Article published online: 2023-02-22

Health Literacy and Clinic-Epidemiological Profile of Patients with COVID-19-Associated Mucormycosis: A Questionnaire-Based Study

Michell Gulabani[1] Richa Chauhan[1] Diksha Gaur[1] Swati Das[1] Megha Bajaj[1] Ashok Kumar Saxena[1]

[1] Department of Anaesthesia and Critical Care, University College of Medical Sciences, Delhi, India

Ann Natl Acad Med Sci (India) 2023;59:36–48.

Address for correspondence Richa Chauhan, MBBS, DNB Anaesthesia, Department of Anesthesia and Critical Care, University College of Medical Sciences, Guru Teg Bahadur Hospital, Dilshad Garden, Delhi, 110095, India (e-mail: drrichsilverdust@gmail.com).

Abstract

Background The patient partnership is desirable for the optimal management of comorbidities. This became significant more so during the coronavirus disease 2019 (COVID-19) crisis wherein health infrastructure was overburdened.

Objectives The aim of this study was to estimate the clinicoepidemiological profile, health literacy regarding predisposing risk factors, and disease management in patients with COVID-19-associated mucormycosis (CAMCR).

Materials and Methods A structured questionnaire-based study on randomly chosen 100 microbiologically proven patients of CAMCR, consisting of 38 multiple choice questions, was designed with each answer having a patient and assessor response to it.

Results A male predilection was seen (68%) with rhino-orbital (73%) being the commonest anatomic site. Forty-nine percent of the study participants had pre-existing diabetes of which 62% did not carry out regular blood sugar monitoring and in 18%, blood sugars were controlled prior to COVID-19. Thirty-five percent of patients with mild COVID-19 illness were treated with unwarranted steroids and 56% of patients had fluctuating blood sugar levels, during COVID-19 illness.

Seventy-nine percent of patients were not vaccinated against COVID-19, 16% only partially vaccinated. Seventy-one percent of patients were not aware of red flag signs and of mucormycosis with 8% presenting early, on noticing nasal symptoms.

Conclusion This study observed diabetes as the most common comorbidity in patients with CAMCR. A lacuna in the health literacy of diabetics presenting with CAMCR was found. Additionally, knowledge regarding glycemic control during COVID-19 illness with or without the use of steroids and awareness of the "red flag" signs of CAMCR were mostly lacking. Interventions to improve awareness amongst patients with diabetes should help in optimal glycemic control, and avoid potential complications like severe COVID-19 illness, and mucormycosis.

Keywords
- awareness
- diabetes
- epidemiology
- patient education

article published online
February 22, 2023

DOI https://doi.org/10.1055/s-0042-1760288.
ISSN 0379-038X.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Mucormycosis (MCR) referred to as "black fungus" results from inhalation of fungal spores in patients with a weakened immune system.[1] The second wave of coronavirus disease 2019 (COVID-19) in India resulted in an unprecedented outbreak of MCR.

India has had the maximum disease load of MCR even in pre-COVID-19 times, although it remained largely unrecognized.[2] Rhino-orbitocerebral mucormycosis (ROCM) is the most common clinical form and diabetes mellitus (DM) is the biggest risk factor,[3] so much so that MCR has become a diabetes-defining illness.[4] It became a "notifiable disease" in May 2021.[2] India has a major global burden of uncontrolled diabetes.[5] It leads to mortality and morbidity associated with diabetes.[6] It increases the risk of COVID-19 infection and also complications. COVID-19, in turn, can induce acute-onset diabetes in some individuals with no history of diabetes.[7,8] India contributed to approximately 71% of the global cases of MCR in patients with COVID-19 based on published literature from December 2019, to the start of April 2021.[9] Diabetes has been identified as the most common comorbidity in COVID-19 patients in India.[10]

The patient partnership is desirable for optimal management of comorbidities, and health awareness for prevention and timely identification of potential disease complications. This became significant more so during the COVID-19 crisis wherein health infrastructure was overburdened.

Patients presenting early have MCR limited to the nose and paranasal sinuses and can be salvaged with antifungals accompanied by endoscopic surgery.[1,5] Owing to this, sound patient knowledge of predisposing risk factors and early symptom identification should lead to early detection and timely intervention, thereby improving patient outcomes.[5] The second wave of COVID-19 in India provided flourishing grounds for MCR.[9] Its association with COVID-19 is an entity demanding further research.

In the literature search, studies in various developing countries with a high diabetic burden reported awareness in less than half of their study participants and also highlighted the importance of patient awareness and their participation in the effective management of diabetes and prevention of its potential complications.[11,12] However, studies to assess awareness of MCR per se have been found lacking.[13]

Studies analyzing adverse health complications in diabetes revealed decreased incidence in patients where prevention and early detection of diabetes were practiced.[14]

However, studies evaluating the impact of awareness in MCR prevention among diabetic patients are deficient in literature.

In the present study, we aimed to provide a comprehensive assessment of MCR in the backdrop of COVID-19, to highlight the clinicoepidemiological profile, effect of health literacy on predisposing risk factors, and disease management in patients with COVID-19-associated mucormycosis (CAMCR), during the second wave of COVID-19 pandemic in India.

Materials and Methods

This cross-sectional study was conducted using a structured questionnaire in a tertiary care government hospital, during June-August 2021. Institutional ethics committee approval was obtained, IECHR-2021-50-S-R2, and the study was registered under Clinical Trial Registry of India, CTRI/2021/09/036452.

On the basis of a pilot study, 15 to 50% of patients had reasonable knowledge about various factors associated with CAMCR. Taking this value as reference, minimum required sample size with a 10% margin of error and 5% level of significance was 97 patients. To reduce the margin of error, total sample size taken was 100.

The formula used was:

$$N \geq (p(1 - p))/(ME/z_{\alpha})^2$$

Where, Z_{α} = value of Z at a two-sided alpha error of 5%, ME = margin of error, and p = proportion of patients who had reasonable knowledge about various factors associated with the disease.

The inclusion criteria were microbiologically proven MCR, serologically confirmed cases of COVID-19, and age group of 18 to 70 years. Exclusion criteria were MCR not associated with COVID-19, other fungal infections, and patients on invasive ventilation. One-hundred study participants were randomly chosen patients, and written and informed consent obtained. They answered a questionnaire (with 38 questions) with input from his/her attendant, if and when required. All the answers were then verified through the file and other available records by an assessor who was one of the investigators of the study. The structured questionnaire was prepared by the investigators using the existing literature on the awareness and knowledge of patients about their comorbidities and their complications. This was reviewed by senior investigators of the institutional ethics committee and a statistical validation was obtained (►**Annexure 1**). A pilot study was carried out and the questionnaire (►**Annexure 2**) was subsequently modified according to the responses obtained by the participants, so as to optimally simplify the questions for laymen and remove any ambiguity. The questionnaire was bilingual (Hindi and English) with both verbal and written consent forms. Blood sugars were defined as "controlled" when blood sugar values were 80 to 140 mg/dL before meals and less than 200 mg/dL, 2 hours after meals.

Presentation with MCR was defined as "early," when a patient presented to a clinician on noticing the symptoms of nasal cavity involvement.[5]

Awareness of symptoms of MCR was considered complete when being aware of red flag symptoms and considered incomplete if aware only of the advanced symptoms.[5] The assessor's response obtained following verification of health records, where ever available and applicable, was taken as the final response. In case of unavailability of records to verify a patient's response, the patient's response was documented and used in data analysis. In cases where neither the patient was able to recall nor the records were available to verify, the response was documented as "no records."

Statistical Analysis

The data entry was done in a Microsoft Excel spreadsheet and the final analysis was done using the Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, United States, version 21.0. Percentages were calculated for descriptive statistics. For statistical significance, a *p*-value of less than 0.05 was considered.

The inter-kappa agreement analysis was done to ascertain the association between the responses obtained from the patient and from the assessors, thereby mitigating any potential recall bias at the patient's end and also verifying the completeness of the hospital record keeping. Kappa's score derived ranged from poor to very good (0.20–1.00).

Results

The study participants were constituted of 21% young adults (18–39 years of age), 48% middle-aged (40–59 years age), and 31% old adults (≥ 60 years of age). The mean age with CAMCR was 50.85 years (24–77 years). Male predilection was seen, forming 68% of the study population. 41% of patients had wage-earning jobs, and 29% were housewives. The majority of patients hailed from upper lower (34%) and lower-middle (30%) socioeconomic strata of modified Kuppuswamy classification[15] (►**Table 1**). The most common anatomical site seen was rhino-orbital (73%; ►**Table 2**).

The most common chronic medical condition encountered was DM, seen in 49% of patients, either alone or in combination with other comorbidities (►**Table 3**). Sixty-two percent of the pre-existing diabetics in our study sample did not carry out regular blood sugar monitoring, while 38% did. Among the latter, 51% had uncontrolled blood sugars and in 18%, blood sugar was controlled. Moreover, 31% of patients were unaware of blood sugar values and also could not produce any health records (►**Table 4**). Fifty-nine percent of study subjects received systemic steroids during COVID-19 illness. Twenty-nine percent subject were unaware and did not have health record-keeping regarding steroid use (►**Annexure 2**).

The association between COVID-19 disease severity and steroid treatment was assessed by Fisher's exact test (►**Table 5**). It showed that 35% of study patients with mild COVID-19 disease were treated with systemic steroids. In addition, 45% of patients with mild disease were unaware and did not have health records to ascertain steroid

Table 1 Sociodemographic profile of study subjects

Sociodemographic characteristics	*n* (%)/ Mean ± SD
Age (years) Young adults (18–39 years age), middle-aged adults (40–59 years age), old adults (≥ 60 years age).	50.86 ± 12.67 21% 48% 31%
Gender, *n* = 100	
Male	68%
Female	32%
Occupation, *n* = 100	
Blue collar	41%
Housewife	29%
White collar	16%
Business	9%
Farmer	59%
Socioeconomic status, *n* = 100	
Upper	2%
Upper middle	28%
Upper lower	34%
Lower middle	30%
Lower	6%

Abbreviation: SD, standard deviation.

Table 2 Clinical presentations

Clinical form, *n* = 100	
Rhino	3
Cerebral	1
Rhinocerebral	2
Rhino-orbital	73
Rhino-orbital-pulmonary	10
Rhino-orbital-cerebral	11

Table 3 Chronic medical illness in study subjects

H/o Chronic medical illness, *n* = 100	%
DM1	1
DM2	33
DM2 + HTN	11
DM2 + HTN + CAD	1
DM2 + HTN + COAD	1
DM2 + HTN + HepC	1
DM2 + HTN + hypothyroid	2
HTN	5
Hypothyroid	1
No comorbidity	44

Abbreviations: CAD, coronary artery disease; COAD, chronic obstructive airway disease; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; Hep C, hepatitis C; HTN, hypertension.

Table 4 Blood sugar control among pre-existing diabetics

n = 49	%
Blood sugar controlled	18
Uncontrolled	51
No records	31

Table 5 Association of steroid treatment with disease severity

Steroid treatment	Mild ($n = 40$)	Moderate ($n = 24$)	Severe ($n = 36$)	Total	*p*-Value
No	8 (20%)	2 (8.33%)	2 (5.56%)	12 (12%)	0.001[a]
Yes	14 (35%)	16 (66.67%)	29 (80.56%)	59 (59%)	
Don't know	18 (45%)	6 (25%)	5 (13.89%)	29 (29%)	
Total	40 (100%)	24 (100%)	36 (100%)	100 (100%)	

Abbreviation: COVID-19, coronavirus disease 2019.
[a]The association between COVID-19 disease severity and steroid treatment was assessed by Fisher's exact test and was statistically significant with *p*-value of 0.001.

Table 6 Association of COVID-19 vaccination with the severity of COVID-19 illness

COVID-19 vaccination	Mild ($n = 40$)	Moderate ($n = 24$)	Severe ($n = 36$)	Total	*p*-Value
No	30(37.97%)	23(29.11%)	26(32.91%)	79(100%)	0.009
1 dose	8(50%)	0(0%)	8(50%)	16(100%)	
2 doses	2(40%)	1(20%)	2(40%)	5(100%)	
Total	40(40%)	24(24%)	36(36%)	100(100%)	

Abbreviation: COVID-19, coronavirus disease 2019.
Of the unvaccinated study participants, 37.97% had a mild COVID-19 illness and 32.91% had a severe disease.
In the fully vaccinated category (5 patients), 2 patients suffered severe disease. The association was statistically significant with a *p*-value of 0.009.

treatment in them. The association showed a statistically significant *p*-value (0.001). In 47% of the study patients, blood sugar monitoring was done during COVID-19 illness with or without a history of steroid use. In 36%, no blood sugar monitoring was done and 17% patients were unaware and had no pertaining records (►**Annexure 2**).

Fifty-six percent of study subjects had fluctuating blood sugar levels during COVID-19 illness with or without steroid use. Nine percent of them had blood sugars in the normal range. Thirty-five percent of patients were unaware of the blood sugar values and had no health record-keeping (►**Annexure 2**).

Mild and moderate COVID-19 illness was found in 40 and 24% of study subjects respectively, being severe in 36% (►**Annexure 2**). Sixteen percent of the study subjects received only 1 dose of COVID-19 vaccination and 5% had received both doses.

The association between COVID-19 vaccination status and severity of COVID-19 disease was analyzed (►**Table 6**). Of the unvaccinated, 32.91% had severe disease. In the fully vaccinated category (5 patients), two patients suffered severe disease. The association was clinically significant with a *p*-value of 0.009.

Knowledge about the initial symptoms of MCR was lacking in 71% of subjects. Eleven percent had incomplete information about the red flag signs of MCR and were aware only of the symptoms of the advanced disease, while 18% reported awareness of red flag symptoms and signs of MCR (►**Annexure 2**).

Eight percent of the subjects presented early with symptoms of MCR. Initiation of treatment within 5 to 10 days of symptom onset of MCR was done in 25% of the study patients (►**Annexure 2**). A significant *p*-value (< 0.0001) and very good kappa score (0.896) in agreement analysis regarding the onset of symptoms and initiation of treatment for MCR (►**Table 7**).

The agreement analysis between patient and assessor for blood sugar monitoring (►**Table 8**) and blood sugar control (►**Table 9**) during COVID-19 illness and or while on steroid treatment showed a significant *p*-value (<0.001) and a very good kappa agreement (0.882 and 0.714 respectively). The analysis regarding the severity of COVID-19 illness (►**Table 10**) was good ($k = 0.798$).

Discussion

The study patients presenting with CAMCR were more commonly middle-aged, males, belonging to the upper-lower class of modified Kuppuswamy classification, doing wage-earning jobs. The most frequently involved anatomical site was rhino-orbital (►**Tables 1**, **2**). DM was the most common underlying illness (►**Table 3**).

Studies have identified male predilection[2,16–19] and middle age group (45–55 years) as most commonly affected with MCR in pre-COVID-19 times similar to that for our patients with CAMCR,[16,17] as well as for other studies involving patients with CAMCR.[5,20]

Jeong et al in a global meta-analysis in non-COVID-19 times observed ROCM as the most common presentation, in 34% of patients.[11] Likewise, ROCM was also the most common clinical variant globally when associated with COVID-19 but in increasingly higher numbers, in 76%.[18] This was unlike in the pre-COVID-19 times wherein a disparate presentation was seen in the clinical distribution of MCR, with ROCM as the most common variant in developing countries,[2,17,20,21] but not the developed countries.[22]

Thus, we observed that the epidemiology and clinical form (►**Table 2**) of patients with MCR in correlation with

Table 7 Inter-rater kappa agreement between patient and assessor for the duration between mucormycosis symptom onset and initiation of treatment

Patient	Assessor							Total	*p*-Value	Kappa
	0–5 D ($n=6$)	5–10 D ($n=14$)	10–15 D ($n=20$)	15–20 D ($n=10$)	20–30 D ($n=4$)	30–40 D ($n=5$)	40–50 D ($n=2$)			
0–5 D	6 (9.84%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (9.84%)	<0.0001	0.896
5–10 D	0 (0.00%)	14 (22.95%)	1 (1.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	15 (24.59%)		
10–15 D	0 (0.00%)	0 (0.00%)	19 (31.15%)	1 (1.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	20 (32.79%)		
15–20 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (14.75%)	1 (1.64%)	0 (0.00%)	0 (0.00%)	10 (16.39%)		
20–30 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (4.92%)	1 (1.64%)	0 (0.00%)	4 (6.56%)		
30–40 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (6.56%)	1 (1.64%)	5 (8.20%)		
40–50 D	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.64%)	1 (1.64%)		
Total	6 (9.84%)	14 (22.95%)	20 (32.79%)	10 (16.39%)	4 (6.56%)	5 (8.20%)	2 (3.28%)	61 (100.00%)		

Inter-kappa agreement could be carried out in 61 patients, since the pertaining health records were not retrievable in remaining 39 patients.
A significant *p*-value (< 0.0001) was derived with a very good kappa score (0.896) in agreement with analysis regarding the onset of symptoms and initiation of treatment for mucormycosis.

Table 8 Inter-rater kappa agreement between patient and assessor for blood sugar monitoring during COVID-19 illness/steroid use

Value of K	Strength of agreement
< 0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.00	Very good

COVID-19 were similar to that for MCR in a pre-COVID-19 era in India.[2,3,22]

DM was identified as most common underlying disease in patients affected by MCR in pre-COVID-19 times globally[2] as well as in India.[17,19] Jeong et al in a large meta-analysis showed 40 versus 73.5% diabetics globally and in India, respectively, thus, highlighting a much higher prevalence of diabetes with MCR in India.[16] Bala et al prior to the COVID-19 pandemic observed DM to significantly increase the odds of contracting ROCM.[18] Although during COVID-19 pandemic, hyperglycemia due to pre-existing DM or new-onset diabetes has been studied as most important risk factor for CAMCR even in cases outside India.[19,20]

Retrospective studies in India on CAMCR[5,23,24] noted diabetes as the single major comorbidity with Bhanuprasad et al[24] observing diabetes in 97% of CAMCR patients, 40% of which were newly detected. This is in concordance with our findings amongst CAMCR patients (►**Table 3**).

Patel et al[21] observed uncontrolled diabetes to be the most common underlying disease in 67 versus 60.4% in non-CAMCR and CAMCR, respectively. COVID-19 was the only underlying disease in 32.6% of CAMCR patients, comparable to 44% in our study (►**Table 3**). This suggests a possibility of either new-onset diabetes with COVID-19 infection since it induces a diabetogenic state[4] and also increases the risk of associated complications. Furthermore, it may have likely worsened hyperglycemia in pre-existing but undiagnosed diabetics, thereby unmasking diabetes in them[7] which could have been in high number considering abysmal health awareness among Indian population.[6] Thus, DM continues to be the most common underlying illness in MCR both with and without association with COVID-19, with a higher prevalence of uncontrolled diabetes in CAMCR.

India is the diabetic capital of the world, not surprisingly considering dismal health literacy, and health access.[9] This is

Patient	Assessor		Total	*p*-Value	Kappa
	No ($n=16$)	Yes ($n=17$)			
No	15 (45.45%)	0 (0.00%)	15 (45.45%)	<0.0001	0.882
Yes	1 (3.03%)	16 (48.48%)	17 (51.52%)		
Can't Say	0 (0.00%)	1 (3.03%)	1 (3.03%)		
Total	16 (48.48%)	17 (51.52%)	33 (100.00%)		

Abbreviation: COVID-19, coronavirus disease 2019.
Inter-kappa agreement could be done for 33 patients since pertaining health records were not retrievable in the other 67 patients.
The agreement analysis between patient and assessor for blood sugar monitoring during COVID-19 illness and/or while on steroid treatment showed a significant *p*-value (<0.0001) and a very good value of kappa agreement (0.882).

Table 9 Inter-rater kappa agreement between patient and assessor for blood sugar control during COVID-19 illness/steroid use

Patient	Assessor		Total	*p*-Value	Kappa
	No ($n = 19$)	Yes ($n = 3$)			
No	16 (72.73%)	0 (0.00%)	16 (72.73%)	0.0002	0.61
Yes	1 (4.54%)	3 (13.64%)	4 (18.18%)		
Can't say	2 (9.09%)	0 (0.00%)	2 (9.09%)		
Total	19 (86.367%)	3 (13.64%)	22 (100.00%)		

Abbreviation: COVID-19, coronavirus disease 2019.
Inter-kappa agreement could be carried out in 22 patients, since pertaining health records were not retrievable in the remaining 78 patients.
The agreement analysis between patient and assessor for blood sugar control during COVID-19 illness and/or while on steroid treatment showed a significant *p*-value (<0.0002) and a good value of kappa agreement 0.61.

Table 10 Inter-rater kappa agreement between patient and assessor for the severity of COVID-19 illness

Patient	Assessor				*p*-Value	Kappa
	Mild ($n = 24$)	Moderate ($n = 17$)	Severe ($n = 27$)	Total		
Mild	22 (32.35%)	5 (7.35%)	2 (2.94%)	29 (42.65%)		
Moderate	1 (1.47%)	12 (17.65%)	0 (0.00%)	13 (19.12%)		
Severe	0 (0.00%)	0 (0.00%)	25 (36.76%)	25 (36.76%)	< 0.0001	0.798
Can't say	1 (1.47%)	0 (0.00%)	0 (0.00%)	1 (1.47%)		
Total	24 (35.29%)	17 (25.00%)	27 (39.71%)	68 (100.00%)		

Abbreviation: COVID-19, coronavirus disease 2019.
Inter-kappa agreement could be carried in 68 patients, since pertaining health records were not retrievable in remaining 32 patients.
The agreement analysis regarding the severity illness of COVID-19 was obtained as good (k= 0.798).

also reflected in our study with the fact that 62% of pre-existing diabetics were found not carrying out regular blood sugar monitoring. Furthermore, 51% of pre-existing diabetics had uncontrolled blood sugars, and 31% were both unaware of their glycemic control and also did not maintain health records (►**Table 4**). Though hemoglobin A1c aids in better defining diabetes blood sugar control, it was available in the medical records for a few patients only and hence was not used. However, when available, it was found to be abnormal.

Another major risk factor identified is corticosteroid use, especially in diabetics resulting in complex immune dysregulation.[25,26] In pre-COVID-19 times, Skiada et al[22] noted MCR with corticosteroid use in 46% of patients. It was noted to be the most common predisposing factor in a meta-analysis by Jeong et al.[16] John et al[20] observed the use of systemic corticosteroids in 97.56% of patients with CAMCR. In our study, 59% of patients had been treated with steroids, while they were positive for COVID-19. Out of the 51 non-diabetics, 59% had received steroids for COVID-19. Twenty-nine percent of patients were neither aware of steroid use nor had records for the same.

However, 29% of patients had no awareness and also maintained no health records to provide information on steroid medication prescription (►**Annexure 2**). The association between COVID-19 disease severity and steroid treatment was assessed and was statistically significant with *p*-value of 0.001(►**Table 5**).

We observed that 35% of patients with mild disease had been treated with systemic steroids. Furthermore, 45% of patients with mild COVID-19 illness had neither awareness nor documents pertaining to steroid use. These findings highlight the unwarranted and unrestrained use of steroids. COVID-19 scare and restricted access to a health facility during the COVID-19 crisis may have resulted in self-treatment with over-the-counter steroids.

In 47% of study subjects, blood sugar monitoring was carried out during COVID-19 illness with or without treatment with steroids. Seventeen percent of the patients were unaware and had no record-keeping to verify their glycemic monitoring. Furthermore, 56% of study subjects had fluctuating blood sugar levels during COVID-19 illness, while 9% of them had blood sugars in the normal range. Thirty-five percent of patients were unaware of the blood sugar values and had no health record-keeping (►**Annexure 2**).

Our observations are corroborated by Gianchandani et al[27] who found very high blood sugar levels in CAMCR patients. The inter-kappa analysis on blood sugar monitoring during COVID-19 illness with or without treatment with systemic steroids shows a significant *p*-value and a very good kappa agreement (0.81–1.00; ►**Table 8**). This further signifies that the information obtained from patients was accurate and also a good record keeping as retrieved from the case sheets of the patients.

Mulakavalupil et al[28] showed that low-dose steroids with strict glycemic control completely eliminated risk of MCR in

COVID-19. On assessing the disease severity, mild and moderate COVID-19 illness was found in 40 and 24% of subjects, respectively (►**Annexure 2**).

Even mild COVID-19 can induce a proinflammatory milieu, which can further lead to lowering insulin sensitivity.[29] Prolonged hospitalization, broad-spectrum antibiotics, intensive care unit admission, intubation/mechanical ventilation, and surgery are usually seen with severe COVID-19 illness and associated with MCR.[30] Sixty percent of the study patients required hospitalization for a COVID-19 illness of which 30% remained hospitalized for 11 to 20 days.

Primary prevention in the form of vaccination remains the mainstay for mitigating the risks associated with COVID-19 in patients with DM.[31] Seventy-nine percent of the study participants were not vaccinated against COVID-19. A correlation between COVID-19 disease severity and vaccination status of the participants was studied and findings revealed that 33% of unvaccinated patients had severe disease, 38% had mild disease, and 29% had moderate disease. The association was statistically significant with a *p*-value of 0.009 (►**Table 6**). COVID-19 vaccination has been shown to reduce the disease severity. In a retrospective, analysis by Li et al[32] on COVID-19 patients to estimate the effectiveness of vaccination in preventing disease progression, it was concluded that risk of pneumonia and severe disease was lower in fully vaccinated individuals than unvaccinated people. In a case–control study by Tenforde et al,[33] to ascertain the association between prior vaccination and hospitalization for COVID-19 and its progression, the authors concluded that the outcome of mechanical ventilation and death among the vaccinated was less likely. These findings are in concordance with the present study and suggest that the risk of developing severe COVID-19 disease is less with prior vaccination and thus complications like COVID-19-associated mucormycosis are also infrequent. Hence, mild disease does not require hospitalization or steroid treatment thereby immunosuppression and hospital-acquired infections are circumvented. Vaccination has a dual beneficial effect for COVID-19 disease on its severity as well as its further complications like COVID-19-associated MCR that were rampant during the second wave in India.

Average to poor sanitary surroundings during isolation and treatment period was reported by 58% of study subjects. Individuals who have recently recuperated from COVID-19 should ensure stringent personal hygiene.[34] Sixty-nine percent of patients reported wearing cloth protective masks and 9% used no masks, with 21% of patients using soiled masks (►**Annexure 2**). The All India Institute of Medical Sciences had issued guidelines on MCR alerting the public on the alarming symptoms to be watched for to detect early disease.[35]

Seventy-one percent of the study participants had no knowledge and 11% had knowledge only about advanced stage symptoms and could not relate their initial symptoms to the disease (►**Table 1**). In 18% of the aware cases, media through television and newspaper helped spread awareness. Only 6% of patients were alerted to the red flag signs of MCR by their clinicians. Thirty-two percent of patients reported face swelling including eyes as the initial symptom with nasal symptoms in only 11%. Hence, patients presenting with early disease limited to the nasal site were few (8%; ►**Annexure 2**).

Management for MCR was initiated in 25% of the patients within 5 to10 days of the symptom onset. Only in 8% of patients, management was initiated within 5 days of symptom onset. The agreement analysis shows a very good kappa score regarding the onset of symptoms and initiation of management of MCR, further nullifying a recall bias (►**Table 7**).

A delay in the establishment of the diagnosis of MCR resulted in rapid disease progression thereby necessitating more aggressive treatment. Seventy-five percent of the study participants received both medical and surgical treatment by the time they answered the questionnaire (►**Annexure 2**).

Strengthening efforts to enhance health awareness among the general public in various aspects of diabetes care is the key to keeping the associated threats in check. It is prudent to have early initiation of treatment of mucormycosis on strong clinical and radiological suspicion without waiting for tissue confirmation to enable improved outcomes in this rapidly progressive highly debilitating, fatal disease.

The present study having a questionnaire-based design had the limitations of being time-consuming, with participants getting disinterested at times, affecting the essence of the results obtained. Additionally, open-ended questions though few might have been difficult for less educated participants to answer. Other limitations specific to the study entailed records pertaining to the information on pre-existing illnesses, blood sugar charting, and management of MCR were incomplete and missing for so. Follow-up of the patients regarding outcome was not done; therefore, the underlying potential risk factors of the disease could not be correlated to the disease outcome.

The message to take home is that the health literacy of patients having a chronic disease like diabetes plays a key role in optimal control of comorbidity and preventing the associated complications. COVID-19 in its progression and severity affects immunocompromised patients with greater virulence. Hence, strengthening patient education and also health awareness in the general population is paramount to reducing complications entailing COVID-19 such as immunosuppression and MCR. In addition, vaccination against COVID-19 should be encouraged with the use of masks and social distancing should be actively practiced.

Conclusion

Clinicoepidemiological profile of COVID-19-associated MCR was found similar to that not associated with COVID-19, although diabetes was more commonly seen in patients with CAMCR in our study. Health literacy among diabetics had lacunae that resulted in impaired glycemic control. Additionally, awareness for blood sugar monitoring and control during COVID-19 illness with or without the use of steroids was mostly lacking. Knowledge of the "red flag" signs of MCR was incomplete, thereby hampering early disease

recognition. Interventions to improve awareness amongst patients with diabetes should help in optimal glycemic control, and avoid potential complications including severe COVID-19 illness, MCR.

Conflict of Interest
None declared.

References

1 Mishra N, Mutya V, Thomas A, et al. A case series of invasive mucormycosis in patients with COVID-19 infection. Int J Otorhinolaryngol Head Neck Surg 2021;7(05):867
2 Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. Microorganisms 2021;9(03):523
3 Chakrabarti A, Das A, Mandal J, et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol 2006;44(04):335–342
4 Kuchay MS, Reddy PK, Gagneja S, Mathew A, Mishra SK. Short term follow-up of patients presenting with acute onset diabetes and diabetic ketoacidosis during an episode of COVID-19. Diabetes Metab Syndr 2020;14(06):2039–2041
5 Honavar SG. Code Mucor: Guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol 2021;69(06):1361–1365
6 Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep 2020;10(01):14790
7 Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab Syndr 2020;14(06): 2211–2217
8 Singh AK, Misra A. Impact of COVID-19 and comorbidities on health and economics: focus on developing countries and India. Diabetes Metab Syndr 2020;14(06):1625–1630
9 Raut A, Huy NT. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? Lancet Respir Med 2021;9(08):e77
10 Corticosteroid Adverse Effects - StatPearls - NCBI Bookshelf (n.d.). Accessed December 19, 2022, at: https://www.ncbi.nlm.nih.gov/books/NBK531462/
11 Banerjee M, Chakraborty S, Pal R. Diabetes self-management amid COVID-19 pandemic. Diabetes Metab Syndr 2020;14(04):351–354
12 Belsti Y, Akalu Y, Fekadu H, Animut Y. Awareness of complications of diabetes mellitus and its associated factors among type 2 diabetic patients at Addis Zemen District Hospital, northwest Ethiopia. BMC Res Notes 2019;12(01):602. Doi: 10.1186/s13104-019-4637-x
13 Melesie Taye G, Bose L, Beressa TB, et al. COVID-19 knowledge, attitudes, and prevention practices among people with hypertension and diabetes mellitus attending public health facilities in Ambo, Ethiopia. Infect Drug Resist 2020;13:4203–4214
14 Cheng AYCanadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. Can J Diabetes 2013;37 (Suppl 1):S1–S3
15 Saleem S, Jan S. Modified Kuppuswamy socioeconomic scale updated for the year 2021. Ind J Forensic Comm Med 2021;8(01):1–3
16 Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect 2019;25(01):26–34
17 Patel A, Kaur H, Xess I, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect 2020;26(07):944.e9–944.e15
18 Bala K, Chander J, Handa U, Punia RS, Attri AK. A prospective study of mucormycosis in North India: experience from a tertiary care hospital. Med Mycol 2015;53(03):248–257
19 Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel) 2019;5(01):26
20 John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. J Fungi (Basel) 2021;7(04):298
21 Patel A, Agarwal R, Rudramurthy SM, et al; MucoCovi Network3. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. Emerg Infect Dis 2021;27(09): 2349–2359
22 Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. J Fungi (Basel) 2020;6(04): 265
23 Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids-an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multicentric analysis. J Maxillofac Oral Surg 2021;20(03):418–425
24 Bhanuprasad K, Manesh A, Devasagayam E, et al. Risk factors associated with the mucormycosis epidemic during the COVID-19 pandemic. Int J Infect Dis 2021;111:267–270
25 Manesh A, Rupali P, Sullivan MO, et al. Mucormycosis-A clinicoepidemiological review of cases over 10 years. Mycoses 2019;62 (04):391–398
26 Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003;362(9398):1828–1838
27 Gianchandani R, Esfandiari NH, Ang L, et al. Managing hyperglycemia in the COVID-19 inflammatory storm. Diabetes 2020;69 (10):2048–2053
28 Mulakavalupil B, Vaity C, Joshi S, Misra A, Pandit RA. Absence of Case of Mucormycosis (March 2020-May 2021) under strict protocol driven management care in a COVID-19 specific tertiary care intensive care unit. Diabetes Metab Syndr 2021;15(04): 102169
29 Pal R, Bhadada SK. COVID-19 and diabetes mellitus: an unholy interaction of two pandemics. Diabetes Metab Syndr 2020;14 (04):513–517
30 Ezeokoli OT, Gcilitshana O, Pohl CH. Risk factors for fungal coinfections in critically Ill COVID-19 patients, with a focus on immunosuppressants. J Fungi (Basel) 2021;7(07):545
31 Pal R, Bhadada SK, Misra A. COVID-19 vaccination in patients with diabetes mellitus: current concepts, uncertainties and challenges. Diabetes Metab Syndr 2021;15(02):505–508
32 Li M, Liu Q, Wu D, et al. Association of COVID-19 vaccination and clinical severity of patients infected with delta or omicron variants - China, May 21, 2021-February 28, 2022. China CDC Wkly 2022;4(14):293–297
33 Tenforde MW, Self WH, Adams K, et al; Influenza and Other Viruses in the Acutely Ill (IVY) Network. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 2021;326(20):2043–2054
34 Banerjee M, Pal R, Bhadada SK. Intercepting the deadly trinity of mucormycosis, diabetes and COVID-19 in India. Postgrad Med J 2022;98(e2):e108–e109
35 Mucormycosis in COVID-19 | AIIMS Covid Information Portal. (n.d.). Accessed December 19, 2022 at: https://covid.aiims.edu/mucormycosis-in-covid-19/

Annexure 1:

We conducted principal component analysis with Varimax rotation to divide the items into factors. The number of factors retained was derived by considering the magnitude of the eigenvalues, Kaiser's (1960) eigenvalues (>1) rule, the proportion of variance extracted, item content, and the interpretability of the resulting factors. As for factor loading after the Varimax rotation, items with a factor loading less than 0.5 on all factors were excluded. We investigated the internal consistency by calculating Cronbach's alpha and by calculating item-total correlations for each factor that was identified with the factor analysis, and alpha greater than 0.70 was considered acceptable, and optimal item-total correlation was considered to be between 0.2 and 0.5.

Results from the factor analysis indicated that each factor accounts for approximately 40% of the variance. Cronbach's alpha coefficients for various questions in the questionnaire were greater than the accepted number of more than or equal to 0.70.

Calculation of internal consistency (Cronbach's alpha 0.703-0.834) and cross-validation provided evidence of reliability and lack of redundancy of items.

We found that the number of factors, the factor structure, and factors loadings were for the greater part comparable between the first randomly created subsample ($n=25$) and the total sample ($n=100$).

Annexure 2: Patient questionnaire with responses

S No	Question	Possible answers	Replies obtained
1	How many days prior to developing symptoms of "Black fungus," did you have COVID-19 or COVID-19 like illness? $n=100$	0–10 days	33%
		11–20 days	36%
		21–30 days	18%
		31–40 days	9%
		>40 days	4%
2	Where did you get treated for COVID-19? $n=100$	Home	38%
		Hospital	38%
		Home +Hospital	24%
3	How was the overall hygiene of the place of stay while being isolated? $n=100$	Good	42%
		Average	50%
		Poor	8%
4	How many days did you stay at a hospital/COVID-19 care center? $n=100$	<10 days	23%
		11–20 days	28%
		21–30 days	9%
		31–40 days	2%
		NA	38%
5a	Were you treated with steroids like Dexona/ Predmet/Medrol/ Wysolone, $n=100$	Yes	59%
		No	12%
		No records	29%
5b	If yes, you took steroids, $n=59$	As prescription	97%
		As self-medication	3%
5c	If taken steroids as a prescription, prescribed for what duration? ($n=57$)	<10 days	30%
		>10 days	68%
		No Records	2%

(*Continued*)

S No	Question	Possible answers	Replies obtained
5d	If taken steroids as a prescription, took $n = 57$	More no. of days	1%
		More than the prescribed dose	1%
		More days+ More dose	1%
		None	60%
		No records	18%
		NA	19%
6a	Was blood sugar monitored during COVID-19 illness with or without steroid use? $n = 100$	Yes	47%
		No	36%
		Don't know	17%
6b	Was the blood sugar controlled during COVID-19 illness with or without steroid use? $n = 100$	Normal range	9%
		Fluctuating	56%
		No records	35%
7a	Treatment prescribed for blood sugar control during COVID-19 illness with or without steroid use? $n = 100$	OHA	18%
		OHA + insulin	17%
		Insulin	29%
		None	18%
		No records	18%
7b	If OHAs were used then medication names? $n = 35$	Single drug	31%
		Double drug	23%
		Triple drug	6%
		No records	40%
8	How severe was the illness? $n = 100$	Mild RR < 20, Spo2 > 93%	40%
		Moderate RR 20-30, Spo2 > 90%	24%
		Severe RR > 30, Spo2 < 90%	36%
9	What was the CTSS score if you remember, if the CT chest done? n = 100; CTSS score 7 or less (mild) $n = 0$; CTSS score 8–17 (moderate) $n = 22$; CTSS score 18 or more (severe) $n = 11$	10	3%
		11	1%
		12	4%
		13	2%
		14	3%
		15	4%
		16	2%
		17	3%
		18	3%
		19	2%
		20	1%
		21	2%
		22	1%
		23	1%
		24	1%
		NA	36%
		No records	31%

(*Continued*)

(*Continued*)

S No	Question	Possible answers	Replies obtained
10a	Did you receive oxygen therapy? ($n = 100$)	Yes	56%
		No	43%
		Can't say	1%
10b	If yes, received at $n = 56$	Home	4%
		Hospital	80%
		Home +Hospital	16%
10c	Was the oxygen dry or moist? $n = 56$	Moist	80%
		Dry	0%
		Can't say	20%
10d	What type of humidification was used (hospital/home)? $n = 56$	Packaged water/RO water	19%
		Distilled water	7%
		Tap water	6%
		Can't say	13%
		NA	55%
11	Mode of oxygen therapy used? $n = 56$	Simple face mask	38%
		Tight mask with straps (Bipap)	13%
		Nasal prongs	5%
		NA	44%
12	Any other treatment received?	Remdesivir	9%
		Any other treatment	35%
		No records	56%
13	For what duration was treatment taken for COVID-19, including hospital & home? $n = 100$	<7 days	22%
		7–14 days	36%
		15–30 days	34%
		>30 days	8%
14	COVID-19 vaccination received? $n = 100$	1 dose	16%
		2 doses	5%
		Not vaccinated	79%
15a	Do you have pre-existing diabetes or any other disease for which you have been taking long term medication prior to COVID-19 illness? $n = 100$	Yes	56%
		No	44%
15b	If yes please specify the disease DM/malignancy/HTN/thyroid disorder/CKD/ chemotherapy/immunosuppressants? $n = 56$	DM 1	1%
		DM2	33%
		DM2 + HTN	11%
		DM2 + HTN + CAD	1%
		DM2 + HTN + COAD	1%
		DM2 + HTN + Hep c	1%
		DM2 + HTN + Hypothyroid	1%
		HTN	5%
		Hypothyroid	1%
		NA	45%

(*Continued*)

S No	Question	Possible answers	Replies obtained
16	If pre-existing diabetes, what was the treatment taken? $n = 49$	OHA	35%
		OHA + insulin	3%
		Insulin	1%
		None	10%
		NA	51%
17a	Did you routinely check blood sugars prior to COVID-19 illness, $n = 100$	Yes	28%
		No	72%
17b	If yes, how did you check? $n = 28$	Yes	57%
		No	43%
17c	Did you routinely check blood sugars (in pre-existing diabetics), $n = 49$	Home yes	38%
		Hospital care facility no	62%
18	Was blood sugar controlled? (blood sugar values: 80–140 mg/dL before meals and < 200 mg/dL, 2 hours after meals); $n = 49$	Yes	18.00%
		No	51.00%
		Can't say	31.00%
19	Did you experience any episodes of rapid heart rate, blurry vision, unconsciousness? $n = 49$	Yes	8%
		No	83%
		Can't say	9%
20a	Type of COVID-19 protection mask used? $n = 100$	Cloth	69%
		Surgical	10%
		N-95	9%
		Combination	3%
		No mask	9%
20b	How often was the mask changed/washed? $n = 100$	1-3 days	47%
		4-6 days	24%
		7-14 days	13%
		>14 days	7%
		NA	9%
20c	Was the oxygen mask changed on becoming soiled/wet? $n = 100$	Yes	71%
		No	21%
		NA	8%
21	Did you know about symptoms of black fungus? $n = 100$	Yes	18%
		No	71%
		Incomplete information	11%
22	If yes (complete or incomplete), source of information? $n = 29$	Television/newspaper	62%
		Treating doctor	17.20%
		Internet	13.70%
		Family/Friends	6.89%
23	Were you alerted about the symptoms of mucormycosis before leaving the hospital? $n = 100$	Yes	6%
		No	79%
		NA	15%

(*Continued*)

(*Continued*)

S No	Question	Possible answers	Replies obtained
24	Which symptoms did you notice first? $n = 100$	Face swelling	32%
		Visual disturbances	12%
		SO pain	12%
		Nasal stuffiness	11%
		Vision disturbances + SO pain	10%
		Nasal discharge	7%
		Pain in mandible	6%
		Face numbness	5%
		Blood in cough	2%
		Nasal bleed	1%
		Infraorbital pain	1%
		cough/breathlessness	1%
25	After how many days of diagnosis of mucormycosis was the treatment started? $n = 100$	<5 days	8%
		5–10 days	25%
		10–15 days	25%
		15–20 days	19%
		20–30 days	9%
		30–40 days	7%
		40–50 days	5%
		>50 days	2%
26	What mode of treatment are you being given for black fungus? $n = 100$	Medicine only	23%
		Surgery only	2%
		Both	75%
27	Are you satisfied with the treatment? $n = 100$	Satisfied	84%
		Not satisfied	5%
		Can't say	11%

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; COAD, chronic obstructive airway disease; COVID-19, coronavirus disease 2019; CTSS, CT Chest Severity Score; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; HTN, hypertension; NA, not available; OHA, Oral Hypoglycemic Agent; RO, reverse osmosis; RR, relative risk; SPO2, oxygen saturation; SO, supraorbital.

