

# Incidence of COVID-19-Associated Mucormycosis in COVID-19 Patients after Discharge from the COVID-19 Hospital

Aayush Kulshrestha, Richa Aggarwal<sup>1</sup>, Parul Kodan<sup>2</sup>, Yudhyavir Singh, Rakesh Kumar, Kapil D. Soni<sup>1</sup>, Purva Mathur<sup>3</sup>

Department of Anaesthesiology, Critical Care and Pain Medicine, All India Institute of Medical Sciences, New Delhi, <sup>1</sup>Critical and Intensive Care, JPNATC, All India Institute of Medical Sciences, New Delhi, <sup>2</sup>Department of Medicine, All India Institute of Medical Sciences, New Delhi, <sup>3</sup>Laboratory Medicine, JPNATC, All India Institute of Medical Sciences, New Delhi, India

## Abstract

**Background:** There are studies available on the prevalence of coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM) in hospitalized patients but not on the incidence of CAM in post-discharge patients. The aim of our study was to find the incidence of CAM in the patients discharged from a COVID hospital. **Material and Methods:** Adult patients with COVID discharged between March 1, 2021 and June 30, 2021 were contacted and enquired about sign and symptoms of CAM. Data of all included patients were collected from electronic records. **Results:** A total of 850 patients responded, among which 59.4% were males, 66.4% patients had co-morbidities, and 24.2% had diabetes mellitus. Around 73% of patients had moderate to severe disease and were given steroids; however, only two patients developed CAM post discharge. **Conclusion:** The incidence of CAM post discharge was low in our study, which could be attributed to protocolized therapy and intensive monitoring.

**Keywords:** After discharge, CAM, COVID, COVID-associated mucormycosis, incidence

## INTRODUCTION

Coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM) emerged as the most feared complication of COVID-19 during this pandemic, particularly in India, and became a major public health problem. During the second wave of COVID-19, there was a steep rise in the number of CAM cases, and as of July 20, 2021, India counted 45,432 confirmed cases and 4252 deaths.<sup>[1]</sup> Various studies looked upon the risk factors for CAM.<sup>[2-4]</sup> The most important risk factors appeared to be hyperglycemia because of diabetes mellitus (DM)<sup>[3,4]</sup> or steroid use<sup>[3,4]</sup> and COVID-19 itself.<sup>[5,6]</sup> The other risk factors assumed to be of significance were treatment with anti-IL6 therapies,<sup>[2,4]</sup> the widespread use of antibiotics,<sup>[7]</sup> contaminated oxygen,<sup>[8]</sup> excessive steam inhalation, and zinc therapy.<sup>[9]</sup>

There are published reports of patients who developed CAM while in the hospital or who presented to the hospital with CAM; however, there are no reports on the incidence of CAM in patients discharged from the hospital. The symptoms of CAM usually develop around 10–14 days after symptoms of COVID-19 and may also develop after recovery from

COVID-19,<sup>[2]</sup> by which time most patients are discharged. The aim of our study was to find the incidence of CAM in the patients who were discharged from dedicated COVID-19 hospital after recovery from COVID-19.

## METHODOLOGY

This was a cross-sectional study conducted in the COVID-19 center of AIIMS, New Delhi, after approval from institutional ethics committee. Adult patients with mild, moderate, and severe COVID-19 who remained admitted in the hospital for at least 24 hours and discharged between March 1, 2021 and June 30, 2021 were eligible. All these admitted patients were treated according to the

**Address for correspondence:** Dr. Richa Aggarwal, Additional Professor, Critical and Intensive Care, JPN Apex Trauma Centre, All India Institute of Medical Sciences, New Delhi, India. E-mail: pathakricha@yahoo.co.in

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**How to cite this article:** Kulshrestha A, Aggarwal R, Kodan P, Singh Y, Kumar R, Soni KD, *et al.* Incidence of COVID-19-associated mucormycosis in COVID-19 patients after discharge from the COVID-19 hospital. *Indian J Community Med* 2023;48:364-8.

**Received:** 05-12-22, **Accepted:** 15-02-23, **Published:** 07-04-23

### Access this article online

Quick Response Code:



Website:  
www.ijcm.org.in

DOI:  
10.4103/ijcm.ijcm\_967\_22

national clinical management protocol of COVID-19 by Government of India.<sup>[10]</sup> Discharge criteria were defined as patients who had turned severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-negative via a reverse transcriptase polymerase chain reaction (RTPCR) test or whose clinical symptoms had resolved. They were contacted through telephone or whatsapp 2 months after the date of discharge. Those who responded were included in the study after the consent. They were asked about the sign and symptoms of mucormycosis. A self-designed semi-structured standard questionnaire was used for the sign and symptoms (Appendix 1). All patients with clinical symptoms likely to be CAM were called to the hospital and clinically examined. Wherever appropriate, tissue samples were extracted for fungal KOH mount and other tests if required. The outcome was the number of patients who developed mucormycosis after discharge.

### Data collection and analysis

Demographic data and treatment details of all the included patients were collected from their electronic medical records and daily progress charts. Data collected included demographics, history, co-morbidities, clinical details, and treatment details. The data was summarized and analyzed using STATA (Version 14.0) software and expressed as mean  $\pm$  standard deviation (SD)/median (min, max) and numbers and percentages as appropriate to describe the patient's demographic and clinical characteristics.

### Statistical analysis

Sample size: There are no data available yet on the incidence of mucormycosis in COVID-19 patients discharged from the hospital. Hence, this was an exploratory study wherein we included 'All' the consecutively eligible patients admitted in the hospital over the stipulated time period. The number of admissions varied in different months according to the infections during the second wave of COVID in India.

## RESULTS

During the study period, a total of 1554 adult patients were discharged from the hospital and were contacted; however, 850 patients responded and consented for inclusion in the study.

The demographic data of all the patients are depicted in Table 1. The median age of the patients was 48 years [inter-quartile range (IQR) 34–60], and 59.4% of patients were males. Approximately 2/3<sup>rd</sup> of the patients (66.4%) had one or more co-morbidities, with hypertension being the most common in 276 (32.4%) patients, followed by diabetes mellitus in 206 (24.2%) patients. The patients had varying degrees of severity of COVID-19 [Table 1]. Around 73% of patients had moderate to severe disease and were administered steroids. 36.2% patients required intensive care unit (ICU) admission, and nearly 79% were given antibiotics. The number of patients administered antivirals, immuno-modulatory agents, and antifungals and who underwent surgical procedures is given in Table 1.

**Table 1: Demographics, clinical characteristics, and post-discharge symptoms related to CAM in study patients (n=850)**

Variable	Median (IQR)/Number (%)
Age Median (IQR) (years)	48 (34-60)
Gender	Number (%)
Males	505 (59.4)
Females	345 (40.6)
Comorbidities	Number (%)
Hypertension	276 (32.5)
Diabetes Mellitus	206 (24.2)
Hypothyroidism	83 (9.8)
Coronary Artery Disease	52 (6.1)
Chronic Lung Disease	52 (6.1)
Chronic Kidney Disease	49 (5.8)
Malignancy	42 (4.9)
Chronic Liver Disease	37 (4.4)
Tuberculosis	26 (3.1)
Cerebrovascular Disease	23 (2.7)
Renal Transplant	14 (1.6)
Seizure	10 (1.2)
Rheumatic Heart Disease	10 (1.2)
Clinical Presentation	
Fever	589 (69.3)
Cough	421 (49.5)
Breathlessness	371 (43.6)
Gastrointestinal complaints	141 (16.4)
Loss of Taste	38 (4.5)
Headache	30 (3.5)
Chest Pain	29 (3.4)
Altered Sensorium	22 (2.6)
Neurological Weakness	16 (1.9)
Seizures	5 (0.6)
COVID-19 Severity	
Mild	228 (26.8)
Moderate	360 (42.4)
Severe	262 (30.8)
ICU Admission	308 (36.2)
Oxygen Requirement	620 (73)
Steroids	618 (72.7)
Remdesivir	400 (47.1)
Tocilizumab	7 (0.8)
Antibiotics	673 (79.2)
Antifungals	287 (33.8)
Ventilator	29 (3.4)
Tracheostomy	12 (1.4)
Surgery during hospital stay	70 (8.2)
Neurological Issues during stay	32 (3.8)
Length of Stay (Days)	
Length of Hospital stay	8 (5-13)
Length of ICU stay	9 (6-12)
CAM Symptoms	
Decreased Vision	15 (1.8)
Swelling of Eye	9 (1.1)
Nasal Discharge	6 (0.7)
Eye Pain	6 (0.7)

*Contd...*

**Table 1: Contd...**

Variable	Median (IQR)/Number (%)
Headache	3 (0.4)
Numbness of Face	3 (0.4)
Epistaxis	1 (0.1)
Altered Sensorium	1 (0.1)

CAM – COVID-19-associated mucormycosis; ICU – Intensive care unit

The median duration of hospital stay was 8 days (IQR 5–13) among all the patients, and the median length of ICU stay was 9 (IQR 6–12) days among 308 patients who required ICU care.

Out of 850 patients who responded, only two patients had developed confirmed CAM post discharge from the hospital and required re-admission. The first patient was a 64-year-old hypertensive and diabetic male who was admitted with moderate COVID-19 and required oxygen support in the ICU. He had received a course of steroids and remdesivir and developed CAM 10 days after discharge and 20 days after initial admission. The other patient was a 55-year-old diabetic and hypertensive female who was admitted with mild COVID-19 and developed CAM 20 days after discharge and 30 days after her initial admission.

Among the symptoms related to CAM in other patients, the most common symptom reported was decreased vision (in 1.8% of patients), followed by swelling of eye [Table 1]. All the patients who had symptoms related to CAM were called for clinical examination. Among those who reported, none of them was diagnosed with CAM.

## DISCUSSION

The incidence of CAM in our study population was low, that is, 0.23%. There are no previous studies which have evaluated the incidence of CAM in post-discharge patients; however, the reported prevalence of CAM in hospitalized patients is almost similar, that is, 0.27%, ranging from 0.05% to 0.57%.<sup>[3]</sup>

Diabetes and hyperglycemia are the major risk factors for CAM.<sup>[3-5]</sup> A multi-center COVID-19-Mucor study from India found that 62.7% of CAM patients had uncontrolled diabetes.<sup>[2]</sup> In our cohort, 24.2% patients were diabetic and most of them (82%) developed moderate to severe COVID-19 and received steroids; however, only two patients developed CAM post discharge. The possible reason for such low incidence could be protocolized management and intensive control of blood glucose levels in this at-risk group.

Inappropriate glucocorticoid use has been independently associated with a risk of developing CAM.<sup>[3,4]</sup> The extensive benefits of steroids to reduce mortality and hospital stay for COVID-19 patients have led to their widespread misuse. At our center, steroids were administered to the patients for a short duration of 5–10 days and the blood glucose levels were closely monitored. Hyperglycemia was well controlled with use of intermittent or continuous insulin infusions.

Other at-risk patients for CAM such as patients with malignancy and immuno-suppression were very few in our cohort.

COVID-19 itself has been proposed as an independent risk factor for CAM because of its propensity to cause immune dysregulation.<sup>[5]</sup> Even the patients with mild disease are at risk.<sup>[6]</sup> However, we did not find high incidence among our discharged COVID-19 patients.

Other presumed risk factors for development of CAM are the use of anti-inflammatory agents<sup>[3,4]</sup> and antibiotics<sup>[7]</sup> in COVID-19 patients; however, none of these interventions led to an increase in the incidence of CAM at our hospital. The hyper-inflammatory phases of COVID-19 have been managed with various immuno-modulator therapies, and these may contribute to a period of prolonged immuno-suppression, thereby increasing the risk for mucormycosis. Few published series of CAM reported that tocilizumab was given in 2–4% of all patients.<sup>[3,4]</sup> The use of tocilizumab was limited and restricted at our center, and only seven (0.82%) patients who were included in the study had received tocilizumab. Many experts have questioned the use of antibiotics in COVID-19, with the justification that they disrupt the normal commensal flora that protects against opportunistic infections. Although antibiotics were prescribed to 79.1% of our study patients, they were given for a short duration. Antibiotics were prescribed to patients who had suspected or pre-existing infections and who were administered steroids and immuno-modulators.

Although evidence of a direct relationship between zinc intake and mucormycosis is lacking, experimental studies show that zinc does promote the growth of some isolates of *Rhizopus arrhizus*, as reported by Muthu *et al.*<sup>[9]</sup> In our hospital, all patients received zinc in a dose of 50 mg OD throughout their stay.

Steam inhalation and the use of nebulizers have been widely used in Indian households as routine treatment for COVID-19. The use of poor quality of water and unsterilized equipment has raised the possibility of them contributing to the rise in mucormycosis cases in the country. All patients at our hospital received steam inhalation therapy and nebulization with proper sterilized equipment.

Our study has important implications. The low prevalence of CAM in discharged COVID-19 patients highlights the role of protocolized therapy and intensive monitoring in the management of COVID-19 in the hospital. Despite several risk factors in our study cohort, the incidence was very low in discharged patients. However, there are certain limitations too. We are uncertain about the incidence of CAM in patients who did not respond or did not come for follow-up.

## CONCLUSION

The incidence of CAM in post-discharge patients was low in our study. This low incidence could be attributed to protocolized therapy and intensive monitoring of the patients during the hospital stay.

### Ethical approval

Institutional ethical approval taken.

### Financial support and sponsorship

The study was conducted with Institutional intramural grant.

### Conflicts of interest

There are no conflicts of interest.

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## **APPENDIX 1**

### **Screening questionnaire**

#### **Symptoms Yes/No (if yes then since when)**

Swelling of eye (with side)  
Decreased vision/Blurring of vision  
Drooping of eyelid  
Eye pain  
Facial swelling  
Numbness/tingling of face  
Difficulty in chewing/swallowing  
Jaw pain/tooth ache  
Nasal discharge Blackish/blood tinged/clear  
Nasal stuffiness  
Epistaxis  
Headache  
Irritability  
Altered sensorium  
Fever

#### **Other Post-discharge complaints and duration**

Fever  
Fatigue  
Cough  
Breathlessness  
Need for oxygen  
Chest pain  
Leg swelling  
Any other

#### **Any other hospital admission after discharge**

Cause  
Duration of admission