Predictors for mucormycosis in COVID era: A case-control study from Gujarat

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ABSTRACT

Context: Mucormycosis has been increasingly described in the coronavirus disease (COVID-19) era, however, there is a lack of robust epidemiological studies to understand the predictors for the development of mucormycosis from India. Aims: To document the risk factors of mucormycosis with or without COVID-19 and estimate the strength of association of various risk factors. Settings and Design: A case-control study was conducted in the Ahmedabad districts of Gujarat from June to August 2021. Methods and Material: One hundred participants (25 cases with mucor, 75 without mucor) were enrolled in the study. The cases and controls were then matched based on age and gender. Ethical approval was sought from the Institutional Ethics Committee of the Indian Institute of Public Health Gandhinagar, Gujarat, India. Statistical Analysis Used: Data were collected using the Epi Collect 5 application, and the descriptive, inferential analysis was done using the SPSS version 21 statistical software. Results: About 68% of the cases were from a rural area and had past comorbidity conditions. About 80% of the cases reported a previous history of COVID-19, whereas 67% of the controls reported the same. The factors which remained significant after applying the hierarchical model were rural residents (OR = 3.2 [95% CI: 1.05–10.3]) and history of oxygen therapy (OR = 5.42 [95% CI: 1.24–23.8]). Conclusions: This study concludes that mucormycosis is independent of the COVID-19 status. Rural residents and oxygen therapy were found to be the most significant risk factors for mucormycosis. The findings of this study are also not conclusive to establish an association; thus, further exploration and in-depth research with larger samples are recommended.

Keywords: Case-control, COVID-19, India, mucormycosis

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has caused a global pandemic of the coronavirus disease (COVID-19). More than 222 million confirmed COVID-19 cases worldwide with over 4.5 million deaths as of September 9, 2021, have been reported.¹ The COVID-19 pandemic can cause life-threatening pneumonia with associated coinfections. The evidence reported that the COVID affected people with pre-existing comorbidity are prone to develop severe opportunistic infections such as oropharyngeal candidiasis, pneumocystis jiroveci pneumonia, pulmonary aspergillosis, bloodstream candida infections, and mucormycosis.²⁻⁴ Among other complications, mucormycosis is one of the significant complications that is debatable during this COVID-19 era.

Mucormycosis is a deadly fungal infection and has shown an increasing trend during the COVID-19 pandemic globally and...
more so in India.[7] The overall mortality rate is approximately 50%, although early identification and treatment can lead to better outcomes. Data show more than 4,000 people with COVID-associated mucormycosis (CAM) in India—the highest globally.[7,8] The complications might lead to death as it resides as a symbiotic of the nasal mucosa and can germinate in the nasal cavity, paranasal sinuses to invade the palate, orbits, and brain.[9,10] The literature cites complex reciprocity/interaction of the factors including uncontrolled pre-existing diabetes, new onset of diabetes during the COVID management, rampant and irrational overuse of steroids, irrational use of broad-spectrum antibiotics, prolonged Intensive care unit (ICU) stay, and the presence of other comorbidities such as hematological malignancies, use of immunosuppressants, and solid organ transplant.[5,8,11–14] The increasing trend of CAM might be because COVID-19 itself causes an immunosuppressed state, and to a greater extent, the COVID management trend in India.[8,12,13]

In India, the prevalence of mucormycosis is estimated as 140 per million population, which is about 80 times higher than the prevalence in developed countries.[16] The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population. As of June 8, 2021, India recorded 28,252 mucormycosis cases. Among them, 86.0% had a history of COVID-19, and 62.3% had diabetes.[17]

Although mucormycosis has been increasingly described in COVID-19 patients, it is also reported in non-COVID patients. Hence, there is a lack of robust evidence on the risk factors for developing mucormycosis among the COVID and non-COVID patients. The predominant risk factors for CAM such as inappropriate steroid therapy and uncontrolled diabetes have been documented in the literature. While 32.6% of the patients had no diabetic history, 79% of them received steroid therapy.[18] A better understanding of the risk factors of mucormycosis can help the primary physicians in the prevention, early diagnosis, and management of the patient at risk of developing mucormycosis.

To date, most of the studies conducted are based on the review of the literature, systematic review, case studies, and case series, but there is a lack of robust epidemiological studies to understand the predictors in the form of risk factors for the development of mucormycosis, especially from India. Thus, the present study aims to document the risk factors of mucormycosis with or without COVID-19 and to estimate the strength of association of the various risk factors.

Materials and Methods

Study Design: A case-control study was conducted in the Ahmedabad district of Gujarat, India, from June to August 2021. The cases were defined as patients affected with mucormycosis during March–May 2021 and identified through snowball sampling. The details of mucor cases were retrieved from the registry available with the designated pharmacists for the sale of scheduled drugs as notified by the state government.

The mucor patients who were hospitalized in different hospitals of Ahmedabad or discharged within 7 days during the reference period of March–May 2021 were included as cases. The control of the cases was either a neighbor or household contacts or hospitalized patients for any other problems in the same hospital.

Sample Size: A total of 100 participants were enrolled in the study. A total of 25 cases and 75 controls (1:3), irrespective of COVID, diabetes status, were enrolled in the present study. The controls were matched based on age and gender.

The mucor cases with age >18 years, hospitalized or discharge before 7 days of interview (between March and May 2021), and willing to participate were enrolled in the study. Severely ill patients were excluded from the study. Only survivors were included in the study.

Data collection and analysis

The data were collected using a pretested questionnaire. The demographic characteristics, morbidity, hospitalization, and lab test details were obtained through the questionnaire. Various factors like a history of diabetes, COVID-19, hospitalization for COVID, oxygen therapy, steroid therapy, occupation, etc., were also documented to identify the risk factors for developing mucormycosis. The clinical manifestations and treatment details of mucormycosis were also documented. Information on amphotericin B prescription and consumption was retrieved from the case papers. The patients were interviewed using a structured pretested questionnaire. Data were collected using the Epi Collect 5 application, and the descriptive, inferential analysis was done using the SPSS version 21 statistical software.

Ethical approval was sought from the Institutional Ethics Committee of the Indian Institute of Public Health Gandhinagar, Gujarat, India. The permission from the hospital authority was obtained before data collection.

Results

Sociodemographic characteristics of cases and controls

A total of 25 cases (mucor positive) and 75 controls (mucor negative) were enrolled in the present study. Out of the total 25 cases, the majority were males (80%) and above 40 years. A majority (80%) of the cases had a history of COVID-19 and were hospitalized for its management except for three (15%) cases. Most (92%) of the mucor cases had a loss of vision and the remaining 8% had maxillary necrosis and sinusitis.

As presented in Table 1, among the cases, the majority were from rural areas, whereas in the control group, the majority were
from urban areas. Among the cases, most of the participants were engaged in a private job or retired, and 20% were farmers, whereas, among the control group, the majority (60%) were engaged in a private job or had their own business. The history of comorbidities was higher among the cases in comparison to the control groups. Out of a total of 25 cases, 68% had a history of comorbidities like hypertension or diabetes. The majority (64%) of the cases were diabetic, whereas the proportion of diabetic patients among the control group was 21%.

The details of COVID-19 and its management were also documented for further risk factor analysis. Out of a total of 25 cases, 80% of the patients had a history of COVID-19, whereas, among the control, 67% of the cases had COVID-19. In comparison to control, the history of oxygen therapy was higher among the cases. Most (80%) of the mucor cases had a history of steroids, whereas half of the controls had received steroids. The consumption of antibiotics was also higher among the cases compared to the controls. Sixty percent of the cases had a history of consumption of doxycycline whereas 76% had taken azithromycin, and 48% received remdesivir.

The cases and controls were compared to identify the possible risk factors for mucor, and the odds ratio was calculated. The cases and controls were compared based on sociodemographic variables like the place of residence, history of comorbidities, diabetes, medication, steroid, and oxygen therapy. As presented in Table 2, the people who reside in rural areas have three times more risk of developing mucor compared to the urban residents (OR: 3.7, 95% CI: 1.05–10.3) and the finding was statistically significant. The diabetic patients have six times more risk of mucormycosis compared to non-diabetics and the finding is highly significant (OR: 6.55, 95% CI: 0.63–75.2). Other risk factors are a history of oxygen therapy, steroids, and antibiotics like azithromycin.

The logistic regression indicated that the odds of having mucor is three times more among the rural residents (OR = 3.2 [95% CI: 1.05–10.3]) and it remains significant after controlling the confounding factors (P = 0.04) [Table 2]. The patients with a history of oxygen therapy are having a five times higher risk of having mucormycosis compared to the patients without oxygen therapy (OR = 5.42 [95% CI: 1.24–23.8]) with statistically significant. The diabetic patients (OR = 6.85 [95% CI: 0.63–75.2]) are having seven times more risk of developing mucormycosis compared to non-diabetic patients. However, the finding was not statistically significant. The possible contributing factor is comorbidities as it was reflected in the logistic regression model.

**Discussion**

This is possibly the first report from India that identified the associates of mucormycosis with the perspective of COVID-19. The present research shows that the place of residence and oxygen therapy are important risk factors for developing mucormycosis. Unfortunately, there is no substantial evidence available about the association between oxygen therapy and mucormycosis. Previous study revealed that the fungus colonization is predominantly aggravated by the use of steam inhalation or high-flow oxygen, contamination from the use of industrial oxygen, low-quality
The present study shows that the people residing in a rural area are at a higher risk of developing mucormycosis compared to the urban residents, however, one of the probable reasons for the same is the referral of mucor patients from the rural area to the hospitals of Ahmedabad for tertiary care.

There is no robust evidence on the incidence of mucormycosis with age or gender-dependency. However, this study, along with a study done by Pan American Health Organization/World Health Organization (PAHO/WHO) documented higher CAM among the males and 40-year age group. It may be a reflection of a higher prevalence of COVID-19 among Indian males. In contrast, there are lesser odds of having CAM for those who had taken tablet ivermectin and tablet fabiflu during the COVID management, but no firm evidence was found for this observation.

This study documented that diabetes and the use of corticosteroids during the COVID management were strong predictors. Several other studies conducted during the pandemic and even before the pandemic supported the findings for the same. In addition, the literature cites that the mucormycosis cases were higher among the COVID-positive with a history of hospitalization. In contrast, our study observed mucormycosis in COVID-positive with a history of home isolation and hospitalization and also among COVID-negative patients. Hence, it should be noted that the correlation between all these predictors and the incidence of fungal infections in hospitalized COVID-19 patients may be explored by other confounding risk factors for fungal infections, such as the patients’ history of pulmonary disease, comorbidities, and mechanical ventilation.

In concluding, the authors revealed that most of the evidence reported in the COVID pandemic era about the potential role between the immunosuppressants and fungal infections is from case studies, case reports, or minimal sample size. Such a small study size may not represent enough statistical power and may lead to false conclusions. Further meta-analysis of additional retrospective and randomized control studies or extensive sample size studies needs to be conducted to understand the immunosuppressants’ role in predisposing COVID-19 patients to fungal coinfections. There are several limitations of the study. One among the others is the smaller sample size. Thus, the generalizability of the findings of this study is limited to the specific geographic setting. Data were collected as per the hospital records, not prospectively.

This study concludes that mucormycosis is independent of the COVID-19 status. Considering the other risk factors, oxygen therapy and rural residents were found to be the most significant risk factors. There is a lack of evidence on the association between oxygen therapy and mucormycosis. However, a recent study reported the indirect link between mucormycosis and the use of oxygen humidifiers as the hospital water is a potential reservoir for fungi. Therefore, further prospective studies are recommended to understand the association between oxygen therapy and mucormycosis.

There is a need of increased awareness among primary care physicians about the various risk factors for mucormycosis. With the knowledge of risk factors, they can prevent the occurrence of such infections and can manage patients effectively which may lead to less morbidity and mortality.

Acknowledgments
We wish to thank the team of experts from the Indian Institute of Public Health Gandhinagar for providing valuable inputs and feedbacks to the final draft of the manuscript. We would like to thank the key stakeholders who provided the vital information on patient data.

Key Messages
Mucormycosis is independent of the COVID-19 status. Oxygen therapy and rural residents were found to be the most significant risk factors for mucormycosis. However, this study fails to establish the association for those risk factors and is recommended for future large-sample studies.

Table 2: Inferential analysis on predicting the risk factors for the mucormycosis status studied in Gujarat, India, during June-August 2021

| Characteristics          | Cases n=25 (%) | Controls n=75 (%) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|--------------------------|----------------|-------------------|-------------------|----------------------|
| History of COVID         | 20 (80%)       | 50 (67%)          | 2.0 (0.67-5.95)   | -                    |
| Rural residence          | 17 (68%)       | 29 (38.7)         | 3.3 (1.29-8.80)*  | 3.2 (1.05-10.3)*     |
| History of diabetes      | 16 (64%)       | 16 (21%)          | 6.55 (2.44-17.5)** | 6.85 (0.63-75.2)     |
| History of comorbidity   | 17 (68%)       | 25 (32%)          | 4.25 (1.61-11.1)** | 0.85 (0.08-9.2)      |
| History of oxygen therapy| 12 (48%)       | 11 (15%)          | 5.37 (1.95-14.7)** | 5.42 (1.24-23.8)*    |
| History of steroids      | 20 (80%)       | 42 (56%)          | 3.14 (1.06-9.26)*  | 1.61 (0.23-11.34)    |
| History of remdesivir    | 12 (48%)       | 25 (33%)          | 1.84 (0.73-4.63)   | 0.39 (0.09-1.75)     |

Antibiotic consumption

| Medication      | Cases n=25 (%) | Controls n=75 (%) | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------|----------------|-------------------|-------------------|----------------------|
| Azithromycin    | 19 (76%)       | 37 (49%)          | 3.25 (1.16-9.05)*  | 1.81 (0.35-9.3)      |
| Ivermectin      | 9 (36%)        | 35 (47%)          | 0.64 (0.25-1.63)   | -                    |
| Dosycycline     | 10 (60%)       | 30 (27%)          | 1.00 (0.39-2.51)   | -                    |
| Fabiflu         | 8 (32%)        | 34 (45%)          | 0.56 (0.21-1.47)   | -                    |

Significance levels at P<0.05, **<0.01, ***<0.001
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. Available from: https://covid19.who.int/. [Last accessed on 2021 Sep 09].
2. Sarkar S, Gokhale T, Choudhury S, Deb A. COVID-19 and orbital mucormycosis. Indian J Ophthalmol 2021;69:1002-4.
3. Farnoosh G, Alishiri G, Hosseini Zijoud SR, Dorostkar R, Jalali Farahani A. Understanding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19) based on available evidence-A narrative review. J Mil Med 2020;22:1-11.
4. Chowdhary A, Tarai B, Singh A, Sharma A. Multidrug-resistant candida auris infections in critically ill coronavirus disease patients, India, April-July 2020. Emerg Infect Dis 2020;26:2694-6.
5. Salehi M, Ahmadikia K, Badali H, Khodavaisy S. Opportunistic fungal infections in the epidemic area of COVID-19: A clinical and diagnostic perspective from Iran. Mycopathologia 2020;185:607-11.
6. Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19. Cureus 2020;12:10-4.
7. Global Action Funds for fungal Infection. Doctors Around the World Call for Rapid Response to Deadly Mucormycosis (the so-called “black fungus”) Found in COVID Patients in India.-Gaffi | Gaffi-Global Action Fund for Fungal Infections. Available from: https://gaffi.org/doctors-around-the-world-call-for-rapid-response-to-deadly-mucormycosis-the-so-called-black-fungus-found-in-covid-patients-in-india/. [Last accessed 2021 Dec 20].
8. Agnihotri AK, Vij M, Aruoma OI, Yagnik VD, Bahorun T, Villamil ME, et al. The double trouble: COVID-19 associated mucormycosis a focused review and future perspectives. Glob J Med Pharm Biomed Update 2021;16:4.
9. Mohindra S, Mohindra S, Gupta R, Bakshi J, Gupta SK. Rhinocerebral mucormycosis: The disease spectrum in 27 patients. Mycoses 2007;50:290-6.
10. Ferguson BJ. Mucormycosis of the nose and paranasal sinuses. Otolaryngol Clin North Am 2000;33:349-65.
11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
12. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus disease (COVID-19) associated mucormycosis (CAM): Case report and systematic review of literature. Mycopathol 2021;186:289-98.
13. Paul S, Kumar R, Meena V, Ramprasad A, Garg P, Keri V, et al. Clinical characteristics and outcomes of 16 cases with COVID19 and mucormycosis: Experience from a tertiary care center in India and review of literature. Research Square 2021. Available from: https://doi.org/10.21203/rs.3.rs-533347/v1 [Last Accessed on 2021 Sep 17].
14. Sen M, Lahane S, Lahane TP, Parekh R, Honavar SG. Mucor in a viral land: A tale of two pathogens. Indian J Ophthalmol 2021;69:244-52.
15. Selarke L, Sharma S, Saini D, Sharma S, Batra A, Waghmare VT, et al. Mucormycosis and COVID-19: An epidemic within a pandemic in India. Mycoses 2021;64:1253-260.
16. WHO. Mucormycosis. Available from: https://www.who.int/india/emergencies/coronavirus-disease-(covid-19)/mucormycosis. [Last accessed on 2021 Sep 17].
17. Moona AA, Islam MR. Mucormycosis or black fungus is a new fright in India during covid-19 pandemic: Associated risk factors and actionable items. Public Health Pract (Oxf) 2021;2:100153.
18. Chakrabarti A. The recent mucormycosis storm over Indian sky. Indian J Med Microbiol 2021;39:269-70.
19. Rao VUS, Arakeri G, Madikeri G, Shah A, Oeppen RS, Brennan PA. COVID-19 associated mucormycosis (CAM) in India: A formidable challenge. Br J Oral Maxillofac Surg 2021;59:1095-8.
20. Chanda A. COVID-19 in India: Transmission dynamics, epidemiological characteristics, testing, recovery and effect of weather. Epidemiol Infect 2020;148:e182.
21. Fazeli MA, Rezaei L, Javadirad E, Ianfar K, Khosravi A, Saman JA, et al. Increased incidence of rhino-orbital mucormycosis in an educational therapeutic hospital during the COVID-19 pandemic in western Iran: An observational study. Mycoses. 2021;64:1366-77.
22. Sharma S, Grover M, Bhargava S, Samdani S, Kataria T, Post coronavirus disease mucormycosis: A deadly addition to the pandemic spectrum. J Laryngol Otol 2021;135:442-7.
23. Singh Y, Ganesh V, Kumar S, Patel N, Aggarwala R, Soni KD, et al. Coronavirus disease-associated mucormycosis from a tertiary care hospital in India: A case series. Cureus 2021;13:e16152.
24. Ravan S, Agrawal G, Leuva P, Modi P, Amin K. Rise of the phoenix: Mucormycosis in COVID-19 times. Indian J Ophthalmol 2021;69:1563-8.
25. Pakdel F, Ahmadikia K, Salehi M, Tabari A, Jafari R, Mehrparvar G, et al. Mucormycosis in patients with COVID-19: A cross-sectional descriptive multicentre study from Iran. Mycoses 2021;64:1238-52.
26. Patel A, Agarwal R, Rudramurthy SM, Shevkani M, Xess I, Sharma R, et al. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Emerg Infect Dis 2021;27:2349-59.
27. Patel A, Kaur H, Xess I, Michael JS, Savjo J, Rudramurthy S, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect 2020;26:944.e9-15.
28. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A National Strategy to Diagnose Coronavirus Disease 2019-Associated Invasive Fungal Disease in the Intensive Care Unit. Clin Infect Dis. 2021 Oct 5;73(16):e1634-e1644. doi: 10.1093/cid/ciaa1298. PMID: 32860682; PMCID: PMC7499527.
29. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N, et al. COVID-19-associated mucormycosis: An updated systematic review of literature. Mycoses 2021;64:1452-9.