

# Etiology and Clinical Manifestations of Mucormycosis during the COVID-19 Pandemic

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**Abstract:** *Mucormycosis is an aggressive infection caused by the fungi of order Mucorales, class Zygomycetes. It is an angio-invasive fungus found freely in environment. Mucor infection is associated with impaired immune function; patients with uncontrolled diabetes, cancer, organ transplant recipients and those on immunosuppressants are vulnerable for developing mucormycosis. The incidence of mucormycosis India is estimated to be much higher than that of the developed countries as is, however, there has been an exponential rise in incidence of mucormycosis following the COVID-19 pandemic. The common feature among the affected patients was that they had a history of or active COVID-19 infection as well as high dose steroid administration. A combined medical and surgical approach was adapted for the treatment. Early diagnosis and aggressive treatment formed the mainstay of management*

**Keywords:** Mucormycosis, COVID-19, Amphotericin B, Modified Denker's approach

## 1. Introduction

Mucormycosis is a rare, but fulminant fungal infection, caused by fungi belonging to the order of Mucorales. The causative fungi for mucormycosis are ubiquitous, usually found in soil and decomposing matter, it usually does not affect healthy individuals. People with compromised immune system are affected. The most commonly affected are those with diabetic ketoacidosis, organ transplant recipients, hematological malignancies, and glucocorticoid therapy. Inhalation is the most common route of infection, hence nose and paranasal sinuses are most commonly affected and hence rhino-cerebral mucormycosis is the most commonly encountered subtype. Rhino-mucormycosis falls under acute invasive fungal sinusitis. Other forms of mucormycosis are pulmonary, gastrointestinal, dermatological and disseminated.

As per the WHO estimates the global burden of mucormycosis is about 1.7 cases per million whereas in India it is 140 per million, 80% higher than the developed countries. However, a further surge in the incidence was seen in India following the COVID-19 pandemic. The primary factors responsible for this are deemed to be the impairment of the immune function due to the COVID-19 infection and the indiscriminate use of glucocorticoids. This unforeseen surge in the number of cases has also provided a rare opportunity to analyze this rare disease.

In this study, we are focusing on rhino-orbito-cerebral mucormycosis. It remains one of the most difficult diseases to manage, with a high rate of morbidity and mortality. Diagnosis is based on a detailed history, and clinical examination, with radiological and histo-pathological correlation. The management of choice remains a combination of medical and surgical modalities, often requiring multi-departmental efforts.

Our study aims to analyse the epidemiology of

mucormycosis and to evaluate the etiopathogenesis of mucormycosis and associated co-morbidities, precipitating factors, diagnostic modalities, and the various medical and surgical treatment options.

This is a retrospective observational study conducted at a tertiary care center in Gujarat. The patients presenting with signs and symptoms of mucormycosis between the period of April 2021 to October 2021 were candidates for this study. The study comprised of a total of 250 patients who were diagnosed cases of mucormycosis. The data is obtained from the hospital records. A detailed proforma was filled out, which included the history, clinical findings, investigations and treatment provided. The patients were followed up to 3 months after discharge.

### **Inclusion Criteria:**

Diagnosed cases of mucormycosis presenting during the study period.

### **Exclusion criteria:**

Patients who are not willing for participation, unwilling for admission or referred to higher centre without admission.

### **Pathophysiology:**

Rhino cerebral mucormycosis is an acute, often fatal infection caused by fungi of the family mucoraceae. The principal pathogens in this family are rhizopus, mucor and of absidia species [1]. The causative organism is ubiquitous within the environment. They are found in soil, decaying vegetation and other organic matter. Infection most often develops in individuals with immunologically compromising conditions which are frequently the result of diabetes mellitus, cancer, chemotherapy or administration of immunosuppressive medications following organ transplantation [2-4]. Other predisposing factors include renal failure, severe burns, malnutrition, neutropenia and treatment with desferoxamine [5]. Patients without an underlying abnormality or apparent predisposition have also been affected. The incidence of disease has not been

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demonstrated to vary based on age or gender. The predisposition of patients with diabetes to acquire the disease may be particularly related to hyperglycemia and the presence of ketoacidosis is presumed to induce a neutrophil defect, resulting in reduced phagocytosis and chemotaxis [6]. Nasal infection follows the inhalation of aerosolized fungal spores that may deposit in the nasal turbinate and extend into adjacent paranasal sinuses and orbit. The pathogens are prone to invade and spread along blood vessels particularly arteries. The fungus proliferates within the internal elastic lamina, dissecting it from media. As the hyphae penetrate the endothelium, thrombotic arteritis, infarction, hemorrhage and extensive tissue necrosis follows [7]. Involvement of the internal carotid artery, cavernous sinus and ophthalmic artery is common. Involvement of venous and lymphatic structures occur later in course of illness. Patients with rhinocerebral mucormycosis usually presents as acute sinusitis with fever, nasal congestion, purulent nasal discharge, headache and facial pain. All sinuses can become involved and spread to adjacent structures such as palate, orbit and brain usually progresses rapidly. The hallmarks of spread of disease beyond the sinuses are tissue necrosis of the palate resulting in palatal eschars, destruction of turbinate, perinasal swelling and cyanosis of the facial skin overlying the involved sinuses. Black necrotic intranasal or palatal eschar is highly suggestive of the disease but it occurs in only 40-50 % of those affected.

#### Clinical features:

##### *Nose and Paranasal sinus:*

Clinical features include: nasal discharge (blackish or bloody), epistaxis, headache, facial pain and facial swelling.

Nasal discharge in mucormycosis is often thick and blood stained occasionally nasal blockage is also present. Frank epistaxis can also be present. Occasionally crusting and necrosis can be encountered in anterior rhinoscopy itself. However, a formal nasal endoscopy should be done for all patients.

Necrosis on endoscopy is diagnostic of mucormycosis, however in many cases the nasal endoscopy can be completely normal. Para nasal sinus tenderness and facial swelling are also present.

##### *Ophthalmological symptoms:*

Clinical features include: Chemosis, proptosis, ptosis, lid edema, diplopia, restricted or absent eyeball movement, blurring or loss of vision and abscess formation.

Ptosis, restricted eye movements, ophthalmoplegia, diplopia due to involvement of cranial nerves III, IV and VI associated with cavernous sinus involvement.

Chemosis, lid oedema, proptosis, cellulitis or orbital abscess are due to direct invasion of orbit from the nasal cavity and paranasal sinuses. There is marked inflammation, of the orbit and the peri-orbital region with a very rapid progression from chemosis to orbital abscess.

Loss of vision occurs due to thrombosis of ophthalmic artery, which leads to ischemia of the optic nerve. There may be isolated loss of vision without any other signs of inflammation.

#### *Central nervous system*

Clinical features include: drowsiness, irritability, altered sensorium, photophobia, diplopia, neck rigidity, projectile vomiting, hemiplegia, focal neurological deficits and cranial nerve palsies.

These can be broadly divided into two categories:

- **Infective:** These are due to meningitis, encephalitis, extradural and subdural brain abscess and these are usually due to the direct invasion into the cranium. It can occur directly by the cribriform plate, foramen rotundum or the orbits. Features seen include irritability, drowsiness, altered sensorium, photophobia, neck stiffness, focal neural deficits, projectile vomiting and convulsions etc.
- **Thrombo-embolic:** These are due to the vascular complications of mucormycosis which is mainly depends upon the area of the involvement. There may be neural deficits, hemiplegia, convulsions and cranial nerve palsies.
- **Palatal features:**
- **Clinical features include:** Non healing ulcers, necrotic patches, frank eschar, swelling over the hard palate, oro-antral fistula and loosening of teeth.

This occurs due to angioinvasion and compromised vascular supply of the palate. Swelling of the hard palate and alveolar process occurs due to marrow edema of the palate.

#### **Investigations and Diagnosis**

##### *Potassium hydroxide mount:*

The diagnosis of mucormycosis is based on microbiology, radiology and histopathological testing. For microbiology, KOH mount and fungal cultures are done; KOH mount is a primary screening tool and combined with clinical grounds treatment can be started. The specimen collected is transported in normal saline. Once it reaches the laboratory, the specimen is kept over a slide with a drop of 20% KOH. KOH is a strong alkali and it clears the tissue and makes fungal elements prominent. Mucorales can be seen as aseptate hyphae. The results are available within 3-4 hours and as early as an hour however it is merely a screening method as it only talks about the presence or absence of fungal elements and doesn't point towards the species. For that, fungal culture is necessary. Differentiating fungal elements from artifacts requires expertise. Furthermore, specimen may be contaminated [8].

##### *Fungal culture:*

Similar to fungal KOH, the sample for fungal culture is transported in normal saline. It is mounted on SDA (sabourou dextrose agar) and incubated at 25-30°C. Fluffy white, brown or gray colored Colonies appear within 24 to 96 hours. They are further observed under microscope and identification is done based on the presence of aseptate or sparsely septate hyphae and branching if present, at 90° and

spherical sporangium. Lactophenol cotton blue is used for better visualization. Fungal hyphae appear blue as cotton blue dye stains the chitin. Even though diagnostic, low culture positivity rate, heavy inoculum requirement and risk of contamination of sample do not make it a suitable diagnostic tool. Moreover, treatment initiation should not wait for culture results [9].

#### ***Histological examination***

This test distinguishes fungus as pathogen or a contaminant as fungal hyphae can be seen invading blood vessels. The specimen for histopathological examination is sent in formalin. Fungus can be observed in routine H&E and with special stains like PAS and GMS, which help in highlighting the fungal wall. Mucorales are seen as ribbon like aseptate hyphae with few septation. However, diagnosis is based on morphologic testing and can be frequently confused with other fungus species such as aspergillus. The testing may take several days by which the patient may have expired [9].

#### ***Computed Tomography:***

The main role of a CT scan is to know the bony anatomy of the paranasal sinuses and bone involvement. It can also be used as an alternative in patients where performing MRI is not feasible. A contrast enhanced CT scan of paranasal sinus, orbit with brain with axial and coronal sections can be performed. There may be sinus opacification or nodular thickening, infiltration of periantral fat planes indicating extent of the disease and bony erosion. CT can be performed in a shorter span than MRI, is non-invasive and painless. However, MRI is preferred over CT as soft tissue intraorbital and intracranial extension and vascular invasion can be seen better on an MRI [10].

#### ***Magnetic resonance imaging:***

MRI PNS, Orbit and brain is important for evaluation of extent of the disease particularly for intraorbital and intracranial extension [10]. The patient is positioned in supine position. T1 and T2 weighted images with fat suppression and gadolinium contrast are done of which T2 weighted images with fat suppression and gadolinium enhanced scans are very useful. Necrosed portion appears hyperintense on T2 and hypointense with contrast as seen in black turbinate sign. It needs surgical removal; MRI therefore helps in planning of surgical debridement as well.

Diffusion weighted images (DWI) aids in the diagnosis. Angioinvasion by fungus can lead to thrombosis and infarction as in central retinal artery, vessels supplying frontal and parietal lobes. Death of tissue leads to oedema causes diffusion restriction which appears hyperintense. With this even developing infarcts can be diagnosed and prognosis of a patient can be known beforehand.

MRI is contra-indicated in patients with electrical or magnetic implants like cardiac pacemaker, cochlear implants, intracranial aneurysmal clips unless made of MRI compatible, relatively in pregnancy, can't be done in people with an altered renal function test, EGFR should be more than 30 for doing an MRI. It requires a longer time than CT and in few cases the patient may not be cooperative for that much amount of time.

#### **Management Protocol:**

The principles of treatment of mucormycosis are:

##### ***Reversal of immunocompromised state***

It is critical to reverse or prevent the immunocompromised status of the patient. Immunosuppressive dosages or stopped if at all possible. Aggressive treatment to rapidly restore euglycemia and normal acid-base status is critical in diabetics in ketoacidosis. This is an essential part of management, as the continued immunocompromised state blunts the effect of antifungals and also makes the patient vulnerable to residual disease and future recurrences.

##### ***Early initiation of systemic antifungal therapy***

Initiation of systemic antifungal therapy within 5 days after diagnosis of mucormycosis was associated with improvement in survival, compared with initiation of the therapy at >6 days after diagnosis.

##### ***Aggressive Surgical debridement***

Surgical debridement is primarily to reduce fungal load, the removal of devitalized tissue also improves perfusion of systemic antifungals. It further prevents the disease progression and involvement of vital structures.

The most of the patients were between 51-60 years of age, the Average age being 53.4 years, maximum age being 94 years and minimum, 19 years. 64.4% (n=161) patients were males and 35.6% (n=89) were females (Figure 1).

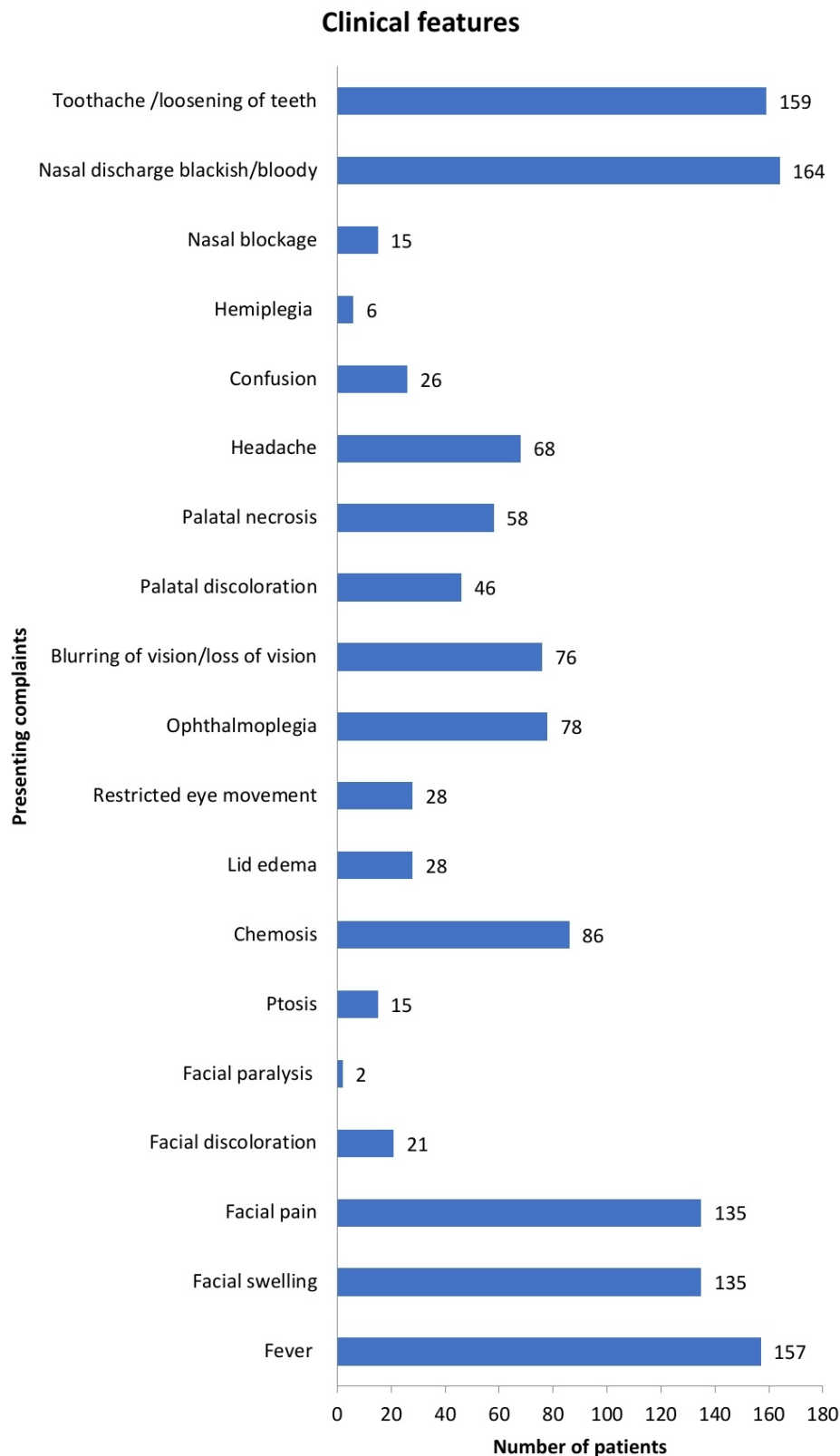


Figure 1: Age distribution

**Clinical Features:**

Fever (62.8%) was seen in 62.8% (n=157). Nasal features included nasal discharge 65.6% (n=164) which tended to be purulent, blackish or bloody, facial pain 54% (n=135), facial swelling 54% (n=135), sinus headache 27.2% (n=68) and nasal blockage 6% (n=15).

Orbital involvement was seen in 31.2% (n=78) of the patients. Ophthalmological features include ptosis 6% (n=15), chemosis 34.4% (n=86), lid edema 11.2% (n=28), restricted eye movements 11.2% (n=28), ophthalmoplegia 31.2% (n=78), impairment or loss of vision 30.4% (n=76).

Palatal involvement was present in 36% (n=90) patients, and causes toothache or loosening of teeth 36% (n=90), palatal necrosis 23.3% (n=58) and palatal ulcers 18.4% (n=46). Involvement of the central nervous system was present in

26.4% (n=66), causes the following features drowsiness 4.3% (n=11), irritability 3.8% (n=10), nausea and vomiting 3.4% (n=9), photophobia 3.4% (n=9), neck rigidity 2.6% (n=7), and hemiplegia 2.4% (n=6) (Figure 2).

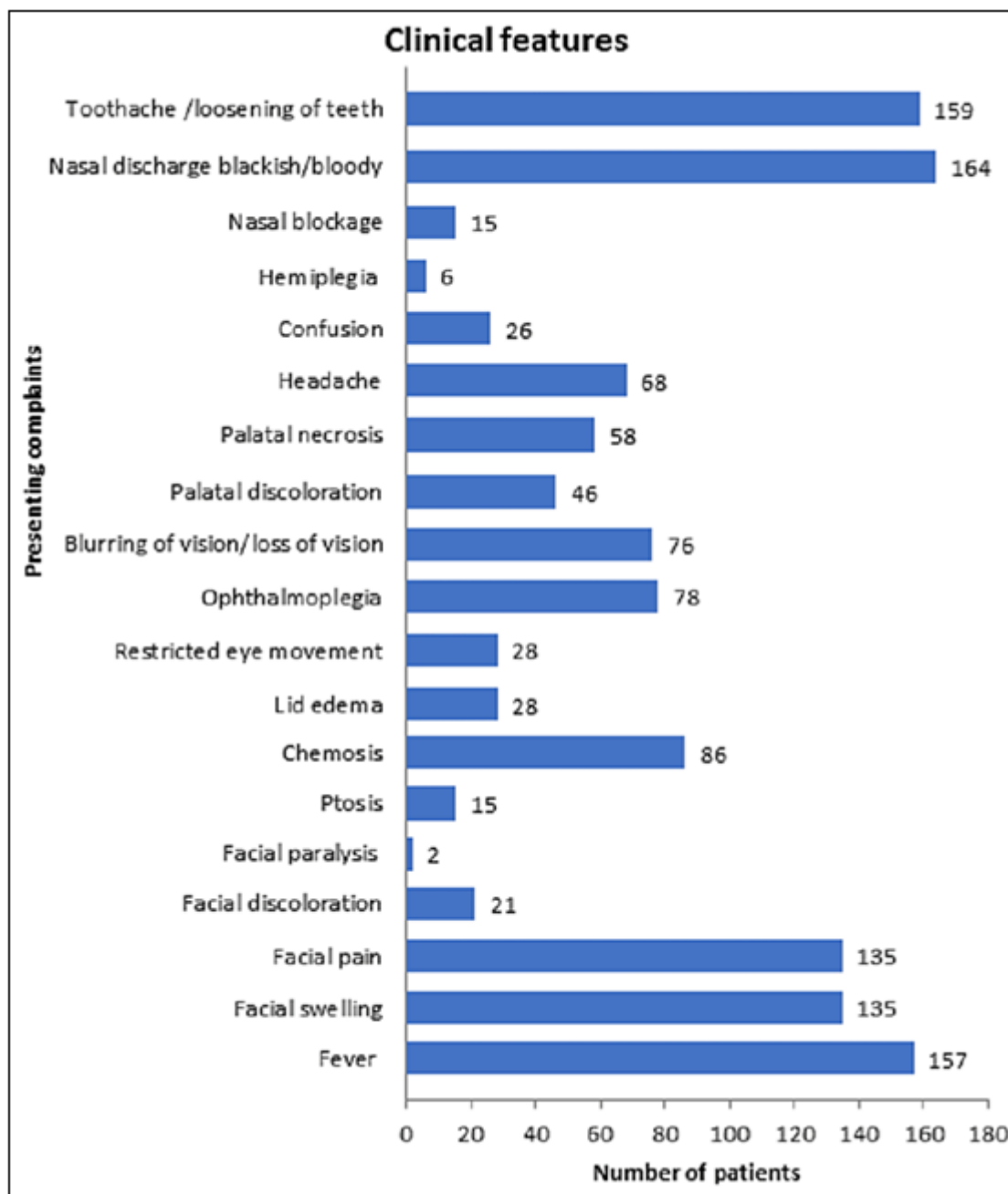


Figure 2: Clinical features

**Investigations:**

Nasal endoscopy showed necrosis in 63.2% (n=158) patients, purulent discharge in 30.4% (n=76) and was normal in 6.4% (n=16) patients.

The potassium hydroxide mount (KOH) was used as a screening tool. Fungal elements were seen in 44.8% (n=112) of the patients on KOH. While histopathology was positive in 80.4% (n=201) of the patients.

MRI was the preferred investigation in our institute, although ideally it should be performed in conjunction with the CT scan of the paranasal sinuses. The MRI is useful for the assessing the extent of the disease and the CT scan is required for the bony anatomy of the paranasal sinuses (Figure 3).

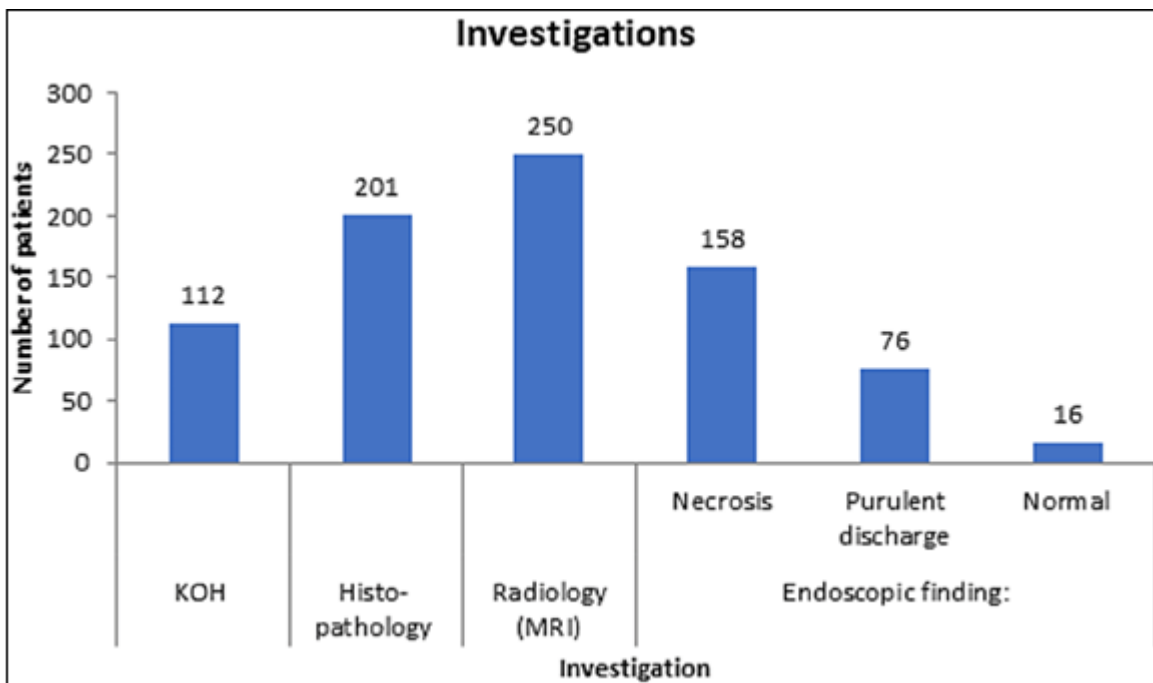


Figure 3: Investigations

The MRI findings showed maxillary involvement in 86% (n=251), ethmoidal in 40% (n=100), sphenoidal in 12.4% (n=31), frontal in 8.4% (n=21), retromaxillary in 28.4% (n=71), pterygopalatine in 27.2% (n=68). Intracranial involvement was seen in 26.4% (n=66) and intraorbital in 16.4% (n=41) patients.

**Co-morbidities:**

Uncontrolled diabetes mellitus, seen in 85.6% (n=214), still remains the most commonly associated co-morbidity. However, COVID-19 infection appears to be an emerging risk factor, as 72.8% (n=182) patients had either recovered from or had active COVID-19 infections. 116 patients (46.4%) had a history of steroid administration. 42.8% (n=107) patients had a history of oxygen administration and 2 patients had other immunosuppressive diseases (Figure 4).

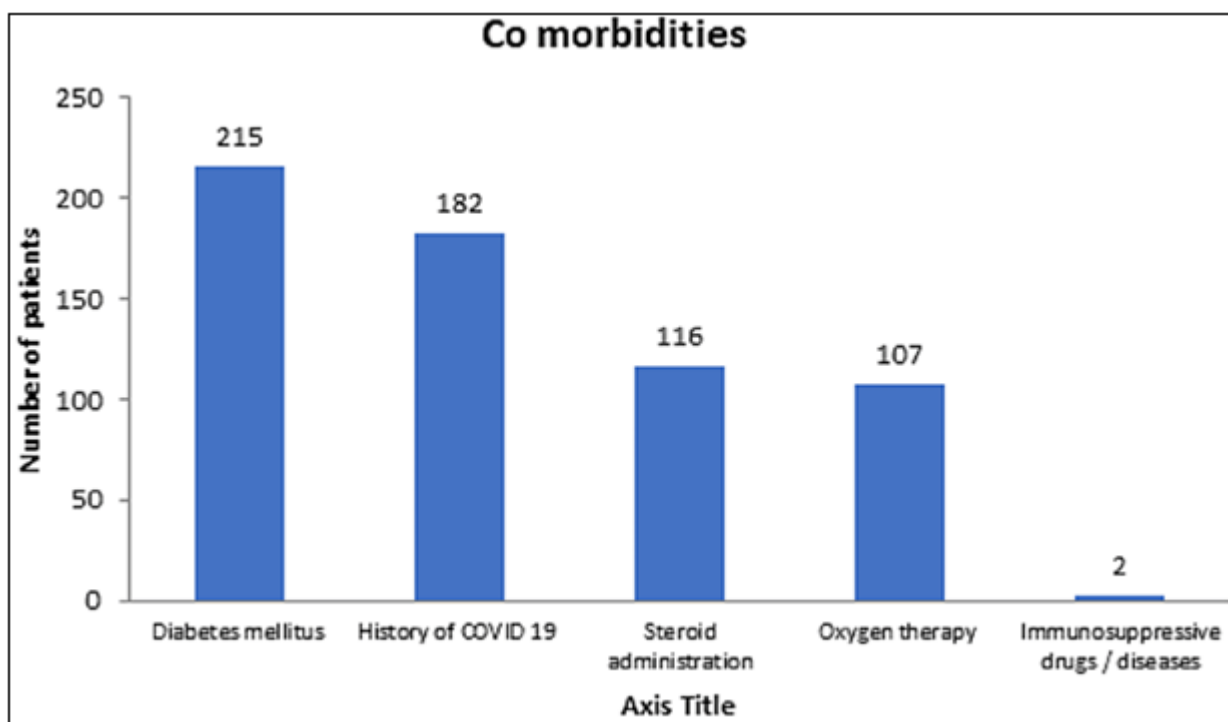


Figure 4: Co-Morbidities

**Management:**

74.2% (n=187) patients underwent surgical intervention, while the 25.2% (n= 63) patients were treated with Injection

Amphotiricin B only. The mortality was much higher in the patients treated with Injection Amphotiricin B only.



Endoscopic partial maxillectomy via Modified Denker's approach was performed in 37.2% (n=93), Endoscopic debridement by sinus surgery was performed in 35.6% (n=89), and external approach by lateral rhinotomy in 0.8% (n=2) patients.

8.4% (n=21) patients had a stay of less than 1 week, 69.2% (n=173) of the patient's required hospital stay of 5 weeks, 18.4% (n=46) patients for 8 weeks and 4% (n=10) patients for more than 8 weeks (Figure 5).

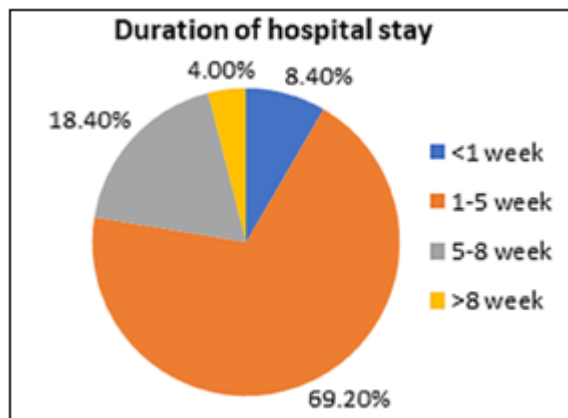


Figure 5: Duration of Hospital Stay

The mortality rate was 38% (n=95), 54 of these were unoperated and 16.4% (n=41) were operated for surgical debridement.

Mucormycosis remains one of the most fatal infections of our times. It is also very rare; the exact incidence remains a matter of some debate. The incidence remains high in India [10]. However, there was an unprecedented increase in the number of cases following the second wave of COVID-19 particularly in India [11].

In our study we found that the most commonly affected age group was between 51-60 years of age, with a male predilection. Most studies had patients who were >50 years of age, while the younger age groups were affected less commonly. This is owing to the fact that the older population has a higher number of associated co-morbidities, mainly uncontrolled diabetes [12]. Other co-morbidities like hematological malignancies, immunosuppressive drugs are also more common on older age groups. However pediatric cases have also been reported, but all of these had some kind of disorders which affected the immune function.

The diagnosis and management of mucormycosis proved to be a challenge, and with the sudden increase in the number of patients, even more so. However, it also provided an opportunity to study the disease and establish management protocol for the same.

History of diabetes mellitus [10-17] and COVID-19 [11] were seen in most of the patients, as was history of steroid administration. It remains to be seen if there is a direct causative association between COVID-19 and mucormycosis, or if it simply because of steroid induced diabetes.

Uncontrolled diabetes by far remains the most commonly associated incriminating factor. In an immune-competent person the infection by these fungi can be warded off by neutrophils, these are however dysfunctional in immune-compromised state. Hence mucormycosis is common in patients with neutropenia or impaired neutropenic function. On the other hand, diseases which primarily affect the lymphocytic functions, like AIDS do not have a particularly increased risk of developing mucormycosis [11].

There was a high index of suspicion for patients with history of COVID-19, diabetes or steroids administration. Thorough history and clinical examination including nasal endoscopy were undertaken. Any suspicious lesion was biopsied and sent for KOH and histopathology. In obvious cases, Amphotericin B was started, without awaiting KOH and histopathology reports.

MRI was the radiological investigation of choice, especially for orbital involvement [17]. MRI is also superior to CT scan for meningeal and cavernous sinus involvement [18]. Ideally MRI should be carried out in conjunction with CT scan for mucormycosis, for identifying the extent of the disease as well as the bony anatomy.

Strict glycemic control is maintained. Medical treatment alone is not sufficient, surgical debridement is necessary in conjunction to it [6, 7].

Surgical debridement should be undertaken as early as possible, and it is imperative to have a recent MR imaging of the patient. Operating without the MR imaging there is a high probability of leaving some disease behind, as it has been observed that the infection spreads even beyond intact bony margins. This is especially true for the retro-maxillary and retro-orbital region. Interdepartmental co-ordination is required in cases with alveolar and orbital involvement. It was however found that most of the cases with early intracranial did not require neurosurgical intervention. Modified Denker's procedure was employed in most of the cases, with satisfactory results. As modified Denker's approach provides excellent exposure intra-operatively and for post operative surveillance.

The number of complications increased greatly due to COVID-19 infection. This has been shown to affect the respiratory reserve and greatly increases the requirement for ventilatory support. Similarly, the mortality rate was increased because of COVID-19 associated complications.

## 2. Limitations of the Study

Since there aren't many studies on mucormycosis, with number of subjects as large as our study, the results cannot be compared adequately. The efficacy of Isavuconazole could not be elicited, as it was difficult to procure because of high cost.

In conclusion in our study, we found that there a definite increase in the incidence of mucormycosis in patients with COVID-19 infection. The most commonly affected population was > 50 years of age, with a male predominance. The most common pre-disposing factor still

remains uncontrolled diabetes, but the corticosteroid administration for treating mucormycosis has also been implicated. Early treatment with antifungal agents and surgical debridement proved to be helpful in improving the prognosis of the patients. Modified Denker's procedure has proved to be very well suited for patients with mucormycosis, as it is an endoscopic procedure but provides very good exposure and clearance of diseased areas. Mortality is greatly increased in patients undergoing medical line of management only. Hence early and aggressive debridement has been advised even in complicated cases and cases with intracranial extension.

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