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Risk factors for COVID-19 associated mucormycosis in India: A case control study

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic had led to an increase in a surge of mucormycosis in COVID-19 patients, especially in India. Diabetes and irrational usage of corticosteroids to treat COVID-19 were some of the factors implicated for COVID-19-associated mucormycosis (CAM). We designed this case-control study to identify risk factors for mucormycosis in COVID-19 patients. The study was conducted at a private tertiary care center in western India. Data were extracted from records of COVID 19 patients (January–May 2021) and divided into two groups: Those with proven or probable mucormycosis, and those without mucormycosis with a ratio of 1:3. A binary logistic regression analysis was done to assess potential risk factors for CAM. A total of 64 CAM and 205 controls were included in the analysis. Age and sex distribution were similar in cases and controls with the majority of males in both the groups (69.9%) and the mean age was 56.4 (±13.5) years. We compared the comorbidities and treatment received during acute COVID-19, specifically the place of admission, pharmacotherapy (steroids, tocilizumab, remdesivir), and the requirement of oxygen as a risk factor for CAM. In a multivariate analysis, risk factors associated with increased odds of CAM were new-onset diabetes (*vs.* non-diabetics, adjusted odds ratio [OR] 48.66, 95% confidence interval [CI] 14.3–166), pre-existing diabetes (*vs.* non-diabetics, aOR 2.93, 95%CI 1.4–6.1), corticosteroid therapy (aOR 3.64, 95%CI 1.2–10.9) and home isolation (*vs.* ward admission, aOR 4.8, 95%CI 2–11.3). Diabetes, especially new-onset, along with corticosteroid usage and home isolation were the predominant risk factors for CAM.

Lay Summary

This study revealed new-onset diabetes, pre-existing diabetes, corticosteroid therapy, and home isolation as risk factors for COVID-19-associated mucormycosis. Avoiding the use of corticosteroids in non-severe COVID-19 disease coupled with proper blood sugar monitoring and control will help to reduce the CAM burden.

Keywords: mucormycosis, COVID-19 associated mucormycosis, risk factors of mucormycosis, SARS CoV-2, diabetes

Introduction

The incidence of mucormycosis has been increasing globally over the last 2 decades, notably in European countries (France, Switzerland, Belgium), the USA, and India.[1] The rise in incidence has been attributed to the growing population of solid organ transplants, hematologic malignancies, and diabetes. The estimated prevalence of mucormycosis is 14 cases per 100 000 population in India, which is nearly 70 times higher than the global burden.[2]

Diabetes remains the predominant risk factor for mucormycosis in India.[2,3] COVID-19 pandemic led to a surge of mucormycosis cases in COVID-19 patients, especially in India.[4–7] Diabetes and irrational corticosteroid usage in managing COVID-19 have been implicated for COVID-19 associated mucormycosis (CAM).[5,6,8] Several published reports have described the risk of new-onset diabetes and uncontrolled hyperglycemia in those with pre-existing diabetes during acute COVID-19.[9,10] Corticosteroids are lifesaving drugs and are recommended by the World Health Organization (WHO) for the treatment of COVID-19 patients with hypoxia. Apart from worsening hyperglycemia, corticosteroid usage can also affect neutrophil/macrophage functions thus contributing to increasing the risk of mucormycosis.[11,12] Besides corticosteroids, COVID-19 patients may have been given additional immunosuppressive agents like tocilizumab or baricitinib to treat the cytokine storm. So far, though, we don't have any evidence that the use of these immunosuppressive agents can increase the risk for mucormycosis.[6] Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) virus is itself known to produce significant immune dysregulation affecting both the innate and adaptive immune systems. A dysfunctional innate immune system may facilitate tissue invasion and angioinvasion by mucorales.[13]

Hyperglycemia, new-onset and worsening of pre-existing diabetes, indiscriminate corticosteroid usage, and immune dysregulation could be COVID-19-specific factors that could

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provide a fertile ground for mucormycosis in these patients, in a high-burden country like India. We designed this case-control study to identify risk factors for mucormycosis in COVID-19 patients.

Methods

Research question: To identify risk factors for COVID-19-associated mucormycosis.

Study design and setting: We conducted this case-control study at a private tertiary care center in western India. Data were extracted from records of COVID 19 patients (January–May 2021) and divided into two groups: (1) Those with proven or probable mucormycosis. (2) Those without mucormycosis with a ratio of 1:3.

Case definition and eligibility: We defined proven mucormycosis in a patient with compatible clinical and radiological features and direct microscopic examination of tissue/sterile material showing typical hyphae of Mucorales and histopathological examination showing invasive hyphae in the tissues with or without positive fungal culture. Probable mucormycosis was defined as patients with direct microscopy from a sputum/BAL or Mucorales culture-positive from sputum/BAL/sinus tissue without histopathological evidence. We also categorized cases with histopathology showing characteristic fungal hyphae without direct microscopy or culture patients as probable mucormycosis.

Source population: Patients admitted to the private tertiary care hospital for treatment of acute COVID-19 and/or post COVID-19 medical complications (Controls) or CAM (Cases) were enrolled for this study. COVID-19 diagnosis was arrived at by positive reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen testing from respiratory specimen. Adult patients aged >18 years diagnosed with CAM were categorized as cases and recovered COVID-19 cases without mucormycosis were taken as controls.

Patients' demographic data comorbidities, treatment received for acute COVID-19 including the need for oxygen, ICU/ward treatment, immunosuppressant used (steroids and tocilizumab) were recorded. In CAM cases, clinical profile including site of mucormycosis, diagnostic modalities, and treatment for mucormycosis were retrieved from hospital records and entered in a structured case report form.

Treatment procedures for CAM: Liposomal Amphotericin B (L-AmB) 5 mg/kg or amphotericin B deoxycholate (D-AmB) 1 mg/kg was used as induction therapy for 4–6 weeks to treat CAM patients followed by tablet posaconazole 300 mg twice a day loading dose followed by 300 mg once a day or tablet isavuconazole 200 mg three times a day for 2 days followed by 200 mg once a day as a step-down therapy. Patients who are intolerant to L-AmB/D-AmB were stepped down to oral posaconazole or isavuconazole during induction treatment. CAM patients diagnosed in the month of May 2021 received erratic induction therapy because of the non-availability of amphotericin preparations. Erratic induction treatment for mucormycosis was described for patients who received a few days of L-AmB or D-AmB and started on tablet posaconazole or isavuconazole. Again, after a few days, once L-AmB or D-AmB was available, patients received combination therapy with either posaconazole or isavuconazole along with amphotericin preparation. We stopped oral agents, once the amphotericin supply was ensured and restarted at the end of completion of 4–6 weeks of amphotericin.

Table 1. Site of infection, diagnostic modalities, species distribution and treatment of CAM cases.

Site of disease	N = 64
Paranasal sinus	35 (54.7%)
Paranasal sinus with upper jaw	10 (15.6%)
Paranasal sinus with skull base	5 (7.8%)
Rhino-orbital-cerebral mucormycosis	5 (7.8%)
Rhino-orbital mucormycosis	4 (6.2%)
Pulmonary	5 (7.8%)
Diagnostic modalities	
Direct microscopy (KOH preparation)	54 (84.4%)
Culture	40 (62.5%)
Histopathology	59 (92.2%)
Mucorales species (n = 40)	
Rhizopus arrhizus	23 (57.5%)
Rhizopus microspores	3 (7.5%)
Rhizopus species	4 (10%)
Cunninghamella	1 (2.5%)
Mucorales	9 (22.5%)
Treatment	
Liposomal Amphotericin B	49 (76.6%)
Amphotericin B deoxycholate	12 (18.8%)
Posaconazole	34 (53.1%)
Isavuconazole	6 (9.4%)
Sequential antifungal*	35 (54.7%)
Sinoscopic debridement	52 (81.3%)

*Sequential antifungal is defined when patient initiated with amphotericin B and followed by oral azole (posaconazole or isavuconazole) treatment.

Statistical analysis: Continuous variables were expressed as mean (standard deviation) and the difference between the two groups was assessed using a two-tailed independent sample *t*-test. Categorical variables were described as proportions and compared using the Chi-squared test. Odds ratios were calculated for binomial variables from contingency tables and from univariate regression for continuous variables. Potential risk factors included in binary logistic regression using the backward LR method were age, sex, diabetes mellitus, cardiovascular disease, renal disease, corticosteroid use, tocilizumab, remdesivir, place of admission, and oxygen therapy. We considered the level of significance at 0.05. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 26.0.

This study received institutional ethics clearance vide letter SHEC/AP/Mucormycosis study/212-2021.

Results

A total of 77 cases admitted with a diagnosis of proven and probable CAM were enrolled in the study as cases and 261 COVID-19 cases admitted during the same time and had recovered without mucormycosis were selected as controls. We excluded 13 CAM cases and 56 controls from analysis because of incomplete data. So, a total of 64 cases and 205 controls were included in the final analysis. Out of 64, 52 had proven and 12 had probable mucormycosis. The distribution of the CAM cases as per the site of mucormycosis, diagnostic modalities, species, and treatment is described in Table 1.

The mean duration of CAM diagnosis after COVID-19 was 23.43 ± 9.3 days (range: 5–50 days). Majority of the cases (92.2%) had paranasal sinus (PNS) involvement. Further distribution of site of involvement is

Table 2. Demographic, comorbidities and acute COVID-19 treatment profile of CAM and Controls.

	Total (N = 269, n (%)	CAM (N = 64) n (%)	Controls (N = 205) n (%)	*P*-value	Odds Ratio (95% CI)
Age*	56.4 ± 13.5	55.7 ± 11.9	56.6 ± 14	.62	0.99 (0.97–1)^
Female	81 (30.1)	14 (21.9)	67 (32.7)	.119	1.73 (0.9–3.4)
Male	188 (69.9)	50 (78.1)	138 (67.3)		
Comorbidity (other than DM)	166 (61.7)	38 (59.4)	128 (62.4)	.662	0.88 (0.5–1.6)
Diabetes	123 (45.7)	48 (75)	75 (36.6)	<.001	5.2 (2.8–9.8)
Known case of DM	94 (34.9)	26 (40.6)	68 (33.2)	.295	1.38 (0.8–2.5)
Newly diagnosed DM	29 (10.8)	22 (34.4)	7 (3.4)	<.001	14.82 (5.9–36.9)
Cardiovascular diseases	151 (56.1)	36 (56.3)	115 (56.1)	.999	1 (0.6–1.8)
Lung disease	10 (3.7)	0	10 (4.9)	.124	
Renal disease	17 (6.3)	3 (4.7)	14 (6.8)	.77	0.67 (0.2–2.4)
Home isolation	34 (12.6)	17 (26.6)	17 (8.3)	<.001	4 (1.9–8.4)
Admitted to ward	183 (68)	43 (67.2)	140 (68.3)	.983	0.95 (0.5–1.7)
Admitted to ICU	52 (19.3)	4 (6.3)	48 (23.4)	.002	0.22 (0.1–0.6)
Oxygen therapy	140 (52)	34 (53.1)	106 (51.7)	.957	1.06 (0.6–1.9)
No supplemental Oxygen	129 (48)	30 (46.9)	99 (48.3)	.078	
Low flow devices	98 (36.4)	29 (45.3)	69 (33.7)		
High flow therapy	42 (15.6)	5 (7.8)	37 (18)		
Systemic steroid	224 (83.3)	58 (90.6)	166 (81)	.085	2.27 (0.9–5.6)
Remdesivir	213 (79.2)	44 (68.8)	169 (82.4)	.022	0.47 (0.2–0.9)
Tocilizumab	24 (8.9)	2 (3.1)	22 (10.7)	.078	0.27 (0.1–1.2)

*(Mean ± SD), ^Univariate logistic regression

shown in Table 1. Pulmonary mucormycosis was diagnosed in five patients, of which four had probable mucormycosis (Sputum or BAL showed fungal hyphae with or without culture positive). A total of 15.6% of CAM patients had mixed fungal infections (one had *Acremonium* species and the rest all had *Aspergillus* coinfection). *Rhizopus species* (75%) were the commonest species isolated. In all, 22.5% and 10% of cultures reported *Mucorales* and *Rhizopus species* but further identification was not performed.

Treatment: Majority (76.6%) of patients received liposomal amphotericin B (L-AmB) for their initiation treatment, and 18.8% received amphotericin B deoxycholate (D-AmB). A total of 19 (29.7%) CAM patients in the month of May 2021 received erratic induction therapy because of a shortage of antifungal agents. In all, 54.7% of cases received oral posaconazole or isavuconazole after 4 weeks of induction treatment with amphotericin. 52 (81.3%) CAM cases underwent sinoscopic debridement. The outcome in CAM patients (n = 64) was assessed at 12 weeks and categorized as a clinical improvement (60.9%), disease progression (7.8%), death (4.7%), and loss to follow-up (26.6%). The respective outcomes were assessed against the two treatment modalities: amphotericin monotherapy (44%, 8%, 8%, 44%) and sequential therapy of amphotericin followed by posaconazole/isavuconazole (73%, 8%, 5%, 14%). The difference in outcomes across the two therapies was significant (Fisher's $P = .033$).

The demographic data, comorbidities, and COVID-19 treatment profile of the cases and controls are shown in Table 2. Age and sex distribution were similar in cases and controls. Majority were males and the mean age was 56.4 (±13.5) years. The proportion of cases with diabetes mellitus was significantly higher among cases as compared with controls ($P < .001$) and associated with a 5.2 (95%CI: 2.8–9.8) times higher odds for CAM. Newly diagnosed diabetes was significantly higher in the CAM cases (34.4%) as compared with controls (3.4%) ($P < .001$) and significantly associated with CAM with OR of 14.8 (95%CI: 5.9–36.9). Prevalence of any other comorbidity was similar among cases and controls. For the treatment of acute COVID-19, 73.5% of home isolated and 84.7% of indoor (both ward and ICU) patients had received corticosteroids.

Table 3. Multivariate analysis of risk factors for CAM.

	Adjusted Odd's Ratio	95%CI	*P*-value
Diabetes mellitus			<.001
No DM	Reference		
New DM	48.66	14.3–166	<.001
Known case of DM	2.93	1.4–6.1	.004
Type of admission			.032
Ward admission	Reference		
ICU admission	0.11	0.03–0.4	.002
Home isolation	4.8	2–11.3	<.001
Steroid therapy	3.64	1.2–10.9	.021

Diabetes was more common in home isolated (58.8%) as compared with indoor patients (43.8%). Multivariate analysis of risk factors and adjusted OR are described in Table 3.

We compared the treatment received during acute COVID-19 illness, specifically the place of admission, pharmacotherapy (steroids, tocilizumab, remdesivir), and requirement of oxygen for any impact on CAM. The selection of hospital-based controls led to a higher proportion of hospital-based prior COVID-19 management among controls, while a higher proportion of CAM cases had received treatment at home. The odds of CAM among home isolated patients were high (OR 4, 95%CI: 1.9–8.4). Patients who received oxygen therapy with a high flow nasal cannula, non-invasive ventilator, or invasive ventilator were categorized into high-flow oxygen group while those who received oxygen by nasal cannula, mask, or non-rebreathing mask were classified into low-flow oxygen group. A higher proportion of controls had required high flow oxygen as compared with cases, but the overall requirement of oxygen therapy was similar among the cases and controls. We analyzed three pharmacological interventions (remdesivir, tocilizumab, and corticosteroids) as risk factors for CAM.

Remdesivir usage was higher among controls (82.4%) as compared with cases (68.8%) and the difference was statistically significant. The odds of developing CAM among those who received remdesivir were 0.47, 95%CI (0.2–0.9) but adjusted odds were not significant (Table 3). A higher proportion of controls used tocilizumab (10.7%) as compared with cases (3%), but this difference was insignificant with an odds ratio of 0.27, 95%CI (0.1–1.2). corticosteroids were used to treat acute COVID-19 in 83.3% of the study patients. No significant difference in corticosteroid use in CAM (90.6%) as compared with controls (81%) was found in univariate analysis, but the adjusted OR 3.64, 95%CI (1.2–10.9) was statistically significant (Table 3).

In multivariate analysis, diabetes, patients who received home isolation care during COVID-19 and corticosteroid therapy were found to be independently associated with CAM as shown in Table 3. Newly diagnosed diabetes cases had significantly higher odds of developing CAM (34.1, 95%CI: 6.7–174.4), more than patients with pre-existing diabetes (2.93, 95%CI: 1.4–6.1) when compared with non-diabetics. ICU treatment had significantly lower odds for the development of CAM (0.11, 95%CI: 0.03–0.4) whereas home isolation had higher odds (4.8, 95%CI: 2–11.3) as compared with ward admission. Those receiving systemic corticosteroid therapy were at higher odds of developing CAM (3.64, 95%CI: 1.2–10.9).

Discussion

The clinical profile of CAM patients was similar to previously published studies with predominant PNS involvement (92.2%). Noteworthy features in CAM patients were diseases restricted to only PNS (54.7%), PNS with upper jaw (15.6%), and PNS with skull base (7.8%) involvement. This was more common in CAM compared to non-COVID-19 mucormycosis.[2,3] Toothache and loosening of teeth was the presenting feature of patients with upper alveolus involvement. These features are not commonly seen in non-COVID-19 mucormycosis patients.[2,3] Early diagnosis of mucormycosis in patients recovering from COVID-19 illness is a plausible explanation for patients with the limited disease to PNS with a small number of cases having orbital and brain involvement. Apart from early reporting of their symptoms to the treating doctor, Indian media has also been highlighting mucormycosis symptoms widely and alerting patients for any symptoms of mucormycosis. Culture yielded Mucorales growth in 62.5% of our patients. *Rhizopus* was the commonest species identified as a cause of CAM as described in a previous Indian study.[2,3]

Results of this case-control study revealed three risk factors for CAM viz. diabetes, type of admission for COVID-19 management, and corticosteroid therapy. Diabetes and diabetic ketoacidosis are prominent risk factors for mucormycosis in India and other low-middle income countries, while hematological malignancies are the leading cause of mucormycosis in high-income countries.[2,14,15] Diabetes (73.5%) has been reported as a leading risk factor for mucormycosis in a multicenter study on the epidemiology of mucormycosis in India.[2,3] New-onset diabetes has been reported in up to 20.9% of mucormycosis in studies from India.[3,5] In the current study, new-onset diabetes (34.4%) during COVID-19 diagnosis was more significantly associated with CAM as compared with patients with pre-existing diabetes, which is consistent with our previous multicenter study performed during the months of September–December 2020 on COVID-19 associated mucormycosis from India.[5] Possible mechanisms for the new-onset diabetes leading to more mucormycosis are systemic inflammation, cytokine activation and resultant insulin resistance possibly leading to stress hyperglycemia. Direct viral/immune destruction of islet cells with decreased insulin production has also been implicated for new-onset diabetes and poor glycemic control.[9,10] COVID-19 can also act as an infectious trigger that could decompensate and precipitate diabetic ketoacidosis in patients with new-onset diabetes.[16]

The present study found patients who received COVID-19 treatment at home isolation to be having higher odds of developing CAM. This may be because of prolonged hyperglycemia which remained unrecognized as patients may not have an access to frequent glucose monitoring. Corticosteroid usage for COVID-19 treatment would have further aggravated blood sugar levels. Systemic corticosteroid treatment also affects the qualitative function of neutrophils and macrophages, an important first-line defense against the development of mucormycosis and other invasive fungal infections.[11,12] Similarly, hyperglycemia also affects neutrophil function and plays a critical role in the pathogenesis of mucormycosis.[17] Triad of new-onset diabetes/pre-existing diabetes, unrecognized during home isolation COVID-19 care, and worsening glycemic control with corticosteroids in COVID-19 patients provide a fertile microenvironment for the germination and tissue invasion by Mucorales spores. Zero CAM patients during the peak of CAM outbreak were reported from a single center-study from Western India by the implementation of protocol-based corticosteroid usage and strict glycemic control.[18] We did not study SARS CoV-2 itself as a risk factor for mucormycosis as our study was not designed for the same. It is possible that the virus might play a role in increased susceptibility of mucormycosis by increasing the expression of glucose regulated protein 78 (GRP-78) which is used by Mucorales for tissue and angioinvasion.[19,20] The role of GRP78 in the establishment of cellular invasion by viral infections is well described. SARS CoV-2 spike glycoprotein uses host cell ACE-2 and GRP78 receptor to bind and internalize.[20]

Adhesive tapes, wooden tongue spatula, and contaminated linen have all been implicated in healthcare-associated mucormycosis with small hospital outbreaks.[21] During CAM outbreak in India, industrial oxygen, contaminated humidifier, oxygen tubings, and masks used in patients' treatment had been implicated.[8] Our study clearly showed that oxygen therapy received during COVID-19, both high flow and low flow has no association to CAM. Tocilizumab treatment for cytokine release storm in severe COVID-19 was also not associated with CAM in our study, in fact, more controls had received tocilizumab as compared with CAM cases, and this was not statistically significant. There are a few gaps in our understanding of the CAM surge in India. Why only India has reported a high CAM case burden? Why Gujarat, Maharashtra, Rajasthan, Karnataka, Tamil Nadu, Andhra Pradesh, Madhya Pradesh, and Delhi reported high CAM cases as compared with other states of India.[22] One explanation for this differential surge could be differential spore counts in the outdoor and indoor environment. A study conducted before the COVID-19 pandemic and another one after CAM outbreak did suggest a higher outdoor spores count compared with indoor.[23,24] Rooms with window air-conditioner (AC) has higher spores compared with central AC and non-AC rooms in the indoor settings.[24] Another study has also described seasonal variation in the spores count. *Mucorales* spores had been detected at

0.68–1.12 cfu/m^3 in indoor and 0.73–8.60 cfu/m^3 in outdoor air of India with pre-dominance of main pathogenic species *Rhizopus arrhizus*.[24] The most recent multicenter study also has shown variation in the environmental spores count in the different zones of India with highest spores count in the north and south India compared with west and east Indian centre.[23] Further studies looking at COVID-19 specific risk factors, such as GRP78 expressions in PNS tissue of CAM *vs.* non-CAM and healthy patients, COVID-19 associated dysregulation in the innate immune system may help us understand the increased susceptibility of COVID-19 patients to mucormycosis.

Limitations of our study: This is a small single-center study, and multicenter larger studies are needed to validate our findings. CAM cases received treatment of acute COVID-19 treatment elsewhere, including home care under family physicians' supervision, while most controls received treatment at a tertiary care center—there could be a bias here. Study patients' corticosteroid dosage and duration were not analyzed. The study design precludes assessment of SARS-CoV-2 as a risk factor.

Conclusions

New-onset diabetes was the predominant risk factor for CAM in our study with corticosteroid usage and home isolation care for COVID-19 being other important ones for mucormycosis in COVID-19 patients. Clinicians need to adopt a very judicious approach and follow treatment guidelines for COVID-19, especially regarding the use of corticosteroids in non-severe COVID-19 disease. This, coupled with diligent blood sugar monitoring and glycemic control for home-isolated patients will help reduce the CAM incidence.

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Declaration of interest

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