

## Original Research Article

# COVID-19 associated mucormycosis during the second wave of pandemic in South India

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## ABSTRACT

**Background:** The incidence of mucormycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India. As with the other parts of the country, our state also experience surge of mucormycosis cases among COVID-19 patients admitted in our hospitals. The surge of COVID-19 associated mucormycosis (CAM) which was new for the whole medical community with no prior experience. In this context a prospective descriptive study was conducted.

**Methods:** The study was done at a public sector tertiary care hospital in Kerala, South India from April to June 2021 prospectively.

**Results:** During our study period of three months total 40 cases were reported with diagnosis of mucormycosis. Sex wise 29 (72.5%) were males and 11 (27.5%) were females. The mean age was 55.8±16 years. Thirty three (83%) cases were confirmed to be CAM by real time reverse transcriptase polymerase chain reaction (RTPCR) test. Thirty one (79%) of them have got associated risk factor diabetes mellitus. Twenty six (65%) had undergone steroid treatment. Other associated risk factors were hypoxia 10 (25%), zinc supplement 30 (75%), steam inhalation 14 (35%), and intensive care unit (ICU) admission 6 (15%). All the cases were rhino orbito cerebral type. Majority 26 (65%) received medical and surgical treatment. The outcome wise 16 (40%) patients were discharged after cure and case fatality rate was 4 (10%).

**Conclusions:** In our study CAM was highly associated with increasing age above 50, diabetes, steroid use and zinc supplementation. The health care workers and patients should be made aware of the importance of glycemic control, over use of steroids.

**Keywords:** COVID-19 associated mucormycosis, Diabetes mellitus, Steroid use, Zinc supplementation, COVID second wave, South India

## INTRODUCTION

Mucormycosis, caused by a group of moulds called mucormycetes, is a rare but potentially fatal infection if inadequately treated. The incidence of mucormycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India, with at least 14872 cases as of 28 May 2021.<sup>1</sup> After one month by June last as per official sources from government of India it was grown to 40,845 cases and 3129 deaths.<sup>2</sup> Many states including

Kerala already declared it as an epidemic and a notifiable disease to the national health authorities. The Indian council of medical research (ICMR) has released guidelines for the screening, diagnosis, and management of mucormycosis in patients with COVID-19.<sup>3</sup> During the first wave of COVID-19, only 1% secondary infection was caused by any fungus. Since the disease was not included in the list of notifiable disease, no official figures about mucormycosis in COVID-19 cases were released by the union health ministry during the first wave of COVID-19.<sup>1</sup> Even before COVID-19 as per the available reports, India

is the country where maximum cases are reported and the estimated prevalence of mucormycosis was 14 per million populations in India with a mean attributable mortality of 38.2%.<sup>4</sup> In a hospital based study from India, compared to immediate pre COVID period within the first one year of COVID, 2.1 times increase of mucormycosis cases was reported.<sup>5</sup> As with the other parts of the country during the second wave of COVID-19 since April 2021, our state also experience surge of mucormycosis cases among COVID-19 patients admitted in our hospitals.<sup>1,3</sup> Along with COVID-19 wave accompanied by surge, COVID-19 associated mucormycosis (CAM) which was new for the whole medical community with no prior experience. In this context a prospective descriptive study was conducted and the main findings are reported here.

The objectives were to study the epidemiology of mucormycosis, both CAM and non CAM and to study the prevalence of underlying diseases, predisposing, suspected risk factors. The secondary objective was to observe the out comes with respect to the above associated factors.

## METHODS

The study was done at a public sector tertiary care hospital in Kerala, South India during a period of three months from April to June 2021. This was done as a part of “epidemiological study of ongoing COVID-19 pandemic”, which was approved by institutional ethics committee (IEC). The information about the cases were collected daily from the data available from COVID surveillance unit at R PEID cell. Additional data was collected through telephonic calls with patients or their relatives after taking verbal informed consent. A case of mucormycosis was defined as “compatible clinical and radiologic manifestations and demonstration of fungi in the tissue or sterile body fluids of a patient by either direct microscopic visualization or isolation of mucorales”.<sup>6</sup> All the patients reported and admitted in the center with the diagnosis of mucormycosis were included and their data was collected prospectively (n=40). The following details were collected; demographic characteristics, COVID-19 status, underlying disease like diabetes mellitus, malignancy, chronic kidney disease, and coronary artery disease. The symptoms reported by patients, methods of diagnosis and treatment methods. Along with this, their present or past

treatment history of steroids, zinc, oxygen use, steam inhalation were also collected. Using the data, descriptive analysis was done. The quantitative variables are expressed as mean±SD or median±IQR and discrete variables are expressed as frequency and percentage. The significance was tested by appropriate statistical tests.

## RESULTS

During our study period of three months, total 40 cases were reported with diagnosis of mucormycosis. The first case was reported on April 4th and the last case on 29 June 2021. Sex wise 29 (72.5%) were males and 11 (27.5) were females. The mean age was 55.8±16 years ranged from 29 to 80 years. Thirty three (83%) cases were confirmed to be CAM by RTPCR test. The diagnosis was confirmed by microscopy/culture 20 (50%), radiological 16 (40%), clinical 4 (10%) methods. Majority of them, 26 (65%) had developed symptoms of mucormycosis after a gap of >7 days of diagnosing COVID-19.

Thirty one (79%) of them have got associated risk factor diabetes mellitus of which 25 (80.6%) were CAM. Twenty six (65%) had undergone steroid treatment. Other associated risk factors were hypoxia 10 (25%), zinc supplement 30 (75%), steam inhalation 14 (35%) and ICU admission 6 (15%) (Table 1). The reported co morbidities were as follows: coronary artery disease 6, chronic kidney disease 4, chronic liver disease 3, and solid tumor 1. The median duration of symptoms till admission was 9.5 days (2-30 days). Among CAM the median time for onset of mucormycosis following diagnosis of COVID was 26.5 days. The median duration of hospital admission was 25.5 days (2 to 52 days).

All the cases were rhino cerebral orbital type. Majority 26 (65%) received medical and surgical treatment, 11 (27.5%) received medical treatment and 2 (5%) had undergone exenteration. The outcome wise 16 (40%) patients were discharged after cure, 4 (10%) were expired and the rest 20 (50%) were undergoing treatment. Till the date of follow up 22 (55%) had completed >6 weeks of survival after hospitalization. Details of characteristics of the patients, and their relation with main associated risk factors like diabetes and use of steroid use were given in the Table 1.

**Table 1: Relation of diabetes mellitus and steroid use with other COVID-19 associated variables.**

Variables	Total (n=40)	Diabetic (n=31)	Non-diabetic (n=9)	P value	Steroid (n=26)	Non-steroid (n=14)	P value
Age in years mean (SD)	55.78±12.16	55.90±11.33	55.33±15.45	0.89	54.85±11.52	57.5±13.53	0.83
Duration of symptoms prior to admission—days (median-IQR)	9.5 (7–16.5)	10 (7–17)	7 (4–10)	-	8 (6.7–13.5)	10 (6.5–21.5)	-
Duration of hospital stay—days (median-IQR)	25.5 (12.25–38)	26 (13–38)	21 (10.5–36)	-	24 (11.5–38)	30 (14.25–38)	-
Sex—male, n (%)	29 (72.5)	23 (74)	6 (66)	0.68	19 (73)	10 (71)	0.49

Continued.

Variables	Total (n=40)	Diabetic (n=31)	Non-diabetic (n=9)	P value	Steroid (n=26)	Non-steroid (n=14)	P value
<b>COVID positive (%)</b>	33 (82.5)	28 (90)	5 (55)	0.57	26 (100)	7 (50)	<0.01
<b>COVID + to CAM gap &gt;7 days (%)</b>	26 (65)	19 (61)	7 (77)	0.64	20 (76)	6 (43)	<0.01
<b>Risk factors (%)</b>							
Diabetes mellitus	31 (79)	NA	NA	NA	19 (73)	12 (86)	0.66
Steroid use	26 (65)	19 (61)	7 (77)	0.66	NA	NA	NA
Hypoxia	10 (25)	7 (22.5)	3 (33)	0.60	10 (38)	0	<0.01
Zinc use	30 (75)	23 (74)	7 (77)	0.79	26 (100)	4 (29)	<0.01
Steam inhalation	14 (35)	9 (29)	5 (55)	0.34	13 (50)	1 (7)	<0.01
ICU admission	6 (15)	4 (13)	2 (22)	0.60	6 (23)	0	<0.01
Treatment (medical + surgical)	26 (65)	21 (68)	5 (55)	0.65	14 (54)	12 (86)	0.15
<b>Outcome (%)</b>							
Survival >6 weeks*	22 (55)	19 (61)	3 (33)	0.66	17 (66)	5 (35.5)	0.54
Discharge	16 (40)	13 (42)	3 (33)	0.85	12 (46)	4 (29)	0.30
Death	4 (10)	3 (9.6)	1 (11)	0.90	2 (7.7)	2 (14)	0.22

NB: Figures given in brackets ( ) are percentage.

## DISCUSSION

Cases of mucormycosis was not more than background number were reported in this center during the first wave extended from April 2020 to March 2021. All patients (n=40) with CAM was reported from April 2021 corresponding to second wave.<sup>1-3</sup> During the whole period, 14800 COVID patents were undergone inpatient treatment from here. The prevalence of CAM at our center was 0.27% among hospitalized COVID patients which was the same as reported in India.<sup>6</sup>

Sex wise, 29 (72.5%) were males and 11 (27.5%) were females which was almost similar in other places which was 74.6% and 80% corresponds to male predominance of sex wise distribution of COVID-19 admissions.<sup>6,7</sup>

The mean age was 55.8±16 years ranged from 29 to 80 years. At the national level it was 53.4±17 years.<sup>2</sup> Since in COVID-19 cases, old aged people are more admitted in hospitals, this was similar in other reports.<sup>7-9</sup> All over India 68% of the patients were above 45 years.<sup>3</sup>

Since the majority 33 (83%) were with (CAM) we can make sure that COVID-19 directly or indirectly is a predisposing risk factor. At the national level CAM was reported as 67.3% and 85.5% of all reported mucormycosis in the years 2020 and 2021 respectively.<sup>2,6</sup> Due to late reporting of cases to the tertiary hospitals there was increased chances of missing COVID diagnosis in RTPCR tests resulting in more false negatives. Majority of them got secondary infection after a gap of more than 7 days with median 26.5 days after positive COVID tests, which was longer than other areas.<sup>6,9</sup>

## Associated risk factors

Before the pandemic, most common predisposing risk factor associated with mucormycosis was diabetes mellitus in the Asian countries and haematological malignancies and solid organ transplantation in western countries.<sup>8,10,11</sup> Now in COVID-19 patients also the most common attributed risk factors associated with mucormycosis were found to be uncontrolled diabetes, the excessive use of corticosteroids, and long-term stays in the intensive care units.<sup>1,5,7</sup> The hyperglycemia in diabetics may be exacerbated due to affection of the  $\beta$ -cells of the pancreas by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which may be a contributing factor.<sup>11,12</sup>

Here 31 (79%) of them were diabetics. It was 62.7%, 86%, 100% in other studies.<sup>6,7,9</sup> Out of which 25 were CAM and 6 were non CAM.

Here 26 (65%) had undergone steroid treatment. Other studies from India reported steroid treatment as 78.7%, 53%, 80%.<sup>2,6,7</sup> Its use was less reported from Iran 47%.<sup>9</sup> The diabetics conditions were getting worse due to addition of steroids.<sup>12</sup>

The RECOVERY trial served as an approval to use steroids in patients with COVID-19. However, the benefit was specifically shown with low dose, short duration dexamethasone in moderate to severe illness, not for mild cases, a point certainly seemed to have been missed. The indiscriminate use of high doses of and longer duration of corticosteroids, early in the course of the disease without considering the benefit is a possible contributory cause for CAM.<sup>13</sup> The national and state guidelines specifically mention the risk of developing a secondary infection after use of steroids for long time.<sup>3,12,14</sup>

It was evident from our study which reported that only 10 (25%) of the patients had ever undergone oxygen therapy for hypoxia. Correspondingly other studies reported 55.6%, 80% had suffered hypoxia.<sup>6,7</sup> Another chance of getting infected with fungal spores are from intensive care units (ICU) during their stay.<sup>12,13,15</sup> Among our patients only six had ever undergone ICU treatment. For proving this further case control studies or cohorts studies with spores sampling from ICU units may be needed.

Since the beginning to the pandemic, zinc, vitamin C and multivitamins were widely prescribed to COVID-19 patients in all over India. Scientific literatures supported that zinc use would aid in the fungus infection in host cell and this could possibly be a contributory cause.<sup>12-14</sup> Majority of our patients 30 (75%) has been prescribed Zinc supplement which reflects the prescribing pattern of our physicians without evidence.

Since mucormycosis is ubiquitous in our tropical nature, any debridement in nasal mucosa or dryness can promote seeding /attachment of fungal spores in respiratory tract. Among our patients 14 (35%) had used steam inhalation as a preventive measure for COVID-19 in many times a day. It was due to the impact of misinformation which was widely circulating through social media.<sup>16,17</sup>

#### **Other associated co morbidities**

Many co morbidities or their treatments are associated with mucormycosis. Among our patients, six had coronary artery disease, four had chronic kidney disease, three had chronic liver disease and one had malignancy.

CAM can occur either concomitant or sequential.<sup>17</sup> Among CAM, the median time for onset of mucormycosis following diagnosis of COVID is 26.5 days (18 to 118 days), which was reported as less than 18 days nationally, 17 days at state; which was less than 7 days in Iran, which means that here the mucormycosis were affecting COVID cases sequentially.<sup>6,7,9</sup>

All the cases were rhino orbito cerebral type. At the national level it was 58.2%.<sup>6</sup> It has been the most common manifestation even in pre-COVID times and also appear to be the commonest type of CAM observed in the present outbreak.<sup>8,15</sup> It was similarly reported in Iran.<sup>9</sup>

The diagnosis was done by microscopy/culture 20 (50%), radiological 16 (40%), clinical 4 (10%). At national level 82.6% diagnosed by microscopy.<sup>6</sup>

Main symptoms were headache, pain and swelling over face, orbital pain and swelling, visual impairment, proptosis, nasal discharge, nasal obstruction, tooth ache, altered sensorium, ulcer palate, which was similarly reported else.<sup>6,7,9,15</sup>

Majority 65% (26) received medical and surgical treatment, which was 71% at national level.<sup>6</sup> Rest (27.5%)

received medical treatment only. Surgical means nasal endoscopy and debridement or exenteration. The main medical treatment was with liposomal amphotericin B and amphotericin B deoxycholate, which was provided by government free of cost. Isavuconazole/posaconazole were also used for treatment for few cases.

The outcome wise, 12 (30%) patients were discharged after cure, 4 (10%) were died and the rest 24 (60%) were undergoing treatment. All deaths occurred were aged >55 years. The national wide reported mortality was 38.3% after 6 weeks and 45.7% at 12 weeks follow up.<sup>6</sup> As per GOI the case fatality rate was only 7.7% (3129/40845).<sup>2</sup> CFR was 47% from Iran.<sup>9</sup> Among the recovered patients the median duration of hospital stay was 25.5 days (2 to 52 days) pointing that along with high mortality the disease is causing high economic loss also.

Since our center is the only designated public sector tertiary center in the northern part of state where treatment of mucormycosis is provided free by government, majority of the patients from this part of the state (5 districts) and neighboring states (Karnataka, Tamil Nadu) were referred and reported here. So our cases will give a cross sectional representation of patients from south India adding strength to our study.

#### **Limitations**

The data were collected from a tertiary center hospital so the findings may not be generalized. Due to adherence to COVID protocols, we couldn't directly collect the data from patients. We were not able to conduct spore studies by collecting samples from hospital wards, so not able to rule out the chances of getting infections from ICUs. Due to observational nature of our study temporal, causation relationship with factors could not be proved. For finding out the strength of association case control studies must be needed.

#### **CONCLUSION**

Along with COVID-19 cases the incidence of mucormycosis cases were increasingly reported. In our study the disease was highly associated with increasing age above 50, diabetes, steroid use and zinc supplementation. Due to high burden of uncontrolled diabetes in our society and old age population, associated with steroid use, the situation may worsen. The health care workers, and patients should be made aware of the importance of glycemic control, over use of steroids, symptoms of mucormycosis and the importance of early reporting in facilities to undergo treatment. The self-treatment and over the counter treatment (OTC) for COVID-19 should be discouraged. The practicing doctors should be informed and strictly instructed to adhere to the protocol for COVID-19 treatment issued by state government from time to time, take measures to control the over prescription of steroids and to frequently check the glycemic level to maintain it under control.



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