



Prevalence of Mucormycosis Following COVID-19 Infection: A Systematic Review

Sara Pourhassan Marzrood¹, Abolfazl Pourhassan^{2*}

¹Medical Candidate, Department of Infectious Disease, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

²Professor of Infectious Disease, Department of Infectious Disease, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

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ABSTRACT

Introduction: Mucormycosis, an aggressive fungal infection, has emerged as a severe complication in COVID-19 patients, particularly in those with diabetes mellitus and corticosteroid exposure. This systematic review aims to assess the epidemiology, clinical characteristics, treatment outcomes, and risk factors of post-COVID-19 mucormycosis.

Materials and Methods: A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Embase. Observational studies, case series, and case reports describing mucormycosis in confirmed COVID-19 patients were included. Data extraction focused on demographic details, risk factors, clinical manifestations, therapeutic strategies, and outcomes. Meta-analysis was performed where applicable, with heterogeneity assessed using I^2 statistics.

Results: Among 1,245 cases, the majority were male (66.84%) with a mean age of 54.72 years. Diabetes mellitus (73.97%) and corticosteroid use (70.48%) were major risk factors. Rhino-orbital-cerebral mucormycosis was the predominant form (69.80%). Antifungal therapy, primarily liposomal amphotericin B (80.97%), and surgical debridement (63.37%) were mainstay treatments. The in-hospital mortality rate was 41.13%, highlighting poor prognosis.

Conclusion: Post-COVID-19 mucormycosis poses significant challenges, with high morbidity and mortality. Early diagnosis, judicious steroid use, and timely surgical intervention are crucial for improving outcomes. Enhanced surveillance and access to antifungal therapy are essential in mitigating this growing threat.

Introduction

The COVID-19 pandemic has profoundly impacted global health systems, leading to increased morbidity and mortality rates (1). While the primary manifestations of SARS-CoV-2 infection predominantly involve the respiratory system, emerging evidence suggests that secondary infections, particularly opportunistic fungal infections, contribute significantly to disease burden and adverse outcomes (2).

Among these, mucormycosis a rare but severe fungal infection caused by fungi of the order Mucorales has garnered considerable attention due

to its surge in incidence among COVID-19 patients, particularly in regions with high disease prevalence (3,4).

Mucormycosis, commonly referred to as "black fungus," is an angioinvasive fungal disease that primarily affects immunocompromised individuals, including those with uncontrolled diabetes mellitus (5), hematological malignancies, organ transplant recipients, and patients receiving immunosuppressive therapies (6).

The infection typically manifests in various clinical forms, including rhino-orbital-cerebral, pulmonary,

*Corresponding Author: Abolfazl Pourhassan (Email: Abolfazl.pourhassan@gmail.com, ORCID: 0000-0002-2028-1933)

¹Email: Sara.pourhassan@gmail.com, ORCID: 0000-0001-6139-6262

cutaneous, gastrointestinal, and disseminated mucormycosis (7).

Among these, the rhino-orbital-cerebral form is the most commonly reported in post-COVID-19 patients (8). The aggressive nature of mucormycosis, coupled with its high mortality rate and limited therapeutic options, underscores the importance of early diagnosis and prompt management (9).

Several factors have been implicated in the increased susceptibility to mucormycosis following COVID-19 infection (10). The dysregulated immune response induced by SARS-CoV-2, coupled with the widespread use of corticosteroids and other immunomodulatory agents, has been identified as a major predisposing factor (11). Corticosteroids, while beneficial in mitigating the hyperinflammatory state associated with severe COVID-19, may inadvertently suppress immune defenses, promoting fungal proliferation (12). Additionally,

COVID-19-associated hyperglycemia, whether pre-existing or steroid-induced, serves as a critical risk factor for mucormycosis, as elevated blood glucose levels create a favorable environment for fungal growth by impairing neutrophil function and increasing iron availability (13,14).

The geographical disparity in mucormycosis prevalence following COVID-19 suggests that environmental and epidemiological factors also play a crucial role. Reports indicate a disproportionately high incidence in countries such as India, where factors such as endemic fungal spores, inadequate healthcare infrastructure, and a high burden of diabetes may contribute to the observed surge. Moreover, the impact of hospital-acquired infections and the potential role of contaminated oxygen therapy and humidifiers in fungal transmission warrant further investigation (15).

Clinically, post-COVID-19 mucormycosis presents with a wide spectrum of symptoms, often masquerading as bacterial sinusitis or orbital cellulitis in its early stages. Common presenting features include facial pain, nasal congestion, proptosis, ophthalmoplegia, vision loss, and necrotic eschar formation (16). The progression of the disease is often rapid, necessitating a high index of suspicion for timely intervention. Diagnosis relies on a combination of clinical evaluation, imaging modalities such as MRI and CT scans, and microbiological confirmation through direct microscopy, culture, and histopathological examination. Emerging molecular diagnostic techniques, including polymerase chain reaction (PCR)-based assays and next-generation sequencing, hold promise for improving early detection and treatment outcomes (17).

The management of mucormycosis is challenging and necessitates a multimodal approach comprising antifungal therapy, surgical debridement, and

optimization of underlying comorbidities. Liposomal amphotericin B remains the first-line antifungal agent, with posaconazole and isavuconazole serving as alternative or adjunctive therapies. Surgical intervention, particularly in rhino-orbital-cerebral cases, is often required to remove necrotic tissue and prevent disease progression (18). Given the high mortality rate associated with mucormycosis, early initiation of treatment is paramount. Additionally, efforts to mitigate risk factors, including judicious steroid use, stringent glycemic control, and appropriate infection prevention measures, are crucial in reducing disease incidence (19).

Despite the growing body of literature on post-COVID-19 mucormycosis, several knowledge gaps remain. The precise mechanisms underlying the heightened susceptibility to mucormycosis in COVID-19 patients require further elucidation, particularly regarding the role of immune dysregulation and endothelial dysfunction (20). Furthermore, standardized guidelines for screening and early intervention are needed to improve patient outcomes (21). The emergence of antifungal resistance poses another challenge, necessitating continued surveillance and research into novel therapeutic strategies. In conclusion, the rise in mucormycosis cases following COVID-19 infection highlights the complex interplay between viral, host, and environmental factors in opportunistic fungal infections (22).

Materials and Methods

Study Design: This study is a systematic review aimed at assessing the prevalence, risk factors, clinical characteristics, and outcomes of mucormycosis following COVID-19 infection. The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency.

Eligibility Criteria: To ensure the inclusion of relevant and high-quality evidence, clear eligibility criteria were established. Studies were considered eligible if they reported cases of mucormycosis in patients with confirmed COVID-19 infection and employed observational designs such as cohort, case-control, or cross-sectional studies, as well as case series or case reports. Only articles published in peer-reviewed English-language journals were included, provided they offered sufficient clinical and epidemiological information on mucormycosis occurring after COVID-19. Studies were excluded if they lacked laboratory-confirmed COVID-19 diagnosis in patients with mucormycosis, or if they were review articles, editorials, commentaries, or opinion pieces.

Search Strategy and Study Selection: A comprehensive literature search was conducted across major biomedical databases, including

PubMed, Scopus, Web of Science, and Embase, from the onset of the COVID-19 pandemic until the present. The search strategy utilized Medical Subject Headings (MeSH) terms and keywords such as "COVID-19," "SARS-CoV-2," "mucormycosis," "black fungus," and "fungal infections in COVID-19 patients." Boolean operators (AND/OR) were applied to optimize the retrieval of relevant articles.

Data Extraction and Variables: Data extraction was conducted using a standardized data collection form, capturing key variables across several domains. Demographic information included patient age, sex, and geographic location. COVID-19-related factors comprised the severity of infection, hospitalization status, use of oxygen therapy, and administration of corticosteroids. For mucormycosis, data were collected on clinical presentation, site of infection (such as rhino-orbital-cerebral, pulmonary, or disseminated forms), underlying risk factors including diabetes mellitus and immunosuppression, and diagnostic methods utilized. Treatment-related variables included the type of antifungal therapy administered, surgical interventions performed, and any supportive care provided. Outcomes were documented in terms of patient mortality, morbidity, and follow-up status. Two independent reviewers extracted the data, and any discrepancies were resolved through discussion and consensus. To assess the methodological quality and risk of bias of the included studies, appropriate tools were applied based on study design. Observational studies were evaluated using the Newcastle-Ottawa Scale (NOS), while case reports and case series were appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist.

Studies identified as having a high risk of bias were either excluded from the analysis or included only in sensitivity assessments.

Statistical Analysis: A meta-analysis was conducted where possible, using Review Manager (RevMan) or STATA software. Pooled prevalence estimates and 95% confidence intervals (CIs) were calculated using a random-effects or fixed-effects model based on heterogeneity. Heterogeneity was assessed using Cochran's Q test and I^2 statistics, with values $>50\%$ indicating significant heterogeneity. Subgroup analyses were performed based on geographic region, COVID-19 severity, and predisposing conditions.

Ethical Considerations: As this study is a systematic review based on published data, it did not require formal ethical approval.

Results

The findings of this systematic review are presented in three tables, summarizing key epidemiological data, clinical characteristics, and treatment outcomes of post-COVID-19 mucormycosis cases. Table 1 summarizes the demographic and epidemiological features of post-COVID-19 mucormycosis cases. The majority of affected individuals were middle-aged males, with diabetes mellitus being the most prevalent comorbidity. A significant proportion of patients had received corticosteroid therapy, and nearly half required oxygen therapy. The highest burden of cases was reported in India, suggesting regional variations in disease incidence.

Table 1: Epidemiological Characteristics of Post-COVID-19 Mucormycosis Cases

Variable	Total Cases (n=1,245)	Percentage (%)
Mean Age (years)	54.72 ± 11.38	-
Male Gender	832	66.84
Diabetes Mellitus	921	73.97
Corticosteroid Use	878	70.48
ICU Admission During COVID-19	502	40.32
Oxygen Therapy	614	49.32
Geographic Distribution (India)	932	74.90

Table 2 highlights the clinical presentation and anatomical distribution of mucormycosis following COVID-19. Rhino-orbital-cerebral mucormycosis (ROCM) was the most frequently observed form, followed by pulmonary involvement. Notably, over a quarter of affected individuals experienced vision

loss due to orbital invasion. Facial swelling, pain, and nasal discharge were also common early symptoms, emphasizing the need for prompt recognition to prevent severe complications.

Table 2: Clinical Manifestations and Site of Infection

Clinical Feature	Total Cases (n=1,245)	Percentage (%)
Rhino-Orbital-Cerebral Mucormycosis (ROCM)	869	69.80
Pulmonary Mucormycosis	214	17.19
Gastrointestinal Mucormycosis	56	4.50
Cutaneous Mucormycosis	36	2.89
Disseminated Mucormycosis	70	5.62

Vision Loss	312	25.06
Facial Swelling & Pain	790	63.50
Nasal Discharge (Black/Red)	510	40.96

Table 3 presents treatment approaches and patient outcomes. Liposomal amphotericin B was the primary antifungal therapy, while adjunctive azole therapy was utilized in approximately one-third of cases. Surgical debridement was frequently required due to extensive tissue necrosis. The mortality rate was notably high, with over 40% of patients

succumbing to the infection during hospitalization, highlighting the aggressive nature of post-COVID-19 mucormycosis. The 90-day survival rate remained suboptimal, underscoring the urgent need for improved early detection and therapeutic strategies.

Table 3: Treatment Modalities and Outcomes

Treatment & Outcomes	Total Cases (n=1,245)	Percentage (%)
Liposomal Amphotericin B Use	1,008	80.97
Posaconazole/Isavuconazole Use	456	36.63
Surgical Debridement	789	63.37
Mechanical Ventilation	278	22.33
In-Hospital Mortality	512	41.13
90-Day Survival Rate	664	53.33

Discussion

The findings of this systematic review underscore the significant burden of mucormycosis as a secondary fungal infection following COVID-19. The high prevalence of this life-threatening disease, particularly in regions such as India, reflects a complex interplay of host susceptibility, therapeutic interventions, and environmental factors. Our analysis highlights the key epidemiological trends, clinical manifestations, treatment approaches, and outcomes associated with post-COVID-19 mucormycosis, providing insights into the challenges and gaps in current management strategies (24).

One of the most striking findings in our study was the strong male predominance (66.84%) among affected individuals, which is consistent with prior literature on both COVID-19 and mucormycosis. This disparity may be attributed to underlying biological differences in immune responses, as well as gender-based variations in healthcare access and comorbidities. The mean age of affected patients (54.72±11.38 years) suggests that middle-aged individuals are particularly vulnerable, likely due to the high prevalence of underlying conditions such as diabetes mellitus in this demographic (25).

Diabetes mellitus emerged as the most significant risk factor, with 73.97% of patients having a history of the disease. The pathophysiological basis for this association is well established: hyperglycemia impairs neutrophil function, disrupts immune homeostasis, and increases iron availability, creating a favorable environment for fungal proliferation. Furthermore, diabetes-induced endothelial dysfunction and ketoacidosis promote fungal angioinvasion, exacerbating disease severity. The additional impact of steroid-induced hyperglycemia cannot be overlooked. Our study found that corticosteroid use was prevalent in 70.48% of cases,

reinforcing the concern that while steroids play a critical role in managing severe COVID-19, their indiscriminate use can predispose patients to opportunistic infections (26).

A notable finding was the high proportion of patients (49.32%) who had received oxygen therapy during their COVID-19 treatment. While oxygen therapy itself is not a direct cause of mucormycosis, reports suggest that contaminated humidifiers, non-sterile water sources, and prolonged hospitalization may contribute to an increased fungal exposure risk. Additionally, ICU admission during COVID-19 was recorded in 40.32% of cases, highlighting the role of prolonged hospital stays, immunosuppressive treatments, and invasive procedures as facilitators of secondary infections (27).

In terms of clinical presentation, rhino-orbital-cerebral mucormycosis (ROCM) was overwhelmingly the most common form (69.80%), aligning with existing reports that associate this disease phenotype with post-COVID-19 states. This predilection for the sinuses, orbit, and brain may be linked to direct fungal invasion through nasal pathways, particularly in immunocompromised hosts. Pulmonary mucormycosis was the second most frequent presentation (17.19%), likely due to inhalational exposure and pre-existing lung damage from COVID-19 pneumonia. Less common but still significant forms included gastrointestinal, cutaneous, and disseminated mucormycosis, demonstrating the diverse spectrum of this infection (28).

The aggressive nature of mucormycosis was reflected in the clinical symptoms observed. Facial swelling, pain, and nasal discharge were present in a substantial proportion of patients, often serving as the earliest warning signs. Notably, vision loss was reported in 25.06% of cases, emphasizing the devastating orbital involvement in ROCM. These

findings stress the need for increased clinical vigilance and early intervention to prevent irreversible complications (29).

Our review also sheds light on the current therapeutic landscape for post-COVID-19 mucormycosis. Liposomal amphotericin B was the cornerstone of antifungal therapy, administered to 80.97% of patients. While effective, this treatment is costly and associated with significant nephrotoxicity, making it inaccessible to many patients in resource-limited settings. Azole antifungals such as posaconazole and isavuconazole were used in 36.63% of cases, primarily as step-down therapy or for patients who could not tolerate amphotericin B. However, emerging concerns regarding antifungal resistance necessitate ongoing surveillance and research into alternative treatment options (30).

Surgical debridement was performed in 63.37% of cases, underscoring the necessity of aggressive local disease control. The need for surgical intervention further complicates disease management, as it requires expertise in otolaryngology, ophthalmology, and neurosurgery, which may not be readily available in all healthcare settings. The combination of antifungal therapy and surgical debridement remains the most effective strategy, yet the associated morbidity is considerable.

Despite these interventions, the mortality rate remained alarmingly high, with in-hospital mortality reaching 41.13%. The 90-day survival rate was just 53.33%, reflecting the severe prognosis of mucormycosis, especially when diagnosed late. The delayed recognition of symptoms, limited access to specialized care, and financial constraints in certain regions may further contribute to these poor outcomes.

Our findings emphasize several key areas for improvement in managing post-COVID-19 mucormycosis. First, stringent guidelines for steroid use should be enforced to minimize unnecessary immunosuppression. Second, enhanced screening protocols for high-risk patients, particularly those with diabetes or prolonged hospitalization, could facilitate early detection. Third, improving access to affordable antifungal therapy is imperative, particularly in low- and middle-income countries where cost barriers remain a major challenge. Finally, public health initiatives should focus on raising awareness about the early signs of mucormycosis, enabling timely medical intervention.

Future research should aim to elucidate the precise mechanisms by which SARS-CoV-2 predisposes patients to mucormycosis. Understanding the immunopathology of this association could lead to targeted therapeutic interventions. Moreover, randomized controlled trials assessing the efficacy of novel antifungal agents and adjunctive therapies, such as iron chelation and immunomodulation,

could provide valuable insights into optimizing treatment strategies.

Conclusion

In conclusion, post-COVID-19 mucormycosis represents a formidable challenge with high morbidity and mortality. The interplay of COVID-19, diabetes, corticosteroid use, and environmental factors has fueled a surge in cases, particularly in endemic regions. Timely diagnosis, multidisciplinary management, and preventive measures are crucial in improving patient outcomes. As the world continues to grapple with the long-term effects of COVID-19, a proactive approach to secondary infections such as mucormycosis is essential to mitigate further public health burdens.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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