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SYSTEMATIC REVIEW

Mucormycosis in covid-19 disease - a systematic review of the literature

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ABSTRACT

Background and aims: *There has been a recent significant rise in the incidence of Mucormycosis associated with Covid-19 diseases in India, leading to an increase in disease burden of associated morbidity and mortality on the patients and the health systems. The present study is a comprehensive review of literature summarising the patient demographics, initial presentation, diagnosis, clinical categorization, risk factors, treatment methods, and overall mortality related to Covid-19 associated Mucormycosis reported in published literature.* ***Materials and methods****: PubMed database was searched, and 68 patients from 23 published articles were included and reported according to the PRISMA guidelines. A descriptive summary of the different variables related to Covid-19 associated Mucormycosis was reported.* ***Conclusion****: Rhino orbito cerebral Mucormycosis was the most common clinical presentation identified in Covid-19 disease, while diabetes mellitus with or without ketoacidosis and corticosteroid use remained the most common risk factor. The risk of developing rhino orbito cerebral Mucormycosis was significantly higher in diabetic Covid-19 patients. Mortality was higher in patients treated with antifungal drugs only compared to the antifungal drug plus surgery group.*

Keywords*: Covid-19 disease; Mucormycosis; Systematic review.*

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INTRODUCTION

The assessment and appraisal of the epidemiology of secondary infection of Mucormycosis in patients with Covid-19 disease have become an indispensable requirement because Mucormycosis in Covid-19 patients further complicates the efficacious treatment and recovery of the Covid-19 patients. It also adversely affects the future quality of life of patients infected with invasive fungal infections needing surgical interventions like orbital exenteration, loss of vision, and facial disfiguration.

The European Confederation of Medical Mycology (ECMM) states that Mucormycosis or Zygomycosis is an opportunistic infection caused by a fungus of the order Mucorales. The risk factors identified specific to this invasive fungal infection are an impaired and dysregulated immune status associated with Diabetes Mellitus, Neutropenia, Hematopoietic stem cell transplant, solid organ transplant, trauma, and patients with CARD9 deficiency, chronic granulomatous diseases, and HIV. A broad spectrum of clinical manifestations has been reported ranging from rhino-orbito-cerebral, pulmonary, cutaneous and skin, gastrointestinal, disseminated Mucormycosis, renal and abdominal Mucormycosis, and Mucormycosis of bones and joints, mainly involving extracranial bones and joints by direct injection.[1]

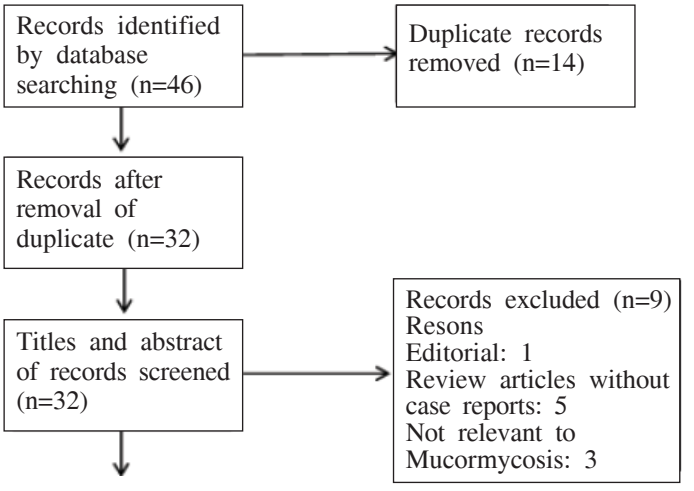
In India, uncontrolled diabetes, trauma, diabetic adults on dialysis, malnourished or premature children on broad-spectrum antibiotics with abdominal mass, distension, or bilious vomiting with or without gastrointestinal bleeding, have been identified as the risk factors linked to Mucormycosis.[2] There has been a significant rise in the incidence of secondary invasive fungal infections of Mucormycosis in India's second wave of Covid-19 disease. Therefore, the present literature review aims to shed some light on the diagnosis, underlying risk factors, clinical manifestations, and overall mortality of Mucormycosis associated with Covid-19 disease.

MATERIALS AND METHODS

The present review has been conducted complying with the PRISMA Guidelines.[3] We conducted a systematic search in PubMed from January 2020 to July 2021 using the keywords "Covid-19", "Novel Coronavirus infection", "SarsCov 2", and "Mucormycosis", "Mucorales", "Zygomycosis", "Rhizopus", "Mucor".

Eligibility: Inclusion criteria were the presence of Mucormycosis following the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria in laboratory-confirmed Covid-19, having adequate records of diagnosis, site of infection, underlying medical conditions, treatment, and patient outcome.[4]

Data collection and variables: Data collection was done using standardized forms and compared. Data retrieved included country of origin of the publication, patient information including patient demographics, past medical history, Covid-19 disease status, diagnosis of secondary or concurrent Mucormycosis, time for sequential Mucormycosis in Covid-19 patients, site of infection of Mucormycosis, overall mortality. Categorization into Rhino Orbital Cerebral, Pulmonary, Gastrointestinal, and Cutaneous was done following the previous guidelines.[5]



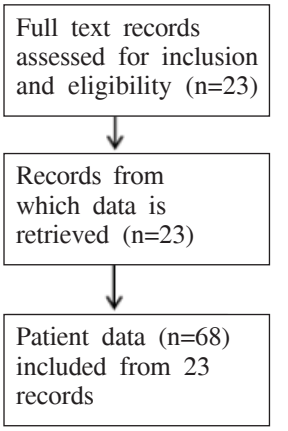


Figure 1 PRISMA diagram demonstrating methodology

RESULTS

Out of the 56 articles identified in the initial database search, 23 articles showing data of 68 patients were included in the final study for assessment (**Figure 1**). The maximum cases of Mucormycosis associated to Covid-19 patients were identified in India (52/68,76.4%), followed by USA (5/68,7.4%), Iran (4/68,5.9%), Italy (1/68,1.5%), Brazil (1/66,1.5%), Mexico (1/66,1.5%), Austria (1/66,1.5%), France (1/66,1.5%). The numerical distribution of each Covid-19 disease-associated Mucormycosis, i.e., Rhino orbito cerebral, Pulmonary, Cutaneous, Gastrointestinal in different countries, is displayed in graph 1. The group of "Rhino orbito cerebral" Mucormycosis signifies patients have isolated and different combinations of involvement of either sinus (maxillary, ethmoid, sphenoid) or sinus and orbit or sinus and cerebral or sinus, orbit and cerebral. The list of articles that have been included in this study is given in the supplementary material (**Figure 1**).

Patient demographics

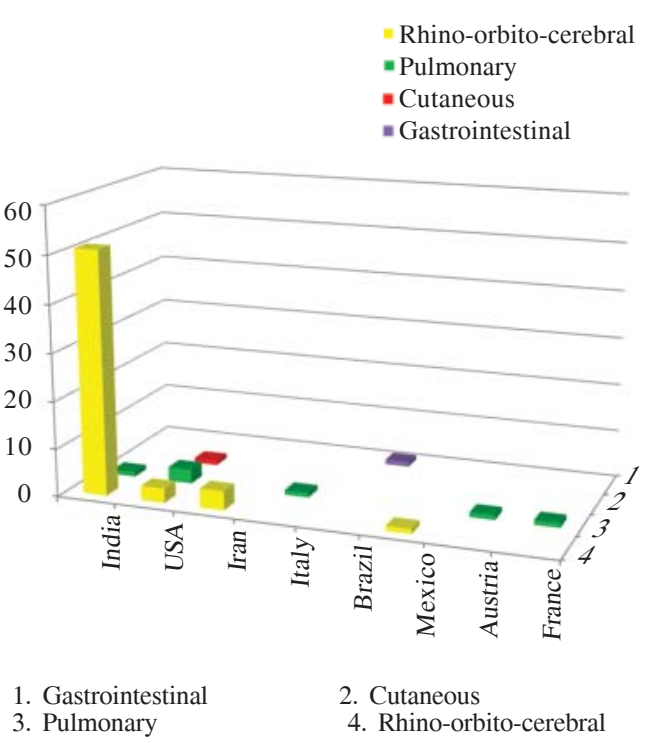
The age range observed in the patients with Covid-19 disease-associated Mucormycosis was from 24 to 86 years. The percentage of male patients was 73.5%(50/68), and that of female patients was 26.5%(18/68).

Comorbidities and risk factors

The associated comorbidities observed in the patients infected with Mucormycosis concurrent or sequential to Covid-19 are diabetes mellitus with and without ketoacidosis, asthma, hypertension, hyperlipidaemia, ischemic cardiomyopathy, secondary acute myeloid leukaemia, end-stage renal disease with haemodialysis, solid organ transplant(heart), autologous hematopoietic stem cell transfer after follicular lymphoma. Among these, the comorbidity most associated with Mucormycosis in Covid-19 patients was diabetes mellitus with or without ketoacidosis (85.3%, 58/68). Systemic corticosteroids in the treatment protocol for moderate or severe Covid-19 were the most observed risk factor (85.3%, 58/68).

In the patients with diabetes mellitus as an underlying medical condition, Rhino orbito cerebral Mucormycosis was the dominant clinical presentation, with 93%(54/58) of patients showing symptoms of this clinical category, followed by Pulmonary Mucormycosis (5%, 3/58) and cutaneous Mucormycosis (2%, 1/58). Among the non-diabetic Covid-19 patients, Rhino orbito cerebral Mucormycosis was also the more dominant clinical presentation, i.e., 60% (6/10).

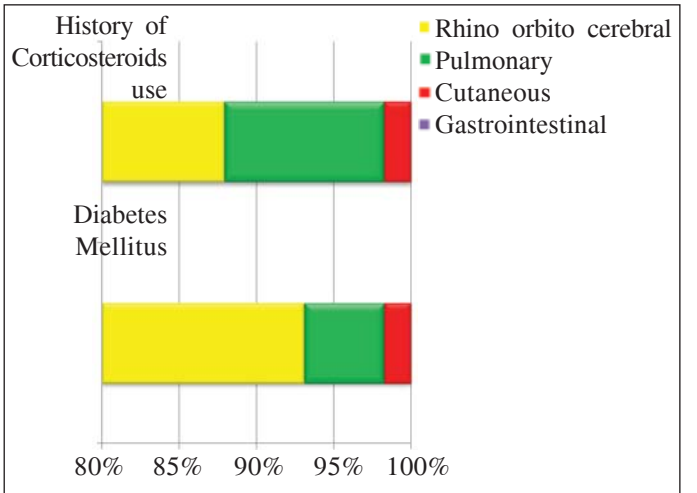
Similarly, among the patients, who had a history of corticosteroid administration during the treatments of Covid-19 disease, Rhino orbito cerebral Mucormycosis was the dominant presentation (87.8%, 51/58) followed by pulmonary Mucormycosis (10.3%, 6/58) and cutaneous Mucormycosis (2%, 1/58). Similarly, 90% (9/10) of patients without any history of corticosteroid use also had Rhino orbito cerebral Mucormycosis (**Figure 2**, **Figure 3**).



1. Gastrointestinal
2. Cutaneous
3. Pulmonary
4. Rhino-orbito-cerebral

	India	USA	Iran	Italy	Brazil	Mexico	Austria	France
Rhino-orbito-cerebral	51	3	4			1		
Pulmonary	1	3		1			1	1
Cutaneous		1						
Gastro-intestinal						1		

Figure 1 Country-wise distribution of different categories of Mucormycosis associated with covid-19



	Diabetes Mellitus	History of Corticosteroids use
Rhino orbito cerebral	54	51
Pulmonary	3	6
Cutaneous	0	0
Gastrointestinal	1	1

Figure 2 Risk association of diabetes mellitus and corticosteroids use with different clinical categories of Mucormycosis in Covid-19 disease.

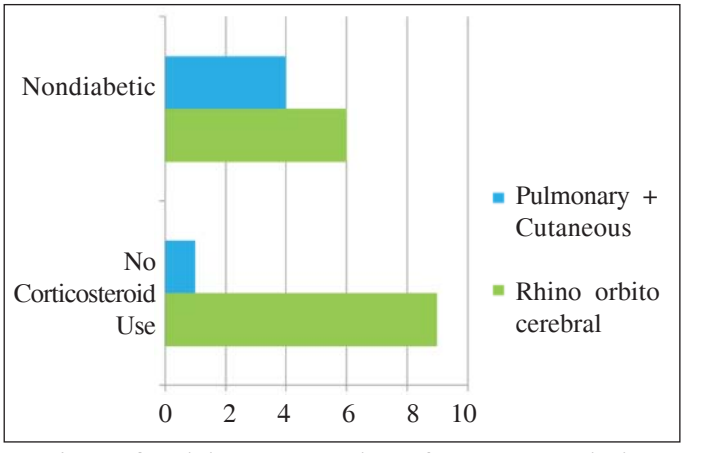


Figure 3 Clinical presentation of Mucormycosis in Covid-19 patients without diabetes mellitus and patients with no history of corticosteroid use

Symptoms at initial presentation

A wide range of symptoms has been reported at the initial presentation of Mucormycosis associated with Covid-19 disease. These include black eschar on the skin and hard palate, progressive bilateral vision loss, periorbital pain, ophthalmoplegia, proptosis, ptosis commonly unilateral, facial pain commonly unilateral, tenderness of sinus, nasal congestion, necrosis of palatal bone, odontalgia, otalgia, dyspnea, cough, hemoptysis, burning micturition, time of initial presentation.

Covid-19 patients displayed initial symptoms of Mucormycosis both 'concurrently' and 'sequentially'. Concurrent cases were those who had been diagnosed with Covid-19 disease and Mucormycosis simultaneously. Sequential patients were those diagnosed with Covid-19 disease first and then showed the initial symptoms of Mucormycosis at least 48 hours later with a median time of 11 days (range 1-42 days).

Mucormycosis in active vs recovered patients of Covid-19

60% (41/68) of patients having Mucormycosis had recovered from Covid-19 diseases at initial presentation, while 40% (27/68) of patients had active Covid-19 disease at the time of initial presentation of Mucormycosis (**Figure 3**).

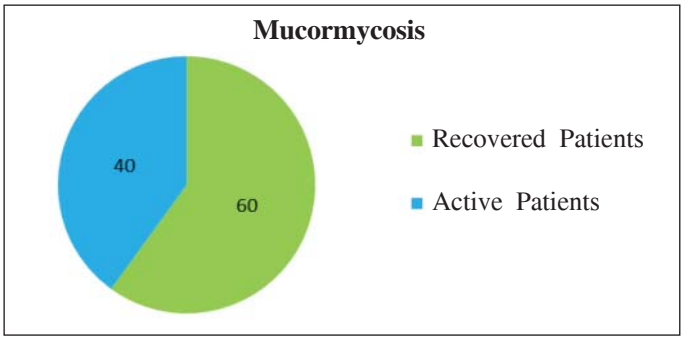


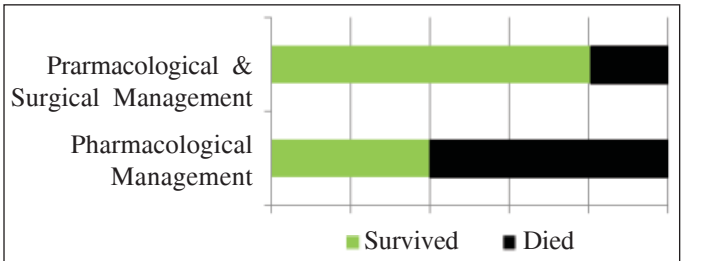
Figure 3 Pie-diagram showing the percentage of active vs recovered patients of Covid-19 having Mucormycosis.

Methods of diagnosis

The methods of diagnosis of Mucormycosis that were reported included CT scan, MRI, Sinonasal Endoscopy with tissue debridement, Sampling Biopsy (e.g., endoscopic, or CT-guided), and respiratory sample (tracheal aspirate, Bronchoalveolar lavage fluid (BALF), Direct microscopy with special stains (e.g. PAS-periodic acid Schiff, GMS-Grocott-Gomori's methenamine-silver strain), Potassium hydroxide test (KOH), molecular identification techniques like Fungal qPCR, matrix-assisted laser desorption/ ionization-time of flight (MALDI-TOF).

Treatment methods

The treatment methods reported by the included studies were pharmacological management using antifungal drugs only or pharmacological and surgical management. Conventional Amphotericin B, liposomal Amphotericin B, Posaconazole, Isavuconazole alone or accompanied with gross surgical debridement, maxillectomy, orbital exenteration, paranasal sinus irrigation with diluted amphotericin B, etc. remained the mainstay of treatment. Fifty-six patients were reported to be treated with antifungal drugs plus surgery, of which 11(20%) died. Ten patients were treated with antifungal drugs without surgery, of which 6(60%) died. 2 patients died without either form of treatment (**Figure 4**).

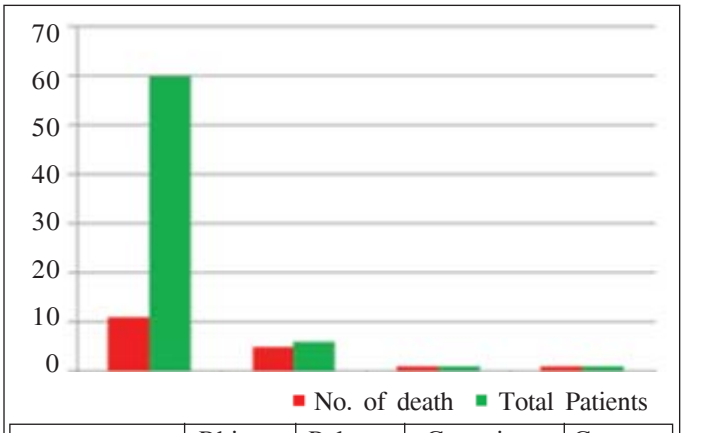


	Pharmacological Management	Prarmacological & Surgical Management
Survived	4	45
Died	6	11

Figure 4 Survival vs death rate in two treatment groups

Overall mortality

Death was reported in 40%, i.e., 18 out of 45 patients in which the mortality status was specified. 11 out of 60 patients with Rhino orbito cerebral Mucormycosis associated with Covid-19 disease died, whereas 5 out of 6 patients of the pulmonary Mucormycosis category succumbed to death. Death was reported in both patients suffering from cutaneous and gastrointestinal Mucormycosis in Covid-19 disease (**Figure 5**).



	Rhino orbito cerebral	Pulmo-nary	Gastrointes-tinal	Cutane ous
No. of death	11	5	1	1
Total Patients	60	6	1	1

Figure 5 Overall mortality in different clinical categories of Covid-19 associated Mucormycosis

DISCUSSION

The interplay between the pathogenic mechanism of Mucormycosis and the host defence system in normal individuals prevents the infection of host tissues by these invasive fungi, which are otherwise ubiquitous to their surrounding environment. The following conditions are conducive for the pathogenic fungi to cause infection.[6]

- Iron sequestration from the host for growth and sustenance, especially in a hyperglycemic and acidic environment.
- Evade the primary phagocytic defence mechanism via circulating neutrophils and tissue macrophages.
- Angioinvasion via adherence and damage to the endothelial cells resulting in vascular occlusion and thrombosis.

The countrywide distribution indicates that the number of Mucormycosis associated with Covid-19 cases in India is higher as compared to other nations, with diabetes mellitus and systemic corticosteroid administration as the most significant risk factor, which is like the study findings reported by TM John et al.,[7] Cornely et al.,[1] Hariprasath Prakash et al.,[3] in non-Covid-19 patients.

Elevated levels of available serum iron have been found in patients with systemic acidosis like Diabetic ketoacidosis due to increased release of binding proteins, which supports the growth of Rhizopus spp of Mucorales. A rise in the level of ferritin in Covid-19 has been reported by Bo Zhou et al.,[8] which also contributes to the increase in available serum iron, creating a favourable environment for the fungi to grow.

The covid-19 disease may also increase the risk of development of Diabetic ketoacidosis, as was observed in SARS CoV-1 infection, where the damage of pancreatic islets resulting in acute diabetes and DKA was found.[9] The diabetogenic state in SARS CoV-2 infection can be associated with higher expression of ACE -2 receptors in pancreatic islets. Also, insulin resistance increases later in Covid-19 disease due to cytokine storm.[10,11] Euglycemic diabetic ketoacidosis has also been reported in Covid-19 patients with Type 1 diabetes,[11] which can provide favourable conditions for developing Mucormycosis in Covid-19 patients due to the underlying state of systemic acidosis. Therefore, the risk of developing Mucormycosis in people with diabetes should not be ruled out despite reasonable glycemic control. The present study also observed that 15% of Covid-19 patients had Mucormycosis without any history of diabetes or diabetic ketoacidosis.

Systemic corticosteroid as a risk factor for Mucormycosis in Covid-19 was observed in the present study. Corticosteroid as an individual risk factor for Mucormycosis has been reported by Roden MM et al.,[12], Skiada A et al.,[13], Lanternier F et al.,[14] in non-Covid-19 patients.

The Glucose-regulated protein (GRP78), expressed in the endothelial cells of blood vessels, was identified to act as a receptor that mediates penetration through and damage of endothelial cells by Mucorales. Surface expression of GRP78 was observed to be enhanced by an increased concentration of serum glucose and iron, like that observed in diabetic ketoacidosis. This creates a favourable environment for receptor binding by Mucorales to invade and damage the endothelial. A recent study by R Sabirli et al.,[15] reported elevated expression of GRP78 in Covid-19 disease, which also establishes a possible link between the increased incidence of Mucormycosis infection and Covid-19 disease.

Consistent with previous findings in non-Covid patients,[6] Rhino orbito cerebral presentation was the most prevalent type of Mucormycosis in the present review. The risk of Rhino orbito cerebral Mucormycosis in diabetic patients of Covid-19 was higher than other types of Mucormycosis in the present study, which is similar to the previous study by Spellberg et al.[6]

The development of Mucormycosis in Covid-19 patients without a history of corticosteroid use or diabetes mellitus could raise the question of treating Covid-19 disease as an independent risk factor for Mucormycosis. The European Confederation of Medical Mycology (ECMM) 1's global guidelines has identified immunosuppression as a risk factor for Mucormycosis. Immune dysregulation has been thoroughly investigated and reported in Covid-19 disease. Carolina Lucas et al.,[16] reported, in their study, that the patients with moderate Covid-19 disease displayed a progressive decrease in type 3 immunity (antifungal) which is orchestrated by the

ROR ãt induced cytokines IL 17, IL22 secreted by ILC3, Th17 cells responsible for neutrophil-mediated clearance of extracellular bacteria and fungi.[16] The dysregulated immune system with a progressive decrease in total lymphocytes, CD4+ T cell, CD8+ T cell, B cell, Natural killer cell, direct infection of T cells by SARS COV 2, endothelial cell damage by Covid-19[17] could explain the occurrence of Mucormycosis in the 15% Covid-19 patients in the present study. They had no history of diabetes mellitus or corticosteroid use.

The present study observed a 40% mortality rate in Mucormycosis associated with Covid-19, which is lesser than the 46% mortality rate of Mucormycosis observed in non-Covid-19 patients. The mortality was higher in the pharmacological treatment group than in the pharmacological plus surgical management group in the present study, which follows the previous studies.[7]

CONCLUSION

The opportune diagnosis and immediate treatment of Mucormycosis in suspected cases are essential factors in reducing the mortality and morbidity associated with infection. Maintaining a high degree of suspicion in Covid-

19 patients presenting any symptoms of Mucormycosis or having a history of diabetes, steroid usage, or other immunosuppressive conditions is recommended. The role of prophylactic usage of antifungal drugs in high-risk patients should be further investigated.

Authors' contribution

We declare that the authors mentioned in this paper did the work, and we will bear all liabilities about claims relating to the content of this article.

Data Availability

The data used to support the findings of this study are included in the article.

Conflict of Interest

None declared.

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Supplementary Materials

Nil.

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