

# Association of Risk Factors among Nasal and Orbital Mucormycosis in Coronavirus Disease 2019 Infection: A Cross-Sectional Study

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## Abstract

**Purpose:** To study the risk factors of mucormycosis and analyze their association among nasal and orbital mucormycosis in Coronavirus disease 2019 (COVID-19) infection.

**Methods:** All patients diagnosed of rhino-orbito-cerebral mucormycosis (ROCM) with previous COVID-19 infection were included in the study. The details such as age, sex, presence of co-morbidities, and serum ferritin levels were collected. ROCM patients were classified into two groups, nasal mucormycosis (stage 1 and 2 of ROCM) and orbital mucormycosis (stage 3 and 4 of ROCM), and data were collected. Duration of COVID-19 symptoms, the time interval between COVID-19 infection and onset of ROCM symptoms, computed tomography severity score (CTSS) and usage of steroids were collected accordingly. The collected data were compared between nasal group and orbital group.

**Results:** Among 52 patients, 15 patients had nasal and 37 patients had orbital mucormycosis. Forty-one patients were more than 40 years, 43 patients were males. Seven out of ten risk factors were found to be significant on comparing nasal and orbital group. Patients of age more than 40 years ( $P = 0.034$ ), elderly diabetics ( $P = 0.014$ ), poor control of diabetes ( $P = 0.003$ ), high serum ferritin levels ( $P = 0.043$ ), duration between COVID-19 and mucormycosis of more than 20 days ( $P = 0.038$ ), CTSS of more than 9/25 ( $P = 0.020$ ), and steroid usage during COVID-19 infection ( $P = 0.034$ ) are prone to develop orbital mucormycosis. On multivariate logistic regression analysis, these variables did not emerge as independent risk factors.

**Conclusions:** Patients with severe COVID-19 infection along with other associated risk factors can be prone to develop severe forms of mucormycosis. We did not find them to be statistically significant on multivariate analysis. In the future, large scale studies are needed to know their significance.

**Keywords:** Computed tomography severity score, Coronavirus disease 2019, Rhino-orbito-cerebral mucormycosis

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## INTRODUCTION

Mucormycosis is an infectious disease caused by the member of *Mucorales*.<sup>1</sup> The spores of these fungi are found naturally in the soil or air. The transmission of the fungi in the hospital can be through the ventilators, bed linens, and unsterilized oxygen pipes. The predominant clinical manifestations of mucormycosis vary from host

to host, with rhino-orbito-cerebral, pulmonary, cutaneous, and gastrointestinal infections being the most common.<sup>2</sup> Mucormycosis causes a life-threatening infection in patients with compromised immunity and various comorbidities such as diabetes mellitus, hematological malignancies, and postorgan transplantation.<sup>3</sup>

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The recent pandemic by Coronavirus disease 2019 (COVID-19) can have varied clinical presentations ranging from mild infection to deadly pneumonia.<sup>4</sup> Although no definite treatment is available, corticosteroids play a major role in reducing the inflammatory markers and improving the symptoms, while at the same time, making the person prone to opportunistic infections by inducing immunosuppression.<sup>5</sup> Taking advantage of the vulnerability of the patient to secondary infections, the mucor spores germinate into hyphal forms in the paranasal sinuses (PNS). From here, it spreads by local tissue destruction and angioinvasion. The time of presentation of mucormycosis in COVID-19 patients ranges from a few weeks postviral infection to occurring concurrently with the viral infection. The severity differs from patient to patient. Through this study, we aimed to analyze the association between the severity of the COVID-19 infection and that of orbital mucormycosis.

## METHODS

This is a retrospective, cross-sectional study conducted at a tertiary care hospital from April 2021 to September 2021 after getting Institutional Human Ethics Committee approval.

All post COVID-19 patients who presented to our hospital with any signs or symptoms of rhino-orbito-cerebral mucormycosis (ROCM), (possible, probable, and proven) were included in the study after obtaining consent. Possible ROCM was diagnosed, if patient had typical signs and symptoms of ROCM.<sup>6</sup> Probable ROCM was diagnosed, if clinical features were supported by diagnostic nasal endoscopy findings, contrast-enhanced magnetic resonance imaging (MRI), or computed tomography (CT) scan.<sup>6</sup> Proven ROCM is defined as clinicoradiological features along with microbiological confirmation on direct microscopy and/or culture or histopathology with special stains or molecular diagnostics.<sup>6</sup> All patients of non-COVID-19 mucormycosis, nonmucor infection, chronic renal failure, and patients on immunosuppressant therapy were excluded from the study.

Details of all risk factors such as age, sex, presence of comorbidities, time of onset of COVID-19 symptoms, date of positivity of COVID-19 by reverse transcriptase-polymerase chain reaction, CT Severity Score (CTSS), serum ferritin levels, usage of steroids, duration between COVID-19 symptoms and ROCM symptoms, and the stage of mucormycosis were collected. Patients having high CTSS score and history of usage of steroids during the COVID-19 infection were considered to have had a severe form of COVID-19 infection.

At the time of presentation, the patients with probable ROCM (based on clinical and radiological findings with MRI brain, PNS and orbit with contrast), possible, and proven ROCM were divided into two groups: Nasal mucormycosis, i.e., stage 1 and 2 ROCM (15 patients) and orbital mucormycosis, i.e., stage 3 and 4 ROCM (37 patients).<sup>7</sup> The orbital group was considered the severe form of ROCM in our study. Each risk factor was assessed separately between these two groups.

The patients were divided into less than 40 years and more than 40 years. Diabetics were divided into newly diagnosed diabetics and already known diabetics who were on treatment. As per glycosylated haemoglobin (HbA1c) values, diabetics were divided into good control (HbA1c <8) and poor control (HbA1c >8), based on classification given by Anetor *et al.*<sup>8</sup> Other comorbidities such as the history of hypertension or coronary artery disease were noted. Based on serum ferritin levels, patients were divided into those with normal levels (<300 ng/ml) or raised levels (>300 ng/ml).

Detailed COVID-19 history was taken. The duration between COVID-19 symptoms to mucormycosis symptoms ranged from 0 to 60 days; hence, they were divided into patients presenting in <20 days or patients presenting more than 20 days, following Ramaswami *et al.*'s study, as they found a median time of 20 days in developing mucormycosis.<sup>9</sup> History of usage of steroids during COVID-19 infection was noted. During COVID-19 infection, steroid therapy was started as per the institution protocol. Forty mg methylprednisolone was given once daily and tapered over a period of 15 days in patients not requiring oxygen supplement. In patients, who need oxygen supplement, 80 mg methylprednisolone was given and tapered accordingly.

CTSS on high-resolution CT of the lung ranged from 0 to 25 and was divided into <9/25 and more than 9/25.

## Statistical analysis

Collected data were analyzed with Chi-square test and logistic regression analysis.  $P < 0.05$  indicated the statistical significance using SPSS software (IBM SPSS Statistics for Windows, Version 24.0; IBM Corp., Armonk, NY, USA).

## RESULTS

Among 52 patients, 15 patients had nasal mucormycosis and 37 patients had orbital mucormycosis. About 78.8% were more than 40 years and 82.69% were males. In the study population, 65.3% were already known diabetics and 75% had poor control of diabetes. Raised serum ferritin levels of more than 300 ng/ml were noted in 67.3% individuals. About 55.7% presented after 20 days of developing COVID-19 symptoms, with 51.92% having a CTSS score of more than 9/25 [Table 1].

The median age was 49 years (inter-quartile range [IQR]: 41–56.5). The median duration between COVID-19 and onset of mucormycosis was 21 days (IQR: 8–25.5).

A total of ten risk factors were analyzed between nasal and orbital groups. Seven out of ten risk factors were found to be significant on univariate analysis. Patients of age more than 40 years ( $P = 0.034$ ), already known diabetics ( $P = 0.014$ ), poor control of diabetes ( $P = 0.003$ ), high serum ferritin levels ( $P = 0.043$ ), duration of more than 20 days, between COVID-19 and onset of mucormycosis ( $P = 0.038$ ), CTSS of more than 9/25 ( $P = 0.020$ ), and steroid usage during COVID-19 infection ( $P = 0.034$ ) were more prone to develop

**Table 1: Most common associations seen in rhino-orbito-cerebral mucormycosis patients**

Clinical features	n=52 patients, n (%)
Age of >40 years	41 (78.8)
Males	43 (82.7)
Already known diabetics	34 (65.3)
HbA1c of >8	39 (75)
Raised serum ferritin levels (>300 ng/mL)	35 (67.3)
COVID-19 to onset of mucormycosis of >20 days	29 (55.7)
CTSS of >9/25	27 (52)
Stages of ROCM	
Stage 1	2 (3.8)
Stage 2	13 (25)
Stage 3	34 (65.3)
Stage 4	3 (5.7)

CTSS: Computed tomography severity score, COVID-19: Coronavirus disease 2019, ROCM: Rhino-orbito-cerebral mucormycosis, HbA1c: Glycosylated hemoglobin

orbital mucormycosis [Table 2]. Males were more in number compared to females, but even then, there was no statistical significance in developing orbital mucormycosis compared to nasal mucormycosis.

Risk factors showing  $P < 0.05$  on univariate analysis were subjected to multivariate analysis. On multivariate logistic regression analysis, these variables did not emerge as independent risk factors [Table 3].

## DISCUSSION

A staging system was proposed by Honavar *et al.* that follows the anatomical progression of ROCM from nasal mucosa, PNS, orbit, and central nervous system (CNS).<sup>6</sup> Stage 1 is involvement of nasal mucosa, stage 2 is involvement of PNS, stage 3 is involvement of the orbit, and stage 4 is the involvement of CNS.<sup>6</sup> This staging helped us in dividing the patients into two groups, i.e. nasal and paranasal involvement as the nasal group; orbital and cerebral involvement as the orbital group.

Diffuse involvement of the PNS and the orbit is seen commonly.<sup>7</sup> Among the orbits, the predominance of the medial orbit involvement is witnessed, due to its spread through the nasolacrimal duct or the lamina papyracea. Apical involvement may not have fulminant signs and symptoms. Early signs of orbital apex involvement may be white eye with subtle proptosis, ptosis, other cranial nerve palsies, regional hypoesthesia, and diminution of vision.<sup>7</sup> Early diagnosis of the above helps minimize the risk of progression to the cavernous sinus.<sup>7</sup>

Of 2826 patients of mucormycosis, Sen *et al.* found out that males (71%) were affected more than females, attributing the majority to the greater outdoor exposure and mean age of 51.9 years.<sup>7</sup> Similarly, we also found that 82.69% of the study population were males with a mean age of 50.7 years.

**Table 2: Risk factor analysis between nasal and orbital mucormycosis**

Risk factors	Nasal group n=15 patients (%)	Orbital group n=37 patients (%)
Age		
<40 years	6 (40)	5 (13.5)
>40 years	9 (60)	32 (86.4)
$\chi^2$ (P)		4.489 (0.034)
Sex		
Males	14 (93.3)	29 (78.3)
Females	1 (6.6)	8 (21.6)
$\chi^2$ (P)		1.668 (0.197)
Diabetes mellitus		
Newly diagnosed	9 (60)	9 (24.3)
Old diabetics	6 (40)	28 (75.6)
$\chi^2$ (P)		6.002 (0.014)
HbA1c		
<8	8 (53.3)	5 (13.5)
>8	7 (46.6)	32 (86.4)
$\chi^2$ (P)		9.026 (0.003)
Hypertension		
Present	7 (46.6)	11 (29.7)
No	8 (53.3)	26 (70.2)
$\chi^2$ (P)		1.353 (0.245)
Coronary artery disease		
Present	3 (20)	7 (18.9)
No	12 (80)	30 (81)
$\chi^2$ (P)		0.008 (0.929)
Serum ferritin levels		
<300 ng/mL	8 (53.3)	9 (24.3)
>300 ng/mL	7 (46.6)	28 (75.6)
$\chi^2$ (P)		4.082 (0.043)
COVID-19 to mucor duration		
<20 days	10 (66.6)	13 (35.1)
>20 days	5 (33.3)	24 (64.8)
$\chi^2$ (P)		4.302 (0.038)
CTSS		
<9/25	11 (73.3)	14 (37.8)
>9/25	4 (26.6)	23 (62.1)
$\chi^2$ (P)		5.387 (0.02)
Steroid usage during COVID-19		
Yes	6 (40)	5 (13.5)
No	9 (60)	32 (86.4)
$\chi^2$ (P)		4.489 (0.034)

Level of significance set at  $P < 0.05$ . CTSS: Computed tomography severity score, COVID-19: Coronavirus disease 2019, HbA1c: Glycosylated hemoglobin,  $\chi^2$ : Chi-square test

Patel *et al.* found that diabetes mellitus was the dominant predisposing factor in all forms of mucormycosis.<sup>10</sup> Ramaswami *et al.* observed that diabetes mellitus (70%) and steroid use (70%) during the COVID-19 infection were the common risk factors for mucormycosis.<sup>9</sup> In our study, all patients with COVID-19-associated mucormycosis were found to be diabetics (100%). Of all the diabetics, 65.3% were already

**Table 3: Multivariate analysis**

Serial Number	Risk factors	Univariate analysis		Multivariate analysis	
		$\chi^2$	P	P	OR (95% CI)
1	Age	4.489	0.034	0.92	1.1 (0.07-17.9)
2	Sex	1.668	0.197	-	-
3	Diabetes	6.002	0.014	0.18	5.6 (0.42-76.3)
4	HbA1c	9.026	0.003	0.052	32.3 (0.97-1078.5)
5	Hypertension	1.353	0.245	-	-
6	Coronary artery disease	0.008	0.929	-	-
7	Serum ferritin	4.082	0.043	0.16	5.4 (0.49-58.7)
8	COVID-19 to mucor duration	4.302	0.038	0.07	14.8 (0.79-279.1)
9	CTSS	5.387	0.020	0.07	14.9 (0.78-286.2)
10	Steroid usage	4.489	0.034	0.41	0.2 (0.006-8.54)

$P < 0.05$  on univariate analysis were subjected to multivariate analysis.

CI: Confidence interval, CTSS: Computed tomography severity score, COVID-19: Coronavirus disease 2019, OR: Odds ratio, HbA1c: Glycosylated hemoglobin

known diabetics and 75% had poor control of diabetes with HbA1c of more than 8%.

There will be glycosylation of transferrin and ferritin causing reduction in iron-binding secondary to hyperglycemic states. Along with hyperglycemia, acidosis presents a summative effect leading to increase in free iron levels. This increase in free iron levels allows the mucor to thrive. Hence, diabetes mellitus was considered one of the major risk factor for mucormycosis.<sup>11</sup> Coronavirus can enter islets using angiotensin-converting enzyme 2 as its receptor and damages islets causing acute diabetes.<sup>12</sup>

Singh *et al.* observed that mucormycosis was seen both in people who were active (59.4%) and recovered (40.6%) from COVID-19.<sup>13</sup> A systematic review done by Pal *et al.* found that a prior history of COVID-19 was present in 37% of patients with mucormycosis developing after an initial recovery.<sup>14</sup>

In our study, mucormycosis was found in 34.6% of active COVID-19 infection and 65.3% in the postrecovery phase patients.

Ramaswami *et al.* found that median duration of 20 days (IQR: 13.5–25) was present between the onset of COVID-19 symptoms and the onset of COVID-19-associated mucormycosis symptoms.<sup>9</sup> In our study, we found the median duration between COVID-19 and mucormycosis to be 21 days (IQR: 8–25.5).

A systematic review done by Pal *et al.* found that glucocorticoid usage was reported in 85% of cases.<sup>14</sup> In our study, in contrast, we found 21% of them had a history of usage of steroids during COVID-19 infection. The difference can be due to the insufficient information of patients on the treatment taken outside our institution for COVID-19 infection.

After the COVID-19 pandemic, India reported a majority of the COVID-19-induced mucormycosis.<sup>15</sup> The higher prevalence

of mucormycosis in India was imputed to the environmental factors such as tropical, sub-tropical humid climate, and high temperatures.<sup>16</sup> COVID-19 produces a hypoxic environment with high glucose levels, high levels of ferritin, and attenuated phagocytic activity of leukocytes due to immunosuppression by the virus itself and the corticosteroids used in the management. This setting is highly conducive for the fungal spores to germinate and proliferate.<sup>13</sup>

Even though diabetes plays a major role in the COVID-19-induced mucormycosis, tissue hypoxia, excessive use of corticosteroids, antibiotics, and environmental exposure (hot and humid environment) can have an additive effect.<sup>13,17</sup> Tissue hypoxia caused by COVID-19 infection, with partial tissue infarction, are more prone for fungal angio-invasion.<sup>18</sup> Overuse of antibiotics during COVID-19 treatment can suppress the normal bacterial flora and facilitates invasion of fungi.<sup>18</sup>

Analyzing the severity of COVID-19 infection in patients with mucormycosis may help in identifying the at-risk individuals and in predicting the prognosis. Our study analyzed COVID-19 severity by high CTSS and usage of steroids during COVID-19 infection, and compared it with the ROCM severity, considering orbital group as the severe form of ROCM (stage 3 and 4 of ROCM). Even though steroid usage and CTSS score were statistically significant on univariate analysis, they did not turn out to be independent risk factors for developing severe forms of ROCM on multivariate analysis. Hence, we conclude, that multiple factors are associated with severe forms of mucormycosis, and more elaborate studies are needed to assess the individual risk factors.

Most of the studies analyzed the risk factors of mucormycosis, but the strength of our study is that we have analyzed the risk factors for nasal and orbital mucormycosis separately. This helps us know which patients will develop severe forms of the disease. The study has added novelty in performing multivariate logistic regression to remove the effect of confounding.

Sen *et al.*'s study was a multi-centric study of all over India.<sup>7</sup> We have considered the above study as a reference study in collecting the data, and ours is a single institution study, from South India. In our study, we have analyzed the risk factors for severe form of mucormycosis, so that early diagnosis and treatment can be instituted. Moreover, our study also analyzed the severity of COVID-19 by CTSS and steroid usage and compared it with mucormycosis severity, considering orbital group to be a severe form of ROCM.

The limitations of our study are a small sample size, combining nasal and paranasal into one category and orbital and cerebral into another category, and having a low number of patients in nasal mucormycosis group compared to orbital mucormycosis group. In the future, we will plan a multi-centric study and analyze the risk factors for all four stages of mucormycosis separately.

Patients with severe COVID-19 infection along with other associated risk factors can be prone to develop severe form of mucormycosis. We did not find them to be statistically significant on multivariate analysis. In the future, large-scale studies are needed to know their significance.

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### Conflicts of interest

There are no conflicts of interest.

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