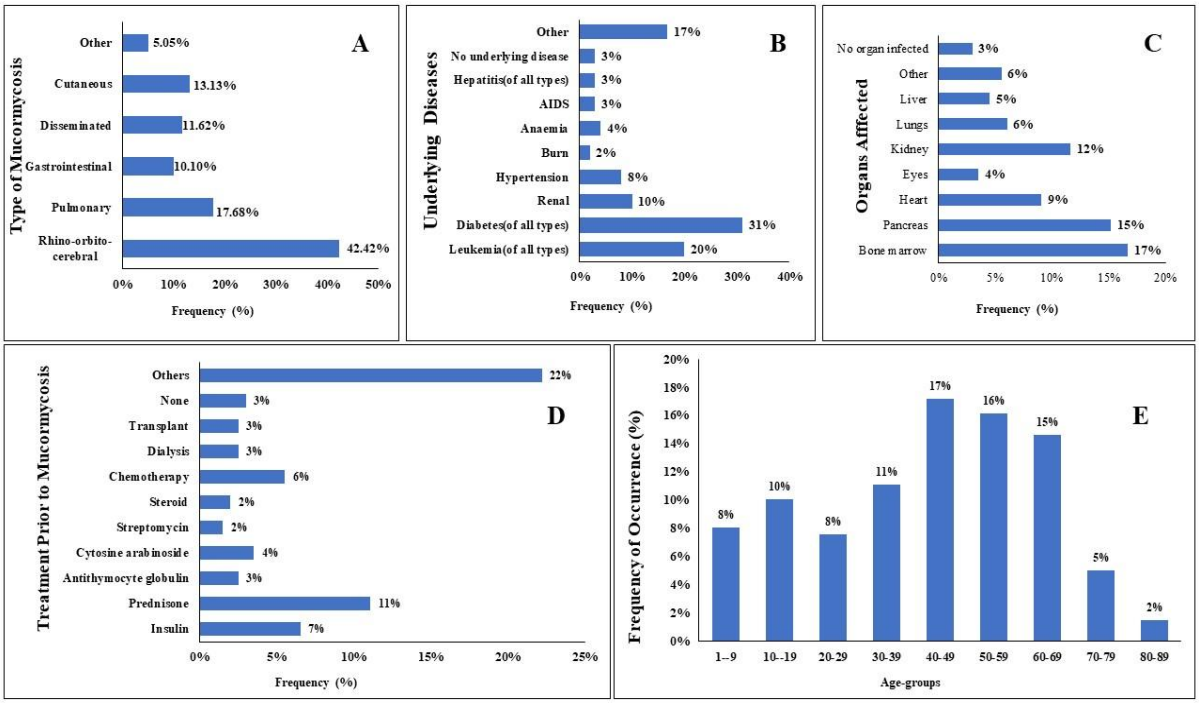

Figure 2 Total number of case histories analysed = 198; (2A) Occurrence of mucormycosis in patients; (2B) Underlying diseases prior to diagnosis of mucormycosis; (2C)Most affected organs before diagnosis of mucormycosis; (2D) Influence of drugs for underlying diseases on mucormycosis patients; (2E) Various age groups affected by mucormycosis

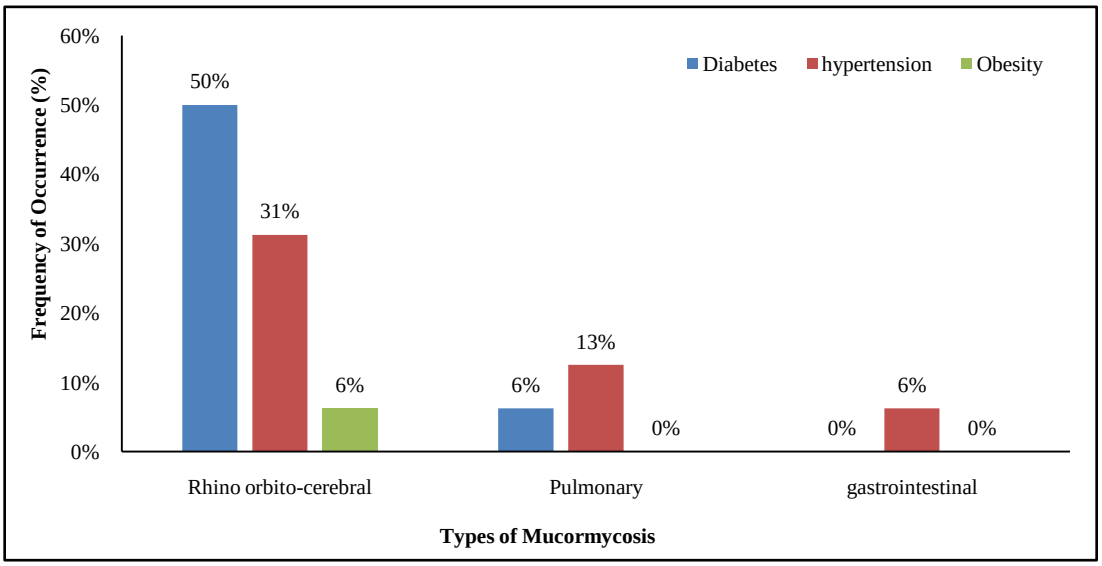

Figure 3 Comparison of types of mucormycosis in post COVID-19 patients with various underlying medical factors (Total number of case histories analysed = 16)

(Figure 2D). Prednisone, a corticosteroid widely used by immunocompromised patients, was found to make diabetic patients more vulnerable to mucormycosis infection due to its adverse effects. Similarly, chemotherapy disrupts the normal growth and development of immune cells and the renewal of epithelial cells, rendering the host more susceptible to pathogenic attacks (Teoh and Pavelka, 2016).

It was also observed that individuals with competent immune systems have been infected by mucormycosis. The apparent depressed immune response in these individuals may be due to a biphasic response to sepsis, where an initial hyperinflammatory response is followed by immune paralysis, leading to neutrophil deactivation and placing the individual at high risk of mucormycosis (Bassetti and Bouza 2017). In terms of

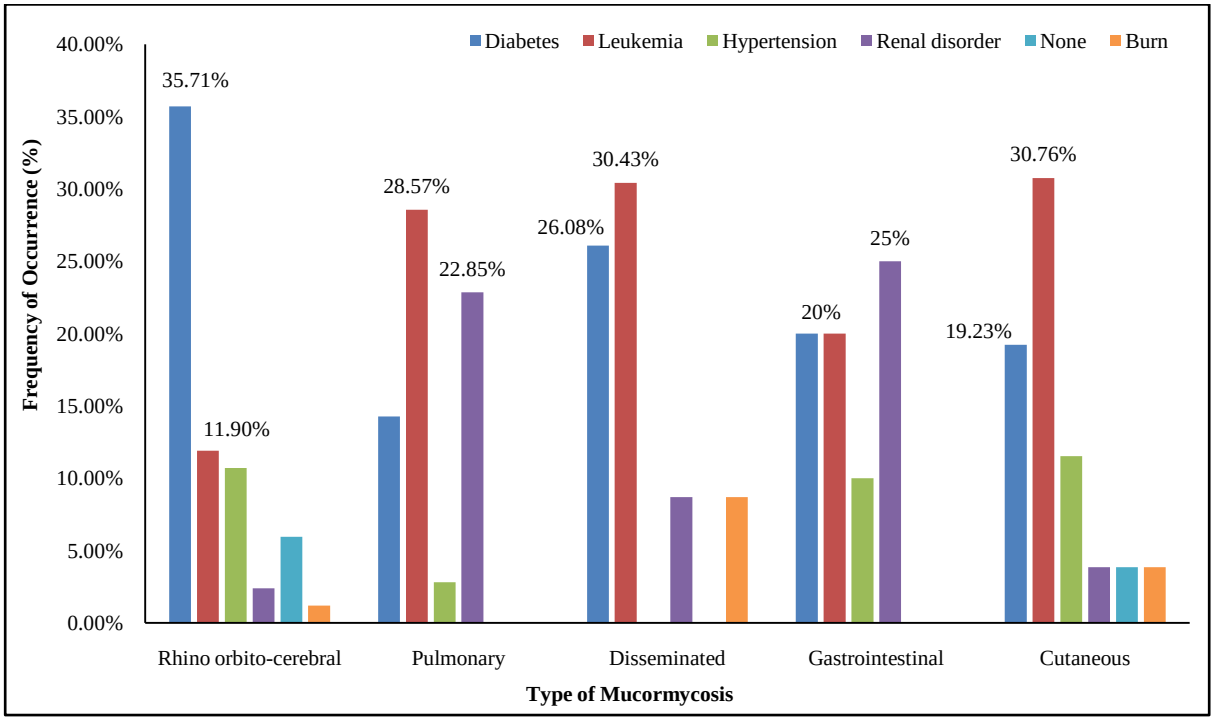

Figure 4 Comparison of types of mucormycosis with various underlying medical factors. Total number of case (histories analysed = 198)

susceptibility, the age groups most at risk of mucormycosis were patients between the ages of 40-49 years (17%), followed by those in the 50-59 years age group (16%) and the 60-69 years age group (15%) (Figure 2E). Age significantly impacts susceptibility to fungal infections due to immunological changes, administration of immunosuppressive medication, antibiotics, underlying chronic conditions, and solid organ transplantation (Kauffman 2001). Furthermore, a study on the correlation between underlying conditions and the type of mucormycosis showed that diabetes played a significant role in rhino-orbito-cerebral mucormycosis patients (35.71%). Leukemia was more prevalent in cutaneous (30.76%), disseminated (30.43%), and pulmonary mucormycosis (28.57%). Renal disorders had the highest association with gastrointestinal mucormycosis (25%) (Figure 3 & 4).

Conclusion

Mucormycosis is a rare and deadly fungal disease caused by inhaling fungal spores known as mucormycetes. The rarity of the disease makes it challenging to conduct large clinical trials. It has a very high mortality rate and is treated with antifungal agents such as isavuconazole, amphotericin B-based drugs, or posaconazole combined with surgical intervention. Several types include rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated mucormycosis. Among COVID-19 patients, rhino-orbito-cerebral and pulmonary mucormycosis are most common. Certain groups, such as diabetic and immunocompromised patients, are more susceptible. The study showed that rhino-orbito-cerebral mucormycosis is most commonly diagnosed, and diabetes is the most frequent underlying condition. Age is also a determining factor. The study did not deeply explore the effect of various drugs taken for underlying conditions on the disease due to limited data, but it would be beneficial for future studies to do so.

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Conflict of Interest

Nil

Authors' contributions

Srishti Sen and Shubhangi Tiwari contributed equally to acquire data and perform the analysis. These authors performed the literature survey and wrote the entire manuscript. Sinjini Banerjee contributed to data acquisition by studying various case histories. Mihir Ghosh critically reviewed and corrected the manuscript. Boudhayan Bandyopadhyay conceived the idea of this research project and played a critical role in guiding the authors in this entire work.

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