

“MuCovid-21” study: Mucormycosis at an Indian tertiary care centre during the COVID-19 pandemic

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Background Mucormycosis has been reported in several Indian states with the second wave of COVID-19 from January 2021 onwards. This prospective study was conducted with the objective of defining the contribution or association of various known and many suspected factors in the incidence of this disease during the ongoing pandemic.

Method The study included 464 adults with mucormycosis. Basic demographic data were collected. Patient history of COVID infection, its severity, duration of treatment, and oxygen use was taken to assess the association. History of use of antibiotics, steroids, antivirals, biologicals, and other complementary treatments was sought. History of diabetes and other comorbidities was noted. Patients were investigated for mucor confirmation using a nasal swab KOH mount, nasal endoscopy with biopsy, and radiological investigations were done to assess the extent.

Results Out of 464 patients, 175 were known diabetics, and 157 were treated with steroids during COVID infection. Out of 287 post-COVID patients, 125 (44%) had rhino-mucormycosis (RM), 102 (35%) had rhino-oculo-mucormycosis (ROM) and 60 (21%) had rhino-oculo-cerebral-mucormycosis (ROCM). 162 did not have a history of COVID, of which 93 (57%) had RM, 48 (30%) had ROM and 21 (13%) had ROCM.

Conclusion This study has showed that COVID was not the only factor contributing to mucor, rather other factors such as diabetes, steroid use etc. were also contributory. Many patients who were suffering from mucormycosis did not have a history of COVID. Advanced age, ROCM, and ICU admission were associated with increased mortality.

Keywords: RM, ROM, ROCM, diabetes, glucocorticoids, COVID

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Introduction

Mucormycosis is a serious but rare fungal infection caused by mucormycetes (mold). Infection occurs by encountering the fungal spores from the environment. It usually occurs in individuals who have comorbid conditions or immunocompromised conditions. The fungus can enter the skin through cuts, burns, or different type of trauma to the skin. The fungal hyphae invade the blood vessels, causing tissue thrombosis and necrosis in a rapid progression (Figures 1 and 2).¹⁻³

It is rare, affecting around 1.7 people per million population each year. It is more prevalent in India (0.14 cases per 1,000 population), and its incidence is increasing at a greater rate.⁴ Increased incidence of mucor was reported in India after the second wave of COVID from January 2021 onwards.

The sudden surge in cases was unexpected but in many individuals, the cause could easily be explained by diabetes, immuno-suppression with contribution from the COVID virus itself. Simultaneously there were many cases without any obvious pre-disposing factors. Due to the unexpected rise in COVID cases in late January 2021, India registered an increased use of evidence-based, experimental and a few unproven interventions by patients themselves and sometimes by treating physicians to counter this pandemic or the fear associated with it.

The clinical course of COVID were complicated by superadded infections which are more harmful to the patients. The most common superadded infections were bacterial, but the emergence of fungal infections was of major concern. In the early part of the COVID pandemic, less than 1% of secondary

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Figure 1 Shows a patient with right-sided orbital swelling, blackening of right sided face and nose with loss of vision in the right eye, patient had no history of previous COVID infection but was known to have chronic liver disease and alcoholism. **Figure 2** Shows a patient with bilateral orbital swelling with loss of vision, with swelling and tenderness of the bilateral maxillary area and swelling around the forehead, possible fungal extension, diagnosed as ROCM, newly diagnosed diabetes mellitus, with a post-COVID status.



fungal infections were recorded.^{5,6} Comorbid conditions, glucocorticoids and the use of antibiotics were greater than desired clinical dosing, and a lapse in infection control were factors leading to secondary mucormycosis in COVID patients.⁷ Awareness increased among treating physicians and microbiologists after an abrupt rise in the incidence of fungal infection during the second wave of COVID.^{8,9} An analysis done in hospitalised COVID patients reported $\approx 6\%$ fungal infections.¹⁰ An increased incidence of mucor in India was reported from different cities during the second wave of the COVID pandemic. A city in South India reported around 18 cases simultaneously, which raised our concerns about mucormycosis in post-COVID patients.¹¹⁻¹³ Mucormycosis is mainly associated with the immunocompromised status of patients; the most common comorbidity was diabetes but COVID in India provided the necessary ingredient, as India has greater incidence of mucor, this combination of COVID with diabetes led to an abrupt surge of mucor in the country.^{12,14}

This analysis was conducted with the objective of defining the association between COVID and various other factors such as uncontrolled diabetes, the use of more than desired clinical dosing of antibiotics and steroids, and other immune-compromised status. COVID was major part of this analysis.

Methods

Study design

This was an observational study to appraise the various factors which resulted in an abrupt surge of mucormycosis during the COVID-19 pandemic (second wave) in India.

The present analysis was done at a tertiary level post graduate institute in central India, where a separate multidisciplinary team was constituted for treatment of this disease. All adult patients presenting with clinical history, symptoms and signs suggestive of mucor with radiologically and/or microbiologically confirmed cases admitted from 8/5/2021 to 8/7/2021 to clinical departments of our hospital were included in our analysis after taking an informed consent from the patients/attendants.

Participants

Adults presenting with symptoms and signs of facial swelling (unilateral/bilateral), headache, fever, black lesion on the face, nasal bridge or inside the mouth that quickly becomes more severe, sinus congestion, shortness of breath, cough, abdominal pain, delirium, coma were considered. Clinical cases were confirmed by nasal endoscopy findings, KOH stain, histopathology findings and radiological investigations.

Mucormycosis was diagnosed based on clinical findings, KOH stain and histopathology findings showing non-septate hyphae, which are ribbon like and broad based with wide-angle branching and radiological investigations. COVID-19 was confirmed in patients by RT-PCR or rapid antigen test (RAT) from samples taken from the nasopharynx. Individuals presenting with mucormycosis directly without any previous history of COVID were also included in our study.

Assessments

We used a structured proforma to collect the following details: demographic data along with COVID-19 history, severity, duration of symptoms, different sites of involvement of mucor, hospitalisation (ICU/ward stay) or advised home

isolation history during COVID was also recorded. We investigated the treatment offered to patients. We asked about the history of antibiotics use, glucocorticoids, antiviral drugs, biologicals, and other alternative treatments for COVID. Participants were asked about oxygen mask use, canula, cylinders and humidifiers. A history of comorbidities was sought. Investigations included nasal swab KOH mount, CD4 cell count, HIV antibody test, COVID antibody test in individuals who did not have a history of COVID-19 and who were COVID antigen negative, HbA1c, diagnostic nasal endoscopy (DNE) and biopsy, radiological investigations, and outcome in respect to mortality. All this information was noted and analysed.

Statistical analysis

Data were entered into Microsoft excel spreadsheets and studied using open source software. Continuous data were expressed as mean and standard deviations (SD). Categorical data were expressed as percentages.

Ethical approval

The analysis protocol was reviewed, and ethical approval was granted by the Ethics Committee of the institution (No. EC/MGM/AUG-21/21, Dated 21 August). Written informed consent was obtained from the patient/guardian for publication of this paper (including images, case history and data).

Results

In our analysis of 464 patients, one patient was younger than 20 years, 28 (6%) were 21-30 years, 91 (20%) were 31-40 years, 163 (35%) were 41-50 years, 88 (19%) were 51-60 years and 93 (20%) were older than 60 years. 316 (79%) were male and 148 (21%) were female (Table 1).

Out of 464 patients, 287 (62%) were post COVID, 15 (3%) were COVID antigen negative, and 162 (35%) did not have a history of COVID (of which 120 were antibody positive). 29 (6%) were vaccinated and 435 (94%) were non-vaccinated. 123 (27%) patients had less than 10 days duration between COVID and mucormycosis, 79 (17%) patients had 10-20 days duration between COVID and mucor, and 85 (18%) patients had more than 20 days duration between COVID and mucormycosis, and 162 (35%) patients did not have a history of COVID-19. Out of a total of 464 patients, 66 (14%) were hospitalised in the ICU, and 135 (29%) were hospitalised in a ward for COVID previously, while 101 (22%) were treated at home (home isolation), and 162 (35%) did not receive any treatment (Table 2).

163 (35%) out of 464 admissions had less than or equal to seven days history of glucocorticoid use during COVID, 94 (20%) had more than seven days history of use, 207 (45%) did not have a history of steroid intake. 280 (60%) (majority) individuals managed with antibiotics during COVID and 97 (21%) with remdesivir, 57 (12%) with favipiravir, 74 (16%) with zinc tablets, 10 (2%) with biologicals, 12 (2.5%) with plasma/IVIG, and 162 (34%) patients did not have a history

Table 1 Age and gender distribution

Age (years)	Number of patients (%)
<=20	1
21-30	28 (6%)
31-40	91 (20%)
41-50	163 (35%)
51-60	88 (19%)
>60	93 (20%)
Gender	Number of patients (%)
Male	316 (79%)
Female	148 (21%)

Table 2 History of COVID status, COVID vaccination status, duration between COVID-19 and mucor symptoms, and hospitalisation status (COVID)

COVID status	
COVID status	Number of patients (%)
Post COVID	287 (62%)
COVID negative	15 (3%) (antibody positive)
No history of COVID	162 (35%) (120 antibody positive)
Total	464

COVID-19 vaccination status	
Vaccination status	Number of patients (%)
Not vaccinated	435 (94%)
Vaccinated	29 (6%)
Total	464

Duration between COVID-19 and mucor symptoms	
Duration in days	Number of patients (%)
COVID negative	15 (3%)
<10 days	123 (27%)
10-20 days	79 (17%)
>20 days	85 (18%)
No history of COVID	162 (35%)
Total	464

Hospitalisation status (COVID)	
Hospitalisation	Number of patients (%)
Hospitalisation	66 (14%) ICU admission 135 (29%) ward admission
Home isolation	101 (22%)
No treatment	162 (35%)
Total	464

Table 3 History of steroid use, drug use, mask reuse, use of alternative medicine

Steroid use		
Use	Duration (days)	Number of patients (%)
Yes	≤7	163 (35%)
	>7	94 (20%)
No		207 (45%)
Total		464

Drug use	
Drug	Number of patients (%)
Antibiotics	280 (60%)
Zinc	74 (16%)
Remdesivir	97 (21%)
Febiflu	57 (12%)
Biologicals	10 (2%)
IVIG/plasma	12 (2.5%)
No history of any treatment	162 (35%)
Total	464

Mask reuse	
Reuse	Number of patients (%)
Yes	47 (10%)
No	417 (90%)
Total	464

Alternative medicine used	
Used	Number of patients (%)
Yes	32 (7%)
No	432 (93%)
Total	464

of treatment. Out of the 464 patients, 417 (90%) did not have a history of mask reuse and 47 (10%) did have a history of mask reuse. 32 (7%) individuals had a history of treatment with alternative medicine during COVID (Table 3).

Out of 287 post-COVID participants, 61% were known diabetics, 19% were newly diagnosed and 20% were non-diabetic. Out of 162 patients who did not have a history of COVID, 72 (44%) were known diabetics, 58 (35%) were newly diagnosed, and 32 (20%) were non-diabetic. There were 15 COVID-negative individuals, of which 8 (53%) were previously diagnosed as diabetic, 3 (20%) were newly diagnosed, and 4 (27%) were non diabetic. Of 287 post-COVID participants, 125 (44%) had RM, 102 (35%) had ROM, and 60 (21%) had ROCM. Of 15 COVID-negative individuals, 5 (33%) had RM, 6 (40%) had ROM, and 4 (27%) had ROCM. Of 162 patients who did not have a history of COVID, 93 (57%) had RM, 48 (30%) had ROM, and 21 (13%) patients had ROCM. Of the 464

Table 4 Clinical examination including diabetes status, anatomic site of involvement and CD4 count

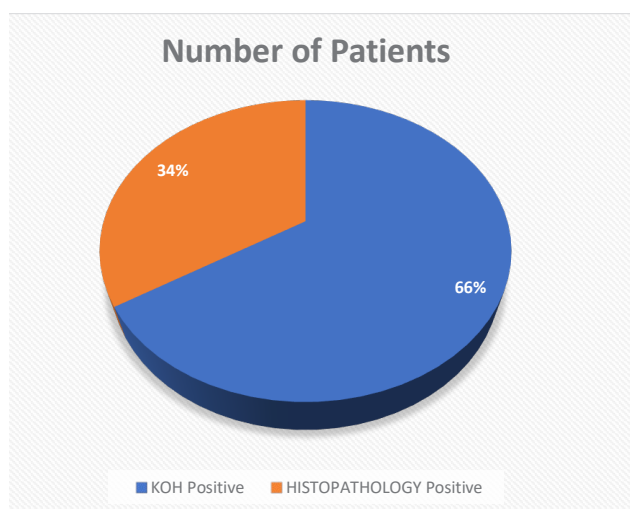
Diabetes status			
	Number of post-COVID patients (%)	Number of COVID-19 negative patients (%)	Number of patients with no history of COVID-19 (%)
Known diabetic	175 (61%)	8 (53%)	72 (44%)
Newly diagnosed diabetic	54 (19%)	3 (20%)	58 (35%)
Non-diabetic	58 (20%)	4 (27%)	32 (20%)
Total patients	287	15	162

Anatomic site of involvement			
Type of involvement	Number of post-COVID patients	Number of COVID-negative patients	Number of patients with no history of COVID
Rhino-mucormycosis	125 (44%)	5 (33%)	93 (57%)
Rhino-oculo-mucormycosis	102 (35%)	6 (40%)	48 (30%)
Rhino-oculo-cerebral-mucormycosis	60 (21%)	4 (27%)	21 (13%)
Total patients	287	15	162

CD4 count		
	Total	HIV status
<200	5 (5%)	Negative
200-500	35 (38%)	Negative
500-1000	49 (52%)	Negative
>1000	5 (5%)	Negative
Total	94	Negative

patients, HIV tests performed on 94 patients were negative, a CD4 count was done in 94 patients, and 49 (52%) had a CD4 count between 500-1000, 35 (38%) had a CD4 count between 200-500, 5 (5%) had a CD4 count less than 200 and 5 (5%) individuals had a CD4 count greater than 1000 (Table 4).

In 162 patients, the KOH mount was positive (Figure 3), and 83 were histopathology positive. A total of 464 patients were admitted, 60 died, out of which the majority (48 [80%]) were ROCM and 12 (20%) were ROM. No deaths occurred in patients with RM (Table 5). Maximum mortality occurred at age older than 50 years (37 [62%]), 41-50 years mortality was 9 (15%), 31-40 years mortality was 12 (20%), 21-30 years mortality was 2 (3%), no mortality occurred younger than 20 years (Table 6). 15% mortality was reported in 374 diabetic patients, 16% mortality was reported in 257 admissions with a history of

Figure 3 KOH stain and histopathology positive patients**Table 5** Anatomic site involvement and mortality association

Anatomic site of involvement	Number of patients (%)	Total number of patients (%)
Rhino-mucormycosis	223 (48%)	0
Rhino-oculo-mucormycosis	156 (33.6%)	12 (20%)
Rhino-oculo-cerebral-mucormycosis	85 (18.4%)	48 (80%)
Total	464	60 (13%)

Table 6 Age distribution of mortality

Age (years)	Mortality Number of patients (%)
<=20	0
21-30	2 (3%)
31-40	12 (20%)
41-50	9 (15%)
>50	37 (62%)

Table 7 Mortality associated with diabetes, steroid use, ICU admissions

Associations	Number of patients	Mortality Number of patients (%)
Known diabetic	255	38 (15%)
Newly diagnosed diabetic	115	19 (16%)
Total diabetics	370	57 (15%)
Steroid usage	257	41 (16%)
ICU admission	241	60 (25%)

glucocorticoids use, and 25% mortality was reported in 241 ICU admissions (Table 7).

Discussion

The incidence of mucormycosis increased from May 2021 in India. We credit this increase mostly to the COVID-19 pandemic (second wave). The majority of cases had less than 10 days' gap between COVID and mucormycosis. The inappropriate dosing of glucocorticoids and antibiotics were mainly linked to this epidemic. During the COVID pandemic (second wave), glucocorticoids and antibiotics were used in greater quantity than the desired clinical dosing. The death rate was around 60 (13%) out of 464 admissions, which was less compared to other centres.¹¹ Advanced age (older than 50 years), ICU admissions, and involvement of the brain in mucormycosis has been linked to higher mortality. The use of antifungals is mainly linked to an improved survival rate, since its proactive adequate use to treat mucormycosis.

In our analysis, 316 (79%) patients affected by mucormycosis were men, as seen in previous studies.¹⁵⁻¹⁷ We observed diabetes as one of the important underlying comorbidities in both COVID-associated mucor and in individuals who did not have a history of COVID. SARS-CoV-2 mainly affects insulin producing cells (B-cells) of the pancreas, which causes diabetes.^{18,19} The COVID antibody test was positive in individuals who did not have a history of COVID, and who had negative COVID antigens but had signs and symptoms of COVID. HbA1c levels were also measured in all diabetic participants, which predicted that many individuals had uncontrolled diabetes. Out of 287 post-COVID patients, 61% (majority) were known diabetics, 19% were newly diagnosed and 20% were non-diabetic. Out of the 162 patients who did not have a history of COVID, 44% were known to be diabetic, 35% were newly diagnosed, and 20% were non-diabetic. Of 15 COVID-negative patients, 53% were known to be diabetic, 20% were newly diagnosed, and 27% were non-diabetic.

We believe that glucocorticoids use could be linked to mucor as it down regulates macrophages and neutrophils, causing further deterioration of the immune system in fighting infection, which increases the likelihood of secondary infections. Glucocorticoids causes high blood sugar, which provides an acidic medium for mucormycosis. Around 435 (94%) of the patients were not vaccinated with covishield or covaxin (COVID vaccines), which could be the reason for the mucor infection. It is possible that COVID causes immune dysregulation, ultimately predisposing individuals to mucor, however, this is unproven.²⁰⁻²² During the recovery phase from COVID infection, there is a persistence of immune dysregulation which may be linked to fungal infection. Use of biologicals in the treatment of COVID has been suspected as a linking factor for fungal infection.²³ Only 10 (2%) of individuals received biologicals during COVID out of the 464 admissions.

Our study suggests advanced age as a major factor related to hospitalisation, respiratory system failure, admissions in ICU, and glucocorticoid use in COVID.^{24,25} Being older


than 50 years was major factor related to mortality in our institute. We did not observe many cases of pulmonary and gastrointestinal mucor. As there are minimum cases showing involvement of respiratory and gastrointestinal systems, we think it could be due to the complications of COVID or treatment related to COVID, rather than a sole modification in the respiratory or gastrointestinal systems. Several pulmonary or gastrointestinal mucor cases have not been diagnosed because it is difficult to obtain respiratory or gastric samples in critical patients admitted to ICU.

The treatment involves antifungal therapy to be started as soon as possible and surgery of the infected part, where feasible. The major drawbacks in the treatment of mucor were the financial conditions of the individuals and the gap in treatment protocol. They could not afford costly antifungals (liposomal amp-B, posaconazole). Data suggest a lower mortality rate in patients of mucor when treated with a combination of both antifungals and surgery (19-44%), when compared with only antifungal therapy (50-61%).²⁷ Posaconazole was mainly used when we did not see a favourable response after giving Amp-B.²⁸ An analysis from South India of the safety and efficacy assessment of posaconazole in an ROCM study showed no mortality; around 66.6% were completely cured, and the rest of the individuals showed improvement in their condition.²⁹ The new antifungal isavuconazole has shown similar effectiveness to Amp-B. It is recent to the Indian market and its effectiveness still requires assessment.³⁰ The overall death rate due to mucor is 28-52% in India,³¹ and the death rate specifically for ROCM is 31-49%, but in our analysis the death rate for ROCM was 48 out of a total 464 patients (10%).^{32,33}

Timely and appropriate dosing of antifungals and surgery, where feasible, are essential in the treatment of mucor. Out of 464 patients admitted, around 241 (52%) patients received an injection of AMP-B, and around 156 (33.6%) were treated with intravitreal AMP-B. Around 223 (48%) patients received posaconazole. The evidence is not very clear about the advantages and disadvantages of combining antifungals for mucormycosis treatment.²⁵ Early and aggressive surgery along with antifungals was linked to better survival in the ROCM group in our study, and previous studies also revealed the same outcome.²⁶ The optimal dose and duration of antifungals are not clear in mucormycosis management. An RCT could be done to assess the results of combining antifungals in mucormycosis management. Around 7% of mucormycosis patients were managed with alternative medicine during their COVID infection.

Our study has certain limitations, the first being we analysed the evidence collected from a single centre. The major factor related to mucor in our study was diabetes, which is similar

to other countries such as Mexico, China, Iran, Bangladesh, and Pakistan which also had more cases of mucor due to diabetes.³⁴ Further analysis is required to compare evidence of more cases of diabetes and mucor from different countries, particularly from the USA and Europe, where mucor is mainly seen in malignancies, especially hematological and after organ transplantation.³⁵ Contamination from ventilators, air conditioning units, and construction works has caused mucor in the past.³⁶ The burden of spores of mucormycetes could not be estimated in our institute.³⁷ Lastly, we have limited evidence on the timing of the use of antifungals, surgery, or duration/dose of sequential antifungals, which can be factors related to outcome in mucormycosis. Factors such as genetic predisposition could explain why there is high occurrence of mucor infection in India. Thus, analysis of the epidemiology of mucor associated with COVID from countries other than India, i.e. those countries affected by mucor during COVID-19, is urgently needed.

In conclusion, our study has several points of interest regarding mucormycosis in relation to COVID. Advanced age (over 50 years) is related to a higher risk for mortality – 48 (80%) out of total mortality (60) reported in ROCM. 25% mortality reported out of 241 ICU admissions. One hundred and sixty two patients did not have a history of COVID infection, but they were COVID antibody positive, underscoring the fact that there must be some underlying exposure to the COVID antigen. Around 80% patient had dysglycemia, which suggests diabetes as an independent factor related to mucor, possibly because chronic hyperglycemia can compromise the immunity. The COVID pandemic (second wave) leading to mucor in India, glucocorticoids and antibiotics used in greater quantity than the desired clinical dosing, could be other factors, and a debate about unhygienic delivery of oxygen to individuals with COVID are presumed to be potential causes behind the sudden surge of mucormycosis. Industrial oxygen use is presumed to be one factor related to the abrupt surge in this disease, because there is a dissimilarity in the manufacturing of both industrial and oxygen used for medical purposes. Due to a shortage of medical oxygen during the COVID pandemic, doctors used industrial oxygen. However, most individuals with mucor without a known history of infection leaves a gap and the need for further analysis of complex immunopathological studies of patients with COVID prone to mucor, suggesting a direct alteration in cellular immunity due to novel COVID which needs further appraisal. 

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