

## Original Research Article

# COVID-19 associated mucormycosis and COVID-19 vaccination status

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## ABSTRACT

**Background:** Mucormycosis is lethal angio invasive fungal infection affecting mainly the immunocompromised individuals. During second wave of COVID-19 pandemic there was rise in number of rhino-orbito-cerebral (ROCM) cases in both COVID-19 affected patients and patients who recovered from COVID-19 infection. This study was conducted to know the anatomical site and extent of involvement in head and neck region in both COVID-19 vaccinated and unvaccinated individuals.

**Methods:** A retrospective descriptive study was conducted between May 2021 and November 2021 at Bowring and lady Curzon hospital, Shri Atal Bihari Vajpayee medical college and research institute, Bangalore, Karnataka, India. 358 patients with post-covid RTPCR negative rhino-orbital mucormycosis were included in the study. The demographic data, COVID-19 vaccination status and anatomical sites of involvement in the patients was collected and analysed.

**Results:** 4 (1.11%) patients were fully vaccinated with 2 doses of covid vaccine, 18 (5.02%) patients were partially vaccinated, 336 (93.85%) were unvaccinated. Majority of the patients were in the age group of 41-60 years in all the groups. In unvaccinated group, majority of the patients presented with stage II/III disease (48.51%; 39.88% respectively) and 39 (11.60%) patients with stage IV ROCM.

**Conclusions:** The extent and severity of ROCM was higher in COVID-19 unvaccinated patients as compared to vaccinated group. Further studies are required to determine the role of COVID-19 vaccine in reducing the severity of the of ROCM.

**Keywords:** COVID-19 associated mucormycosis, COVID-19 vaccine, Covaxin, Covishield, Mucormycosis

## INTRODUCTION

Mucormycosis is a rare, opportunistic fungal infection which causes angio-invasive disease leading to aggressive necrosis and infarction of the involved tissues.<sup>1</sup> A study in 2019 based on computational modelling revealed that the prevalence of mucormycosis in India before the COVID-19 pandemic was 140 cases per million, translating to a mean of 171,504 cases in Indian population.<sup>2</sup>

Underlying predisposing factors include uncontrolled diabetes mellitus, immunocompromised status, systemic use of corticosteroids, pre-existing respiratory pathology, cancer, and stem cell transplant.<sup>5</sup> The rhino-orbito-cerebral type is the most common form of the disease in India, followed by the pulmonary and cutaneous types.<sup>6</sup>

India began its COVID-19 vaccination programme on 16 January 2021, operating 3,006 vaccination centres on the onset. The first phase of the rollout involved health workers and frontline workers, including police,

paramilitary forces, sanitation workers, and disaster management volunteers. Two vaccines were available: covishield and covaxin.<sup>7</sup>

The next phase of the vaccine rollout covered all residents over the age of 60, residents between the ages of 45 and 60 with one or more qualifying comorbidities, and any health care or frontline worker that did not receive a dose during phase 1.<sup>8</sup> From 1 April, eligibility was extended to all residents over the age of 45.<sup>9</sup> On 19 April, it was announced that the next phase of the vaccination programme would begin on 1 May, extending eligibility to all residents over the age of 18.<sup>10</sup>

During the second wave of the COVID-19 pandemic in India, an increase in fungal infections, predominantly rhino-orbito-cerebral mucormycosis (ROCM), has been documented.<sup>3</sup> India had reported more than 47,000 cases of mucormycosis in three months (May to July 2021), and the actual figures were likely to be higher.<sup>4</sup> A recent multicenter retrospective study of CAM among hospitalized COVID-19 patients estimated prevalence at 0.27%.<sup>11</sup>



**Figure 1: Rhino-orbital mucormycosis.**

SARS-CoV-2 infection causes endothelial dysfunction due to direct viral invasion and host inflammatory response causing apoptosis of endothelial cells. Predisposing factors for mucorales spores to germinate in COVID-19 affected patients include a fertile host environment of hypoxia, hyperglycemia (diabetes, new onset hyperglycemia, steroid-induced hyperglycemia), acidosis (metabolic or diabetic ketoacidosis), high free iron levels, impaired phagocytic activity of white blood cells, ciliary dysfunction, cytokine storm (associated with insulin resistance and hyperglycemia), thromboinflammation (SARS-CoV-2 mediated, steroid-mediated or comorbidities), along with additional risk factors like prolonged hospitalization with or without mechanical ventilation.<sup>19</sup> In this view this study was conducted to determine the COVID-19 vaccination status of CAM patients and severity of the disease.

## METHODS

A retrospective descriptive (record based) study was conducted between May 2021 and November 2021 at Bowring and lady Curzon hospital, Shri Atal Bihari Vajpayee medical college and research institute, Bangalore, Karnataka, India. 358 patients with post covid RTPCR negative ROCM who had histopathologically and/or radiologically proven mucormycosis [European Organization for Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG group) criteria] were included in the study.<sup>12</sup> RTPCR positive ROCM patients were excluded from the study.

After obtaining approval from the institutional ethics committee, the patients fulfilling the inclusion criteria were enrolled for the study and were divided into three groups based on COVID-19 vaccination status: completely vaccinated (2 doses), partially vaccinated (1 dose) and unvaccinated group. Patient's demographic details, clinical features, laboratory test results, radiological reports and details of medical and surgical interventions performed were collected using a detailed proforma.

Extent and severity of CAM was based on staging of ROCM by Honavar et al.<sup>13</sup> Stage 1- involvement of the nasal mucosa; stage 2- involvement of the paranasal sinuses, perisinus inflammation; stage 3- involvement of the orbit; stage 4- involvement of the central nervous system. The subsites of involvement were studied in all three group of patients to correlate severity of disease. Data collected in the proforma was collated in MS Excel and analysed statistically using SPSS software version 24 and are presented in the form of tables, percentages.

## RESULTS

The demographic data of the patients is presented in Table 1.

**Table 1: Demographic data of the patients.**

<b>Total number of patients</b>	<b>358</b>
<b>Age group</b>	13-80 years
<b>Median age</b>	46 years
<b>Sex</b>	Male- 268 (74.86%)
	Female- 90 (25.13%)
<b>Past history of COVID-19 infection</b>	358 (100%) patients

### COVID-19 vaccination status

4 (1.11%) patients were fully vaccinated with 2 doses of covid vaccine, 18 (5.02%) patients were partially vaccinated, 336 (93.85%) were unvaccinated. Majority of the patients were in the age group of 41-60 years in all the groups (Table 2).

**Table 2: COVID-19 vaccination status and age distribution of the patient.**

Age group (years)	Completely vaccinated	Partially vaccinated	Unvaccinated
≤45	1 (25%)	1 (5.6%)	70 (20.8%)
45-50	0	5 (27.7%)	104 (30.9%)
51-60	1 (25%)	4 (22.2%)	107 (31.8%)
61-70	0	6 (33.3%)	40 (11.9%)
>70	2 (50%)	2 (11.1%)	15 (4.5%)
<b>Total</b>	<b>4</b>	<b>18</b>	<b>336</b>

**Table 3: COVID-19 vaccination status and stage of ROCM.**

Stage of ROCM	Completely vaccinated	Partially vaccinated	Unvaccinated
<b>Stage I</b>	0	0	0
<b>Stage II</b>	3 (75%)	14 (77.78%)	163 (48.51%)
<b>Stage III</b>	1 (25%)	2 (11.11%)	134 (39.88%)
<b>Stage IV</b>	0	2 (11.11%)	39 (11.60%)

**Table 4: COVID-19 vaccination status and anatomical site of involvement.**

Anatomical site	Subsite	Completely vaccinated	Partially vaccinated	Unvaccinated
<b>Nose</b>	Nasal floor	0	1 (5.6%)	17 (5%)
	Nasal septum	0	1 (5.6%)	13 (3.8%)
	Inferior turbinate	0	3 (16.7%)	112 (33.3%)
	Middle turbinate	3 (75%)	10 (55.6%)	69 (20.5%)
	Superior turbinate	0	1 (5.6%)	49 (14.5%)
	Nasopharynx	0	1 (5.6%)	8 (2.4%)
<b>PNS</b>	Maxillary sinus	4 (100%)	12 (66.7%)	234 (69.6%)
	Ethmoid sinus	2 (50%)	14 (77.8%)	225 (66.9%)
	Sphenoid sinus	0	10 (55.6%)	144 (42.8%)
	Frontal sinus	1 (25%)	10 (55.6%)	153 (45.5%)
<b>Orbit</b>	Periorbita only	1 (25%)	2 (11.1%)	114 (33.9%)
	Orbital walls	1 (25%)	1 (5.6%)	39 (11.6%)
	Extraocular muscles	0	1 (5.6%)	51 (14.24%)
	Optic neuritis	0	1 (5.6%)	20 (5.9%)
<b>Pterygopalatine fossa</b>		0	1 (5.6%)	26 (7.7%)
<b>Infratemporal fossa</b>		0	1 (5.6%)	27 (8%)
<b>CNS</b>	Meninges	0	1 (5.6%)	39 (11.6%)
	Brain parenchyma (abscess)	0	2 (11.11%)	20 (6.32%)
	Cavernous sinus	0	2 (11.11%)	25 (7.44%)
<b>Palate</b>		0	5 (27.78%)	133 (39.58%)
<b>Mandible</b>		0	1 (5.55%)	6 (1.78%)
<b>Cutaneous</b>		0	2 (11.11%)	7 (2.08%)

In the vaccinated group, 3 patients had taken 2 doses of covishield and 16 patients 1 dose of covishield. 1 patient was completely vaccinated with covaxin and 2 patients had received 1 dose of covaxin.

#### **Extent/severity of ROCM**

Completely vaccinated individuals presented with stage II (3;75%), stage III (1;25%) ROCM. In partially vaccinated individuals, 14 (77.78%) patients presented with stage II, 2 (11.11%) patients with stage III, 2 (11.11%) patients with stage IV ROCM. In unvaccinated

patients, 163 (48.51%) patients presented with stage II, 134 (39.88%) patients with stage III, 39 (11.60%) patients with stage IV ROCM (Table 3). Anatomical subsites of involvement is depicted in Table 4.

#### **DISCUSSION**

In India, during the second wave of the COVID-19 pandemic, there was a surge in number of CAM cases. A systematic review conducted by Musuza et al observed that CAM constitutes 0.3% of COVID-19 coinfections.<sup>15</sup>

We conducted a single centre retrospective study of 358 patients with ROCM. Majority of the patients were middle aged males. It has been hypothesized that the effect of oestrogen might be protective in systemic fungal infection, which could have led to lower incidence in females.<sup>14</sup>

In our study, majority of the patients were unvaccinated (93.85%). In this group, majority of the patients presented with stage II/III disease (48.51%; 39.88% respectively) and 39 (11.60%) patients with stage IV ROCM.

In a study conducted by Dravid et al, 46 (78.0%) CAM patients were not vaccinated, 9 (15.3%) patients had received covishield (1 dose), 2 (3.4%) covishield (2 doses), 1 (1.7%) patient had received covaxin (1 dose), 1 (1.7%) received covaxin (2 doses). 24 (40.7%) patients presented with stage II, 8 (13.6%) with stage III, 26 (44.1%) with stage IV ROCM.<sup>16</sup> In a study conducted by Selarka et al. majority were men (n=35, 74.5%), and the mean age was 55±12.8 years. Majority of subjects (n=31, 66.0%) had not been vaccinated for COVID-19. 14 (29.8%) and 2 (4.3%) patients were vaccinated with 1 dose and 2 doses of COVID-19 vaccine respectively. 19 (40.4%), 19 (40.4%), 9 (19.1%) patients presented with stage II, III, IV ROCM respectively.<sup>17</sup>

The most common anatomical subsite involved in our study was maxillary sinus followed by ethmoid sinus, frontal sinus, sphenoid sinus in all the groups. In the orbit, periorbita was involved commonly followed by extraocular muscles. Orbital involvement presented with different stages of cellulitis and may progress to involve the brain. Intracranial involvement was commonest in the unvaccinated group presenting with meningitis (11.6%), cavernous sinus thrombosis (7.44%), brain abscess/encephalitis (6.32%). It can occur by spread of the disease through cribriform plate of the ethmoid bone or orbital apex. The occurrence of palatal bone (39.58%) and mandible (1.78%) involvement in the unvaccinated group was higher as compared to partially vaccinated or fully vaccinated patients.

The prevalence of CAM was high during the second wave of COVID-19 pandemic in India.<sup>4,11</sup>

COVID-19 vaccination was not available for all the age groups during the period.<sup>11</sup> Combination of uncontrolled diabetes, hyperglycemia (COVID-19 and steroid induced) was hypothesized to the risk of development of mucormycosis by following mechanisms: a) induction of defect in neutrophil-macrophage phagocytic system; b) upregulation and increased expression of GRP78 receptor in humans and their interaction with specific protein CotH3 on fungal surface c) hyperglycation of iron sequestering proteins leading to disruption in iron sequestration and increased delivering of iron to mucorales.<sup>18</sup> The extent and severity of CAM was

comparatively high in unvaccinated patients in our study as found in other studies also.<sup>16,17</sup>

There was a limitation of the study. The total number of unvaccinated individuals were comparatively higher due to phase-wise distribution of covid vaccine during the pandemic. Hence, large sample multicentric studies are required to determine the protective role of covid vaccine in preventing or reducing the severity of CAM.

## CONCLUSION

The extent and severity of ROCM was higher in COVID-19 unvaccinated patients as compared to vaccinated group. Further studies are required to determine the role of COVID-19 vaccine in reducing the severity of the of ROCM.

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