

# Mucormycosis in COVID-19 Patients: A Tertiary Care Experience

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## Abstract

**Introduction:** Zygomycetes consisting of Mucorales order is a group of fungal infections. These species cause life threatening opportunistic fungal infections mucormycosis. This infection is highly prevalent in immunocompromised. During the 2<sup>nd</sup> wave of Covid 19 pandemic corticosteroid treatment was used which has been linked to development of Mucormycosis. In our tertiary care teaching hospital we saw that patients suffering from Covid-19 infections developed mucormycosis. We present these cases in our study. To study the clinical, demographical, and Laboratory parameters in Covid-19 patients with Mucormycosis. **Material and Methods:** Retrospective Study. All biopsy proven cases of Mucormycosis (which developed after Covid-19 infection) were included. Relevant Clinical Demographics and Laboratory data was retrieved from the available case sheets. The data was tabulated in Excel sheet and further reviewed. **Results:** A total of 22 patients were diagnosed as suffering from mucormycosis majority were unvaccinated. 11 patients out of 22 (50%) started manifesting mucormycosis within one week of COVID infection. All the patients who had only single comorbidity (22.72%) suffered from mild disease and patient who had more than one comorbidity suffered from moderate (27.27%) to severe (50%) COVID infection. **Conclusion:** It is suggested that patients with Covid-19 infection are at risk for development of opportunistic fungal infections like Mucormycosis. Hence the physicians who are involved in treating such patients must be mindful of the fact that mucormycosis can develop in them. Histopathology helps in establishing a concrete diagnosis of Mucormycosis.

**Keywords:** COVID-19, fungal, mucormycosis

## INTRODUCTION

Zygomycetes consisting of Mucorales order is a group of fungal infections. These species cause life-threatening opportunistic fungal infections and mucormycosis. This infection is highly prevalent in immunocompromised.<sup>[1]</sup> During the second wave of the COVID-19 pandemic, corticosteroid treatment was used which has been linked to the development of mucormycosis. The steroids affect the activity of macrophages due to which macrophages are not able to stop the germination of these fungal spores.<sup>[2]</sup> The clinical spectrum of its presentation progresses systemically in an aggressive fashion in the human body and affects multiple organs.<sup>[3,4]</sup>

In our tertiary care teaching hospital, we saw that patients suffering from COVID-19 infections developed mucormycosis. We present these cases in our study. This study aims to study the

clinical, demographical, and laboratory parameters in COVID patients with mucormycosis.

## MATERIALS AND METHODS

### Study design

This study was a retrospective study.

### Duration of study

This study was conducted from April 2021 to September 2021.

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**Sample size**

The sample size of this study is 22 cases.

**Inclusion criteria**

All biopsy-proven cases of mucormycosis (which developed after COVID-19 infection) were included in the study.

**Method of collection of data**

Relevant clinical, demographics, and laboratory data were retrieved from the available case sheets. The data were tabulated in an Excel sheet and further reviewed.

**Statistical analysis**

Statistical analysis will be done with student *t*-test and ANOVA using the SPSS version 26 (IBM Corp. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

**Ethical consideration**

Complete confidentiality regarding the subject’s information was maintained.

**RESULTS**

Twenty-two patients were diagnosed as suffering from mucormycosis, and the majority were unvaccinated. Eleven patients out of 22 (50%) started manifesting mucormycosis within 1 week of COVID infection [Table 1].

Patients who had comorbidity such as diabetes mellitus (DM) (*n* = 6), chronic kidney disease (CKD) (*n* = 4), chronic obstructive pulmonary disease (COPD) (*n* = 3), and hypertension (*n* = 3) suffered from mucormycosis with in 1<sup>st</sup> week of admission [Table 2a-d].

All the patients who had only single comorbidity (22.72%) suffered from mild disease, and patients who had more than one comorbidity suffered from moderate (27.27%)-to-severe (50%) COVID infection.

Three/five (60%) patients with single comorbidity required steroids, whereas 14/17 (82.35%) patients with greater than one comorbidity required steroids.

About 92.3% of DM, 100% cases of CKD, 100% cases of COPD, and 100% cases of hypertension were on continuous oxygen [Table 5].

Seven/ten (70%) cases with computed tomography (CT) value of reverse transcription-polymerase chain reaction (RT-PCR) test <20 showed a severe degree of COVID-19 infection [Table 6a].

Majority of cases in 12/13 (92.30%) who showed CT value of RT-PCR test <20 were on steroids [Table 6b].

Thirteen/seventeen (76.47%) cases who had CT value <20 needed oxygen [Table 6c].

Total leukocyte count (TLC) count was higher in 21/22 (95.45%) cases who had the onset of mucormycosis in <5 weeks [Table 7].

Low lymphocyte count was seen in 21/22 (95.45%) cases who had onset of mucormycosis in <5 weeks [Table 8].

About 10/21 (47.61%) cases with severe degree of COVID-19 infection showed higher values of interleukin (IL)-6 as compared to 11/21 cases (52.38%) who had lesser IL-6 levels and were mild to moderate in severity [Table 9a].

IL-6 levels were more in 17/21 (80.95%) cases who required oxygen therapy [Table 9b].

IL-6 levels were higher in 11/21 (52.38%) cases with the onset of mucormycosis <1 week [Table 9c].

D-dimer levels were higher in 10/18 (55.55%) cases with the onset of mucormycosis <1 week [Table 10] C-reactive protein (CRP) levels were highest in 10/19 (52.63%) cases who were severe in the severity of COVID 19 infection followed by 5/19 (26.31%) cases who were moderate in severity and were lowest in 4/19 (21.05%) cases [Table 11].

Thirteen/twenty-two (59.09%) patients were blood group A positive.

Positive patients suffered from severe COVID infection (8/13, i.e., 61.53%) [Table 12a].

Positive patients suffered from severe COVID infection, 8/13 (61.53%) needed steroids [Table 12b].

**Table 1: The onset of mucormycosis**

	The onset of mucormycosis (after COVID-19 infection)			Total
	<1 week	3-5	≥5	
Unvaccinated	11	7	1	19
Vaccinated (first dose)	0	3	0	3
Total	11	10	1	22

**Table 2: Comorbidity with the onset**

The onset of mucormycosis (after of COVID-19 recovery)	DM		Total	CKD			COPD			Hypertension		
	Yes	No		Yes	No	Total	Yes	No	Total	Yes	No	Total
<1 week	6	5	11	4	7	11	3	8	11	3	8	11
3-5	7	3	10	0	10	10	2	8	10	0	10	10
≥5	0	1	1	0	1	1	0	1	1	0	1	1
Total	13	9	22	4	18	22	5	17	22	3	19	22

DM: Diabetes mellitus, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease

Positive patients suffered from severe COVID infection, 10/13 (76.92%) needed oxygen [Table 12c].

Non-A blood group showed higher CRP, IL-6, and prothrombin time (PT) value compared to A blood group though D-dimer was more in blood group A [Table 13].

## DISCUSSION

Diabetes, hypertension, smoking, and another comorbidity status single/multiple have been existing for decades. Out of this, DM is known to develop superadded bacterial and fungal infections. However, none of them had the extent of mucormycosis that had been reported worldwide, particularly in India. This article makes an attempt to bring out precipitating factors and the possible reason as to why and what changes were brought about by COVID-19 that suddenly led to an increased number of mucormycosis cases at unprecedented levels.

A total of 22 patients were diagnosed as suffering from mucormycosis and the majority were unvaccinated. Only three patients who received vaccination but had multiple comorbidities such as DM and COPD also developed superadded mucor infection. A reduction in CD4+ T-lymphocytes has been observed which is responsible for opportunistic fungal infections in these cases.<sup>[5-8]</sup>

It was also found that 11 patients out of 22 (50%) started manifesting mucormycosis within 1 week of COVID infection. None of the patients had any mucormycosis beyond 5 weeks of recovery. However, patients who had comorbidities such as DM (six cases), CKD (four), COPD (three), and hypertension (three) suffered from mucormycosis within 1<sup>st</sup> week of admission. It was also pertinent to find that all these patients were on steroids and oxygen. The

treatment plan included steroids for critical COVID patients. The steroids were responsible for hyperglycemia and the development of invasive fungal infections.<sup>[9-11]</sup>

All the patients who had only single comorbidity (22.72%) suffered from mild disease and patients who had more than one comorbidity suffered from moderate (27.27%)-to-severe (50%) COVID infection [Table 3]. Three/five (60%) patients with single comorbidity required steroids, whereas 14/17 (82.35%) patients with greater than one comorbidity required steroids [Table 4]. About 92.3% of DM, 100% cases of CKD, 100% cases of COPD, and 100% cases of hypertension were on continuous oxygen [Table 5a-d]. Significant angiotensin-converting enzyme (ACE)-2 receptor expression has been seen in such groups of patients with single or multiple comorbidities and helps in viral entry into the host cells.<sup>[12]</sup>

CT values of the RT-PCR test were also compared with different parameters. CT value had no relation with clinical manifestations such as fever slurred speech, numbness, pain, nasal blockage, or nasal ulceration. Seventy percent of patients who had a severe form of COVID-19 had CT values <20. 92.20% were on steroids and 76.47% needed oxygen. Such low values have been directly linked to the possibility of a flared disease. It has been observed and documented that the test of choice for making a prompt definitive diagnosis is the RT-PCR test. The amount of viral load can be ascertained by measuring CT value which has an inverse relationship with each other.<sup>[13-15]</sup>

It was also interesting to note that total leukocyte count was higher in 95.45% of cases whose onset of mucormycosis was <5 weeks. Increased leukocyte count in such patients is responsible for the activation of the cellular phase of acute inflammation which finally culminates in massive production of cytokines and extensive damage to organs.<sup>[16,17]</sup>

In spite of this high TLC count, 95.45% of patients had lymphocytopenia. The steroids, on the one hand, led to an increase in white blood cell count in particular neutrophilia, and on the other hand, also cause lymphopenia. Since T lymphocyte is the backbone of cell-mediated immunity, any disruption in their levels will lead to decreased immune response and complications in the disease process.<sup>[18,19]</sup>

About 47.61% of cases who had a mean IL-6 level of 42.09 pg/ml had a severe degree of COVID infection; 52.38% had a lesser level of IL-6 rise and were mild to moderate in severity. COVID-19 infection causes severe inflammation which leads to cytokine storm. IL-6 plays multiple roles which

Severity of COVID-19 infection	Single comorbidity, n (%)	>1 comorbidity, n (%)
Mild	5/22 (22.72)	0
Moderate	0	6/22 (27.27)
Severe	0	11/22 (50)

Steroid usage	
Single comorbidity, n (%)	>1 comorbidity, n (%)
3/5 (60)	14/17 (82.35)

Oxygen requirement	DM			CKD			COPD			Hypertension		
	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	12	6	18	4	14	18	5	13	18	3	15	18
No	1	3	4	0	4	4	0	4	4	0	4	4
Total	13	9	22	4	18	22	5	17	22	3	19	22

DM: Diabetes mellitus, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease

**Table 6: Cycle threshold value with other variables**

a. Ct value with the severity of COVID-19 infection				
Ct value of RT-PCR test	The severity of COVID-19 infection			Total
	Mild	Moderate	Severe	
10-15	1	1	4	6
15-20	1	3	3	7
20-25	2	1	2	5
25-30	1	1	1	3
Total	5	6	10	21

b. Ct value with steroids				
Ct value of RT-PCR test	Steroids		Total	P
	No	Yes		
10-15	0	6	6	0.012
15-20	1	6	7	
20-25	2	3	5	
25-30	3	0	3	
Total	6	15	21	

c. Ct value with oxygen requirement				
Ct value of RT-PCR test	Oxygen requirement		Total	P
	Yes	No		
10-15	6	0	6	0.001
15-20	7	0	7	
20-25	4	1	5	
25-30	0	3	3	
Total	17	4	21	

RT-PCR: Reverse transcription-polymerase chain reaction, Ct: Cycle threshold

**Table 7: Relation of total leukocyte count with the onset of mucormycosis**

Onset of mucormycosis	Mean (TLC)	n
<1 week	27,250	11
3-5	25,790	10
≥5	13,000	1
Total		22

TLC: Total leukocyte count

**Table 8: Lymphocytes with onset of Mucormycosis**

Onset of Mucormycosis (after covid-19 recovery)	Mean Lymphocyte (%)	n
<1 week	17.18	111
3-5 week	19.40	10
>5 week	34.00	1
Total	18.95	22

include proinflammatory which results in cytokine storm and also has a role in tumorigenesis.<sup>[20]</sup>

It was also found that 80.95% of mucor cases had high IL-6 and were dependent on oxygen. IL-6 levels were also very high in 52.38% of mucormycosis cases who developed mucormycosis within 1 week. Only one case who had the lowest rise of IL-6 developed mucormycosis after 5 weeks. All the patients

**Table 9: Interleukin-6 with other variables**

a. IL-6 with severity		
Severity of COVID-19 infection	Mean IL-6 (0-6.4 pg/ml)	n
Mild	38.6200	5
Moderate	29.7167	6
Severe	42.0900	10
Total	37.7286	21

b. IL-6 with oxygen requirement		
Oxygen requirement	Mean IL-6	n
Yes	42.0235	17
No	19.4750	4
Total	37.7286	21

c. IL-6 with the onset of mucormycosis		
The onset of mucormycosis (after of COVID-19 recovery)	Mean IL-6	n
<1 week	51.0727	11
3-5	25.0778	9
≥5	4.8000	1
Total	37.7286	21

IL-6: Interleukin-6

**Table 10: D-dimer with the onset of mucormycosis**

Onset of mucormycosis	Mean D-dimer (0-0.50)	n
<1 week	2.3850	10
3-5	1.0250	8
Total	1.7806	18

who developed mucormycosis within 1 week also had higher D-dimer levels (55.5%). Similarly, the CRP level was high in severe COVID cases (52.63%) followed by 26.3% of cases who had a moderate-to-severe disease. CRP values rise significantly in active inflammatory processes like COVID-19 which acts as a perfect soil for the development of mucormycosis.<sup>[21]</sup>

When we analyzed the blood group, we found that majority of cases 59.09% were in blood group A. Out of this, 61.53% suffered from severe COVID infection and 76.92% were dependent on oxygen and 61.53% needed steroids. No study could be found in the literature which could depict the relationship between blood group and mucormycosis infection. ACE is specifically inhibited by human natural anti-A antibodies in respiratory tissue due to which out of all blood groups, A blood group patients are most prone to this infection. Angiotensin II stimulates an inflammatory cascade in the alveoli which in turn destroys the alveolar cells and is responsible for the development of hypoxia.<sup>[22]</sup>

The clinical signs and symptoms have no relation to the blood group. It was interesting to note that non-A blood group showed higher CRP, IL-6, and PT values compared to A blood group though D-dimer was more in blood group A. It has been documented that due to a higher level of von Willebrand factor in patients with blood group A as compared to non-A blood groups; the A blood group subset is prone to develop more defects in hemostasis and thrombosis.<sup>[23-25]</sup>

**Table 11: C-reactive protein with severity**

Intensity of COVID-19 infection	Mean	n
Mild	46.50	4
Moderate	52.60	5
Severe	56.30	10
Total	53.26	19

**Table 12: Blood group with other variables****a. Blood group with infection severity**

Blood group	Severity of COVID-19 infection			Total
	Mild	Moderate	Severe	
A	2	3	8	13
B	1	0	2	3
AB	1	1	1	3
O	1	2	0	3
Total	5	6	11	22

**b. Blood group with the use of steroids**

Blood group	Steroids		Total
	No	Yes	
A	5	8	13
B	2	1	3
AB	0	3	3
O	0	3	3
Total	7	15	22

**c. Blood group with oxygen requirement**

Blood group	Oxygen requirement		Total
	Yes	No	
A	10	3	13
B	2	1	3
AB	3	0	3
O	3	0	3
Total	18	4	22

**Table 13: Mean values of prothrombin time, interleukin-6, D-dimer, and C-reactive protein in A versus non-A blood groups**

Blood group	Mean value of PT	Mean value of IL-6	Mean value of D-dimer	Mean value of CRP
A	15.30	27.60	1.85	39.75
Non-A	16.27	51.22	1.66	76.42

PT: Prothrombin time, IL-6: Interleukin-6, CRP: C-reactive protein

## CONCLUSION

The multidisciplinary team of doctors who are involved in treating COVID patients must be mindful of the fact that mucormycosis can develop in them. Since it is a life-threatening angioinvasive disease, timely diagnosis and management of the patient can reduce the mortality rate. It is imperative that one must adhere to strict guidelines while administering steroids to such group of patients and prevent the development of such deadly infections.

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## Conflicts of interest

There are no conflicts of interest.

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