Original Article

Mucormycosis and diabetes in the times of COVID-19: A Mumbai-based observational study

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Abstract

Background: There is a significant increase in the number of mucormycosis cases in the setting of the coronavirus disease 2019 (COVID-19) pandemic. This study was undertaken to understand the clinical profile of such patients and the risk factors associated with increased mortality of this already deadly infection. **Materials and Methods:** A retrospective observational study was conducted by including microbiologically confirmed cases of mucormycosis with the background of COVID-19 infection (COVID-19–associated mucormycosis [CAM]). Data was segregated into those of survivors versus non-survivors and the two groups were analyzed for various risk factors. Early and late CAM were also compared. **Results:** The case fatality rate was 21.73% (5/23 patients). Case fatality in early CAM was 33.3% versus 9.1% in late CAM. Rhino-orbital-cerebral mucormycosis (P = 0.01) and cranial nerve involvement (P = 0.0482) were associated with increased mortality. Diabetes and poor glycemic control were the common factors in all patients. Early CAM patients were more likely to have orbital or cerebral involvement (P = 0.0065). Patients having chronic liver disease had a higher risk of mortality (P = 0.0395). Sequential treatment or concurrent dual drug therapy with a combination of antifungal drugs was independently associated with better survival (P = 0.0395). The average duration of treatment with amphotericin-b required for cure by survivors was 29.05 ± 17.05 days. The average duration of treatment with isavuconazole/posaconazole for survivors was 50.32 ± 25.23 days. **Conclusion:** Early CAM had a higher case fatality rate. Patients had better recovery rates with sequential or dual antifungal treatment. The raised incidence and mortality in the COVID-19 pandemic is probably related to the COVID-19–induced immunosuppression with associated diabetes and excessive use of steroids.

Keywords: COVID-19, COVID-19–associated mucormycosis, mucormycosis

Introduction

An incremental change in the incidence of mucormycosis has been observed in recent years with an increase in the spectrum of susceptible populations. This susceptible population includes not only patients with uncontrolled diabetes, but also patients with a compromised immune system (posttransplant, chemotherapy or malignancy induced, etc.). This rise in incidence has been noticed more so in the Asian continent.[1] The estimated incidence of mucormycosis before the pandemic per million population was different in different continents. The incidence in Europe ranged from 0.2 cases in Denmark to 95 cases in Portugal, whereas it was three cases in the USA and 140 cases per million in India.[1]

White *et al.* from the UK reported a 26.7% incidence of invasive fungal disease in a multicenter prospective cohort of coronavirus disease 2019 (COVID-19) intensive care patients.[2] During the second COVID-19 wave in India, there were numerous reports of mucormycosis infections in patients suffering from or having

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suffered COVID-19 in the recent past (COVID-19–associated mucormycosis [CAM]).[3] Similar to non-CAM, CAM commonly affects the rhino-orbital region, followed by rhino-orbito-cerebral, pulmonary, and then other sites, with cutaneous mucormycosis having an incidence of less than 0.026%.[3]

The present study aims to understand the epidemiology of CAM (early and late CAM), including the incidence of CAM among COVID-19 patients admitted in the institute, risk factors prevalent among the CAM patients, site of infection in CAM, treatment, and outcomes by comparing the survivors with non-survivors. The primary care physician needs to identify CAM patients at the earliest for prompt treatment, keeping in mind the high morbidity and mortality of such patients.

Materials and Methods

Study design and setting

This study, conducted at a tertiary hospital in Mumbai, India, is a retrospective observational study. Data was collected for all confirmed mucormycosis cases among patients afflicted with COVID-19, who reported from December 2020 to June 2021. The study was approved by the Institutional Ethics committee.

Study subjects and definitions

A case of CAM was defined as one having compatible clinical or radiologic manifestations and demonstration of fungi in the tissue or sterile body fluids by microbiological or histopathologic identification [Figure 1a and b] with ongoing or recent history of COVID-19 infection. COVID-19 diagnosis was considered in patients who tested positive by reverse transcription polymerase chain reaction (RT-PCR) or had a positive rapid antigen test or had clinical and radiological findings suggestive of COVID-19 pneumonia along with positive COVID-19 antibodies with no prior history of vaccination.

The incidence of CAM was calculated as the total number of CAM cases admitted at our institution divided by the number of COVID-19 patients treated at our center during the study period. The authors classified CAM cases as early when mucormycosis was diagnosed <14 days after COVID-19 diagnosis and late or post COVID-19 mucormycosis when mucormycosis diagnosis occurred >14 days after COVID-19 diagnosis.

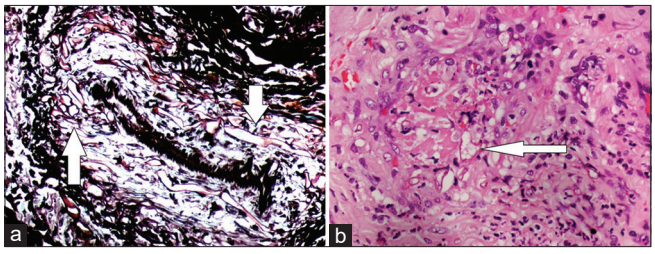

Figure 1: Mucormycosis histopathology images: (a) Grocott's methenamine silver stain showing angioinvasion (arrow) and (b) hematoxylin–eosin stain showing broad aseptate fungal hyphae (arrow)

COVID-19 severity was analyzed as per the COVID-19 treatment guidelines from NIH.[4]

Treatment details

Glucocorticoid use was classified as appropriate when used as per the Recovery trial.[5]

Patients received liposomal amphotericin-b (5 mg/kg/d) or amphotericin-b-deoxycholate (1 mg/kg/d). Oral triazoles were given for variable duration depending on the site of mucormycosis, radiologic resolution, and clinical response. Antifungal therapy was classified as a combination when the patient received two agents, that is, amphotericin-b with any triazole, concurrent when both amphotericin-b and triazoles were used simultaneously, and sequential when triazole was used after amphotericin-b.

Statistical methods

Data was tabulated, and correlation analysis was done for mucormycosis-associated mortality with various risk factor–related variables. Comparative analysis was done by dividing the study population into two groups of survivors and non-survivors.

Microsoft Excel-16 was used for statistical calculations as follows:

a. Chi-square test or Fischer's-exact test was used to test the association of columns and rows in tabular data and in the case of qualitative, categorical data.
b. Two-tailed unpaired *t*-test was used to compare differences between statistical means of quantitative measurements.
c. Pearson's correlation was used to identify any correlation between two variables.

A P value of < 0.05 was considered significant.

Results

During the study period, a total of 24 mucormycosis cases were admitted to our institute. One case was excluded because of no confirmed diagnoses on histopathology or culture or smear. Of the remaining 23, all had CAM, which was confirmed microbiologically or via histopathology. The baseline characteristics of the study population are mentioned in Table 1.

CAM incidence

Four out of 23 patients were admitted to our institute for COVID-19 infection and developed mucormycosis. These four patients were among the 1930 patients admitted for COVID-19 infection at our hospital. Hence, the incidence of CAM was 0.21% for the period from December 2020 to June 2021. The rest of the patients were transferred to our institute from elsewhere or admitted only for CAM.

Timeline of CAM

The timeline of CAM is given in Tables 2 and 3.

Table 1: Comparison of baseline characteristics and comorbidities in CAM survivors versus CAM non-survivors

Parameters	Overall (*n*=23)	Survivors (*n*=18)	Non-survivors (*n*=5)	*P*
Age (in years)	55.69±13.79	56.27±13.14	53.6±17.47	0.7786
Gender	Male (19)	15	4	1
	Female (4)	3	1	
Average HbA1c levels (%)	9.58±2.14 (*n*=21)	9.46±2.22 (*n*=17)	10.1±1.99 (*n*=4)	0.6043
Average highest blood sugar level during admission for mucormycosis (mg/dl)	342.7±85.34 (21)	348.56±77.63 (17)	319.25±122.8 (4)	0.5486
Prevalence of comorbidities (%)				
Newly detected DM during COVID-19 or mucor admission	6	5	1	1
Previously known DM	17	13	4	
HTN	14	12	2	0.348
IHD	2	2	0	1
CKD	2/23	2	0	1
CLD	2/23	0	2	0.0395*

CAM=COVID-19–associated mucormycosis, CKD=chronic kidney disease, CLD=chronic liver disease, COVID-19=coronavirus disease 2019, DM=diabetes mellitus, HTN=hypertension, IHD=ischemic heart disease. *n*=number of participants; **P* is statistically significant

Table 2: Comparison of various prognostic parameters in CAM survivors and non-survivors

Parameters	Overall (*n*=23)	Survivors (*n*=18)	Non-survivors (*n*=5)	*P*
Length of stay for COVID-19–related illness (days)	16.61±14.83	16.72+16.77	16.2+3.77	0.9466
Mean duration from the onset of COVID-19 symptoms to mucormycosis diagnosis (days)	19.78±12.18	20.72±12.40	16.4±12.01	0.4957
Mean duration from the onset of mucormycosis symptoms to mucor diagnosis (days)	12.34±10.42	13.38±10.84	8.6±8.62	0.3760
The average dose of first-day steroids in survivors versus non-survivors (equivalent to dexamethasone in mg)	12.60±7.52	12.6±5.27	12.61±8.164	0.99
Average duration of steroids received (in days)	10.17±4.18	10.16±4.42	10.4±3.65	0.912
Number of patients with early CAM	12	8	4	0.3168
Number of patients with late CAM	11	10	1	
Antifungals in sequence or dual antifungals versus single antifungal only	20	18/18	3/5	0.0395*
Secondary bacterial infections	6	3	3	0.0886
Average lymphocyte count at the time of diagnosis (/ml)	1201.74±571.14	1262.22±598.72	984±441.5	0.0825
Average leukocyte count at the time of diagnosis (/ml)	11,032.608±5074.46	10,065.55±3679.93	14,514±8044.54	0.3470
Average duration of hospital stay in days	25.04±16.13	27.26±16.85	14.5±5.20	0.11
Total duration of treatment in days	59.30±41.88	68.95±39.67	13.5±5.45	0.006*
Average duration of amphotericin-b in days	26.04±17.03	29.05±17.05	11.75±7.27	0.04*
Average duration of isavuconazole/posaconazole in days	41.86±29.59	50.32±25.23	1.75±2.36	0.035*
Need for ICU admission	15	10	5	0.1221

CAM=COVID-19–associated mucormycosis, COVID-19=coronavirus disease 2019, ICU=intensive care unit. *n*=number of participants; **P* statistically significant

Eleven of 23 patients were late CAM cases, while 12 were early CAM cases. Seven out of 11 late CAM patients developed CAM after 1 month. The average duration between the development of COVID-19 infection and symptoms of CAM was 19.43 ± 12.34.

Predisposing factors

Three patients received voriconazole for suspected aspergillosis before developing CAM. All but one patient received steroids. One of the non-survivors had recently been diagnosed with renal cell carcinoma (RCC). Among the survivors, one was a known case of hepatitis-B and one patient had thalassemia minor (not transfusion dependent). Three patients had hypothyroidism.

a. Steroids [Table 2]: Steroids were indicated in 15 patients, but only three patients received steroid treatment (dose and duration) as per the Recovery trial.[5] All three of these patients survived ($P = 1$, Chi-square analysis). Thirteen out of 23 CAM patients received higher than recommended doses and another six patients received steroids for more than 10 days. The average duration of steroids received by these 13 patients was 10.32 ± 3.33. Seven patients received steroids when there was not any indication for it. There was no significant difference in the average duration of steroids between survivors and non-survivors (unpaired *t*-test) [Table 2]. The average first-day starting dose was more than the recommended dose in 78.26% (18/23) of patients.
b. Diabetes mellitus [Table 1]: All patients having CAM were diabetic. Four were diagnosed during admission for mucor treatment. Two were diagnosed during admission for COVID-19 treatment. Seventeen patients were known diabetics. One patient had presented with diabetic ketoacidosis with mucormycosis symptoms after receiving high-dose steroids during admission for COVID-19.
c. Blood sugar control [Table 1]: All patients reported poor control of blood sugar during COVID-19 admission.

Table 3: Comparison of early CAM and late CAM

Parameter	Early CAM (*n*=12)	Late CAM (*n*=11)	*P*
Secondary infections	3	3	1
Average length of stay for COVID-19 (in days)	13.92±11.24	19.54±18.08	0.3763
Average steroid duration (in days)	10.33±3.869	10.09±4.7	0.89
Glycemic control (HbA1c %)	9.31±2.02	9.366±1.79	0.947
Initial steroid dose (equivalent to dexamethasone units, mg)	11.16±6.26	14.85±7.92	0.227
COVID-19 severity (number of patients in each group)			0.225
Mild	0	1	
Moderate	6	2	
Severe	2	5	
Critical	4	3	
ICU admissions for COVID-19	4	6	0.780
Hypoxemia during COVID-19			0.685
Nil	5	3	
Up to 4 l/min	3	2	
Up to 10 l/min	0	2	
NIV/intubation	4	4	
Site of mucor			0.006*
Nasal and paranasal sinus regions	1	7	
Rhino-orbital	5	3	
Rhino-orbital-cerebral	6	0	

CAM=COVID-19–associated mucormycosis, COVID-19=coronavirus disease 2019, ICU=intensive care unit

However, individual readings of blood sugar levels during COVID-19 illness were not available for all patients, but the HbA1c reading of 21 patients was available. Glycemic control during mucor admission was far from adequate [Table 1] (unpaired *t*-test).

d. Only one patient had received injection tocilizumab during COVID-19 infection treatment.
e. The comorbidity profile is presented in detail in Table 1 (Chi-square analysis).

Analysis of COVID-19 severity, hypoxemia, computed tomography severity index for COVID-19–associated lung involvement, and intensive care unit admission in CAM patients

As per the NIH[4] criteria, patients were segregated into mild, moderate, severe, and critical, based on the severity of COVID-19. On analysis, there was no statistically significant association between COVID-19 disease severity, need for intensive care unit (ICU) admission (15/23), and degree of hypoxia in CAM patients and mucormycosis mortality ($P = 0.759$, $P = 0.115$, and $P = 0.55$, respectively, Chi-square analysis).

There was no significant association with computed tomography (CT) severity index on high-resolution computed tomography (HRCT) for COVID-19 lung involvement and mucormycosis mortality ($P = 1$, Chi-square analysis). One patient had COVID-19 associated with Guillain–Barre syndrome and one patient had critical illness neuropathy; both these patients recovered.

Clinical manifestations and site of involvement

The clinical manifestations and site of involvement are presented in Tables 4 and 5.

The nasal and paranasal sinus regions were the most common sites involved in mucormycosis (8/23) [Figures 2a, b, and 3b], followed by rhino-orbital (7/23) [Figures 2a and 3a] and rhino-orbito-cerebral (7/23) regions [Figures 2b and c] and one cutaneous mucormycosis. Our study did not have any case of pulmonary or abdominal mucormycosis. Symptoms of mucormycosis in the study population are described in Table 4 (Chi-square analysis). There was a statistically significant positive correlation between site involvement and mortality, with higher mortality seen in orbital and cerebral involvement ($r = 0.45$, $P = 0.018$) [Table 5] (Pearson's correlation)). Cranial nerve involvement was also observed to have a poorer prognosis ($P = 0.0482$, Chi-square analysis) [Table 4].

Treatment

Liposomal amphotericin-b was used in 22/23 patients. One patient received conventional amphotericin-b (deoxycholate). Posaconazole and isavuconazole were used as step-down/sequential or concurrent therapy in 20/23 patients (concurrent- 11/23 and sequential- 9/23). The remaining two patients received only liposomal amphotericin-b. Patients received amphotericin-b (liposomal or deoxycholate) in a discontinuous fashion either due to lack of availability in the month of May–June or because they had amphotericin-b–induced acute kidney injury. Irrespective of the above, treatment continuation was not disrupted, as an alternative agent was used. Barring one, every patient underwent debridement once only at the start of therapy. One patient succumbed to CAM before debridement took place. Only one patient underwent two sessions of debridement, but at two different sites. This was followed by regular nasal and sinus washings, the frequency of which was decided on a case-to-case basis by the ENT

Table 4: Comparison of survivors and non-survivors for clinical symptoms and radiological site of CAM

Parameter	Overall (*n*=23)	Survivors (*n*=18)	Non-survivors (*n*=5)	*P*
Nasal symptoms	8	8	0	0.1221
Eye symptoms	16	11	5	0.697
Palatal involvement	2	2	0	1
Symptoms of pain in jaw cheek	11	10	1	0.3168
Cranial nerve involvement	5	2	3	0.0482*
Cutaneous symptoms	1	1	0	1
Site of mucor in case of non-cutaneous mucor on MRI				
Nasal and paranasal sinus regions	8	7	1	0.422
Rhino-orbital	9	8	1	
Rhino-orbital and cerebral	6	3	3	

CAM=COVID-19–associated mucormycosis, COVID-19=coronavirus disease 2019, ICU=intensive care unit, MRI=magnetic resonance imaging. *n*=number of participants; **P* statistically significant

Table 5: Correlation of mucormycosis mortality and morbidity with various risk factors

Correlation of mucormycosis mortality and morbidity with various risk factors (Pearson's correlation)	*r*	*P*
The gap between COVID-19 diagnosis and mucormycosis symptoms	0.312	0.147
HbA1c levels	0.303	0.18
Site of mucor involvement (mild- sinusitis, moderate- orbital involvement, severe- cerebral involvement)	0.486	0.01*
Duration of DM in years	0.3955	0.062
Early versus late CAM	0.116	0.95
ICU	0.25	0.24

CAM=COVID-19–associated mucormycosis, COVID-19=coronavirus disease 2019, DM=diabetes mellitus, ICU=intensive care unit. **P* statistically significant

surgeon (this was not so for the two unconscious patients who were also on the ventilator). The endpoint of debridement was to see healthy non-necrotic tissue. In comparison, patients who received dual antifungals (concurrent or sequential) fared better than those who did not receive them ($P = 0.0395$, Chi-square analysis) [Table 2]. However, initiation of therapy with dual versus single agent showed no significant benefit in terms of mortality ($P = 0.3428$, Chi-square analysis) [Table 2]. Three patients underwent orbital exenteration and one patient underwent decompression of the eye for orbital involvement. The average duration of hospital stay and treatment duration is presented in Table 2. The average duration of treatment with amphotericin-b in survivors having nasal and sinus involvement, rhino-orbital involvement, and rhino-orbital and cerebral involvement was 17.29 ± 8.67, 36.63 ± 25.76, and 43.5 ± 2.12 days, respectively. Upon clinical recovery (i.e., improvement in symptoms and signs), amphotericin-b was stopped and treatment was continued with either isavuconazole or posaconazole. The total duration of treatment in survivors with nasal and sinus involvement ($n = 7$), rhino-orbital involvement ($n = 8$), and rhino-orbito-cerebral ($n = 2$) involvement was 49.86 ± 21.57, 85.63 ± 56.41, and 102 ± 0 days, respectively.

The deciding factor for the duration of treatment was the resolution of disease on radiological imaging (magnetic resonance imaging [MRI] scan) and clinical examination via nasal and sinus examination by endoscopy to visualize healthy tissue.

COVID-19 vaccination

Three out of the 18 survivors had been vaccinated with one dose of Covishield vaccine (ChAdOx1 nCoV-19 AZD1222), compared to none in the non-survivors group ($P = 1$, Chi-square analysis).

Discussion

In the present study, the incidence of CAM was 0.21%. This is much more compared to pre-pandemic data, where the incidence was 0.014% in the Indian population.[6] Patel *et al.*[3] reported the incidence of CAM as 0.27% with 187 patients having CAM, which is an almost twofold increase in the incidence of mucormycosis from the previous year in India. Another study had an incidence of 3.36% CAM in hospitalized patients of COVID-19.[7] Chakrabarti *et al.*,[8-10] in three studies, showed an increasing trend of mucormycosis from a single Indian center during successive periods, with an increase in annual incidence from 12.9 cases per year in 1990 to 89 cases per year in 2015.

In the present study, 82.6% of CAM patients were males; this is much more when compared to other studies that reported 74.6%[3] and 46.9%[7] males in their study. The mean age of the present study population was 55.69 years, with 28 years being the age of the youngest and 77 years being the age of the eldest.

Diabetes mellitus was the most common underlying comorbidity for all CAM patients in the present study, with 73.9% of patients being known diabetic patients and the others being newly diagnosed patients. A pre-pandemic study reported diabetes to be present in 77% of mucormycosis patients.[11] There is a possibility that COVID-19 affects the beta cells of the pancreas, hence leading to secondary diabetes mellitus.[12] The possibility of undiagnosed diabetes needs to be considered, given the fact that India is known to be the diabetic capital of the world.[13,14] Furthermore, excess use of steroids for treatment of COVID-19 could be causing secondary diabetes, especially in those already in a state of insulin resistance or pre-diabetes. Of the 26.1% of patients in our study who had newly diagnosed diabetes, only one patient had a glycosylated hemoglobin value of less than 7%. Therefore, the possibility of preexisting diabetes or prediabetes needs to be considered. The average HbA1c was

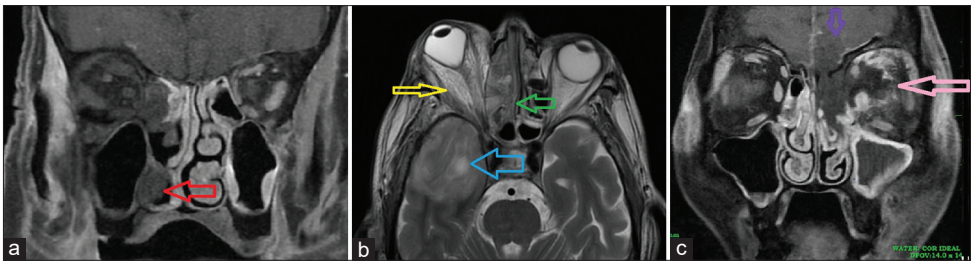

Figure 2: (a) MRI image depicting non-enhancement of inferior turbinate representing black turbinate sign as seen in acute invasive mucormycosis. (b) Heterogenous T2-hyperintense area in the right temporal lobe suggestive of evolving abscess (blue arrow) with extraocular muscle involvement, retro-orbital fat stranding, proptosis, and deformed globe, suggestive of orbital cellulitis (yellow arrow). Right-sided ethmoid air cells have T2-hypointense areas suggestive of fungal sinusitis (green arrow). (c) Image showing infiltration of medial wall of left orbit with extension into orbit with orbital fat stranding (pink arrow) and involvement of extraocular muscles. Non-enhancing left optic nerve with diffusion restriction is seen. The image shows contiguous infection from the sinus cavity into the frontal lobe, indicating destruction of the cribriform plate. Left frontal infarct secondary to the spread of infection via cribriform plate (purple arrow) is seen. MRI = magnetic resonance imaging

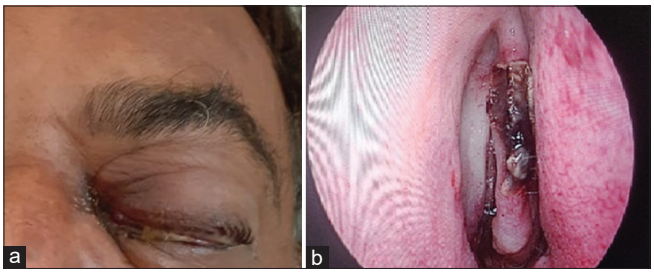

Figure 3: (a) Orbital cellulitis secondary to CAM in one of the patients and (b) FESS image of another patient with infected right middle turbinate. CAM = COVID-19–associated mucormycosis

9.58 ± 2.14, which is similar to the value of 9.06 ± 2.19 as stated by Mishra *et al.*[7]

Two out of 23 patients had chronic liver disease (CLD). One of them was incidentally detected on an HRCT scan for assessing lung involvement of COVID-19 pneumonia. Both the patients succumbed to mucormycosis. Patients with decompensated liver cirrhosis have an increased susceptibility to develop opportunistic infections like rhino-cerebral mucormycosis due to an alteration of neutrophils' chemotaxis and phagocytosis.[15,16] In the present study, presence of CLD was a marker for poor prognosis (P = 0.0395). Case reports point to the fact that mucormycosis carries high mortality in patients with liver cirrhosis despite aggressive treatment.[17]

Among the 23 cases of our study, only three received appropriate duration and dose of steroids as per the Recovery trial.[5] Steroids were indicated in 15 of 23 patients, but 22 of the 23 patients received steroids. Steroid-induced hyperglycemia in a diabetic patient coupled with the immunosuppression produced by steroids can contribute to secondary infection with mucormycosis.[18] However, in the present study, no significant correlation was found between the dose and duration of steroids and the mortality associated with mucormycosis (P = 0.99 and P = 0.912, respectively).

One diabetic patient who did not receive any steroids during COVID-19 treatment still developed rhino-orbital mucormycosis. Although this is a small number, other studies do report CAM in patients who did not receive any steroids; nor did they have any diabetes.[3] The possibility of COVID-19 infection causing immunosuppression by affecting innate immunity is to be kept in mind.[19]

The mean duration of onset of mucormycosis from the onset of COVID-19 was 19.78 ± 12.18 in the present study. A Pune-based study[7] observed that 65.6% of patients (21/32) were late CAM patients. Patel *et al.*[3] noted that 84.27% of patients had late CAM. The present study noted an almost equal number of patients having early and late CAM, that is, 12 and 11, respectively. Both groups were comparable in terms of COVID-19 severity, hyperglycemia, ICU admissions, and steroid duration and dose. Early CAM was more likely to have cerebral and orbital involvement, whereas late CAM was more likely to have disease involving nasal and paranasal sinus regions (P = 0.00615). Further studies will be required to understand the causative factors required to develop early versus late CAM.

The case fatality rate was 21.74% in our study. The case fatality rate in early CAM (33.3%) was higher compared to late CAM (9.1%). COVID-19 severity, lung involvement on HRCT, degree of hypoxemia, and the time interval between COVID-19 and mucormycosis did not seem to impact mucormycosis-associated mortality in our study. Cranial nerve involvement and rhino-orbital-cerebral involvement were associated with poorer prognosis (P = 0.048 and P = 0.01, respectively). Despite early diagnosis and aggressive combined surgical and medical therapy, the prognosis for recovery from mucormycosis is poor.[20] Independent risk factors for mortality include disseminated infection, renal failure, and infection with *Cunninghamella* species.[20] However, in the present study, both patients with chronic kidney disease had a favorable outcome.

Overall mortality from rhino-orbital-cerebral mucormycosis ranges from 16% to 62%, with the best prognosis found in patients with infection confined to the sinuses and the worst prognosis found in patients with cerebral involvement.[20,21] Four out of six patients in the present study having cerebral

involvement succumbed to mucormycosis, that is, our study had a 66.66% case fatality rate for cerebral mucormycosis. Moreover, there was a statistically significant correlation between mortality and orbital and cerebral involvement ($P = 0.01$). Seven of eight patients having nasal and sinus region involvement survived in the present study (12.5% case fatality rate). We believe this patient died due to complications of his comorbidities (RCC and CLD) rather than mucormycosis. Prognosis is improved in cases of nasal and sinus involvement with early surgical debridement, and survival has been reported to be around 91%.[22] The survival rate in the present study is 87.5%, similar to Nithyanandam S *et al* study.[22]

Appropriate and timely antifungal therapy and surgical resection are the cornerstones in mucormycosis management. Debridement of the sinuses is necessary in all cases of rhino-orbital-cerebral mucormycosis, and this was performed for all but one of our patients. The average total duration of treatment in the present study was 59.30 ± 16.13 days. This was much less in non-survivors as most of them were early CAM patients and thus could not complete their treatment before succumbing to CAM. The average duration of hospital stay in the present study was 25.04 ± 16.13 days. However, this does not reflect the total duration of treatment as combination therapy with isavuconazole or posaconazole made it easier to continue treatment post-discharge. The role of combination antifungal treatment in mucormycosis is not supported by evidence.[23] However, in the present study, patients who received concurrent or sequential dual therapy fared better. This finding is corroborated by other studies.[3] We believe this finding would help the primary care physician in decision-making for the treatment.

Limitations and strengths of our study

The present study is a single-center study with limited cases of mucormycosis and may not represent the full picture of the current state of the world. This study did not have adequate cases of mucormycosis before the pandemic to compare CAM with non-CAM. This study did not have non-diabetic CAM patients, nor were there adequate numbers of cases to explore other risk factors. Moreover, we do not have outcomes of CAM at 24 weeks. However, our study provides useful insights into the demographic and clinical profile of CAM. Despite the sample being small, we did a comparative analysis of early CAM versus late CAM. This study also analyzed the total duration of antifungal treatment required by patients having mucormycosis at different sites. To the best of our knowledge, the latter two findings are a novel data not previously published.

Conclusion

The key findings of the study are as follows.

The case fatality rate was 21.73% (5/23 patients) in the present study; there was no change in 2-, 4-, 8-, and 12-week mortality rate. Diabetes with poor glycemic control along with non-judicious steroid use was a common factor in all patients. Early CAM patients were more likely to have orbital or cerebral involvement with a higher (33.3%) case fatality rate than late CAM (9.1%) patients. Patients having CLD or rhino-orbital-cerebral involvement had a higher risk of mortality. The average duration of treatment required by survivors was 68.95 ± 39.67 days. The present study reiterates that sequential or dual drug therapy treatment with a combination of antifungal drugs was independently associated with better survival.

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Conflicts of interest

There are no conflicts of interest.

References

1. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel) 2019;5:26.
2. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, *et al.* A National strategy to diagnose Coronavirus Disease 2019-Associated invasive fungal disease in the intensive care unit. Clin Infect Dis 2021;73:1634-44.
3. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, *et al.* Multicenter epidemiologic study of Coronavirus Disease-associated mucormycosis, India. Emerg Infect Dis 2021;27:2349-59.
4. COVID-19 Treatment Guidelines.nih.gov. About the guidelines: Guideline PDFs; [Updated 2021 Oct 27]. An official website of the National Institutes of health. Available from: https://www.covid19treatmentguidelines.nih.gov/. [Last accessed on 2021 Oct 29].
5. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.
6. Chakrabarti A, Dhaliwal M. Epidemiology of mucormycosis in India. Curr Fungal Infection Rep 2013;7:287–92.
7. Mishra Y, Prashar M, Sharma D, Akash, Kumar VP, Tilak TVSVGK. Diabetes, COVID- 19 and mucormycosis: Clinical spectrum and outcome in a tertiary care medical center in Western India. Diabetes Metab Syndr 2021;15:102196.
8. Chakrabarti A, Das A, Sharma A, Panda N, Das S, Gupta KL, *et al.* Ten years' experience in zygomycosis at a tertiary care centre in India. J Infect 2001;42:261–6.
9. Chakrabarti A, Das A, Mandal J, Shivaprakash MR, George VK, Tarai B, *et al.* The rising trend of invasive zygomycosis in

patients with uncontrolled diabetes mellitus. Med Mycol 2006;44:335-42.

10. Chakrabarti A, Chatterjee SS, Das A, Panda N, Shivaprakash MR, Kaur A, *et al.* Invasive zygomycosis in India: Experience in a tertiary care hospital. Postgrad Med J 2009;85:573–81.
11. Priya P, Rajendran T, Geni V. Mucormycosis in a tertiary care center in South India: A 4-year experience. Indian J Crit Care Med 2020;24:168-71.
12. Müller JA, Groß R, Conzelmann C, Kruger J, Merle U, Steinhart J, *et al.* SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021;3:149–65.
13. Tripathy JP, Thakur JS, Jeet G, Chawla S, Jain S, Pal A, *et al.* Prevalence and risk factors of diabetes in a large community-based study in North India: Results from a STEPS survey in Punjab, India. Diabetol Metab Syndr 2017;9:8.
14. Pandey SK, Sharma V. World diabetes day 2018: Battling the emerging epidemic of diabetic retinopathy. Indian J Ophthalmol 2018;66:1652-3.
15. Pellicelli AM, D'Ambrosio C, Villani R, Cerasari G, Ialongo P, Cortese A, *et al.* Liver cirrhosis and rhino-orbital mucormycosis, a possible but rare association: Description of a clinical case and literature review. Brazilian J Infect Diseases 2009;13. doi: 10.1590/S1413-86702009000400015.
16. Fiuza C, Salcedo M, Clemente G, Tellado JM. *In vivo* neutrophil dysfunction in cirrhotic patients with advanced liver disease. J Infect Dis 2000;182:526-33.
17. Elsiesy H, Saad M, Shorman M, Amr S, Abaalkhail F, Hashim A, *et al.* Invasive mucormycosis in a patient with liver cirrhosis: Case report and review of the literature. Hepat Mon 2013;13:e10858.
18. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021;15:102146.
19. Gangneux J-P, Bougnoux M-E, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: We should be prepared. J Mycol Med 2020;30:100971.
20. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, *et al.* Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 2005;41:634–53.
21. Kumar M, Poovazhagi V, Anbalagan S, Devasena N. Rhino-orbito-cerebral mucormycosis in a child with diabetic ketoacidosis. Indian J Crit Care Med 2014;18:334-5.
22. Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. Indian J Ophthalmol 2003;51:231-6.
23. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Chen SC-A, *et al.* Contemporary management and clinical outcomes of mucormycosis: A systematic review and meta-analysis of case reports. Int J Antimicrob Agents 2019;53:589-97.