

# Covid-19 and Mucormycosis Superinfection: Prospective, Observational Study in a Single Center

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## Abstract

**Background:** Mucormycosis (MCR) has been increasingly described in patients with coronavirus disease 2019 (COVID-19), but the epidemiological factors, neurological presentation, and outcome of such patients are not well described. **Aims:** To study the patient demographics, presenting symptoms and signs, the role of co-morbidities, medications used to treat COVID-19, and the outcomes of management and to study the spectrum of neuraxis involvement and its outcome. **Methods:** It was a prospective, observational, cross-sectional hospital-based single center cohort study. Confirmed MCR cases with and without COVID-19 were collected. The study was carried out over a period of 3 months from May to July 2021, followed by 3-month follow-up. Information on epidemiological factors, neurological findings, treatment (including medical and surgical treatment), and outcome was recorded. **Results:** A total of 141 patients were diagnosed with MCR, out of which 98 were COVID-associated MCR (CAM). The CAM incidence was 0.39% among COVID-19-positive patients. The MCR case fatality rate at 90 days was 43.9% but was higher for CAM than for non-CAM patients. Older ages (>50 years), diabetes mellitus, multiple risk factors, diabetic ketoacidosis on admission, brain involvement, and history of COVID-19 pneumonitis were associated with a higher risk for death. **Conclusions:** Possibly because of improper usage of corticosteroids, zinc, oxygen, and tocilizumab, there was sudden surge of cases of MCR in the COVID-19 pandemic. Therefore, treating physicians should use the COVID-19 pneumonia regimen judiciously. Neurological involvement itself is a poor prognostic sign, but combined surgical and medical management exhibited better outcome.

**Keywords:** Amphotericin B, COVID-19, Mucorales, mucormycosis, steroid

## INTRODUCTION

Mucormycosis (MCR) occurs because of the fungi belonging to the order Mucorales. Humans acquire the infection predominantly through inhalation of sporangiospores, sometimes by means of ingestion of infected meals or traumatic inoculation.<sup>[1,2]</sup> The fungi in the group of Mucorales are ubiquitous, and morphologically they are broad, aseptate, or sparsely septate ribbon-like hyphae. Eleven genera and approximately 27 species below Mucorales are related to human infections. *Rhizopus arrhizus* is the most common agent inflicting MCR throughout the globe.<sup>[3,4]</sup> MCR is the third most common invasive fungal infection with excessive morbidity and mortality after candidemia and invasive aspergillosis.<sup>[5,6]</sup> The disorder is common in out-of-control diabetic patients of India, in comparison to patients with hematological malignancies and transplant recipients of developed countries.<sup>[7]</sup>

The coronavirus disease 2019 (COVID-19) pandemic, resulting from severe acute respiratory syndrome virus 2 (SARS-CoV-2), has affected greater than 190 million humans worldwide, accounting for over 4.1 million deaths at the day of this report. Although aspergillosis has been stated to complicate intense COVID-19 (the entity is coined COVID-19-related aspergillosis or CAPA), the pathophysiology and the real occurrence of CAPA remains debatable as only a few CAPA cases are biopsy-documented.<sup>[8]</sup> In addition, Mucorales infections are rising as a matter of issue in COVID-19 as poorly

managed diabetes mellitus (DM), and different co-morbidities are danger factors for both severe COVID-19 and MCR.<sup>[9]</sup> The usage of corticosteroids to deal with intense/critical COVID-19 is a well-known risk factor for MCR.<sup>[10]</sup>

Prior to the COVID-19 pandemic, high prevalence of mucor infections is seen, nearly 80 times higher (0.14 per 1000) in India compared to developed countries.<sup>[11,12]</sup> In the second wave of the COVID-19 pandemic, there has been a tremendous increase in the number of MCR cases. This could be because of COVID-19-related illness requiring excessive and extended steroid use leading to DM, immunosuppression, increased ferritin leading to excessive iron load, acidosis, endothelial harm, and use of more than one broad-spectrum antibiotic to prevent or deal with secondary infections.<sup>[13,14]</sup> Because India

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has the second highest number of COVID-19 cases, India has the second highest quantity of DM patients resulting in high incidence of MCR, because of which India noticed massive numbers of MCR, in particular in COVID-19 patients.<sup>[15,16]</sup>

Herein, in the present study, we describe the demographic profile, risk factors in early and late CAM (COVID-19 associated MCR), neurological manifestations, and management. We also study the 3-month outcome profile of MCR patients treated with medical alone versus medical with surgical treatment.

### Study objectives

1. To study the patient demographics, presenting symptoms and signs, the role of co-morbidities, medications used to treat COVID-19, and the outcomes of management.
2. To study the spectrum of neuraxis involvement and its outcome.
3. To compare the prognosis in CAM and non-CAM groups.

### METHODS

**Study Design:** It was a prospective, observational, cross-sectional hospital-based single-center cohort study. The study duration was from May to July 2021. Confirmed MCR cases with and without COVID-19 were collected. The study was approved by the institutional ethical committee.

**Study Subjects and Definitions:** The diagnosis of COVID-19 was made by one of the following methods: reverse transcriptase polymerase chain reaction (RT-PCR) test on nasopharyngeal or oropharyngeal swabs and rapid antigen test. A patient with symptoms and signs of MCR with clinico-radiological features along with microbiological confirmation on direct microscopy or histopathology with special stains in the clinical setting COVID-19-positive status was considered COVID-19-associated MCR (CAM). Patients who were not giving history of COVID-19 were considered as non-COVID-19-associated MCR (non-CAM), and they were checked twice with RT-PCR and were negative.

Early CAM are defined as MCR which were diagnosed  $\leq 10$  days after COVID-19 diagnosis. Late CAM are defined as MCR which were diagnosed  $> 10$  days and  $< 30$  days after COVID-19 diagnosis. The patients who left the hospital against medical advice were excluded from the study.

**Study Procedure:** Patients' demographic characteristics such as age, sex, body mass index (BMI), underlying diseases, such as DM, diabetic ketoacidosis (DKA), hypertension (HTN), ischemic heart disease (IHD), chronic kidney disease (CKD), malignancy, and others were recorded as per pre-structured proforma. Clinical symptoms and signs were recorded at presentation with neurological symptoms. We observed days to the diagnosis of MCR before or after COVID-19, anatomic sites of involvement, and diagnostic modalities used for MCR. The history and duration of treatment including immunosuppressive drugs were recorded. Finally, the outcome was studied at 12 weeks by telephonic conversation or a follow-up visit at hospital.

**Statistical Methods:** The data were analyzed using SPSS 20.0 for MS-Windows (IBM Inc., Chicago, IL) and Microsoft Excel (version 16.49). The descriptive statistics are presented as frequencies and mean. The Chi-square test was used to calculate the *P* value. We considered  $P < 0.05$  statistically significant.

### RESULTS

According to the data from the institutional COVID registry during the study period, that is, from May 2021 to July 2021, the total COVID-19-positive cases reported were 24,906, and out of these, 954 patients needed admission and 227 patients died in the hospital. During the same period, a total of 141 cases developed MCR, and out of these, 98 cases were COVID-19-positive; hence, the incidence rate of CAM was 0.39%.

A total of 141 consecutive MCR diagnosed cases were enrolled in the present study, of which 88 (62.4%) were male and 53 (37.5%) were female. The age group of the patients was between 28 and 71, with a mean age of 45.7 years. Both COVID and non-COVID patients were enrolled, in which CAM were 98 (69.5%) and non-CAM were 43 (30.5%). Of these 98 CAM cases, 66 (67.3%) were male, and the mean age was 49.2 years with a mean BMI of 22.7. Among 98 CAM cases, 17 patients developed MCR with COVID and 81 patients developed MCR after COVID. The mean days of interval was 14.52 days in the CAM group [Table 1].

Any risk factor or co-morbid disease was observed in 116 cases, of which the major causative factor was steroid use (112), followed by DM (66), HTN, and IHD. The steroid use was observed in 86.7% of CAM and 62.7% of the non-CAM group. Fourteen cases (14.2%) of CAM had only a risk factor in the form of steroid use. Among 66 diabetic patients, 25 (37.8%) were newly detected in CAM and five (7.5%) in non-CAM patients. Forty-four had DKA at the time of presentation. Other risk factors and co-morbid illness such as cancer (1.41%), chemotherapy (1.41%), CKD (6.38%), and HIV (0.7%) were also noted. The most common symptom was facial numbness/swelling, which was seen in 111 (78.7%) patients. Other common presentations were dental loosening/pain, nasal discharge (56%), headache (41.8%), ptosis (40%), skin/palatal necrosis (23%), diplopia, facial asymmetry, and altered sensorium. Maxillary sinusitis was seen in all the patients; however, 34% had bilateral peripheral nervous system (PNS) involvement. The mean duration of any symptom with which patients presented was 11 (04–19) days. The rhino-orbital 109 (77.3%) region was the most common MCR site, followed by rhino-orbital-cerebral 32 (22.6%), cutaneous 7 (4.9%), and pulmonary 3 (2.1%). The rhino-orbital site of involvement was the most common in both CAM and non-CAM groups, but rhino-orbital-cerebral involvement was more common in the CAM group [Tables 1 and 2].

MCR diagnosis was made by direct microscopy in 68 (69.3%) patients of CAM and 32 (74.4%) patients of non-CAM.

**Table 1: Touchstone characteristics among patients with MCR**

BASELINE CHARACTERISTIC	TOTAL (n=141)
Mean age (in years)	45.7 (28-71)
Male sex (%)	88 (62.41)
Mean BMI	22.3 (18.6-28.9)
Any risk factor/co-morbid diseases (%)	116 (82.26%)
DIABETES MELLITUS	66 (46.8%)
STERIOD	112 (79.4%)
HTN	58 (41.13%)
IHD	23 (16.31%)
CANCER	2 (1.41%)
CHEMOTHERAPY	2 (1.41%)
CKD	9 (6.38%)
HIV	1 (0.70%)
CLINICAL FEATURES (%)	
Facial numbness/swelling	111 (78.72%)
Nasal discharge	23 (16.31%)
Ptosis	57 (40.42%)
Headache	59 (41.84%)
Dental loosening/pain	79 (56.02%)
Diplopia	32 (22.69%)
Facial asymmetry	16 (11.34%)
Altered sensorium	8 (5.67%)
Skin/palatal necrosis	33 (23.40)
DKA ON ADMISSION (%)	44 (31.2%)
Duration of the symptom (days)	11 (4-19)
MCR with COVID (%)	17 (12.05%)
MCR after COVID (%)	81 (57.44%)
MCR after COVID (mean days)	14.52
SITE OF MCR (%)	
RHINO-ORBITAL (%)	109 (77.30%)
RHINO-ORBITAL-CEREBRAL (%)	32 (22.69%)
PULMONARY (%)	3 (2.12%)
CUTANEOUS (%)	7 (4.96%)
RENAL (%)	0
DISSEMINATED (%)	3 (2.12%)
COVID-19-SPECIFIC THERAPY	
ZINC (%)	110 (78.01%)
VITAMIN C (%)	67 (47.5%)
IVERMECTIN (%)	51 (36.17)
TOCILIZUMAB (%)	14 (9.92%)
OXYGEN THERAPY (%)	97 (68.79%)
NON-INVASIVE VENTILATION (%)	43 (30.49%)
MECHANICAL VENTILATION (%)	7 (4.96%)

DM - Diabetes Mellitus; HIV - Human Immunodeficiency Virus; IHD - Ischemic heart disease; HTN - hypertension; CKD - chronic kidney disease; AMB - amphotericin B; DKA - diabetic ketoacidosis

Histopathology demonstrated aseptate hyphae, with right angle branching and non-dichotomous branching in 124 (87.9%) in all CAM cases. In the rest of the 17 (12%) patients, diagnosis was made on the basis of classical clinical and radiological presentation. In CAM and non-CAM groups, Liposomal amphotericin B was used in all patients. Stepdown Posaconazole was used in 55.1% of CAM patients and 58.1% of non-CAM patients because of limited availability.

Combined medical and surgical management was performed in 91.8% cases of CAM and 93% patients of the non-CAM group. Major surgery performed was functional endoscopic sinus surgery (FESS) in 90 patients, of which 77.7% cases were of CAM. Twenty eight percent patients underwent PNS debridement, and only 2.8% patients were treated with orbital exenteration. The mean duration of hospital stay for CAM is 29.32 days, and that for non-CAM is 24.12 days. In the hospital, the mortality was 22.4% in CAM and 11.65% in non-CAM. The total mortality at 3 months was of 62 (43.9%) cases, out of which 42 (67.7%) were of the CAM group [Tables 2 and 3].

Among the neurological manifestations of MCR, major presentation was of cranial nerve palsy in 50 (51%) patients of CAM and 20 (46.5%) patients of non-CAM with the most common trigeminal nerve involvement (sensory more than motor) in 70 (49.6%) cases. Extra-ocular movement abnormalities were seen in (50.21%), of which lateral rectus involvement was the most common. Bilateral extra-ocular movement restriction was observed in 11 (7.8%) cases. Optic nerve involvement was observed in 20 (14.1%) cases, which was bilateral in four (20%). Lower motor neuron (LMN) facial palsy was seen in 16 patients. The second most common neurological manifestation was headache (41.8%), followed by ischemic stroke (23.4%), cavernous sinus thrombosis (16.3%), cerebral abscess (5.6%), and an altered mental status (5.6%), and none of the patients presented with hemorrhagic stroke [Table 4].

Factors predicting death at 3 months among patients with MCR were statistically significant in DM, DKA at admission, and rhino-orbital-cerebral involvement. Combined medical and surgical management may be a better option for survival [Table 5].

## DISCUSSION

Our study revealed that males (62.4%) and middle age groups (40 to 60 years) were more affected as observed in previous studies.<sup>[4,17,18]</sup> Most of the patients had one or more than one risk factor/co-morbid illness. It was surprising that 25 (17.7%) patients in our study had no risk factor or any co-morbid illness. Similarly, in a study by Patel *et al.*,<sup>[17]</sup> from the data of 465 cases of MCR without COVID-19 in India, 11.8% did not have any predisposing factors. This is important in patients presenting with signs and symptoms of MCR in the absence of any underlying comorbidity which is rare, and it mandates further study of virus-host interactions and search for other potential risk factors.

Steroid was the most common and important risk factor associated with CAM (86.7%) in our study. Early and more frequent use of corticosteroids that exacerbated glucose homeostasis may have predisposed patients to MCR. Corticosteroid use is a key risk factor for opportunistic mycoses, including MCR.<sup>[13]</sup> Over-usage of steroids was independently associated with the development of early CAM as all the 30 cases in our study had history of steroid use. We

**Table 2: Touchstone characteristics among patients of CAM and non-CAM**

VARIABLES (%)	CAM (n=98) (69.5%)	NON-CAM (n=43) (30.5%)	P
Mean Age	49.2	43.7	<b>0.01</b>
MALE SEX	66 (67.34%)	22 (51.16%)	
BMI	22.7	25.1	
SITE OF MCR (%)			
RHINO-ORBITAL	69 (70.4%)	40 (93.02%)	0.07
RHINO-ORBITAL-CEREBRAL	30 (30.61%)	2 (4.65%)	0.06
PULMONARY	2 (2.04%)	1 (2.3%)	0.42
CUTANEOUS	7 (7.14%)	0	<b>0.01</b>
DISSEMINATED	3 (3.06%)	0	<b>0.01</b>
RISK FACTOR/CO-MORBID DISEASE (%)			<b>0.001</b>
DM	59 (60.20%)	7 (16.27%)	
STEROID	85 (86.73%)	27 (62.79%)	
HTN	42 (42.85%)	26 (60.46%)	
IHD	15 (15.3%)	8 (18.6%)	
CANCER	2 (2.41%)	0	
CHEMOTHERAPY	2 (2.41%)	0	
CKD	7 (7.14%)	2 (4.65%)	
HIV	1 (1.02%)	0	
Multiple risk factor	50 (51.02%)	19 (44.18%)	
COVID-19-SPECIFIC THERAPY (%)			
STEROID	85 (86.73%)	27 (62.79%)	<b>0.002</b>
REMDESEVIR	60 (61.2%)	21 (48.83%)	<b>0.001</b>
TOCILIZUMAB	14 (14.28%)	0	<b>0.0001</b>
OXYGEN THERAPY	62 (63.97%)	35 (81.39%)	<b>0.05</b>
NON-INVASIVE VENTILATION	22 (22.44%)	21 (48.83%)	0.95
MECHANICAL VENTILATION	5 (5.1%)	2 (4.65%)	<b>0.014</b>
ZINC	80 (81.63%)	30 (69.76%)	<b>0.01</b>
VITAMIN C	51 (52.04%)	16 (37.2%)	<b>0.003</b>
IVERMECTIN	25 (25.51%)	26 (60.46%)	<b>0.01</b>
MICROSCOPY (%)	68 (69.3%)	32 (74.4%)	
HISTOPATHOLOGY (%)	88 (89.7%)	36 (83.7%)	
SINUS INVOLVED (%)			
Maxillary	98 (100%)	43 (100%)	
Frontal	46 (46.93%)	19 (44.18%)	
Ethmoid	50 (51.02%)	25 (58.13%)	
Sphenoid	35 (35.71%)	12 (27.9%)	
Bilateral	40 (40.78%)	12 (27.9%)	
Treatment (%)			
Liposomal AMB	98 (100%)	43 (100%)	<b>0.012</b>
Posaconazole	54 (55.1%)	25 (58.13%)	0.78
Step-down anti-fungal therapy	54 (55.1%)	25 (58.13%)	0.89
Intraorbital amphotericin	15 (15.3%)	12 (27.9%)	0.75
Surgery (%)	90 (91.83%)	40 (93.02%)	<b>0.01</b>
FESS	70 (49.64%)	20 (46.51%)	
Debridement	20 (14.18%)	20 (46.51%)	
Orbital exenteration	3 (3.06%)	1 (2.3%)	
Combined medical and surgery	90 (91.83%)	40 (93.02%)	0.12
Duration of hospital stay (days)	29.32	24.12	<b>0.01</b>
Hospital stay mortality (%)	22 (22.44%)	5 (11.6%)	<b>0.001</b>
90-day mortality (%)	42 (48.97%)	20 (46.5%)	<b>0.17</b>

DM - Diabetes Mellitus; HIV - Human Immunodeficiency Virus; IHD - ischemic heart disease; HTN - hypertension; CKD - chronic kidney disease; AMB - amphotericin B; FESS - Functional endoscopic sinus surgery. \*Statistically significant values are highlighted in bold

found that some of the patients were neither diabetic (39) nor steroid-exposed (13), so whether COVID-19 itself causes immune dysregulation and predisposes patients to invasive

MCR remains an unproven possibility and needs further study.<sup>[19-21]</sup> DM was another common underlying co-morbid illness. The mean glycated hemoglobin value (5.7%) at



**Table 3: Touchstone characteristics among patients of early and late CAM**

VARIABLE	EARLY CAM (n=30)	LATE CAM (n=68)	P
Mean Age (in years)	54.8	45.3	0.01
Male Sex	22	44	0.001
Risk factor (%)			0.01
DM	19 (63.33%)	40 (58.82%)	
STEROID	30 (100%)	55 (80.8%)	
HTN	11 (36.66%)	29 (42.64%)	
IHD	5 (16.66%)	10 (14.7%)	
CANCER	2 (6.66%)	0	
CHEMOTHERAPY	2 (6.66%)	0	
CKD	2 (6.66%)	5 (7.35%)	
HIV	1 (3.33%)	0	
SITE OF MCR (%)			0.81
RHINO-ORBITAL	22 (73.33%)	47 (69.11%)	
RHINO-ORBITAL-CEREBRAL	4 (13.33%)	26 (38.23%)	
PULMONARY	2 (6.66%)	0	
CUTANEOUS	1 (3.33%)	6 (8.82%)	
DISSEMINATED	0	3 (4.41%)	
COVID-19-SPECIFIC THERAPY (%)			
STEROID	30 (100%)	55 (80.8%)	<b>0.01</b>
REMDESEVIR	17 (56.66%)	43 (63.23%)	0.62
TOCLIZUMAB	0	14 (20.5%)	<b>0.001</b>
OXYGEN THERAPY	22 (73.33%)	40 (58.82%)	<b>0.01</b>
NON-INVASIVE VENTILATION	6 (20%)	16 (23.52%)	<b>0.05</b>
MECHANICAL VENTILATION	0	5 (7.35%)	<b>0.04</b>
ZINC	27 (90%)	53 (77.94%)	0.44
VITAMIN C	21 (70%)	30 (44.11%)	0.23
IVERMECTIN	6 (20%)	19 (27.94%)	0.96
Treatment (%)			
Liposomal AMB	30 (100%)	68 (100%)	<b>0.09</b>
Posaconazole	20 (66.6%)	34 (50%)	<b>0.07</b>
Step-down anti-fungal therapy	20 (66.6%)	34 (50%)	<b>0.07</b>
Surgery (%)			
FESS	20 (66.6%)	50 (73.52%)	<b>0.04</b>
DEBRIDEMENT	7 (23.3%)	13 (19.11)	0.11
EXENTERATION	0	3 (4.41%)	<b>0.04</b>
Combined medical and surgery (%)	27 (90%)	63 (92.64%)	0.81
90-Day mortality (%)	17 (56.6%)	45 (66.17%)	<b>0.01</b>

DM - Diabetes Mellitus; HIV - Human Immunodeficiency Virus; IHD - ischemic heart disease; HTN - hypertension; CKD - chronic kidney disease; AMB - amphotericin B; FESS - Functional endoscopic sinus surgery. \*Statistically significant values are highlighted in bold

admission for all newly detected diabetes cases (n = 25) in the CAM group was in the normal range, so we can say that these patients did not have DM before CAM developed. In a multi-center study on MCR in India,<sup>[4]</sup> 57% of patients had uncontrolled DM and 18% had DKA; in contrary to this, the cases of DM were less in our study (46.8%), although we observed more patients with DKA (31.2%). SARS-CoV-2 has

shown to affect the beta cells of the pancreas, possibly causing DM and ketoacidosis.<sup>[22]</sup> Zinc was used very frequently in COVID-19 treatment, and its association as a possible risk factor with MCR in both early and late CAM groups was analyzed. In this study, 78% had the history of zinc intake for a minimum period of 2 weeks. Pathogenic fungi make use of a variety of transporters and specialized zinc captors to survive.<sup>[23]</sup> Apart from this, oxygen therapy was the third common treatment in early CAM, whereas remdesivir was in the late CAM group. In 98 cases of CAM, 63.9% cases had oxygen requirement for COVID pneumonitis. The non-medicated oxygen use, poor hygiene, and failure to change humidifying water frequently may also be risk factors for MCR which are also reported in 14.4% cases in a cohort study of 164 patients.<sup>[24]</sup> Our study shows that 14.2% cases received tocilizumab; however, all these cases were of late CAM. This was because of the COVID-19 treatment protocol or dearth of availability of tocilizumab. Tocilizumab use in COVID-19 has been reported as a risk factor for invasive fungal involvement; however, it was for candidiasis.<sup>[25]</sup> The role of tocilizumab as predilection for MCR is to be studied more widely.

The most common neurological burden because of MCR was cranial nerve involvement (49.6%). The trigeminal nerve was affected most frequently (49.6%), which endorsed Dubey S *et al.*<sup>[26]</sup> observational study, in which they found 47.2% cases of trigeminal nerve involvement. Unilateral cavernous sinus involvement or thrombosis was seen in 21 (14.8%) cases and bilateral in two cases, which could be responsible for a larger number of patients having cranial nerve involvement. According to previous review articles, the frequency of facial paralysis in conjunction with rhino-orbital-cerebral MCR is 11%.<sup>[27]</sup> However, we found a higher incidence of 13.4% with LMN facial palsy and that all of them were diabetic. Although pathophysiology for facial paralysis is not known, some reports indicate that the infection can reach from the pterygopalatine fossa to the inferior orbital fissure, orbital apex, and infratemporal fossa.<sup>[28]</sup> Ischemic stroke was seen in 38 (28.3%), which was more common in CAM (29.5%) in comparison to non-CAM (20.9%). Stroke was concordant to the side of the internal carotid (ICA) involved. The ICA at the level of the cavernous sinus was encased by MCR in 30 cases (78.9%). All strokes were because of ICA involvement at the level of the cavernous sinus. Mechanisms of ICA involvement can be because of external compression, intraluminal obstruction, microscopic angioinvasion, and vasospasm.<sup>[26]</sup>

The management of MCR mainly involves control of risk factors such as uncontrolled DM, early surgical intervention, and medical management with anti-fungal agents. A large review of 929 cases showed that survival was only 3% with no intervention, 57% with surgery alone, 61% with amphotericin deoxycholate, and 70% when treated with both amphotericin and surgical debridement.<sup>[3]</sup> Amphotericin B is the anti-fungal drug of choice for MCR. In our study, all 141 patients received liposomal amphotericin B. The liposomal form is preferred because it is less nephrotoxic and, therefore, higher doses

may be given for a prolonged duration. In our study, 56% of the patients received step-down therapy with posaconazole, which is almost double as compared to a recent multi-center study reported in 2826 patients.<sup>[28]</sup> FESS was the most common operative procedure which was performed in 63.8% of the cases in our study. PNS debridement was performed in 28.3% cases. Orbital exenteration was performed in just 4 (2.8%) cases, and the possible reason behind this is that as most of the patients gave negative consent and a few cases were having severe illness, exenteration was not considered. Intraorbital amphotericin B injection was given in 24 (17%) in patients who were having extensive orbital involvement and not responding with treatment, which was like a previous study where intraorbital amphotericin B injection was provided in 22% of the cases.<sup>[28]</sup> In a study of 2826 patients, PNS debridement as a primary management was performed in 21% and orbital exenteration was performed in 15% patients.<sup>[28]</sup>

As the disease is known to be aggressive, the mortality is more than 50%.<sup>[17]</sup> The results from our study showed that the overall

mortality at 3 months with MCR was 43.9%, which was less as compared to the previous literature.<sup>[17]</sup> The mortality rate for CAM patients was higher (48.9%) than for non-CAM (46.5%) patients. Older ages (>50 years), DM, multiple risk factors, DKA on admission, brain involvement, and history of COVID-19 pneumonitis by Mucorales were associated with a higher risk for death. The combined use of anti-fungal drugs and any type of surgery at any site was associated with significantly improved survival at 12 weeks. The increased risk for death because of COVID-19 itself in CAM patients cannot be ruled out. Although exact pathophysiology is unknown, various reasons could explain this. First, patients with CAM were older (49.2 years) than non-CAM patients (43.7 years). Evidence suggests that an older age imparts an increased risk for hospitalization, respiratory failure, intensive care unit admission, and glucocorticoid therapy in COVID-19.<sup>[22,29]</sup> Second, rhino-orbital-cerebral MCR is a more common involvement site in CAM (30.6%) as compared to non-CAM (4.6%) groups and could be a possible reason for high mortality in the CAM group. Third, COVID-19 itself compromises the immunity and can worsen diabetes control, and some treatments used for COVID treatment (e.g., steroids, remdesivir) can exacerbate hyperglycemia,<sup>[30]</sup> which can lead to severe MCR and higher mortality rates.

Sufferers who underwent combined medical and surgical management had a significantly better outcome, like the previous experience,<sup>[17]</sup> as 79 (56%) cases who survived during this study had combination therapy. However, most of the non-survivor cases had rhino-orbital cerebral involvement and fewer surgeries were performed in the

**Table 4: Neurological manifestations in MCR**

Neurological manifestation (%)	CAM (n=98) (69.5%)	NON-CAM (n=43) (30.5%)
Cranial Nerve Palsy	50 (51.02%)	20 (46.5%)
Headache	45 (45.91%)	14 (32.55%)
Cavernous sinus thrombosis	18 (18.36%)	5 (11.62%)
Ischemic Stroke	29 (29.5%)	9 (20.9%)
Cerebral abscess	8 (8.63%)	0
Altered mental status	6 (6.12%)	2 (4.65%)

**Table 5: Factors predicting death at 12 weeks among patients with MCR**

VARIABLE	SURVIVORS (n=79) (56.02%)	NON-SURVIVORS (n=62) (43.97%)	P
Mean age (years)	47.9	51.2	<b>0.02</b>
Male Sex	40	48	0.914
DURATION OF the SYMPTOM (days)	11.7	13.2	0.623
SITE OF MCR			
RHINO-ORBITAL	72 (91.13%)	37 (59.67%)	<b>0.05</b>
RHINO-ORBITAL-CEREBRAL	8 (10.12%)	24 (38.7%)	<b>0.001</b>
RISK FACTOR/CO-MORBID DISEASES			
DM	26 (32.91%)	40 (64.51%)	<b>0.05</b>
STEROID	62 (78.48%)	50 (80.64%)	0.742
CANCER	1 (1.26%)	1 (1.61%)	1
CHEMOTHERAPY	1 (1.26%)	1 (1.61%)	1
CKD	2 (2.53%)	7 (11.29%)	0.063
HIV	0	1 (1.61%)	
DKA at admission	14 (17.72%)	30 (48.38%)	<b>0.041</b>
Multiple risk factor	19	50	<b>0.003</b>
HTN	51 (54.55%)	17 (27.41%)	0.112
IHD	10 (12.65%)	12 (19.35%)	0.89
Combined medical and surgery	79 (100%)	51 (82.2%)	<b>0.042</b>
COVID-19 +	56 (70.88%)	42 (67.74%)	<b>0.003</b>
Hospital stays (mean days)	34.1	12.3	<b>0.001</b>

Abbreviations: DM - Diabetes Mellitus; HIV - Human Immunodeficiency Virus; IHD - Ischemic heart disease; HTN - hypertension; CKD - chronic kidney disease; AMB - amphotericin B. \*Statistically significant values are highlighted in bold

patient's rhino-orbital-cerebral MCR, which may be because of severity of patient illness or negative consent for intervention. Step-down therapy of anti-fungal agents was almost equally used (58.1%) in non-CAM patients and in CAM patients (55.1%). However, there was an increase in mortality frequency in CAM (48.9%) cases as compared to non-CAM (46.5%) cases.

Finally, our study has some limitations. The first limitation is that we collected data from a single tertiary care center catering the restricted population. Second, the predominant risk factor for MCR in our study was steroid use, but we do not have data on the dosage and duration of steroid use, which is a critical factor for MCR emergence in the COVID-19 era. The power of our study is comprehensive evaluation of all parameters in a large number of patients.

Before having such a large experience of treating MCR cases, we used to have almost 100% mortality for MCR. When we came across initial cases of MCR during this era of COVID-19, in view of our old experience, we were afraid of treating such patients. When large numbers of MCR cases reached to our institute and referred to us, our institute formed a medical board of various specialties including ear–nose–throat (ENT) surgeons and decided to treat comprehensively. At the end of the above study, we were able to save more than 50% cases at 12 weeks and became wiser for future perspectives.

## CONCLUSION

To conclude, because there is a sudden surge of cases of MCR in COVID19, possibly because of improper glucocorticoid usage, treating physicians should ensure use of appropriate drugs and doses in treating COVID-19 patients. Early diagnosis and treatment of MCR can substantially reduce morbidity and mortality. Having high suspicion for MCR in patients with subtle symptoms pertaining to cranial nerve involvement may detect such cases in advance. We found that MCR complicating COVID-19 cases as compared with non-COVID-19 cases had a significantly higher mortality rate. A combined surgical and medical management exhibited a better outcome. A combined approach should always be commenced as early as possible.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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