Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.367520.3876 Volume 31, Issue 7, July 2025
Manuscript ID:ZUMJ-2503-3876
DOI:10.21608/zumj.2025.367520.3876

ORIGINAL ARTICLE

Pathological and Clinical Overview of Mucormycosis: Post-COVID-19 Perspective

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Submit Date 19-03-2025
Accept Date 12-05-2025

ABSTRACT

Background: Mucormycosis is a severe fungal infection caused by Mucorales, it has emerged as a significant post-COVID-19 complication, particularly in immunocompromised individuals. The widespread use of corticosteroids and underlying conditions such as diabetes mellitus have contributed to the increased prevalence of this opportunistic infection. This study aims to evaluate the clinical presentations, risk factors, histopathological findings, and treatment outcomes of mucormycosis in post-COVID-19 patients.

Methods: A retrospective observational study was conducted over three years (2021–2023) at the Faculty of Medicine, Zagazig University. Seventy post-COVID-19 patients diagnosed with mucormycosis were included. Clinical data, imaging findings, and histopathological examination of tissue biopsy samples were analysed. The fungal burden, presence of necrosis, angioinvasion, and perineural invasion were assessed.

Results: 70% of the patients were male, with a mean age of 41–50 years. Diabetes mellitus was the most common comorbidity (98.6%), and 90% had received corticosteroids for COVID-19 treatment. Rhino-orbital mucormycosis was the predominant form (65 cases), with severe fungal load observed in 20% of patients. Angioinvasion and perineural invasion were linked to poorer prognosis. Sinonasal debridement was the most commonly performed intervention.

Conclusions: After analysing the collected clinical and histopathological data of tissue samples, which were processed into paraffin sections, stained using Haematoxylin & Eosin (H&E) and Periodic Acid Schiff (PAS) from the 70 patients by using SPSS version X, we concluded that Post-COVID-19 mucormycosis is associated with significant morbidity and mortality. Uncontrolled diabetes and corticosteroid use are major risk factors. Early diagnosis, aggressive surgical intervention, and antifungal therapy are crucial for improving patient outcomes.

Keywords: Mucormycosis; COVID-19; Diabetes; Corticosteroids; Histopathology.

INTRODUCTION

Mucormycosis is a severe fungal infection caused by fungi of the Mucorales, it has become a growing concern due to its increased prevalence during the COVID-19 pandemic. The primary causative agents include species such as *Rhizopus Arrhizus*, *Mucor spp.*, and *Lichtheimia spp.* These fungi thrive in environments like soil and decaying

organic material and predominantly infect individuals with compromised immune systems. If not promptly treated, the infection progresses rapidly, often leading to significant health complications and high mortality rates [1,2].

The COVID-19 pandemic has significantly contributed to the surge in mucormycosis cases, especially in regions like India, where diabetes mellitus is highly prevalent. Factors such as immune dysregulation caused by COVID-19, the extensive use of corticosteroids, and other predisposing conditions have created an environment conducive to this opportunistic infection. Recognizing these distinctive epidemiological and clinical patterns is essential for enhancing patient care and outcomes [3,4].

The pathogenesis of mucormycosis is multifaceted, involving the pathogen's ability to exploit host vulnerabilities. Conditions such as elevated blood sugar levels, acidosis, and excess iron which are commonly observed in diabetic and post-COVID-19 patients create an environment favourable for fungal growth. Proteins like COTH on the fungal surface enable the pathogen to adhere to and invade host endothelial cells, leading to extensive tissue damage and systemic dissemination [5].

Mucormycosis can present in various clinical forms depending on the site of infection. The rhino-orbito-cerebral form is the most frequently encountered, with symptoms such as facial swelling, nasal congestion, and visual impairment. Pulmonary mucormycosis, which often affects individuals with low neutrophil counts, presents with fever, chest pain, and coughing blood. The cutaneous and disseminated forms are equally severe and highlight the critical need for early detection [6].

The emergence of mucormycosis as a secondary infection during the COVID-19 pandemic underscores the importance of timely and proactive management. Controlling modifiable risk factors, such as poorly managed diabetes and the overuse of corticosteroids, along with improving diagnostic and therapeutic protocols, are critical steps in reducing the impact of this devastating infection [1].

Globally, the increased burden of mucormycosis during the pandemic has highlighted significant challenges in healthcare systems. Multicentre research has revealed strong associations between delayed diagnosis, immune suppression, and poor treatment outcomes, underscoring the urgency of early intervention [3,7].

Recent studies have advanced our understanding of the interplay between COVID-19 and mucormycosis. These investigations have provided new insights into the mechanisms by which COVID-19 exacerbates host vulnerabilities and facilitates fungal proliferation, offering valuable guidance for developing improved preventive and therapeutic strategies [5].

Diagnosing mucormycosis is particularly challenging due to its rapid progression and symptom overlap with other diseases. Imaging techniques like CT and MRI are invaluable for identifying the extent of the infection, while definitive confirmation is achieved through histopathological and molecular diagnostic methods. Differentiating mucormycosis from similar infections, such as aspergillosis or candidiasis, is essential to ensure effective treatment [8].

Histopathological examination plays a crucial role in diagnosing mucormycosis. Typical findings include wide, ribbon-like fungal hyphae without septa and branching at right angles. A distinguishing feature of this infection is the invasion of blood vessels by fungal elements, resulting in vascular thrombosis and tissue necrosis. This aggressive angio-invasion is a key factor contributing to the disease's rapid progression and unfavourable prognosis [8].

Histopathology enables the evaluation of the degree of tissue invasion. This technique is particularly beneficial in

differentiating between mere contaminants, colonizers, and true pathogenic agents, given that Mucorales and other opportunistic fungi are prevalent in the environment. In certain instances, histopathology may represent the sole indication of fungal infection, especially when the pathogen cannot be isolated through culture [9,10].

Despite its diagnostic importance, histopathology alone is insufficient for identifying the specific causative organism, as many fungal pathogens exhibit overlapping morphological features when stained in tissue sections. To achieve accurate identification, additional approaches such as fungal culture, morphological and phenotypic characterization, and molecular diagnostic techniques are essential. Some fungi, such as *Apophysomyces spp.*, pose unique challenges as they may require specific conditions to sporulate in laboratory settings [10] . The aim of this work was to explore the clinical presentations, risk factors, and treatment outcomes of mucormycosis in post-COVID-19 patients

METHODS

A retrospective observational study was carried out over three years (January 2021 to December 2023) in the Oto-Rhino-Laryngology and Pathology departments at the Faculty of Medicine, Zagazig University. The study included 70 patients who had previously contracted COVID-19 and later presented with mucormycosis symptoms within 2–4 weeks of testing positive for the virus. Tissue biopsy samples from these patients were obtained through procedures such as sinonasal debridement, maxillectomy, orbital exenteration, and excision of cutaneous lesions. These samples were sent to the histopathology department for analysis.

Patient data, including age, sex, symptoms, comorbidities, imaging findings, and details of corticosteroid use during COVID-19 treatment, were collected. Additionally, information on the affected anatomical sites and the type of surgical interventions performed was recorded and analysed.

Histopathological examination was conducted on tissue samples, which were processed into paraffin sections, stained using Haematoxylin & Eosin (H&E) and Periodic Acid Schiff (PAS), and then studied in detail. The samples were assessed for the following microscopic features:

1. Fungal morphology.
2. Fungal load, categorized into mild, moderate, or severe based on the number of microscopic fields (400x magnification) showing fungal hyphae.
   - **Mild:** Hyphae observed in fewer than four fields.
   - **Moderate:** Hyphae visible in five to seven fields.
   - **Severe:** Hyphae present in more than eight to ten fields.

   The grading was based on the area with the highest fungal density [11].
3. Presence or absence of tissue necrosis.
4. Evidence of angioinvasion or perineural invasion.
5. Granuloma formation.

The diagnosis of invasive fungal sinusitis was confirmed when hyphal structures were identified in the sinus mucosa, submucosa, blood vessels, or bone.

All patients were followed up in outpatient clinic monthly for six months after surgery.

Ethical code approval: **ZU-IRB #1011 21/1-2025.**

Statistical Analysis

The collected data were analysed using **SPSS version X**. Descriptive statistics, including means, and percentages, were used to summarize patient demographics, clinical characteristics, and histopathological findings. The association between fungal burden, angioinvasion, perineural invasion, and patient outcomes was assessed.

RESULTS

The study was conducted on 70 post-COVID patients who were clinically diagnosed with mucormycosis and later confirmed through histopathological examination. Among these, 49 patients (70%) were male, and 21 patients (30%) were female, resulting in a male-to-female ratio of 7:3 **(Figure 1a)**. The patients' ages ranged from 23 to 70 years, with (30 patients) falling in the 41–50 age group for both genders **(Figure 1b)**. The youngest male and female patients were 23 and 32 years old, respectively, while the oldest male was 70 years and the oldest female was 66 years.

Regarding comorbidities **(Figure 1c)**, diabetes was present in 69 patients, and hypertension was observed in 20 patients. Additionally, 26 patients had co-malignancies and had undergone chemotherapy. The most commonly reported symptoms included facial pain, swelling, and nasal discharge. Mucormycosis primarily affected the sinuses and orbit in (65 cases), with fewer instances involving the cranium (2 cases) and the skin (3 cases) **(Figures 2a, 2b, and 2c) (Figures 3a, 3b).**

Regarding COVID-19 treatment, corticosteroids were administered to 63 patients (90%) **(Table 1).**

Among the 69 diabetic patients analysed, HbA1c levels revealed varying degrees of glycaemic control. A total of 14 patients (20.3%) were classified as having well-controlled diabetes (HbA1c < 7.0%), while another 14 patients (20.3%) fell under moderately controlled (HbA1c between 7.0–8.0%). The majority, 41 patients (59.4%), exhibited poor glycaemic control with HbA1c values exceeding 8.0%.

Additionally, among 26 patients with co-malignancies undergoing chemotherapy, neutrophil counts showed a broad range from 0.1 to 2.0 $\times 10^9$/L, with most values clustering below the normal range, consistent with post-chemotherapy neutropenia.

As regards clinical grading of our rhino-orbito-cerebral patients, 30 patients were grade 1(nasal), 28 patients were grade 2 (paranasal), 10 patients were grade 3 (orbital) and 2 patients were grade 4(intracranial).

Histopathological analysis of tissue samples, stained with H&E and PAS stains when necessary, revealed the characteristic fungal hyphae as broad, aseptate, ribbon-like structures with wide-angle branching. The fungal burden varied, with mild involvement in 18 patients (26%), moderate in 38 patients (54%), and severe in 14 patients (20%). Necrosis was observed in 35 patients (50%), granulomas in 8 patients (11%), angio-invasion in 16 patients (23%), and perineural invasion in 10 patients (14%)**.** The biopsies were taken mostly from the middle turbinate and exenterated eyes**. (Figures 4a, 4b, 4c and 4d).**

Treatment:

All our patients were given liposomal amphotericin B. Sinonasal debridement was carried out soon even before histopathological diagnosis.

The surgeries performed **(Table 2)** included sinonasal debridement only in 49 patients (70%), sinonasal debridement and orbital exenteration in 4 patients (5.7%), and maxillectomy in 6 patients (8.6%). A combination of sinonasal debridement, orbital exenteration, and maxillectomy was performed in 1 patient (1.4%). Orbital exenteration along with maxillectomy was conducted in 3 patients (4.3%), while orbital exenteration alone and craniotomy with lesion excision were each performed in 2 patients (2.85%). Cutaneous lesion excision was done in 3 patients (4.3%).

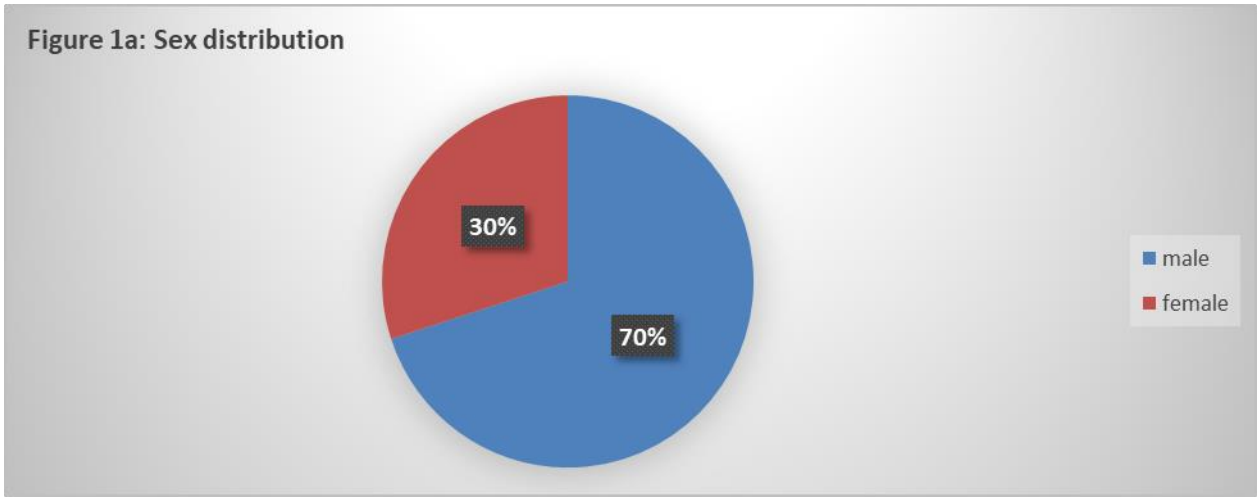
Mortality rate in our cases was 14.3% (10 patients) with disseminated mucormycosis and intracranial complications.

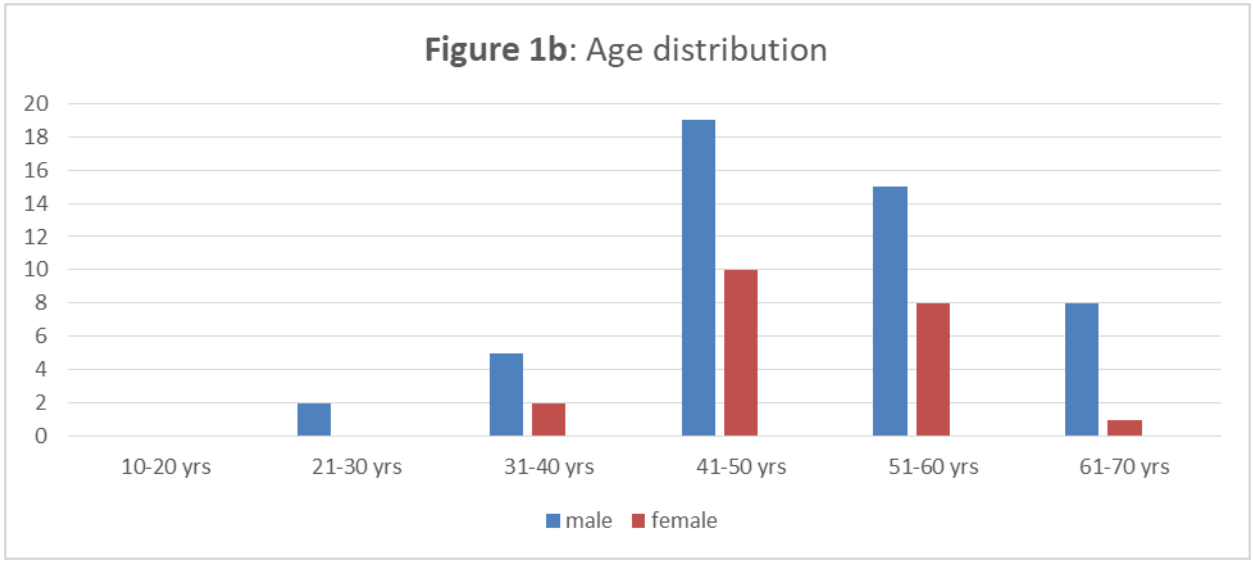
Table 1: Corticosteroids intake for treatment of COVID-19

No. of patients treated with Corticosteroids	No. of patients not treated with Corticosteroids
63	7

Table 2: Types of surgeries performed

	Types of surgeries performed	No. of patients (%)
1	Sinonasal debridement	49 (70%)
2	Sinonasal debridement and orbital exenteration	4 (5.7%),
3	Sinonasal debridement and maxillectomy	6 (8.6%)
4	Sinonasal debridement + orbital exenteration + maxillectomy	1 (1.4%)
5	orbital exenteration and maxillectomy	3 (4.3%)
6	orbital exenteration	2 (2.85%)
7	craniotomy and excision of lesion	2 (2.85%)
8	cutaneous excision of lesion	3(4.3%)





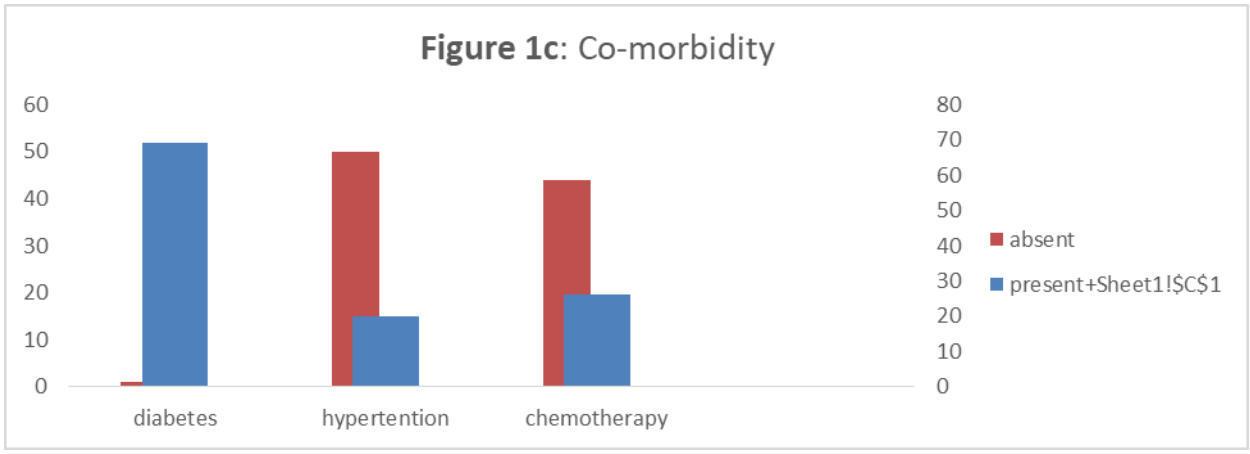


Figure 2a: 43 years old female patient complaining of left nasal obstruction, left facial swelling Facial pain & headache and Lt palatal necrosis. **Figure 2b:** case of 43 years old male patient with facial swelling, area of skin and palatal necrosis on left side. **Figure 2c:** 32yrs old male , complaining of left retro orbital pain , headache , facial hypothesia and nasal regurgitation of food of 1 m duration with gradual onset and progressive course .patient underwent orbital exenteration with subsequent 4 orbital debridement operations

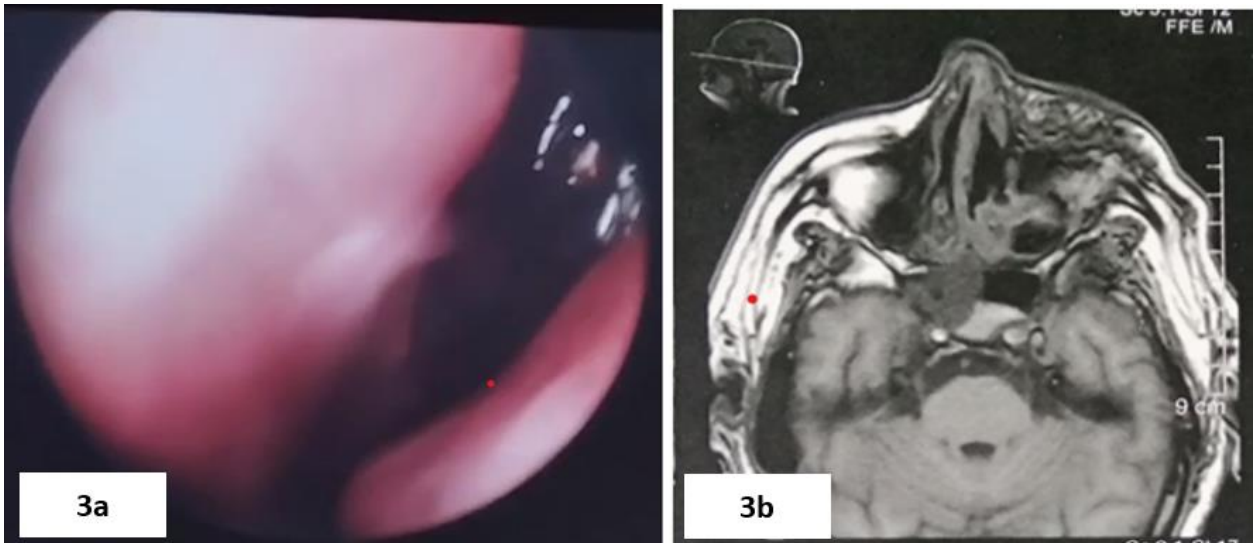
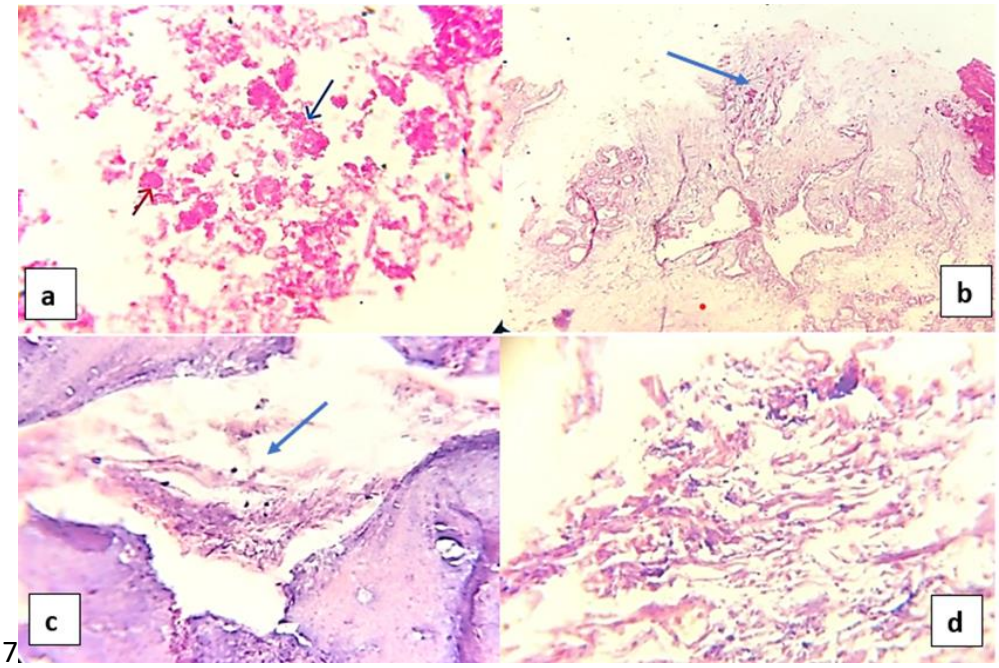


Figure 3a: Endoscopic view of the left nasal cavity shows necrosis of the middle turbinate. 3b: MRI T1 axial view showing right sphenoid opacity with intracranial extension (intracavernous).



Figures 4: a: PAS staining showed numerous ribbon-like, haphazardly branched fungal hyphae and sporangia in tissue section (PAS x40)**. b:** nasal sinus invaded by irregular fungal hyphae(H&E×10).**c:** infarcted bony lamellae invaded by numerous fungal hyphae(H&E×10). **d**: broad hyaline aseptate hyphae with irregular branching, (H&E×40).

DISCUSSION

Mucormycosis is an opportunistic fungal infection that has emerged as a severe complication in post-COVID-19 patients, particularly those with predisposing conditions such as diabetes mellitus and immunosuppression. Diabetes mellitus, especially when uncontrolled or complicated with diabetic ketoacidosis, is a well-established risk factor for mucormycosis. In this study, 98.6% of the patients had diabetes, which corroborates findings from previous research that highlights its critical role in the pathogenesis of mucormycosis [12,13].

Histopathologically, mucormycosis is characterized by non-septate, broad, ribbon-like fungal hyphae that exhibit angioinvasion and necrosis. The study findings revealed a significant association between fungal load and prognosis, with severe fungal load correlating with increased mortality. These results align with the observations of **Goel et al. [**14**]** who demonstrated that a higher fungal burden was indicative of poor survival outcomes in non-COVID rhino-orbito-cerebral mucormycosis.

Angioinvasion was noted in 24% of the patients in this study, and this subset experienced a higher mortality rate. Similar findings have been reported by **Sravani et al.** [15]where angioinvasion was associated with advanced disease and poorer outcomes. Perineural invasion, observed in 16% of patients, was predominantly seen in orbital exenteration specimens and was also linked to increased mortality, reinforcing its role as an indicator of severe disease progression.

The study also identified intracranial involvement in two cases, with fungal

invasion of the brain parenchyma resulting in abscess formation. These cases had poor outcomes, consistent with previous studies highlighting the poor prognosis associated with intracranial mucormycosis. Ethmoid sinus involvement was the most common site of infection followed by the maxillary sinus, these findings are parallel to those reported by **Sharma et al.** [12].

Interestingly, granulomatous responses were observed in 11% of cases and were associated with better survival outcomes. This aligns with reports by **Matiku et al**. [5] which suggest that granulomatous inflammation reflects a stronger immune response and less progression of the disease. However, patients who have multiple high-risk factor and ongoing immunosuppression are likely to have a poor prognosis, with reported mortality rates ranging from 40% to 80%, depending on site and extent of disease [16].

Corticosteroid therapy, used in 90% of the patients for COVID-19 management, was identified as a key risk factor for mucormycosis development. This finding echoes the conclusions of **Watanabe et al**. who emphasized that corticosteroids, while beneficial in managing COVID-19, exacerbate hyperglycaemia and impair immune defences, thereby increasing susceptibility to fungal infections. The combined effect of corticosteroid-induced immunosuppression and hyperglycaemia creates an environment conducive to fungal proliferation [6,9].

The strong association between diabetes mellitus, corticosteroid use, and mucormycosis underscores the need for judicious use of corticosteroids and stringent glycaemic control in COVID-19 patients. The study findings support the need for early diagnosis and aggressive surgical debridement to improve outcomes, as highlighted in the previous multicentre studies[3].

Mortality rate in our cases was 14.3% (10 patients) with disseminated mucormycosis and intracranial complications. This low mortality rate was due to early diagnosis, medical and surgical intervention. After radical surgery, 85.7% of patients achieved local infection control. **Lee et al**. [17] agree with our results.

CONCLUSIONS

Mucormycosis has emerged as a severe post-COVID-19 complication, especially in diabetic and immunosuppressed patients. This study analysed 70 cases at Zagazig University using SPSS version X, revealing a strong link between diabetes (98.6%), corticosteroid use (90%), and disease severity. The infection primarily affected the sinuses and orbit (93%). Histopathological examination was conducted on tissue samples, which were processed into paraffin sections, stained using Haematoxylin & Eosin (H&E) and Periodic Acid Schiff (PAS). Histopathological findings showed fungal hyphae, necrosis (50%), angioinvasion (23%), and perineural invasion (14%).

Uncontrolled diabetes and corticosteroid use significantly contribute to mucormycosis severity. Early diagnosis, strict glycaemic control, and cautious steroid use are essential for better outcomes. Prompt surgical and medical interventions can help to reduce disease progression and mortality, emphasizing the need for proactive healthcare strategies.

Conflict of interest: None.
Financial disclosure: No fund.

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Citation

Mahmoud Hamdy, H., saeed Mustafa Mohammed, M. Pathological and Clinical Overview of Mucormycosis: Post-COVID-19 Perspective.. *Zagazig University Medical Journal*, 2025; (2567-2575): -. doi: 10.21608/zumj.2025.367520.3876