Rhino-orbito-cerebral mucormycosis: patient characteristics in pre-COVID-19 and COVID-19 period*

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Abstract

Background: Rhino-orbito-cerebral-mucormycosis (ROCM), a rare and potentially fatal disease was seen in increasing numbers during the COVID-19 pandemic. This study describes and compares the patient characteristics and outcomes in COVID-19 associated mucormycosis (CAM) and non-COVID-19 mucormycosis (non-CAM).

Methodology: CAM patients (24 cases) were recruited from the COVID-19 period and non-CAM (24 controls) from the pre-COVID-19 period. Clinical data of the CAM group was collected retrospectively with 3 month outcomes prospectively. The non-CAM group data was collected retrospectively. Patient characteristics were compared and risk factors for mortality in ROCM were assessed.

Results: Orbital symptoms [altered vision, restricted eye movements, ptosis] and intracranial involvement were higher in CAM patients on presentation. Similarly, the radiological involvement of orbit (orbital apex, superior orbital fissure) and intracranial cavity (intracranial thrombosis, cavernous sinus) was also higher in CAM patients. Newly detected diabetes was found only in CAM patients (29.2%). Although univariate analysis suggested an increased mortality risk in ROCM patients with orbital involvement, the multivariate analysis showed no increased risk with any of the parameters assessed, including COVID-19 positivity.

Conclusions: Compared to the non-CAM, the disease presentation was severe in CAM with higher frequency of orbital and intracranial involvement. However, with early detection and treatment, the short term survival was comparable in both groups.

Key words: mucormycosis, COVID-19, *Rhizopus*, brain infarction, ophthalmoplegia

Introduction

Acute invasive fungal sinusitis (AIFS), commonly termed as ROCM, is a rare and life-threatening fungal infection caused by fungi of the genus *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella* and *Absidia* of Order- Mucorales, Class- Zygomycetes [(1)]. The infection is thought to originate in the nasal mucosa and spreads to the paranasal sinuses and extra-paranasal sites including the orbit and intracranial region [(2)]. In this rapidly progres-

sive disease, the clinical presentation depends on the extent of tissue involved and leads to increased morbidity and mortality if not detected and treated early [3].

ROCM occurs in patients who are immunocompromised and have impaired neutrophilic response as seen in diabetes mellitus, haematological malignancies, acquired immunodeficiencies, and post organ transplant [4]. The fungi in an acidic environment invade tissue and blood vessels causing thrombosis and eventually necrosis [5].

Ever since the outbreak of Coronavirus infection (COVID-19) pandemic, several opportunistic bacterial and fungal infections [6] have been associated with it. Among this, ROCM has emerged as the single largest entity spiking alongside with the COVID-19 peaks in both the first and second waves. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 attaches to the angiotensin-converting enzyme 2 (ACE2) receptors and enters the nasal epithelial cells. It causes tissue injury by direct viral toxicity, endothelial cell damage, thrombo-inflammation, dysregulation of the immune response, and dysregulation of the renin–angiotensin–aldosterone system [7].

The described clinical features of ROCM include a black or unhealthy nasal mucosa, fever, facial pain, headache, nasal discharge, eye symptoms of ptosis, proptosis, ophthalmoplegia, loss of vision and multiple cranial nerve palsies [8]. As COVID-19 is a relatively new infection and ROCM an uncommon disease, there is not much literature on the differences in the clinical presentations and outcomes between the COVID-19 associated mucormycosis (CAM) and non-COVID-19 mucormycosis (non-CAM) [9]. Moreover, the published data sets selected CAM and non-CAM patients from the COVID-19 pandemic period. Here we fashioned a case -control study to describe the differences in the clinical presentations between CAM (cases) and non-CAM patients (controls, selected from the pre-COVID-19 pandemic period), thereby reducing the possibility of including false negative patients as well as COVID-19 recovered patients. We feel that this would more accurately highlight the true difference between the groups. Risk factors predicting mortality in ROCM were also looked at.

Materials and methods

Study design, participants, and ethics statement

The study conducted at a tertiary centre in South India recruited patients (CAM cohort) who had clinical features with histopathological or microbiologically proven ROCM [10,11] and COVID-19 positivity on SARS-CoV-2 Reverse transcription polymerase chain reaction (RT PCR) testing from July to November 2020. The non-CAM patients were matched for sex, age ± 5 years and pathological diagnosis [acute invasive fungal sinusitis (AIFS) or AIFS + chronic granulomatous fungal sinusitis (CGFS)] to the CAM and were selected from our database (Jan 2014 to Nov 2019, a total of 147 patients). Patients with haematological malignancies were excluded. This study was approved by the institutional review board (IRB. No 13745).

Data collection and comparison of patients in CAM and non-CAM

The surgical and medical treatments were as described previously [11]. Amphotericin was not administered in patients with severely deranged renal parameters or when patients declined therapy. Posaconazole was given as step down therapy. The clinical details, blood parameters, pathological, microbial, radiological, medical and surgical data were collected retrospectively and this was compared between the cohorts. The CAM patients were reviewed 3 months post treatment (outpatient department or contacted on telephone). Diagnostic nasal endoscopy (DNE) was done from at least 6 weeks post-surgery in all patients who survived. Tissue for fungal culture or histopathological examination (HPE) or imaging (computer tomography or magnetic resonance imaging of the paranasal sinus and brain) was done when there was a clinical or endoscopic suspicion of residual disease in patients. Treatment outcome in patients who were alive was classified as good response or residual disease based on the absence or presence of disease on any of the following parameters [DNE- (unhealthy or necrotic nasal tissue was considered residual disease), radiology, HPE, microbiology]. Post treatment data was collected retrospectively in the non-CAM cohort.

Apart from this, the possible risk factors associated with mortality in ROCM such as age, COVID-19 positivity and clinical and radiological involvement of the orbit and intracranial cavity were assessed.

COVID-19 severity was defined as per the institution protocol into 1) mild (any COVID-19 related symptoms without pneumonia or hypoxia and respiratory rate < 24/min), 2) moderate (pneumonia (clinical or radiological) or hypoxia and respiratory rate ≤ 30/min, and SpO2 ≥ 90% on room air and no respiratory distress) or 3) severe (pneumonia and ≥1 of: respiratory rate > 30/min, severe respiratory distress, SpO2 < 90% on room air).

Statistical analysis

Descriptive statistics were reported for patient demographic data. The Pearson Chi-square and Fisher's exact test (less cell count) were used to assess the association between categorical variables. Based on the normality of data, the parametric t test and non-parametric Mann Whitney U test were performed to find difference between two groups. Univariate and multivariate logistic regression was done to assess the risk factors associated with mortality in ROCM. All tests were two-sided at α=0.05 level of significance. All analyses were performed using the software programs SAS (version 9.1 for windows, SAS Institute, Cary, NC, USA).

Table 1. Comparison of comorbidities and clinical features.

		CAM, n=24 No. (%)	non-CAM, n=24 No. (%)	P value
Comorbidities	Diabetes mellitus (DM)	24 (100)	23 (95.8)	1.000
	New onset DM	7 (29.2)	0 (0.0)	**0.009**
	Diabetic ketoacidosis	1 (4.2)	4 (17.4)	0.188
	Hypertension	11 (45.8)	14 (58.3)	0.386
	Chronic kidney disease	3 (12.5)	9 (37.5)	0.093
	Hypothyroid	1 (4.2)	3 (12.5)	0.609
	Bronchial asthma	0 (0.0)	3 (12.5)	0.234
	Coronary artery disease	1 (4.2)	3 (12.5)	0.609
Clinical symptoms	Fever	4 (16.7)	8 (33.3)	0.318
	Headache	15 (62.5)	10 (41.7)	0.149
	Nasal obstruction	7 (29.2)	9 (37.5)	0.540
	Nasal discharge	7 (29.2)	11 (45.8)	0.233
	Facial pain	11 (45.8)	15 (62.5)	0.247
	Facial swelling	8 (33.3)	11 (45.8)	0.376
	Altered facial sensation	9 (37.5)	10 (41.7)	1.000
	Ptosis	9 (37.5)	3 (12.5)	0.093
	Loss/reduced vision	15 (62.5)	3 (12.5)	**0.001**
	Loose tooth	3 (12.5)	8 (33.3)	0.168
	Palatal ulcer	2 (8.3)	3 (12.5)	1.000
	Altered sensorium	3 (12.5)	2 (8.3)	1.000
DNE findings	Nasal crust/polyp	21 (87.5)	20 (83.3)	1.000
Face examination	PNS tenderness	9 (37.5)	4 (16.6)	0.193
	Facial swelling	8 (33.3)	12 (50)	0.242
	Facial sensation	12 (50)	11 (45.8)	0.611
Oral examination	Palatal bulge/ulcer	9 (37.5)	12 (50)	0.383
Eye examination	Periorbital oedema	8 (33.3)	5 (20.8)	0.330
	Ptosis	12 (50)	3 (12.5)	**0.011**
	Proptosis	11 (45.8)	6 (25)	0.131
	Chemosis	8 (33.3)	6 (25)	0.525
	Restricted eye movements	15 (62.5)	7 (29.2)	**0.020**
	Altered vision	15 (62.5)	2 (8.3)	**< 0.001**
	Any clinical orbital involvement	17 (70.8)	8 (33.3)	**0.009**
CNS examination	Delayed IC involvement	6 (25)	1 (4.2)	**0.028**
	Overall IC involvement	10 (41.67)	2 (8.3)	**0.017**

N, number of patients; PNS, paranasal sinus; IC, intracranial; CNS, central nervous system.

Results

Demography and comorbidities

There were 25 patients with ROCM during the study period. Among this, 24 tested COVID-19 positive (CAM) and 1 negative (excluded). None of the patients had a history of invasive fungal sinusitis in the past. These patients did not give a history of ICU admission, intubation or receiving biologics for COVID-19 infection prior to the development of ROCM. The mean age of the CAM was 54.2 years (30-71 years, SD 10.7) and non-CAM was 54.1 years (35-71years, SD 10.3). The matched CAM and non-CAM cohort had 83.3% males and 16.7% females. All patients in the CAM cohort were found to be COVID-19 positive on presentation with 45.8% of them having tested positive elsewhere too. The mean duration of onset of ROCM symptoms after testing positive for COVID-19 was 19 days (range – 7 to 49).

Diabetes mellitus (DM) was the most common comorbidity in both cohorts. Newly detected diabetes was found only in the CAM (29.2%). In the CAM group one patient had pancreatic dia-

Table 2. Imaging findings and biochemical parameters.

Radiological examination		CAM, n=24 No. (%)	non-CAM, n=24 No. (%)	P value
Nose and maxilla	Sinonasal	24 (100)	24 (100)	
	Bilateral involvement	18 (75)	17 (70.8)	0.745
	Hard palate	5 (20.8)	13 (54.2)	**0.017**
	Upper alveolus	2 (8.3)	9 (37.5)	**0.036**
	Maxillary wall erosion	9 (37.5)	16 (66.7)	**0.043**
Orbit	Any radiological orbital involvement	24 (100)	18 (75)	**0.022**
	Orbit bony erosion	8 (33.3)	12 (50)	0.242
	Extraconal	17 (70.8)	20 (83.3)	0.494
	Extraocular muscle	12 (50)	6 (25)	0.074
	Intraconal	10 (41.7)	6 (25)	0.221
	Orbital apex	15 (62.5)	5 (20.8)	**0.003**
	Optic nerve	7 (29.2)	3 (12.5)	0.286
	Superior orbital fissure	12 (50)	1 (4.2)	**< 0.001**
	Inferior orbital fissure	12 (50)	9 (37.5)	0.383
	Nasolacrimal duct	5 (20.8)	6 (25)	0.731
	Proptosis	8 (33.3)	8 (33.3)	1.000
	Abscess in orbit	3 (12.5)	6 (25)	0.267
Intracranial (IC)	Any IC involvement	15 (62.5)	4 (16.7)	**0.003**
	IC direct erosion	1 (4.2)	3 (12.5)	0.609
	IC thrombosis	8 (33.3)	1 (4.2)	**0.023**
	IC infarcts	6 (25)	2 (8.3)	0.245
	Cavernous sinus	12 (50)	1 (4.2)	**0.001**
	ICA narrowing	6 (25)	1 (4.2)	0.097
	Brain abscess	6 (25)	1 (4.2)	0.097
Others	Cribriform plate	3 (12.5)	4 (16.7)	1.000
	Sphenoid	5 (20.8)	2 (8.3)	0.416
	Clivus	1 (4.2)	0	1.000
	Pterygopalatine fossa	17 (70.8)	13 (54.2)	0.233
	Infratemporal fossa	11 (45.8)	8 (33.3)	0.376
	Zygoma	3 (12.5)	3 (12.5)	1.000
	Abscess in other location	6 (25)	1 (4.2)	0.097
Biochemical parameters		**CAM mean (SD)**	**Non-CAM mean (SD)**	
	Haemoglobin*	11.9(2.1)	12.2(2.4)	0.645
	Total count‡	12150.0 (8700.0, 19050)	9150.0 (7275.0, 14150.0)	0.05
	Neutrophils*	75.08 (12.2)	71.46 (11.6)	0.298
	Lymphocytes‡	16.0 (7.0,21.7)	20.0 (10.3, 23.7)	0.265
	Creatinine‡	0.86 (0.70, 1.37)	0.88 (0.65,1.43)	0.861
	Random blood sugar*	273.82 (127.8)	279.5 (117.9)	0.881
	HbA1c*	10.71 (2.2)	10.54 (2.5)	0.805

* Values are Mean (Standard Deviation) and P value from t test.

‡ Values are Median (25th percentile, 75th percentile) and P value from Mann Whitney test; ICA, internal carotid artery; HbA1c, glycated haemoglobin.

betes and the rest had type 2 DM. In non-CAM, the information on the type of DM in one patient was not available and one patient had no DM. Among the remaining patients, one had type 1 DM and all the rest had type 2 DM. In the CAM cohort, 75% had mild, 4.2% had moderate and 20.8% had severe COVID-19 infection. The distribution of other comorbidities were similar in

Table 3. Surgical debridement and medical treatment.

	CAM, n=24 No. (%)	non-CAM, n=24 No. (%)	P- Value
Sinus surgery	23 (95.83)	24 (100)	1.000
Maxillary sinus	23/23 (100)	24 (100)	
Ethmoids	23/23 (100)	24 (100)	
Frontal	18/23 (78.2)	19 (79.2)	0.939
Sphenoid	23/23 (100)	24 (100)	
Middle turbinate	17/23 (74)	15 (62.5)	0.401
Inferior turbinate	15/23 (65.2)	20 (83.3)	0.154
Septum	15/23 (65.2)	6 (25)	**0.005**
Eye surgery	5 (20.8)	3 (12.5)	0.701
Brain surgery	5 (20.83)	0	**0.050**
Maxilla/palatal	6 (25)	15 (62.5)	**0.014**
Amphotericin	23 (95.8)	22 (91.7)	1.000
Posaconazole	19 (79.2)	10 (41.7)	**0.008**

both groups (Table 1).

Patient presenting symptoms and clinical examination findings

Orbital symptoms were higher in the CAM cohort with significant numbers presenting with complaints of visual disturbances (p=0.001). The common presenting symptoms in the CAM were loss/reduced vision and headache whereas it was facial pain and facial swelling in the non-CAM cohort. The other less frequent symptoms among the CAM and non-CAM included retro-orbital pain, epiphora, facial palsy, ear block and ear discharge (Table 1). The most common examination finding present in more than 80% of patients in both cohorts was the presence of unhealthy tissue in nasal cavity. The overall orbital involvement and intracranial involvement was significantly higher in the CAM cohort. Of the 10 patients in the CAM cohort who had intracranial involvement, only 4 had intracranial features at presentation while the other 6 patients developed symptoms after a mean duration of 21.4 days (range, 3-63 days). This delay in development of intracranial features was found to be significant in CAM patients (p=0.028). The mean duration between COVID-19 positivity and development of intracranial features in CAM was 15days (range, 0-63 days) (Table1).

Radiological findings

Complementing the clinical findings, the orbital and intracranial involvement on imaging was higher in the CAM and maxillary sinus erosions more in the non-CAM (Table 2).

Among the 6 CAM patients with brain abscess, 3 had the abscesses in the temporal lobe; 2 in the frontal lobe; 1 patient had abscesses in temporal, frontal, and parieto-occipital lobes. Apart from this, additional intracranial involvement was seen in 5 CAM patients in the form of dural thickening/enhancement, or skull base erosions or perineural extension along skull base to mandibular and maxillary nerves. The only non-CAM patient with brain abscess had temporal lobe involvement.

The location of extra paranasal sinus abscesses included the buccal and masticator spaces, prevertebral space, pterygopalatine space, pterygoid muscles and nasopharynx and this was seen more in the CAM cohort.

Blood parameters

No significant difference was found in the blood parameters (Table 2) between the groups. The control of DM was poor in both the groups as reflected by the mean HbA1c values.

Microbiological and histopathological examination (HPE) findings

Histopathology showed tissue invasion in all the patients. Bony invasion was seen in 66.7% of CAM and 79.2% of non-CAM (p=0.451). In the CAM there were 14 patients with AIFS and 9 patients with AIFS + CGFS (one patient did not consent for surgery). In non-CAM there were 14 patients with AIFS and 10 patients with AIFS + CGFS. All patients with CAM had mucor/broad aseptate fungal hyphae (BAFH) identified on HPE, except one who had associated aspergillus infection (AIFS group). However, aspergillus infection was seen along with mucor in 4 patients with non-CAM [AIFS-(2) and AIFS + CGFS-(2)].

Fungal growth was seen in 95.3% of CAM and 87.5% of non-CAM. Among this, the fungi identified was *Zygomyces*/*Rhizopus* in 91.6% of CAM and 79.2% of non-CAM. The higher detection of *Aspergillus* in non-CAM on histopathology was reflected in fungal cultures where *Aspergillus sp*. grew in 3 patients and in 1 patient in CAM.

Table 4. Risk factors associated with mortality in rhino-orbito-cerebral mucormycosis using logistic regression.

	Univariate Logistic Regression		Multiple Penalized Logistic Regression	
Variables, n= 44	**OR (95%CI)**	**P value**	**aOR (95% CI)**	**P value**
Age(years)	1.05 (0.98, 1.13)	0.219		
Sex (Male)	1.93 (0.20, 18.23)	0.567		
Group (Covid Positive)	1.01 (0.24, 4.10)	1.000	0.41 (0.05, 3.54)	0.4010
Restricted eye movements (yes)	8.36 (1.52, 46.15)	**0.015**	2.95 (0.08, 106.16)	0.5542
Reduced/loss of vision (yes), n=43	5.56 (1.14, 27.01)	**0.034**	2.98 (0.21, 42.51)	0.4211
Any clinical orbital involvement (yes)	5.71 (1.05, 31.07)	**0.044**	1.12 (0.03, 46.84)	0.9516
Any clinical IC involvement (yes)	3.11 (0.67, 14.54)	0.149		
Any radiological orbital involvement (yes)	1.20 (0.12, 12.14)	0.877		
Radiological orbital apex involvement (yes)	4.28 (0.93, 19.65)	0.062		
Any radiological IC involvement (yes)	0.61 (0.14, 2.79)	0.526		

aOR (95%CI): adjusted Odds Ratio (95% Confidence Interval); IC, intracranial.

Bacterial cultures were sent when pus was present and this showed a mixture of bacterial growth in both cohorts. This included *Staphylococcus aureus, Klebsiella sp., Pseudomonas aeruginosa, Escherichia coli*, *Coagulase negative staphylococcus, Enterococcus sp., Streptococcus sp., Morganella sp*. and *Citrobacter sp*. Bacterial growth was, however, seen more in CAM (66.7 %), than non-CAM (37.5%) (p=0.076).

Surgical debridement and medical treatment

Debridement of paranasal sinuses was the most common surgical procedure. Maxillectomy/palatectomy, brain abscess drainage and orbital surgery were done in indicated patients who consented (Table 3). Eight CAM patients, who after admission developed COVID-19 related complications were administered steroids as per the prescribed protocol [12]. The data on steroid administration in patients who tested positive for COVID-19 in outside hospitals prior to ROCM development, however was not available. All patients with DM except two in the CAM and one in the non-CAM required insulin for diabetes control during their treatment course in the hospital.

Follow-up

The patients who did not undergo surgery and did not receive Amphotericin were excluded from follow up and mortality assessments. The 3-month mortality in both CAM (5/22) and non-CAM (5/22) was 22.7%. Two CAM patients with severe COVID-19 disease expired due to acute respiratory distress syndrome (ARDS) in 2 and 4 weeks after admission. One patient who had mild COVID-19 infection expired due to refractory septic shock and metabolic acidosis within a week of admission. The remaining 2 patients with mild COVID-19 died of progressive invasive fungal infection in 5 and 10 weeks. In the non-CAM, 1 patient died of cardiac arrest at 7 weeks; 1 patient had septic shock at 3 weeks; and 3 patients had progressive disease and died in 5 days, 4 and 9 weeks.

Among the survivors, a good treatment response without residual disease was seen in 94.1% of patients in the non-CAM group compared to 58.8% in the CAM group (p=0.015) at 3 months follow-up. The remaining patients in CAM and non-CAM had residual disease and continued to be on antifungals at 3 months.

Among the CAM patients, 40% (2/5) of the patients with severe COVID-19 infection succumbed to the disease while it was 18.8% (3/16) in those with mild COVID-19 infection. This association was however, not significant (p=0.330).

A univariate logistic regression model for mortality risk in ROCM patients showed a significant increase in mortality when there was evidence of clinical orbital (p=0.044) involvement. However, this was not seen on multivariate analysis. None of the parameters tested, including COVID-19 positivity showed increased risk for mortality (Table 4).

Discussion

Substantial differences in the clinical and radiological presentation were noted among the two cohorts. While the CAM cohort was characterized by pronounced orbital and delayed onset intracranial symptoms complemented with imaging features, patients with non CAM presented most commonly with facial pain with greater involvement of hard palate, upper alveolus and maxillary sinus walls on imaging. All patients in the cohort had histopathological evidence of tissue invasion by mucor. However, there was a higher (non-significant) association of Aspergillus infection in the non-CAM cohort and bacterial infection in CAM patients. Though the three-month mortality was similar in both the cohorts, a higher proportion of patients had good treatment response in the non-CAM cohort. None of the factors

analysed, including COVID-19 positivity showed an association with increased risk of mortality in the ROCM patients.

Several recent publications on COVID-19 associated mucormycosis have identified orbital symptoms as a common presentation [13-15] with the Tarjani et al. [14] study showing involvement of orbital apex and cavernous sinus in 24 and 17 of the 58 patients respectively. Consistent with this, we found clinical and radiological orbital involvement to be more in CAM patients in addition to the significant increase in the incidence of intracranial involvement. In contrast , the non-CAM patients in our study presented most commonly with facial pain and facial swelling which was similar to findings in literature during the pre-COVID-19 period (16). Although it is unclear why the orbital and intracranial presentations are more frequent in CAM, it is possible that factors like COVID-19 infection induced prothrombotic state and vascular endothelial inflammation [17] and the accelerated locoregional spread contributed by the increased presence of inflammatory factors such as ferritin in COVID-19 infection and diabetes [15, 18] could have facilitated the spread.

Diabetes mellitus is the most associated comorbidity and independent risk factor in patients with ROCM in the pre-COVID-19 as well as the COVID-19 pandemic period [4, 13, 19]. India, considered as second largest hub of diabetes mellitus also has the maximum number of ROCM cases reported in literature [20]. Although the complex interactions between COVID-19, diabetes and mucormycosis is not well understood, factors such as increased COVID-19 severity, inadequate access to health care facilities and irrational and unsupervised corticosteroid use may have contributed to the surge in COVID-19 associated mucormycosis in the Indian population. Diabetes mellitus was seen in almost all patients in our cohorts. An interesting finding in our study, similar to previous literature is the larger number of new onset diabetes [21] among CAM cohort. Although the pathophysiology for this is unclear, one study attribute it to an increased ACE 2 expression in endocrine pancreas enabling the SARS-CoV-2 entry and potential impairment of insulin secretion [22]. Other factors could be the cytokine storm resulting in insulin resistance, corticosteroids inducing a hyperglycaemic state and viral-induced lymphopenia and endothelial inflammation [13, 23]. Nonetheless, the current study showed uncontrolled diabetes (HbA1c>10) in both the study groups.

The current recommended treatment for ROCM includes surgical debridement and appropriate first line antifungal therapy [10]. Unlike the non-CAM where most patients had a good response to treatment, only a little over 50% of patients in CAM had good response at 3 months in our cohort. Never-the-less, majority of the remaining patients who had residual disease were expected to have a desirable outcome with adequate antifungal therapy and close follow up. The mortality in ROCM largely depends on the extent of the disease, treatment received and patient general condition. A study by Patel et al. [9], which included patients exclusively from the pandemic period, showed comparable death rate at 12 weeks in COVID-19 associated mucormycosis (44.1%) and non-COVID-19 mucormycosis (48.8%). The overall mortality in the CAM and non-CAM in our study was comparable and was close to the mortality (26.5%) of non-COVID-19 mucormycosis in previous studies from our centre [11]. A recent systematic review on CAM reports a mortality of 34% [13].

An increased risk of mortality in ROCM has been reported in patients with intracranial, orbital and pulmonary involvement, advanced age, and renal disease [14, 16]. In CAM patients, increased mortality was seen with orbital involvement and severe COVID-19 infection [24]. Contrary to the reported higher incidence of severe COVID-19 among patients with CAM [23], the current study showed that most patients had only mild COVID-19 infection. However, the mortality among the severe COVID-19 infection was higher (statistically insignificant). Our study showed a poor survival prognosis in patients with orbital involvement of ROCM on univariate analysis. However, this was not seen on multivariate analysis. Interestingly, COVID-19 positivity also did not increase mortality risk in ROCM. These results could be due to our low sample size and lesser number of patients with intracranial complications. The comparable mortality outcomes in the CAM cohort in our study could be due to early detection, better surgical clearance and medical therapies available in the current era. Apart from this, our CAM cohort had only diabetes mellitus as their main associated comorbidity and many of them were new onset diabetes which would have influenced the disease progression and treatment response. Recent studies predicting survival prognosis [25, 26], reinforces the importance of an appropriate and adequate surgical and medical treatment for ROCM.

Limitations

The study describes a short term (3 month) follow up. Patients with comparable disease severity were not chosen in the groups due to the rarity of the disease in pre-COVID-19 period and also because the primary study objective was to compare the clinical presentations. Steroid use for COVID-19 was not included in risk factor analysis for ROCM. Our patients were either diagnosed simultaneously with ROCM and COVID-19 or they were treated for COVID-19 in other hospitals (hence the data on prior steroid use could not be obtained).

Conclusions

Orbital and intracranial involvement was significantly higher in CAM cohort compared to the non-CAM. More number of patients had residual disease in CAM cohort at 3 months. Despite this, the short term survival in CAM cohort was similar to the

non-CAM cohort.

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Authorship contribution

LMC contributed to the protocol development and study design, did data collection, coordinated the study, did primary data analysis, wrote the initial draft of the manuscript and subsequent revision of manuscript. RegiK, LV and RV contributed to the study design and protocol and critically revised the manuscript. RRB, LA, RP and NR contributed to the data collection and provided inputs to the manuscripts. JP, AN, AS, GMV, AM, KG, TG, AL, SGH, RI, JSM, MN, MT, ReshmaK, and SM contributed to the data documentation and provided inputs on subsequent manuscript drafts. RekaK did data analysis and provided inputs to the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest

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None.

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