Mucormycosis outbreak during second wave of COVID-19 in southern India- Clinical and biochemical characteristics from tertiary care hospital

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Abstract

Introduction: The COVID-19 pandemic has been accompanied by a surge in cases of COVID-19-associated mucormycosis (CAM) in India.

Aim: This study aimed to investigate the epidemiological trends, clinical features, risk factors, and outcomes of CAM in a tertiary care center.

Materials and Methods: We conducted a retrospective analysis of CAM cases in our center, focusing on patient demographics, clinical presentations, diagnostic modalities, and associated comorbidities. We also assessed laboratory findings, imaging results, and treatment.

Results: Of the 125 CAM patients, 95 (76%) were male and 95 (76%) were aged between 30 and 60 years. Diabetes mellitus was present in 112 (89.6%) patients and 7 (5.6%) patients were presented with diabetic ketoacidosis. Common clinical presentations included headache in 77 (61.6%), facial pain in 57 (45.6%), and eye pain and swelling in 27 (22.4%). History of steroid therapy and oxygen therapy for COVID-19 management were present in 74 (58.7%) and 52 (41.3%) patients respectively. MRI findings revealed significant mixed organ involvement in 90 (72%) patients with nasal and orbital involvement being the most common in 70/90 (77.7%) patients. In-hospital mortality was observed in 10 (8%) and the cumulative mortality rate after three months was observed in 23 (18.4%) patients.

Conclusion: CAM remains a serious concern during the COVID-19 pandemic, particularly among patients with diabetes and those receiving steroids. Early diagnosis, aggressive treatment, and optimized glycaemic control are crucial in improving outcomes. Efforts should also focus on minimizing the indiscriminate use of steroids and ensuring clean oxygen administration.

Keywords: COVID-19, Mucormycosis, Fungal Infection, SARS-Cov-2, Diabetes Mellitus, Steroid Therapy.

Introduction

Mucormycosis is a relatively rare but life-threatening angio-invasive fungal infection that primarily affects individuals with compromised immune systems. Notably, India has the highest incidence of mucormycosis, with a prevalence of 0.14 cases per 1000 individuals, which is 80 times higher than the global prevalence[1]. The country faced a significant surge in cases during the second wave of COVID-19, with over 51000 reported cases of COVID-19 associated Mucormycosis (CAM) and an estimated mortality rate of approximately 44%[2]. Initially presenting symptoms of mucormycosis often resemble bacterial sinusitis, but the clinical presentation can vary depending on the site of infection. During the CAM outbreak in India, rhino-orbital mucormycosis and rhino-orbito-cerebral mucormycosis were the most frequently observed forms of CAM[3]. The increase in CAM cases during the second COVID-19 wave in India is believed to be the result of multiple contributing factors that require further investigation through scientific research. Factors such as diabetes, the indiscriminate use of steroids and unconventional COVID-19 treatments, extended periods of mechanical ventilation, and the

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use of humidifiers are suspected to have played a role in the surge of CAM cases in India[4]. The high fatality rate associated with CAM is attributed to challenges in timely diagnosis, rapid disease progression, and fatal outcomes. Information concerning the clinical characteristics, features, and management challenges of CAM patients remain limited due to the diversity in disease manifestation and its relatively low incidence compared to other infections. Given the increased prevalence and the serious health risks posed by mucormycosis, this study was undertaken to comprehensively document the clinical features, and the difficulties encountered in diagnosing and managing CAM patients.

Materials and Methods

This study was conducted at a tertiary care center that provided medical care for over 2500 COVID-19 cases, with more than 500 beds allocated for COVID-19 patient treatment during the peak of the pandemic. A retrospective study design was employed for this study. Necessary ethical approval was obtained from the Institutional Ethics Committee (IEC/ 544/ 2021-22).

Individuals diagnosed with mucormycosis between March 2021 and July 2021 were included in the study. All the patients were evaluated for demographic data like age, sex, and COVID-19 status along with their High-Resolution Computed Tomography (HRCT) of the thorax, vaccination status, risk factors like diabetes, steroid and oxygen therapy during their COVID-19 treatment. Clinical symptoms and signs were recorded along with diagnostic nasal and endoscopic findings.

Laboratory parameters for Diabetes like HbA1c to diagnose Old and Denovo diabetes status along with Urine Ketone Bodies (UKB) and acid-based analysis for Diabetic Keto Acidosis (DKA) were also done. Various other parameters like Lactate Dehydrogenase (LDH), Serum Ferritin, D-Dimer, Interleukin 6 (IL-6), C-Reactive Protein (CRP), Human Immunodeficiency Virus (HIV), hepatitis B surface antigen (HBsAg), COVID-19, Immunoglobulin G (IgG), Immunoglobulin M (IgM) antibodies were measured.

MRI paranasal sinus with contrast was done for all the patients along with MRI Brain and HRCT Thorax was done for select cases. All the cases underwent medical and surgical treatment. The Potassium hydroxide (KOH) staining and histopathological report findings were recorded for all the cases who underwent surgery. Follow-up and outcome were measured at one and three months.

Statistical methodology: Categorical variables were expressed in frequency N (%) and continuous variables were expressed as Mean ± SD. One-way ANOVA was used to compare the biochemical parameters between patients with different CAM severity. A p-value <0.05 was considered to be statistically significant.

Results

During the pandemic, our tertiary care center observed 125 COVID-19 patients with mucormycosis. The mean age of the participants was 49.6 ±11.8 years. The demographics of the study population are listed in (Table 1).

Table 1: Patient Demographics

Parameters	Mean ± SD / N (%)
N	125
Age (in years)	49.6±11.8
Age distribution (in years)	
15-20	1 (0.8%)
21-30	6 (4.8%)
31-40	25 (20%)
41-50	37 (29.6%)
51-60	33 (26.4%)
61-70	20 (16.0%)
71-80	3 (2.4%)
Gender	
Male	95 (76%)
Female	30 (24%)
Onset of mucormycosis symptoms following COVID-19 discharge (in weeks)	3.2±1.3
Oxygen received during COVID-19 treatment	52 (41.6%)
Steroids used during COVID-19 treatment	74 (59.2%)
Severity of COVID-19 based on HRCT	
Mild	12 (9.6%)
Moderate	71 (56.8%)
Severe	9 (7.2%)
Status - Vaccinated for COVID-19	Nil
No. of active COVID-19 cases with mucormycosis	5/125 (4.0%)
History of diabetes	112/125 (89.6%)
Newly diagnosed diabetes	52/112 (46.4%)
Pre-existing diabetes	60/112 (53.6%)
UKB	7/113 (6.2%)
DKA	7/125 (5.6%)

UKB: Urine Ketone Bodies; DKA: Diabetic Ketoacidosis; HRCT - High-Resolution Computed Tomography

Nearly three-fourths of the population belonged to the age group between 30 and 60 years with a male preponderance of developing CAM in the cohort (Table 1). The mean onset of mucormycosis occurred typically after 3.2 weeks of COVID-19 diagnosis. In our

study, the mean duration between the initial diagnosis of COVID-19 and the onset of Mucormycosis ranged from 13 to 32 days.

The most common clinical presentation in these patients was headache in 77 (61.6%) patients, followed by facial pain in 57 (45.6%) patients (Fig 1A). Vision obstruction was observed in 27 (21.6%) (Fig 1A) of patients. Nasal endoscopic findings revealed unhealthy mucosa in 87 (69.6%) and crusting in 36 (28.8%) patients (Fig 1B). Palate involvement was observed in 33 (26.4%), with 20/33 (60.6%) of them having unilateral involvement (Fig 1C). Nasal cavity investigations conducted in 35 (28%) patients revealed yellow crustations in 20/35 (57.1%) and black crustation in 15/35 (42.9%) (Fig 1D). Orbital cavity investigations conducted in 76 (60.8%) observed ptosis and lip oedema in 24/76 (31.6%) and 23/76 (30.3%) respectively (Fig 1E).

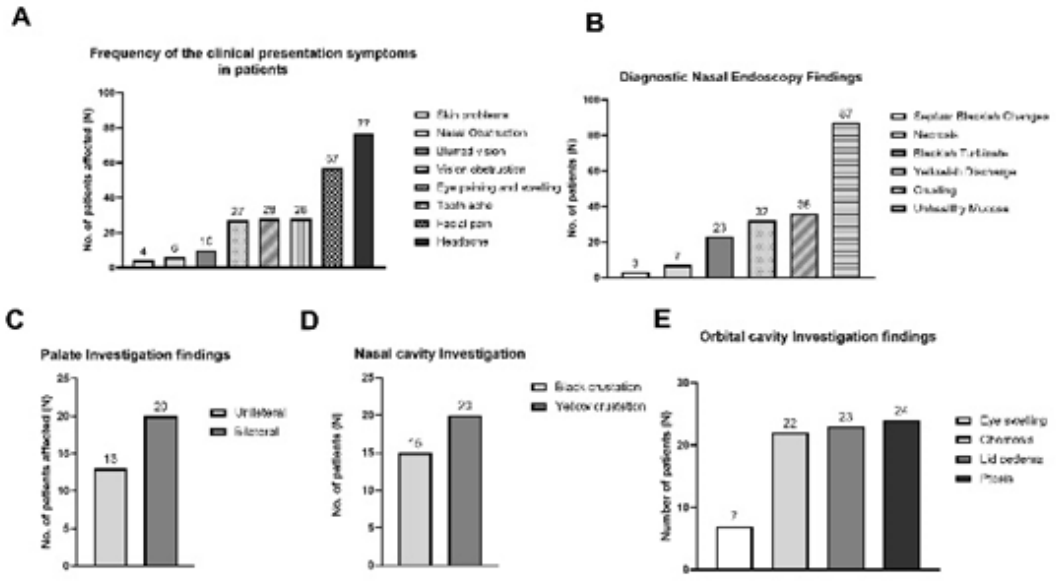

Figure 1 shows the frequency of A) clinical presentations B) Orbital cavity investigation findings C) Palate investigation findings D) Nasal Cavity Investigation E) Diagnostic Nasal Endocopy Findings

Our study on CAM revealed a distinctive distribution of affected organs and organ systems (Fig 2). Mixed organ involvement was observed in 90 (72%) of patients. Nasal and orbital involvement co-occurred in 70/90 (77.7%) and Nasal + Orbital + CNS involvement was observed in 18/90 (20%) of CAM population with mixed organ involvement.

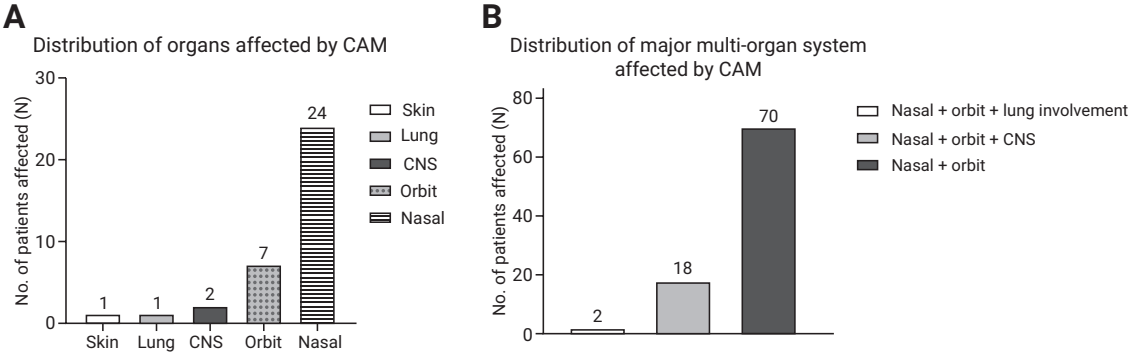

Figure 2:

Figure 2 A) Distribution of organs affected by CAM, B) Distribution of major multi-organ systems affected by CAM

We assessed biochemical parameters (Fig 3) about mucormycosis severity. Elevated levels of inflammatory markers, including D-dimer, serum ferritin, LDH, IL-6, and CRP, were consistently observed upon admission, with higher levels correlating with more severe mucormycosis. Testing for antibody positivity for infections observed that 51 (39.5%) participants tested positive for IgM antibodies and 50 (38.8%) tested positive for IgG antibodies.

One individual tested positive for HbsAg antigen. Biochemical findings revealed that a high proportion of diabetes patients with CAM 75/112 (~67%) (Table 2) had poor glycaemic control.

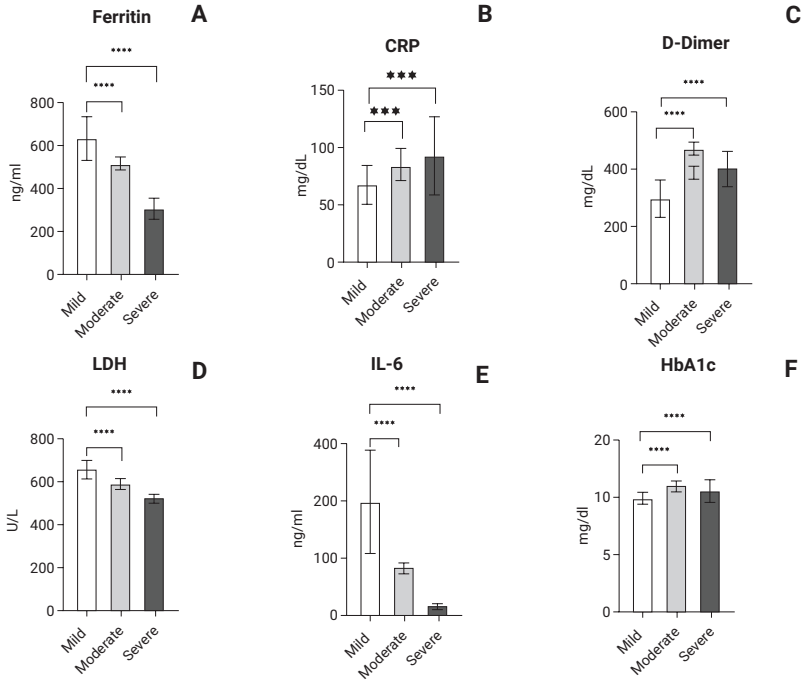

Figure 3:

Figure 3 This figure indicates the levels of A) Ferritin, B) CRP, C) D-Dimer, D) LDH, E) IL-6, and F) HbA1c among patients with mild, moderate and severe CAM.

Table 2: Biochemical findings among COVID-19 patients with mucormycosis

Parameters	Reference range	
Diabetes status		**N (%)**
Prediabetes	**HbA1c:** 5.70 - 6.49%	5 (4.0%)
Diabetes	**HbA1c:** 6.50 - 10.0%	45 (36.0%)
Poor glycaemic control	**HbA1c:** >10.0%	75 (60.0%)
D-Dimer		
Normal	**D-Dimer** ≤ 500.00 ng/mL	87 (69.6%)
Elevated	**D-Dimer** > 500.00	38 (30.4%)
Serum ferritin - Males		
Normal	**Serum ferritin** ≤ 434.00 ng/mL	38 (40.0%)
Elevated	**Serum ferritin** > 434.00 ng/mL	57 (60.0%)
Serum ferritin - Females		
Normal	**Serum ferritin** ≤ 278.00 ng/mL	19 (63.3%)
Elevated	**Serum ferritin** > 278.00 ng/mL	11 (36.7%)
CRP		
Normal	**CRP** ≤ 10.00 mg/dL	12 (9.6%)
Elevated	**CRP** > 10.00 mg/dL	113 (90.4%)
LDH		
Low	**LDH** < 120.00 U/L	10 (8.0%)
Normal	**LDH:** 120-246 U/L	31 (24.8%)
Elevated	**LDH** > 246.00 U/L	84 (67.2%)
IL-6		
Normal	IL-6 ≤ 6.39 pg/mL	11 (8.8%)
Elevated	IL-6 > 6.40 pg/mL	114 (91.2%)

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Table 3: MRI findings among COVID-19 patients with mucormycosis

Sinus involvement	MRI findings	
	Unilateral Sinus Involvement	**Bilateral Sinus Involvement**
	N	**N**
Maxillary sinus	37	92
Ethmoid sinus	40	79
Sphenoid sinus	26	33
Frontal sinus	31	32
Pterygopalatine fossa	10	0
Infra temporal fossa	8	0
Premaxillary tissues	11	0
Parapharyngeal spaces involvement	4	0

MRI findings observed orbital involvement in 90 (70%) of the CAM patients (Table 3).

Table 4: Orbital involvement, Post Op findings and patient outcomes

	N (%)
Orbital involvement	90 (72.0%)
Intracranial involvement	N (%)
Frontal abscess	2 (1.6%)
Focal meningitis	7 (5.6%)
Cavernous sinus area involvement	5 (4.0%)
Infarct	3 (2.4%)
Cribriform plate erosion	5 (4.0%)
Post Op findings	N (%)
Positive for Mucormycetes	90 (72.0%)
Positive for Aspergillus	22 (17.6%)
Mixed with Aspergillus	8 (6.4%)
Mixed with Candida	5 (4.0%)
Patient outcomes	N (%)
During hospital (active) deaths	10 (8%)
Mortality after 3 months	13 (11.3%)
Recovery	102 (81.6%)

HbA1c - Glycated haemoglobin; D- dimer; CRP - C-Reactive Protein, LDH - Lactate Dehydrogenase, IL6, - Interleukin 6; Post-op - Post operation.

Among the 125 patients, 90 (72%) were positive for *Mucormycetes*; 22 (17.6%) were positive for *Aspergillus*; Mucor mixed with *Aspergillus* infection was in 8 (6.4%) and Mucor mixed with *Candida* infection in 5 (4.0%) patients (Table 4).

In-hospital mortality was observed in 10/125 (8%) and mortality rate after three months among discharged individuals was in 13/115 (11.3%) patients. The cumulative mortality rate after three months was at 23/125 (18.4%) (Table 4).

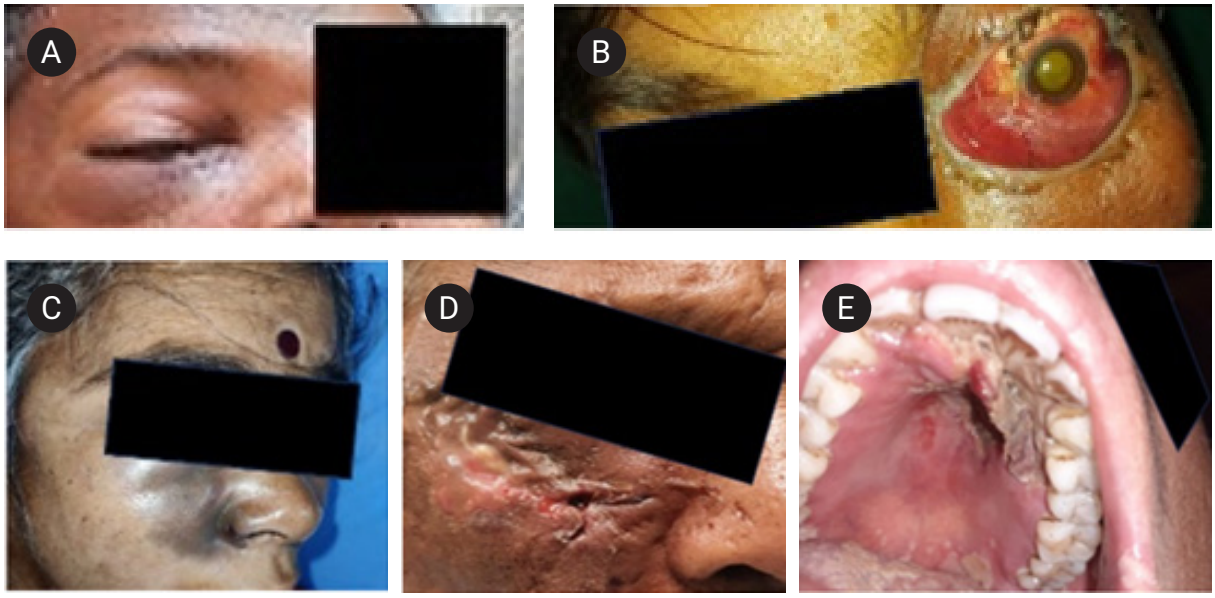


Figure 4 represents the various clinical presentations of Mucormycosis A) Lid Edema B) Chemosis & Proptosis C) Skin discolouration D) Skin ulcer and Sinus discharge, E) palatal ulcer respectively.

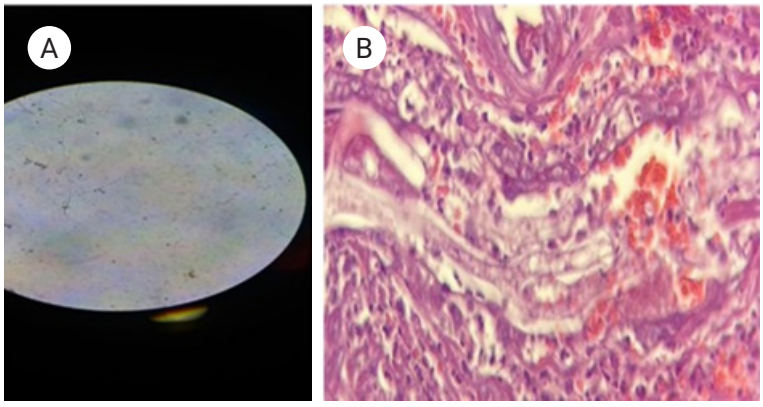
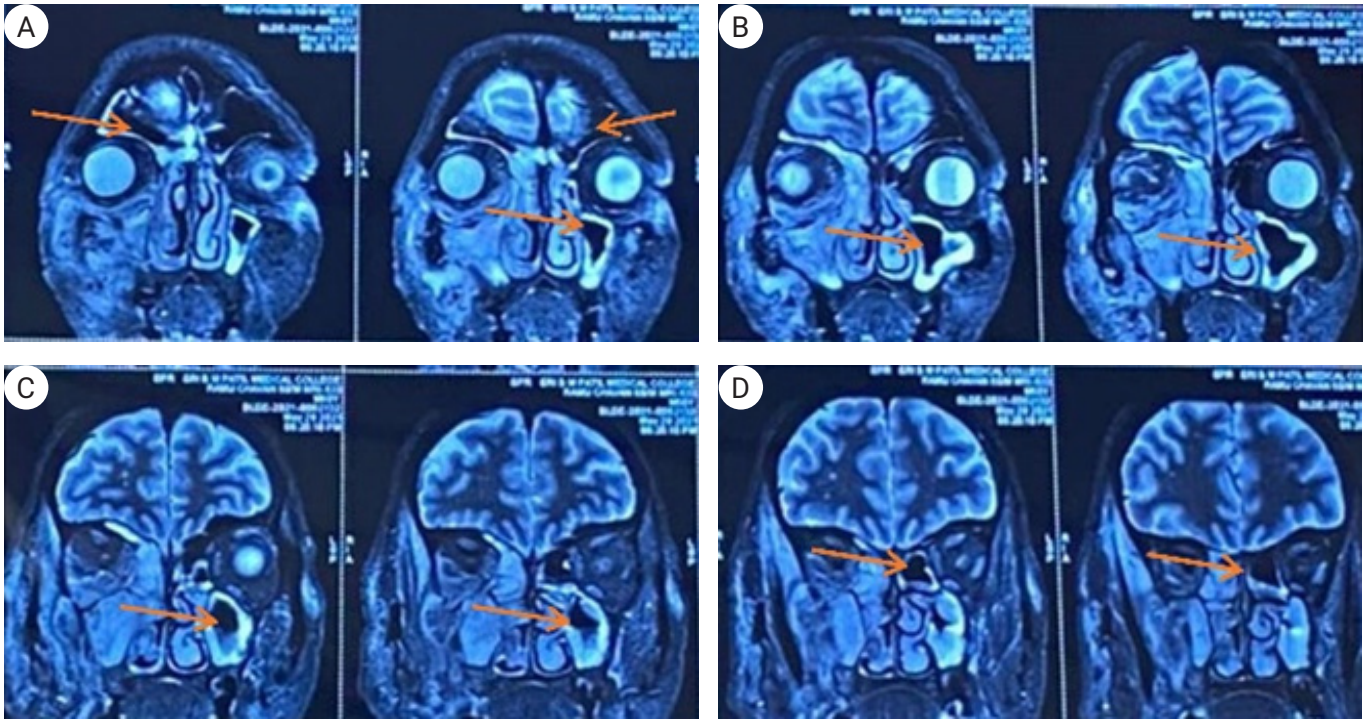
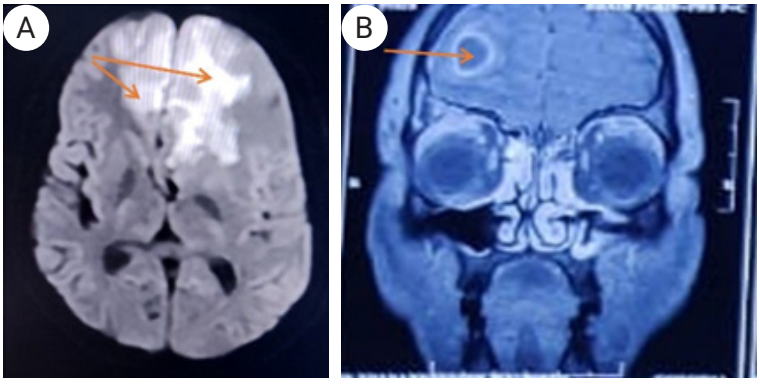


Figure 5 shows the representative images of A) Positive KOH staining B) Positive histopathology for Mucormycosis.



In figure 6, the arrow marks indicate the involvement of A) Right Anterior and posterior Ethmoidal sinus, B) Maxillary sinus, C) Infra orbital area, D) periorbital area and black turbinate.



In figure 7, The arrow marks indicate A) Fronto parietal lobe infarct B) Frontal abscess and ring enhancement.

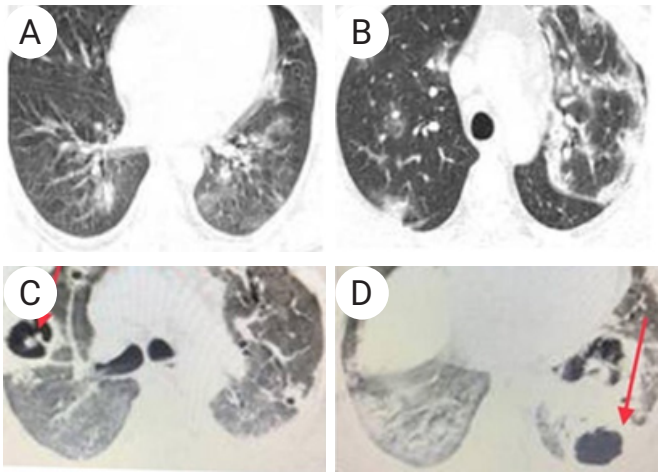


Figure 8 indicates the arrow marks indicate lung involvement in mucormycosis.

Figure 4 represents the various clinical presentations of Mucormycosis including Lid edema, Chemosis & proptosis, skin discoloration, skin ulcer and sinus discharge, and palatal ulcer respectively. Histopathology of tissue samples (Fig 5) from nasal turbinate and sinuses demonstrated tissue necrosis and angioinvasion with vessels thrombosed by non-septate fungal hyphae displaying right-angled branching, which was consistent with Angio invasive Mucormycosis. Figure 6 indicates the representative images of the involvement of rhino-orbital areas in CAM. Figure 7 indicates frontal parietal lobe infarct, abscess, and ring enhancement, while figure 8 indicates the lung involvement in CAM.

Discussion

In this comprehensive study, we aimed to investigate and document the characteristics of Mucormycosis cases within our tertiary care center. Our primary objectives were to elucidate the demographic patterns, clinical manifestations, risk factors, and outcomes of mucormycosis in the context of the COVID-19 crisis.

Throughout the COVID-19 pandemic, our tertiary care institution played a pivotal role in providing extensive healthcare services. During this challenging period, we witnessed a substantial upsurge in Mucormycosis cases. Consequently, our center emerged as one of the recognized referral centers for the treatment of this rare yet life-threatening fungal infection, mucormycosis. Notably, we managed to assemble a significant cohort comprising 125 Mucormycosis cases, recording higher cases than many Indian studies considering a short study duration of 5 months [5,6].

Our study unveiled that the most frequently affected age group among CAM patients was between 30 and 60 years, with the 95 (76%) patients being males. These findings closely parallel those of Nagalli et al. in 2021, which reported similar findings where 89 (77.4%) of the affected population was male, with a mean age of 54.9 years. The high prevalence of uncontrolled diabetes mellitus in India, coupled with the frequent and indiscriminate use of steroids during the COVID-19 pandemic, likely contributed to the elevated incidence of mucormycosis in India during the pandemic[2].

Mucormycosis typically manifested approximately 3.2 weeks after the initial diagnosis of COVID-19. In our study, the mean duration between the initial diagnosis of COVID-19 and the onset of Mucormycosis ranged from 13 to 32 days. This aligns with the findings reported by Nagalli et al., who observed a mean duration of around 16 days between COVID-19 diagnosis and Mucormycosis[7]. Sen and colleagues also found that 44% of patients developed this fungal infection around two weeks after their COVID-19 diagnosis[8]. This pattern of symptom manifestation indicates the need for early screening of opportunistic infections, especially in pandemic situations.

The clinical presentation of Mucormycosis in our study encompassed a variety of symptoms, with the most prevalent complaints being headache in 77 (61.6%), followed by facial pain in 57 (45.6%), eye pain and swelling in 27 (22.4%) and toothache 27 (22.4%). These findings closely resembled findings from another study which indicated that a majority, 35 (74.5%) CAM patients experienced a non-specific localized or generalized headache[9]. Furthermore, Lav Selarka and his colleagues in 2021, which reported that all patients were initially indicative of sinusitis and presented with nasal congestion, with or without discharge[10].

Diagnostic nasal endoscopy examination revealed that 87 (69.6%) patients exhibited unhealthy mucosal changes in the nasal cavity, 36 (28.8%) patients had crusting, and 23 (18.4%) patients displayed blackish turbinate. Septal blackish changes were observed in 3 (2.4%) patients (Fig 1). In our patient cohort, various clinical signs were observed, with nasal and orbital involvement being the most prevalent in 90 (72%) patients (Fig 2A). These results align with previous studies conducted by Nagalli et al. and Chawan et al.[7,11]. In the study by Nagalli et al., clinical signs of mucormycosis predominantly included sinus involvement (79.4%), with the maxillary sinus being the most frequently affected (47.4%). Orbital involvement was noted in 56.7% of patients, and lung involvement occurred in 11.3% of cases. Severe complications observed were cavernous sinus involvement (14.4%) and cerebral issues (12.4%)[7]. Chavan et al. reported clinical presentations of mucormycosis in a cohort where 80% presented with the infection during or within one month of COVID-19. The disease was

classified into stages, with 52% in stage III and 41.3% in stage II. Complications included brain abscesses (5.3%), cavernous sinus thrombosis (8%), facial nerve palsy (4%), and meningitis (1.3%)[11]. A study revealed that the most common DNE findings in the COVID-19 positive group with CAM were black crusts in 52 patients, followed by mucopus in 28 patients, whereas in the COVID-19 negative group, 9 had black crusts and 8 had mucopus. This suggests that nasal discharge and crusting are common presenting symptoms in CAM patients[12]. The presence of black crusts and mucopus could potentially serve as markers for more severe disease progression, necessitating closer monitoring and aggressive management in affected patients.

In the current study, elevated levels of inflammatory markers, including D-dimer, serum ferritin, LDH, IL-6, and CRP, were consistently observed upon admission especially among those with severe CAM (Fig 3). These results are consistent with a study conducted by Goddanti et al. in 2021[13], which reported similar findings, including elevated D-dimer levels (mean ± SD - 671.99 ± 52.94) and increased serum ferritin levels (mean ± SD - 461.31 ± 26.38), both exceeding normal ranges. Antibody examination revealed approximately 40% of the population also tested positive for IgG and IgM antibodies.

Histopathology emerged as a valuable diagnostic tool in our study, allowing confirmation of Mucormycosis. Tissue samples showed the presence of thick, non-septated, ribbon-like fungal hyphae invading tissue, leading to tissue necrosis and angioinvasion. Staining techniques such as hematoxylin-eosin, periodic acid-Schiff stain, and Grocott-Gomori's methenamine silver stain aided in distinguishing true infection from colonization. Additionally, the presence of an inflammatory reaction was indicative of infection rather than commensal fungal colonization, as established in prior research[8,13]. Out of our patient cohort, 90 (72.0%) tested positive for *Mucormycosis*, while 8 (6.4%) showed mixed infections with *Aspergillus*, 5 (3.6%) had mixed infections with *Candida*, and 22 (18%) had infections solely attributed to *Aspergillus*. These findings underscore the diversity of fungal infections encountered in CAM cases.

The most prominent risk factors associated with Mucormycosis in our study included diabetes mellitus (both old and newly diagnosed), oxygen therapy, steroid therapy during COVID-19 treatment, and current COVID-19 infection[14]. Diabetes was identified as the major risk factor and present in 89.6% of cases, followed by steroid therapy (58.7%) and oxygen therapy (41.6%). Current COVID-19 infection was observed in five cases, emphasizing the significance of an immunocompromised state as a key risk factor for Mucormycosis. Notably, a majority of patients with diabetes had uncontrolled diabetes, with an average HbA1c level of 10.5%. Diabetic ketoacidosis (DKA) was present in 7 (5.6%) of patients, suggesting uncontrolled diabetes is a pivotal factor in the outbreak of Mucormycosis in India[8]. Intriguingly, a study conducted by Selarka and colleagues[9], involving 47 CAM patients, reported no cases of DKA, despite a substantial portion of their study population having diabetes. This discrepancy in findings may be attributed to various factors such as differences in patient management protocols, variations in the severity and control of diabetes, differing criteria for diagnosing DKA, and potential variations in the timing of CAM diagnosis relative to the onset of diabetes complications. Firstly, the SARS-CoV-2 virus itself has been demonstrated to infiltrate pancreatic beta cells, leading to necroptosis cell death, and metabolic dysregulation. This contributes to the development of new-onset hyperglycemia and poor control of pre-existing diabetes, potentially increasing the vulnerability to Mucormycosis. Secondly, the cytokine storm associated with COVID-19 can induce insulin resistance, further complicating glycemic management. Additionally, the reduction in absolute lymphocytes and T-cells, especially CD4+ and CD8+ cells, linked to SARS-CoV-2 infection can impact the production of critical cytokines involved in the defense against fungal infections, such as interleukins (Interleukin-4, Interleukin-10, and Interleukin-17) and interferon-gamma. Unfortunately, this immune response mechanism appears to be impaired in COVID-19 patients, rendering them more susceptible to opportunistic fungal infections like mucormycosis[8,15-17].

Another significant risk factor identified in our study for the development of CAM was the administration of steroids[18], which were extensively used in the management of COVID-19 pneumonia. Steroid therapy emerged as the second major risk factor. Steroids are known to reduce phagocytic activity and increase susceptibility to invasive pathogens. Moreover, they can worsen glycemic control[19,20], posing a particular challenge when patients require these medications to manage severe COVID-19 pneumonia or acute respiratory distress syndrome (ARDS).

Additionally, oxygen therapy, especially when administered using unclean humidifiers and industrial (non-medical) oxygen sources, was identified as another potential causative factor in our study. Approximately 60% of our study subjects had a history of oxygen support during their active COVID-19 infection. A study conducted by Mainak Banerjee,

and colleagues shed light on the unforeseen use of industrial oxygen during India's second COVID-19 wave as a potential driver of the CAM surge. Factors such as improper sanitization of oxygen cylinders, the absence of clean and distilled water in oxygen humidifiers, excessive steam inhalation, and the use of non-humidified oxygen may have created conditions conducive to the development of Mucormycosis[21].

MRI findings consistently indicated orbital involvement was observed in 90 (72%) patients. In 25 (20%) patients, there was central nervous system (CNS) involvement, with manifestations such as ischemic stroke, carotid-cavernous fistula, cerebral abscess, and cavernous sinus thrombosis. These results align with the research conducted by Lav Selarka et al. in 2021[9], which reported that nearly all patients displayed signs of pan-sinusitis, and a substantial proportion had an extension of the infection beyond the paranasal sinuses, with orbital involvement being the most common. Involvement of the CNS was observed in a smaller subset of subjects.

The overall mortality rate in our study was observed in 10 (8%) patients. The cumulative 90-day mortality was observed in 23 (18.4%) patients. A meta-analysis comprising six studies with a pooled sample size of 52,916 COVID-19 patients, revealed a high mortality rate (29.6% (95% CI: 17.2-45.9%) among CAM patients[22]. Another study reported the mortality rate of mucormycosis in India is in the range of 28-52%[5]. Our study's lower overall mortality rate of 8% and 90-day mortality rate of 18.4% are favorable when compared to these figures. This discrepancy might be attributed to several factors, including early diagnosis and prompt treatment, better glycemic control among diabetic patients, and more cautious use of steroids during COVID-19 treatment in our study population.

The limitations of the current study include missing data due to the retrospective nature of the study and the single center study design limiting the generalizability of the study findings.

Conclusion

The incidence of mucormycosis during the COVID-19 pandemic is on the rise, leading to significant health challenges. Healthcare providers, especially those caring for severely ill COVID-19 patients with uncontrolled diabetes and corticosteroid treatment, should be vigilant for mucormycosis. It's crucial to prioritize strategies for better glycemic control to improve patient outcomes. Swift initiation of antifungal therapy and surgical intervention can enhance survival rates. We should exercise caution in the widespread use of corticosteroids and broad-spectrum antibiotics, reserving corticosteroids for severe COVID-19 cases to minimize the risk of super-infections. Additionally, expediting COVID-19 vaccination, particularly in regions with a high prevalence of diabetes and limited resources, is paramount to prevent extensive outbreaks, complications, and fatalities during the ongoing pandemic.

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