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**Original Article**

# Mucormycosis, New Causative Agents, and New Susceptible Populations: Review of Cases in a Tertiary Care Hospital in Iran (2007-2021)

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**Abstract**

**Background:** Mucormycosis is an aggressive opportunistic fungal infection that afflicts patients with severe underlying immunosuppression, uncontrolled hyperglycemia and/or ketoacidosis, iron overload, and occasionally healthy patients who are inoculated with fungal spores through traumatic injuries. The epidemiology of mucormycosis has changed after the COVID-19 pandemic, with mucormycosis becoming the most common and the fatal coinfection

**Methods:** In a retrospective, cross-sectional study, 82 hospitalized patients with a definite diagnosis of mucormycosis were reported from 2007 to 2021 in a referral, tertiary care center in Tehran, Iran

**Results:** The number of post-COVID cases increased 4.6 times per year, with 41.5% of patients admitted during the two years of the pandemic. Mucormycosis was more common in women (57.3%), and the most common underlying diseases were diabetes (43.7%), both COVID-19 and diabetes (23.2%), cancer (11%), rheumatic diseases (7.3%), COVID-19 without other underlying diseases (6.1%), and transplantation (4.9%). Rhino-orbito-cerebral Mucormycosis (54.9%) followed by Sino-orbital infection (23.2%) was the most common presentation. There was a significant relationship between the use of immunosuppressive agents and the development of Mucormycosis ($P<0.005$) The average mortality was 41.5%, but this ratio decreased to 35% during the pandemic era.

**Conclusion:** The COVID-19 pandemic caused a 4.6-fold increase in the number of mucormycosis patients, and there was a significant relationship between hyperglycemia, corticosteroid use, and mucormycosis. The death rate during the COVID-19 pandemic has decreased by 6.5%, and during the COVID period, the interval between the arrival of a patient with mucormycosis and the start of the correct treatment was significantly decreased.

**Keywords:** Mucormycosis; Epidemiology; Diabetes mellitus; Corticosteroids; COVID-19

## Introduction

Mucormycosis is the most serious angio-invasive fungal disease with a mortality rate of 30% to 69% (1). The infection primarily affects immunocompromised patients and is rare in healthy people. Diabetes has masked other risk factors in Asia, but post-COVID people, post-tuberculosis patients, and patients with chronic kidney disease are emerging as new risk groups (1,2).

After controlling the waves of COVID-19, health management systems in some countries are facing a surge of COVID-19-associated diseases. COVID-19-associated mucormycosis (CAM) is one of the most important challenges for the health systems of countries such as India and Iran (3).

Rhino-Cerebral Mucormycosis is more common in diabetic patients, while pulmonary Mucormycosis is frequently observed in patients with malignancies and transplant recipients. In a host with a normal immune system, cutaneous Mucormycosis usually occurs after trauma (4). A noteworthy clinical entity, isolated renal Mucormycosis, has only been reported in immunocompromised patients from India and China (5,6). Mild Mucormycosis, as a new clinical entity, has recently been identified in the paranasal sinuses. In recent years, medicine-related mucormycosis has been increasingly reported (7). The presence of foreign bodies in open wounds may be the main cause of Mucormycosis in healthy patients (8).

Major risk factors for Mucormycosis are uncontrolled diabetes mellitus, steroid therapy, persistent neutropenia, deferoxamine therapy, hematopoietic system malignancies/chemotherapy, intravenous drug use, autoimmune disorders, long-term prophylaxis with other antifungals (i.e., voriconazole or echinocandins), and cutaneous or mucous membrane barrier disruption due to trauma, burns, and surgical wounds. However, Mucormycosis has also been reported in patients without the underlying disease (9).

In the aftermath of the COVID-19 pandemic, the high prevalence of invasive rhino-orbital cerebral Mucormycosis (ROCM) infection has been a serious threat. The SARS-CoV-2 infection causes immune cell and cytokine dysregulation, and reckless use of immunosuppressive drugs such as corticosteroids and biologics intensified its destructive effects. The latter gives rise to immune system disturbance and catastrophic Mucormycosis outbreak (10).

Recently, there have been reports of Mucormycosis in patients with SARS-CoV-2 without the previous underlying disease (11). Some authors refer to the term "COVID-associated Mucormycosis" (CAM) as an epidemic that emerges at the heart of the pandemic (12).

Therefore, as the epidemic criteria of Mucormycosis change, national studies are needed to estimate the disease burden on different risk groups, analyze the clinical pattern of the disease, and identify new causative agents. It is difficult to properly diagnose the disease and know all epidemiologic aspects of the area, where medical services are involved in the management of this health crisis (13). We aimed to assess the actual burden of disease in our referral center before the COVID-19 era and during the COVID-19 pandemic to identify possible trends and causes.

## Methods and Materials

In this retrospective, cross-sectional study, we have reported patients admitted with a definite diagnosis of Mucormycosis in the last fifteen years (2007-2021) in a referral, tertiary care center (Loghman Hakim Hospital-Tehran -Iran), and we compared the number of patients and causative agents or predisposing factors of the disease in the pre-COVID and COVID era.

We searched and reviewed the electronic records of patients and retrieved all the granular details of cases, diagnosed with Mucormycosis and COVID-19. Subsequently, we described the patient's characteristics, associated comorbidities, location of Mucormycosis, antifungals and immunosuppressive drug usage, and outcomes. After data

collection, we used SPSS software and experts' opinions for several descriptive reports and information analyses of the pre-pandemic and pandemic period.

The study was approved by the Ethics in Medical Research Committee, IR.SBMU.RETECH.REC.1400.198.

## Results

We identified 82 patients with Mucormycosis in the hospital, of whom 48 patients were in the pre-COVID period (58.5%) In a period of 160 months and 34 patients in the COVID-19 period (41.5%) In the period of 20 months. A comparison of the number of cases showed that COVID-19 era Mucormycosis increased 4.6 times and the average annual number of patients has increased by 360 percent in contrast to the pre-COVID era. Mucormycosis was predominantly observed in women (57.3%), in both with active COVID-19 (21.5%) or in COVID-19 recovered cases (78.5%). Pre-existing diabetes mellitus (DM) occurred in 80.5% of cases, and concomitant diabetic ketoacidosis (DKA) in 15.1% of cases. Five patients (6.09%) had hematological cancers. The use of corticosteroids to treat COVID-19 was reported in 86.7% of CAM cases. Rhino-orbito-cerebral Mucormycosis (54.9%) was the most common presentation, followed by Sino-orbital infection (23.2%). The annual number of patients with Mucormycosis after the COVID-19 pandemic has increased significantly compared to the pre-pandemic era (Fig. 1).

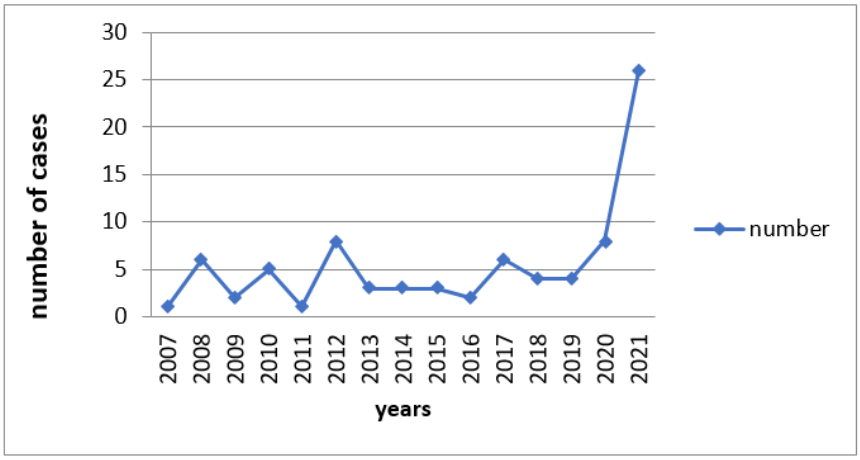


**Fig. 1:** The trend of mucormycosis during 15 years in our center

The average number of hospitalized patients with Mucormycosis before COVID was 3.7 cases per year and after COVID-19 was 28 patients per year. Total mortality was noted in 41.5% of the cases. However, the post-pandemic mortality rate was 35%.

Overall, uncontrolled diabetes was the most important risk factor for Mucormycosis before and after the pandemic. Concomitant diabetes and COVID-19 followed by controlled diabetes (before SARSCOV-2 infection in patients), COVID-19 without DM, and malignancies were the most influential risk factors associated with Mucormycosis during the COVID-19 era (Table 1).

Before the COVID-19 pandemic, risk factors associated with Mucormycosis included uncontrolled diabetes, diabetes in conjunction with the use of immunosuppressive drugs, and hematological malignancies (Table 2).

**Table 1:** Risk factors for mucormycosis in COVID-19 era

| *Risk Factors* | *Percent* |
|---|---|
| Diabetes mellitus (DM) | 43.7 |
| DM and COVID-19 | 23.2 |
| Malignancy | 11 |
| Rheumatologic Disorders | 7.3 |
| COVID-19 ( without underlying disorder) | 6.1 |
| Organ Transplantation | 4.9 |
| No previous underlying disease | 4.9 |

**Table 2:** Risk factors for mucormycosis before COVID-19 era

| *Risk Factors* | *Percent* |
|---|---|
| Diabetes mellitus (DM) | 36.6 |
| Immunosuppressive therapy and DM | 26.8 |
| Immunosuppressive therapy | 9.8 |
| Hematologic malignancy | 7.4 |
| Organ transplantation | 7.4 |
| Trauma and surgery | 4.8 |
| No previous underlying disease | 3.7 |

Prior to COVID-19, there was a significant association between poorly controlled DM and the development of mucormycosis ($P<0.005$). After the COVID-19 pandemic, a significant association was observed between immunosuppressants and the development of mucormycosis in both diabetic and non-diabetic patients ($P<0.005$). Corticosteroids had been the most common immunosuppressive drug used during the 15 years of study. Almost all cases of mucormycosis including diabetics during the SARSCOV-2 infection outbreak, and all cases in 2021 had used corticosteroids (equivalent to 8≤ mg daily dose of dexamethasone for more than 5-6 d).

The number of surviving diabetic patients who did not take immunosuppressive drugs was significantly higher than the number of diabetics who took immunosuppressant ($P<0.005$).

## Discussion

Mucormycosis is a rare and deadly disease that has been troublesome for centuries, but it has never been a major problem for the medical systems in the pre-COVID era. After the COVID-19 outbreak, this life-threatening fungus became the most important co-infection or superinfection with COVID-19 in some countries.

The most important finding reported by several studies is that mucormycosis occurs in patients following a domino-like chain of events. Dysregulation of the immune system begins after infection with SARS-COV2. The next step is corticosteroids or other immunosuppressive drugs to control the immune system's overflow, but these drugs raise the patient's blood sugar levels and downregulate the immune system in a vicious circle (14-16). A compromised immune system along with acidosis caused by increased glucose leads to further growth of opportunistic organisms such as fungi, which subsequently infect the sinuses around the nose, eyes, and brain. This angio-invasive infection kills the patient (17).

In a study conducted in a university hospital in Egypt, mucormycosis was observed mainly in men, and diabetes mellitus, hypertension, and smoking were significantly higher in patients. Steroid dosage was significantly higher among patients with mucormycosis. In this center, 90% of patients died due to mucormycosis (18).

In Germany, the disease is more common in men, (71%), and treatment with steroids, diabetes, and

malignancies represent a group at risk of infection with Mucorales. About 48% of people with no previous underlying disease developed mucormycosis after being infected with COVID-19, and the mortality rate in this study was 59% (19).

In a study conducted in a hospital in India for three months on 75 patients with mucormycosis after COVID-19, 74.7% of mucormycosis patients were men. Among the risk factors, diabetes mellitus, contracting COVID-19, and steroid use were the most common risk factors, and mortality was 25.33%. 5.3% of patients had brain abscesses, 8% of patients had cavernous sinus thrombosis, 4% of patients had facial nerve palsy, and 1.3% of patients had meningitis (20).

A study by Sing et al. describing 101 patients with mucormycosis after COVID-19 (82 from India and 19 from other countries) found that the disease was more common in men with a prevalence of 78.9% and previous diabetes in 80% of patients present and DKA was present in 14.9% of patients and 76.3% of patients received glucocorticoids due to COVID-19. Rhino sinus involvement was present in 88.9% of cases and rhino-orbital involvement in 56.7% of cases and 30.7% of patients died due to this disease (21).

In our study, the incidence of mucormycosis was higher in women than in men. Other findings including the effect of DM, the type of clinical syndrome, the frequency of DKA, and corticosteroid use were similar.

In India, 111 of 131 patients with mucormycosis had a history of COVID-19. Corticosteroids had been prescribed to about 50% of patients. Interestingly, only 6 cases died of Mucormycosis in this case series. The incidence of mucormycosis among COVID-19 patients without risk factors and underlying diseases was found to be very low (7 of 131) (22). The significantly lower mortality was due to earlier diagnosis and treatment. Although this is factual that a high index of suspicion and early management are pivotal, their lower mortality rate (4.5%) versus around 50% universal mortality rate was inconclusive.

In a systematic review, the use of corticosteroids and immunosuppressant contributes significantly to an increase in the number of patients with mucormycosis (23). The Horby's most-cited study in the case of dexamethasone's positive effect on lowering the mortality of COVID-19 with respiratory failure endorses the use of corticosteroids in the management of hospitalized cases (24). However, high dose and long-term glucocorticoids, and administration of these medications in patients without definite indication lead to misuse and negative effects on patients, including immunosuppression and hyperglycemia.

The incidence of mucormycosis in India was reported to be 70 times higher than the global average, and they wrote: "According to an Indian government minister, on May 25, 2021, alone, more than 11,700 patients were reported under mucormycosis care". In their article, they drew attention to the great challenges facing the management of mucormycosis. Four solutions for managing this crisis have been proposed in their article, including 1) Careful control of patients' blood sugar and prevention of the disease through proper use of corticosteroids, 2) Rapid diagnosis while raising the awareness of the treatment team and providing appropriate technologies for them, 3) Early team-based and integrated treatment, 4) post-treatment rehabilitation for patients due to side effects of drugs and surgical procedures.

Our study revealed that mucormycosis has increased significantly during the COVID-19 outbreak, and its important underlying causes have been diabetes/hyperglycemia, corticosteroid treatment, and COVID-19 itself. Unlike other studies, most of our patients were women. The time interval between the patient's arrival and the start of treatment was significantly reduced during the COVID period (Eight hours in days of COVID-19 compared to 26 h in the period before it). The mortality rate has been reported from 90% to 25.33%, but the mortality rate in our patients was 41.5% before the start of the pandemic and 35% after it.

The limitation of our study was retrospectively retrieving the data. To evaluate the definite risk factors of mucormycosis and to find out the causality relationship between SARSCOV-2 infection per

se and mucormycosis, and finally, to realize the relative risk of hyperglycemia with and without underlying DM, corticosteroids (dose and duration), diabetes mellitus with or without acidosis and other possible risk factors, well-design, cohort prospective studies are required.

## Conclusion

There is a significant association between diabetes and mucormycosis. Inconsiderate use of corticosteroids has dramatically increased the number of patients with mucormycosis in the pandemic era. Although the number of patients with mucormycosis has increased, the mortality rate has decreased by 6.5% after the COVID-19 pandemic. This is probably due to differences in the mechanisms of the underlying illness and/ or early detection of mucormycosis and increased awareness and skills of medical and surgical teams. All efforts should be made to maintain optimal glucose and only judicious use of corticosteroids and immunosuppressant in patients with COVID-19.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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