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Epidemiology, clinical presentation and management of COVID-19 associated mucormycosis: A single centre experience from Pune, Western India

Ameet Dravid[1] | Reema Kashiva[2] | Zafer Khan[3] | Balasaheb Bande[3] | Danish Memon[2] | Aparna Kodre[2] | Milind Mane[3] | Vishal Pawar[3] | Dattatraya Patil[3] | Suraj Kalyani[3] | Prathamesh Raut[3] | Madhura Bapte[3] | Charlotte Saldanha[3] | Dinesh Chandak[3] | Teerthagouda Patil[3] | Sateesh Reddy[2] | Krushnadas Bhayani[2] | Laxmi Suresh[2] | Vishnu Dillibabu[2] | Shipra Srivastava[2] | Shubham Khandelwal[2] | Sailee More[2] | Atif Shakeel[2] | Mohit Pawar[2] | Pranava Nande[2] | Amol Harshe[4] | Sagar Kadam[5] | Sudhir Hallikar[6] | Nudrat Kamal[6] | Danish Andrabi[6] | Sachin Bodhale[7] | Akshay Raut[8] | Sangeeta Chandrashekhar[9] | Chandrashekhar Raman[10] | Uma Mahajan[11] | Gaurav Joshi[12] | Dilip Mane[2]

[1]Department of Infectious diseases and HIV/AIDS, Noble hospitals and Research Centre, Pune, MH, India

[2]Department of Medicine, Noble hospital and Research Centre, Pune, India

[3]Department of Critical Care Medicine, Noble hospital and Research Centre, Pune, India

[4]Department of Pathology, Noble hospital and Research Centre, Pune, India

[5]Department of Radiology, Noble hospital and Research Centre, Pune, India

[6]Department of Otorhinolaryngology, Noble hospital and Research Centre, Pune, India

[7]Department of Ophthalmology, Noble hospital and Research Centre, Pune, India

[8]Department of Maxillo-facial surgery, Noble hospital and Research Centre, Pune, India

[9]Department of Anesthesia, Noble hospital and Research Centre, Pune, India

[10]Department of Neurosurgery, Noble hospital and Research Centre, Pune, India

[11]Statistician, VMK Diagnostics private limited, Pune, India

[12]Independent statistical consultant, Chicago, Illinois, USA

Abstract

Background: The second COVID-19 wave in India has been associated with an unprecedented increase in cases of COVID-19 associated mucormycosis (CAM), mainly Rhino-orbito-cerebral mucormycosis (ROCM).

Methods: This retrospective cohort study was conducted at Noble hospital and Research Centre (NHRC), Pune, India, between 1 April, 2020, and 1 August, 2021, to identify CAM patients and assess their management outcomes. The primary endpoint was incidence of all-cause mortality due to CAM.

Results: 59 patients were diagnosed with CAM. Median duration from the first positive COVID-19 RT PCR test to diagnosis of CAM was 17 (IQR: 12,22) days. 90% patients were diabetic with 89% having uncontrolled sugar level (HbA1c >7%). All patients were prescribed steroids during treatment for COVID-19. 56% patients were prescribed steroids for non-hypoxemic, mild COVID-19 (irrational steroid therapy), while in 9%, steroids were prescribed in inappropriately high dose. Patients were treated with a combination of surgical debridement (94%), intravenous liposomal Amphotericin B (91%) and concomitant oral Posaconazole (95.4%). 74.6% patients were discharged after clinical and radiologic recovery while 25.4% died. On relative risk analysis, COVID-19 CT severity index ≥18 ($p = .017$), presence of orbital symptoms ($p = .002$), presence of diabetic ketoacidosis ($p = .011$) and cerebral involvement ($p = .0004$) were associated with increased risk of death.

Conclusions: CAM is a rapidly progressive, angio-invasive, opportunistic fungal infection, which is fatal if left untreated. Combination of surgical debridement and antifungal therapy leads to clinical and radiologic improvement in majority of cases.

Correspondence
Ameet Dravid, Department of Infectious diseases and HIV/AIDS, Noble hospital and research center, Magarpatta city road, Hadapsar, Pune, Pin code – 411013, MH, India.
Email: ameet.dravid@gmail.com

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Amphotericin B, COVID-19 associated Mucormycosis, diabetes mellitus, Posaconazole, Rhino-orbito-cerebral mucormycosis, steroids

1 | INTRODUCTION

In December 2019, Wuhan city in China, became the epicentre of an outbreak of viral pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was designated coronavirus disease 2019 (COVID-19) in February 2020.[1,2] COVID-19 spread rapidly worldwide and India was no exception. By 1 August, 2021, there have been more than 300 million infections and 0.4 million deaths due to COVID-19 in India.[3] With COVID-19, the incidence of secondary bacterial or fungal infections is 8%, with aspergillosis and candida being the most common fungi reported.[4,5] The second COVID-19 wave in India (March 2021 – May 2021), triggered by the Delta variant, has been associated with an unprecedented increase in the cases of COVID-19 associated mucormycosis (CAM).[6,7] Globally, the prevalence of mucormycosis varies from 0.005 to 1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000) in India as per a recent estimate of year 2019–2020.[7-9] Thus, India already had the highest number of mucormycosis cases in the world and its incidence increased exponentially during the second COVID-19 wave. As of 1 August, 2021, 45,374 cases of CAM have been reported in India.[6]

CAM is an uncommon, rapidly progressive, angio-invasive, commonly fatal, opportunistic fungal infection.[9] Unusual alignment of multiple risk factors could be associated with sudden spurt of CAM in India.[10] Dysregulated immune response in COVID-19 characterized by exuberant activation of innate immune system, elevation in systemic inflammatory markers (C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH) and D-dimer, Interleukin—6 (IL-6), soluble IL-2 receptor [IL-2R], IL-10, TNF-α) and depleted adaptive immune response (decline in CD4+ T cell, CD8+ T cell, natural killer cell and decreased interferon Gamma (IFN-γ) expression in CD4+ T cells) could be one of the factors predisposing individuals to CAM.[11] In these patients, the activation of antiviral immunity to SARS-CoV-2 may, paradoxically, potentiate an inflammatory phenotype and thus may favour secondary infections. SARS-CoV-2 has been shown to affect the beta cells of the pancreas, resulting in metabolic derangement, possibly causing diabetes mellitus.[12,13] Uncontrolled DM is a risk factor for both, severe COVID-19 and mucormycosis.[12,13] Steroids, namely Dexamethasone and Methylprednisolone have been extensively used to resolve hyperinflammation and inflammatory lung damage in severe COVID-19.[14-16] Use of steroids can cause hyperglycaemia, suppression of several polymorphonuclear (PMN) leucocyte functions, impairment of phagocytosis by resident macrophages, depletion of T cell immunity and increase risk of mucormycosis.[10] In addition, indiscriminate use of steroids in patients with mild or asymptomatic COVID-19 can be counter-productive and make the person susceptible to opportunistic fungi.[17] Use of immunomodulator therapy such as Tocilizumab (TCZ, IL-6 receptor inhibitor) in combination with steroids for cytokine release syndrome (CRS, cytokine storm) could further aggravate immunosuppression and facilitate breakthrough fungal infection.[18] Thus, the primary reason for this sudden increase in CAM in India appears to be germination of Mucorales spores in an ideal environment of low oxygen (hypoxia), high glucose (diabetes mellitus, new onset hyperglycaemia, impaired fasting glucose or steroid-induced hyperglycemia) and immune dysfunction (mediated by Delta variant of SARS-CoV-2, steroid therapy or background co-morbidities). Acidic environment (metabolic acidosis, diabetic ketoacidosis [DKA]) and high iron levels (excess intracellular iron due to COVID-19 associated hyper-ferritinemia and acidosis facilitating free iron release for Mucorales germination) also seem to contribute to the increase in CAM.[10,19]

The most common form of mucormycosis seen in India during the COVID-19 pandemic was the Rhino-orbito-cerebral (ROCM) one but cases of pulmonary or disseminated mucormycosis have also been reported.[7,20,21] Suspected ROCM requires urgent intervention, because of the often rapidly progressive and destructive nature of the infection. Delayed initiation of therapy is associated with increased mortality.[22,23] Despite treatment, case-fatality rates due to mucormycosis during the pre-COVID-19 pandemic era were already high, ranging from 32% to 70%, according to organ involvement.[22,23] However, in SARS-CoV-2 infection, the mortality maybe even higher. Maximizing survival rates requires rapid diagnostic and therapeutic intervention, including immediate involvement of a multidisciplinary medical, surgical, radiological and laboratory-based team. Multiple case reports[20-35] and retrospective cohort studies[7,36-46] of CAM from India and other countries have already been published. However, description of risk factors, surgical and medical treatment administered, outcomes and complications (especially long-term complications) in patients with CAM has been scarcely reported.[7,37,42] As a result, we planned this retrospective observational cohort study aimed at understanding the epidemiology, clinical presentation, outcomes and long-term complications in patients with CAM admitted at our tertiary level hospital in Pune, Western India during the COVID-19 pandemic.

2 | METHODS

2.1 | Study setting

This retrospective cohort study was conducted at Noble hospital and Research Centre (NHRC), Pune, Western India. NHRC is a tertiary level private hospital designated for clinical management

of COVID-19 patients and management of post COVID-19 complications since 23rd March 2020. Pune is located in the state of Maharashtra, Western India and was one of the epicenters of COVID-19 epidemic in India. As of 1st August 2021, Maharashtra state has reported more than 6.3 million cases of COVID-19 and more than 133,000 deaths.[3] Till 1st August 2021, NHRC has admitted 5439 COVID-19 patients with 391 deaths. Maharashtra state has also reported more than 5000 cases of CAM till 1st August 2021.[6]

NHRC provides clinical care, diagnostic and treatment services to patients at a subsidized cost. Data of all hospitalized patients is entered into an electronic database (Lifeline electronic database, Manorama infosystems, Kolhapur, India).

2.2 | Study population

Patients were eligible for inclusion in this analysis if they were admitted to NHRC between 1st April 2020 and 1st August 2021 and were diagnosed with CAM. COVID-19 was diagnosed in patients if they tested positive for SARS-CoV-2 RNA in respiratory specimens by reverse transcription PCR (RT-PCR) or a positive rapid antigen test. Mild COVID-19 was defined as individuals who have various signs and symptoms of COVID-19 but who do not have shortness of breath, dyspnea, or abnormal chest imaging.[47] Moderate disease was defined as patients who show evidence of lower respiratory disease during clinical assessment or imaging and who have oxygen saturation (SpO_2) 90 to ≤93% on room air. Severe COVID-19 was defined as SpO_2 <90% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, respiratory frequency >30 breaths/min or lung infiltrates >50%.[47] Critical COVID-19 was defined as presentation with respiratory failure (respiratory system failing in its gas exchange functions like oxygenation and carbon dioxide elimination leading to hypoxemia (arterial oxygen tension (PaO_2) lower than 60 mm Hg) and hypercapnia ($PaCO_2$ higher than 50 mm Hg)), septic shock and multiple organ dysfunction. COVID-19 patients were investigated for CAM if they had compatible clinical and radiologic manifestations. CAM was defined as demonstration of Mucorales species in the excised tissue by either direct microscopic visualization (broad ribbon-like aseptate hyphae seen on potassium hydroxide (KOH) or Calcofluor stain), culture isolation (growth of Mucorales species on Sabouraud dextrose agar) or histopathology examination (Mucorales infiltration in affected tissue, angio-invasion and tissue necrosis seen on Hematoxylin and eosin, periodic acid Schiff (PAS), or Gomori methenamine silver stain).[9] Molecular techniques like polymerase chain reaction (PCR) or matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) for identification of Mucorales species grown in culture were not performed. CAM was defined as development of mucormycosis within 3 months of diagnosis of COVID-19.

Data was obtained from electronic health record of each individual admitted with CAM by manual abstraction. It included dates of COVID-19 related hospitalization, demographics, comorbidities, severity of COVID-19 (CT severity index) and treatment received including steroids and immunomodulator therapy. The CT severity index is a scoring system used to assess lung involvement by COVID-19. An approximate estimation is done by visual scoring of each of the five lung lobes seen on a computerized tomography (CT) scan of chest. A score from 1 to 5 is given to each lobe depending on extent of involvement (maximum score- 25).[48] Presenting symptoms of CAM, anatomic site of involvement, diagnostic modalities including microscopy, culture, or histopathology, laboratory investigation data (including inflammatory markers), imaging reports (High resolution computerized tomography scan of chest, paranasal sinuses and brain (HRCT chest, CT PNS and CT brain)), treatment details of anti-fungal drug therapy and surgical debridement, data on use of supplemental oxygen, mechanical ventilation and hospitalization outcomes were also recorded. For all patients diagnosed with CAM, we also scrutinized inpatient case files until hospital discharge, death, or 1st September 2021—the date on which the database was locked—whichever happened first. Systemic complications developing in CAM patients during hospital admission were also noted. All patients who died due to CAM were identified and a death audit to look for cause of death was undertaken. For patients who left the hospital against medical advice, we considered a worst-case scenario for mortality analysis and assumed the patients died. All patients who recovered, got discharged from NHRC and had outpatient follow-up at 15, 30 and 90 days after discharge were identified. Their outpatient follow-up visits were traced from electronic database to look for delayed complications.

2.3 | Management of CAM at NHRC

Treatment protocol for management of CAM at NHRC has been developed after careful consideration of current global and national guidelines.[49,50] As per NHRC protocol, early, radical, surgical debridement of affected site in addition to combination systemic antifungal therapy was utilized for treatment of CAM.

2.4 | Surgical management

Functional endoscopic paranasal sinus surgery (FESS) with debridement of necrosed and diseased sinus tissue and orbital decompression was the most common surgical procedure performed in patients with ROCM. All efforts were made to preserve the eye for as long as possible in view of role of eye to not only provide vision but also its removal causing significant psycho-social problems to patient. In patients with total blindness, proptosis, fixed pupil and eyeball, imaging evidence of orbital involvement (globe/muscles/fat) and/or intracranial spread (superior or inferior orbital fissure involvement), surgical exenteration of the eye was performed.[51] Partial or total maxillectomy was performed in patients with evidence of osteomyelitis of maxilla or alveolar arch. Neurosurgery was performed in case of intracranial spread of

disease with involvement of skull base or formation of basi-frontal lobe brain abscess.

2.5 | Medical management

Combination therapy of Liposomal Amphotericin B (LAmB) and Oral Triazole (predominantly oral Posaconazole) was the most common medical treatment offered to all patients with CAM. LAmB was administered concomitantly with oral Posaconazole. LAmB was initiated at the dose of 5 mg/kg. The dose was increased to 10 mg/kg in case of intracranial spread.[49,50] In the scenario of shortage of LAmB due to surge in CAM cases or non- affordability of patient, other formulations of Amphotericin B (Amphotericin B lipid complex (5 mg/kg/day), Amphotericin B lipid emulsion (5 mg/kg/day) and Amphotericin B de-oxycholate (1 mg/kg/day) were used for patients. The duration of Amphotericin B treatment was decided depending on the site of involvement (3 weeks for only paranasal sinus involvement, 4 weeks for orbital, lung and disseminated mucormycosis and 6 weeks for central nervous system (CNS) mucormycosis). Oral Posaconazole (delayed release tablets, 300 mg twice a day on Day 1 and then 300 mg once a day) was started during hospital admission and continued after discharge from NHRC for a period of 1 to 3 months depending on local control of disease. In patients with concomitant chronic kidney disease, intravenous Posaconazole or Isavuconazole followed by step-down to oral therapy was treatment of choice. Serum Posaconazole levels were performed to guide dosage during oral therapy.

2.6 | Outcomes

Primary endpoint:

1) Deaths in the cohort due to CAM.

Secondary outcomes:

2) Number of patients who had a clinical and radiologic recovery and were discharged from hospital.

3) Patients who required mechanical ventilation (noninvasive or invasive) and Intensive care unit (ICU) admission for CAM.

4) Incidence of systemic complications (including long-term complications) in patients after starting treatment for CAM.

The use of database for clinical research was approved by the institutional review board (IRB) of Noble hospital and Research Centre, Pune, India (Approval number – NHIEC/JUL/2021/251).

2.7 | Statistical methods

Continuous variables were summarized using median and interquartile range (IQR), while categorical variables were summarized using frequency and percentages. Continuous variables were compared using a Mann Whitney U test. Categorical variables were compared using Chi-square test, Proportion test and Fishers' exact test. Baseline and time dependent risk factors significantly associated with death due to CAM were identified by Relative risk analysis. Baseline risk factors included for analysis were age (<60 years or ≥60 years), gender, severity of baseline COVID-19 disease (CT severity index ≥18 versus <18), presence of orbital or central nervous system (CNS) symptoms, presence of diabetic keto-acidosis, presence of intracranial spread (cerebral involvement) and baseline investigations like absolute lymphocyte count (<1000 versus ≥1000 cells/mm^3), C reactive protein (≥50 versus <50 mg/L), D-dimer (≥252 versus <252 mcg/ml) and Ferritin (≥1000 versus <1000 mcg/L). Time dependent risk factors included duration of Amphotericin B therapy (≤3 weeks versus >3 weeks) and development of systemic complications during treatment like acute kidney injury, hepatitis, anemia, thrombocytopenia, osteomyelitis and CNS complications (stroke or cerebritis). The p value ≤0.05 was considered as statistically significant. All data was analyzed by SPSS version 12.0.

3 | RESULTS

During the period between 1st April 2020 to 1st August 2021, 59 patients were diagnosed with CAM at NHRC. Ten patients (16.9%) developed CAM during treatment for COVID-19 at NHRC (hospital admission or home quarantine) while 49 (83.1%) patients were treated for COVID-19 in other hospitals and referred to NHRC for diagnosis and management of CAM. Fifty-eight patients were diagnosed to have ROCM while 1 patient was diagnosed to have renal (disseminated) mucormycosis. Median age of the cohort was 52 (IQR: 41, 61) years and it included 20.3% (12/59) females. Seventeen (28.8%) patients were >60 years of age. Fifty-six (95%) patients had pre-existing or newly diagnosed co-morbidities. Diabetes mellitus (53/59, 89.8%) was the most common co-morbidity seen in our cohort. Of these, 15 patients (28.3%) were newly diagnosed with diabetes mellitus during hospital admission for COVID-19. Two patients were diagnosed to have impaired fasting glucose (Fasting blood glucose between 110 and 125 mg/dl). Pre-existing co-morbidities observed in patients at admission are enumerated in Table 1. Only 3 patients (5.1%) had no co-morbidities prior to developing CAM.

Clinically, 16 patients (27.1%) had mild COVID-19, 29 (49.2%) had moderate COVID-19 and 14 patients (23.7%) had severe or critical COVID-19 prior to diagnosis of CAM. All 59 patients underwent High resolution CT (HRCT) imaging of chest (GE Optima, 128 slice CT scanner) during admission and median CT severity index was 12 (IQR: 8,14.5). CT severity index indicated mild disease (CT severity index: <8) in 18.6% (11/59), moderate disease (CT severity index: 8–14) in 56% (33/59) and severe disease (CT severity index: 15–25) in 25.4% (15/59) of patients.[48] During COVID-19 admission, Remdesivir was prescribed to 67.8% (40/59), intravenous and/or oral steroids were prescribed to 100% and Immune-modulator therapy (Tocilizumab - 5, Barcitinib-2, Idofinib- 1, Infliximab- 2, Bevacizumab - 2 and Itolizumab - 1) was prescribed to 22% (13/59) patients

TABLE 1 Epidemiology of COVID-19 admission in patients with CAM

Baseline characteristics	Total patients (*n* = 59) *n* (%)	Discharged (*n* = 44) *n* (%)	Death (*n* = 15) *n* (%)	*p*-value
Age (Years)				
≤60 years	42 (71.2)	34 (77.3)	8 (53.3)	.077
>60 years	17 (28.8)	10 (22.7)	7 (46.7)	
Median (IQR)	52 (41, 61)	50 (40, 58)	57 (42, 65)	.136
Gender				
Male	47 (79.7)	36 (81.8)	11 (73.3)	.481
Female	12 (20.3)	8 (18.2)	4 (26.7)	
Co-morbidities				
Diabetes mellitus				
Non-diabetic	6 (10.2)	5 (11.4)	1 (6.7)	.216
Known Diabetes Mellitus	36 (61.0)	24 (54.5)	12 (80.0)	
Newly diagnosed DM/ IFG	17 (28.8)	15 (34.1)	2 (13.3)	
Hypertension	24 (40.7)	17 (38.6)	7 (46.7)	.585
Chronic kidney disease	9 (15.3)	6 (13.6)	3 (20.0)	.680
Ischemic heart disease	7 (11.9)	4 (9.1)	3 (20.0)	.355
Chronic liver disease	2 (3.4)	0 (0.0)	2 (13.3)	.061
Stroke	1 (1.7)	0 (0.0)	1 (6.7)	.254
HIV/ Hepatitis B infection	1 (1.7)	1 (2.3)	0 (0.0)	>.999
Obesity	2 (3.4)	1 (2.3)	1 (6.7)	.447
Hypo/hyperthyroidism	3 (5.1)	2 (4.5)	1 (6.7)	>.999
Severity of COVID-19				
Mild	16 (27.1)	12 (27.3)	4 (26.7)	.223
Moderate	29 (49.2)	24 (54.5)	5 (33.3)	
Severe	14 (23.7)	8 (18.2)	6 (40.0)	
HRCT chest COVID severity score				
<18	55 (93.2)	43 (97.7)	12 (80.0)	**.047**
≥18	4 (6.8)	1 (2.3)	3 (20.0)	
Median (IQR)	12 (8, 15)	12 (8, 14)	14 (8, 17)	**.152**
COVID-19 admission Median (IQR)				
Duration of hospitalization (days)	9 (6, 14)	8 (6, 13.5)	10 (7, 15)	.149
Duration of ICU stay (days)	0 (0, 10)	0 (0, 0)	0 (0, 10)	.303
Duration of ventilation (days)	0 (0, 10)	0 (0, 0)	0 (0, 10)	**.046**
COVID-19 vaccine status				
No vaccination	46 (78.0)	34 (77.3)	12 (80.0)	.826
AstraZeneca—1 dose	9 (15.3)	7 (15.9)	2 (13.3)	
AstraZeneca—2 doses	2 (3.4)	1 (2.3)	1 (6.7)	
Covaxin (Bharat Biotech)—1 dose	1 (1.7)	1 (2.3)	0 (0.0)	
Covaxin (Bharat Biotech)—2 dose	1 (1.7)	1 (2.3)	0 (0.0)	

Abbreviations: CAM, COVID-19 associated mucormycosis; DM, diabetes mellitus; HIV, human immunodeficiency virus; HRCT, high resolution computerized tomography; IFG, impaired fasting glucose.

Bold value indicates increased risk of mortality due to Mucormycosis.

(Table 2 and Supplementary file). Methylprednisolone was the commonest prescribed steroid (54 patients, 91.5%, Table 2). Most commonly prescribed dose of Methylprednisolone was 1–2 mg/kg/day in two divided doses for 5–10 days.[52] Ten patients (16.9%) were prescribed 2 different steroids during treatment course for COVID-19. 56% (33/59) patients were prescribed steroids in the absence of hypoxia (irrational or unscientific steroid use). In 5 (5/54, 9.3%) patients, methylprednisolone dose of more than 2 mg/kg/day was prescribed for treatment of severe COVID-19 (excess steroid dose).[52] Eleven patients (18.6%) required ICU admission during treatment of COVID-19. All 11 patients needed ICU for management of respiratory failure. Of these, 7 (11.9%) needed non-invasive or invasive ventilation while four could be managed with low flow supplemental oxygen. Five patients (8.5%) were treated for COVID-19 while in home quarantine and did not require hospital admission. All 5 patients in home quarantine received steroids (irrational or unscientific steroid use) as a part of their treatment regimen. Median duration of hospital admission for COVID-19 was 9 (IQR: 6, 14) days. Thirteen patients (22%) had received COVID-19 vaccination prior to admission (3 patients received 2 vaccine doses and 10 patients received single vaccine dose, Table 1).

Median duration from the first positive COVID-19 RT PCR test to diagnosis of CAM was 17 (IQR: 12, 22) days. Duration was less than 14 days for 22 (37.3%, early CAM) patients while it was ≥14 days for 37 (62.7%, late CAM) patients. Median duration between hospital discharge for COVID-19 to re-admission for CAM was 7 (IQR: 2.5, 15.5) days. Twenty patients (33.9%) were diagnosed to have mucormycosis (suspected fungal sinusitis, ROCM) during hospital admission for COVID-19. Twenty-seven (45.7%) patients were re-admitted less than 14 days after hospital discharge while 12 (20.4%) were re-admitted after more than 14 days. Headache (43/58, 74.1%), hemi-facial pain predominantly maxillary pain (42/58, 72.4%) and facial swelling (33/58, 56.9%) were the three commonest presenting symptoms of ROCM in our cohort (Table 3). Median duration of symptoms prior to hospitalization for ROCM was 6 (IQR: 3, 8.5) days. Seven patients (11.9%) had symptoms for more than 2 weeks prior to diagnosis of ROCM. Fifty-eight patients (99%) had paranasal sinus involvement, 33 (56%) had orbital (eyeball, extra-ocular muscles or orbital cavity) and 26 (44.1%) had cerebral involvement (infarcts, cavernous sinus involvement, dural enhancement, frontal lobe abscess, osteomyelitis and erosion of frontal bone, Table 3). Palatal involvement (palatal necrosis, black eschar or palatal osteomyelitis) was observed in 13 (22%) patients. Median haemoglobin value at diagnosis of CAM was 13.4 (IQR: 11.4, 14.5) mg/dl (Table 4). Median absolute neutrophil count (ANC) was 8100 (IQR: 5248, 11,475) cells/mm^3 and median absolute lymphocyte count (ALC) was 1350 (IQR: 1010, 1750) cells/mm^3. Fourteen patients (24.6%) had ALC <1000 cells/mm^3 while no patient had ANC <1000 cells/mm^3 at admission. Median CRP at admission was 84.7 (IQR: 41,167, 45 patients) mg/L, median D-dimer was 483.5 (IQR: 253.7,1201, 37 patients) mcg/mL

TABLE 2 Steroids and supplemental oxygen used during COVID-19 treatment

Steroids/Oxygen use in COVID-19 treatment	Total patients (*n* = 59) *n* (%)	Discharged (*n* = 44) *n* (%)	Death (*n* = 15) *n* (%)	*p*-value
Steroids given for treating COVID-19				
Intravenous Methylprednisolone	54 (91.5)	40 (90.9)	14 (93.3)	>.999
Intravenous Dexamethasone	4 (6.8)	4 (9.1)	0 (0.0)	.564
Oral Prednisolone	10 (16.9)	8 (18.2)	2 (13.3)	>.999
Oral Deflazacort	1 (1.7)	1 (2.3)	0 (0.0)	>.999
Oxygen given during treatment of COVID-19				
Nasal oxygen by prongs	5 (8.5)	5 (11.4)	0 (0.0)	.315
Nasal oxygen by face mask	1 (1.7)	0 (0.0)	1 (6.7)	.254
Nasal oxygen by NRBM	28 (47.5)	21 (47.7)	7 (46.7)	.943
NRBM (days) Median (IQR)	7 (4, 10)	5 (4, 10)	7 (7, 10)	.369
HFNO	2 (3.4)	1 (2.3)	1 (6.7)	.447
HFNO (days) Median (IQR)	14 (10, 17)	17 (17, 17)	10 (10, 10)	.317
NIV	7 (11.9)	3 (6.8)	4 (26.7)	.062
NIV (days) Median (IQR)	8 (3, 15)	3 (3, 15)	9 (5, 14)	.721
Invasive mechanical ventilation (IMV)	3 (5.1)	0 (0.0)	3 (20.0)	**.014**
IMV (days) Median (IQR)	2 (1, 4)	0 (0, 0)	2 (1, 4)	

Abbreviations: HFNO, high flow nasal oxygen; IMV, invasive mechanical ventilation; IQR, INTERquartile range; NIV, non-invasive ventilation; NRBM, non re-breathing mask.

Bold values indicate increased risk of mortality due to Mucormycosis.

TABLE 3 Baseline characteristics of patients of CAM

CAM	Total patients *n* (%)	Discharged *n* (%)	Death *n* (%)	*p*-value
Total patients	**59**	**44 (74.6)**	**15 (25.4)**	**.0002**
Type of CAM				
Paranasal sinus involvement only	24 (40.7)	24 (54.5)	0 (0.0)	**<.0001**
Paranasal sinus +Orbital involvement	8 (13.6)	7 (15.9)	1 (6.7)	
Paranasal sinus +Orbital + Cerebral	25 (42.4)	13 (29.5)	12 (80.0)	
Paranasal sinus +Cerebral	1 (1.7)	0 (0.0)	1 (6.7)	
Renal	1 (1.7)	0 (0.0)	1 (6.7)	
Symptoms of CAM				
Facial pain	42 (71.2)	32 (72.7)	10 (66.7)	.654
Facial swelling	33 (55.9)	22 (50.0)	11 (73.3)	.142
Headache	43 (72.9)	32 (72.7)	11 (73.3)	>.999
Eye swelling	33 (55.9)	20 (45.5)	13 (86.7)	**.007**
Eye pain	29 (49.2)	17 (38.6)	12 (80.0)	**.007**
Loss of vision	21 (35.6)	9 (20.5)	12 (80.0)	**<.0001**
Ptosis	21 (35.6)	11 (25.0)	10 (66.7)	**.004**
Deviation of angle of mouth	5 (8.5)	3 (6.8)	2 (13.3)	.593
Nasal discharge	15 (25.4)	13 (29.5)	2 (13.3)	.310
Limb weakness	5 (8.5)	1 (2.3)	4 (26.7)	**.013**
Toothache	27 (45.8)	24 (54.5)	3 (20.0)	**.034**
Duration of symptoms (days) Median (IQR)	6 (3, 9)	6 (3, 10)	5 (3, 8)	.488
Duration between 1st positive COVID-19 test and CAM diagnosis				
<7 days	2 (3.4)	2 (4.5)	0 (0.0)	.751
7-14 days	20 (33.9)	14 (31.8)	6 (40.0)	
15-28 days	28 (47.5)	20 (45.5)	8 (53.3)	
>28 days	9 (15.3)	8 (18.2)	1 (6.7)	
Median (IQR)	17 (12, 22)	17 (13, 23)	17 (10, 21)	.676

Abbreviations: CAM, COVID-19 associated mucormycosis; IQR, interquartile range.
Bold values indicate increased risk of mortality due to Mucormycosis.

and median Ferritin value was 857.1 (IQR: 280.5, 1429, 32 patients) mcg/L. Thirteen patients (40.6%) had serum Ferritin level >1000 mcg/L at admission while 11 patients had D-dimer >1000 mcg/mL. Median HbA1C level in our cohort was 9.3 (IQR: 8, 12). Ten patients (10/53, 18.9%) presented with diabetic ketoacidosis. Diagnosis of CAM was made by KOH/calcofluor white staining of nasal scrapings (25/59, 42.4%), fungal culture (5/59, 8.5%) and histopathologic examination of excised tissue from paranasal sinuses (57/59, 96.6%). Mixed mould infection (mucormycosis and aspergillosis) was observed in 3 patients.

Aggressive surgical debridement of involved site and combination anti-fungal therapy was standard of care for all ROCM patients in our cohort. Empirical combination anti-fungal therapy was started after radiologic evidence of invasive sinusitis, pending confirmatory diagnosis by histopathology or culture. Various treatment modalities used in our cohort are mentioned in Table 5. Intravenous (IV) formulations of Amphotericin B (Liposomal, Lipid-complex, Lipid emulsion or Deoxycholate) were the mainstay of antifungal therapy and were prescribed to 91.5% (54/59) patients. In view of the shortage of Liposomal Amphotericin B in India during the second COVID-19 wave, patients ended up getting a combination of Amphotericin B formulations as per availability. LAmB was prescribed to 89.8% (53/59) patients for a median duration of 15 (IQR: 11, 21) days. Amphotericin B de-oxycholate or Conventional Amphotericin B was prescribed to 45.8% (27/59) patients for a median duration of 4 (IQR: 3, 9) days. The median duration of Amphotericin B exposure to patients in our cohort was 21 (IQR: 14, 27) days. All patients were also prescribed concomitant oral triazole therapy (Posaconazole (58/59, 98.3%) or Isavuconazole (5/59, 8.5%)). Median duration for oral triazole therapy was 60 days. FESS with orbital decompression was performed on 94.9% patients. Surgical exenteration of the eye with debridement of orbital cavity was performed in 13 (22%) patients. Partial maxillectomy was performed in 9 (15.3%) patients while Neurosurgery for frontal lobe brain abscess drainage was performed

TABLE 4 Baseline investigations during admission for CAM

Baseline characteristics	Total (*n* = 59) *n* (%)	Discharged (*n* = 44) *n* (%)	Death (*n* = 15) *n* (%)	*p*-value
Laboratory investigations				
Haemoglobin (g/dl)	13.4 (11.4, 14.5)	13.75 (12.05, 14.5)	12.5 (10.9, 13.9)	.169
WBC (per microliter)	10,400 (7000, 14,400)	10,150 (7000, 13,500)	11,900 (7000, 15,400)	.568
Absolute Neutrophil count (ANC)	8100 (5248, 11,475)	7902 (5214, 11,260)	9559 (5250, 13,490)	.447
Platelet count	227,000 (178,000, 308,000)	231,000 (189,000, 308,500)	198,000 (160,000, 308,000)	.186
Blood urea level (mg/dl)	32 (22, 54)	28 (20.5, 49)	41 (27, 92)	**.030**
Serum Creatinine (mg/dL)	1.1 (0.96, 1.27)	1.085 (0.96, 1.205)	1.12 (1.02, 1.61)	.261
Potassium (mmol/L)	4 (3.5, 4.5)	4 (3.5, 4.4)	3.9 (3.2, 4.5)	.656
Absolute Lymphocyte count (ALC, cells/mm^3)				
<1000	14 (24.6)	8 (18.2)	6 (46.2)	
≥1000	43 (75.4)	36 (81.8)	7 (53.8)	
Median (IQR)	1350 (1010, 1750)	1407.5 (1185, 1996.5)	1045 (595, 1308)	**.008**
C-reactive protein (mg/L)				
0-6	2 (4.7)	2 (6.3)	0 (0)	
7-49	9 (20.9)	8 (25)	1 (9.1)	
≥50	32 (74.4)	22 (68.8)	10 (90.9)	
Median (IQR)	84.7 (41, 167)	74.25 (39, 138.75)	173.735 (64.3, 207.5)	**.032**
Ferritin (mcg/L)				
15-150	3 (9.4)	3 (12.5)	0 (0)	
151-1000	16 (50)	13 (54.2)	3 (37.5)	
>1000	13 (40.6)	8 (33.3)	5 (62.5)	
Median (IQR)	857.1 (280.5, 1429)	677.25 (262.55, 1108)	1346.5 (720.55, 1817.5)	.089
D-Dimer (mcg/ml)				
<252	9 (24.3)	7 (25.9)	2 (20)	
253-1000	17 (45.9)	13 (48.1)	4 (40)	
>1000	11 (29.7)	7 (25.9)	4 (40)	
Median (IQR)	483.5 (253.73, 1201.00)	427.1 (237.08, 1071.71)	566.9 (255.48, 20)	.321

Abbreviations: CAM, COVID-19 associated mucormycosis; IQR, interquartile range; SGOT, serum glutamate oxaloacetate transaminase; SGPT, serum glutamate pyruvate transaminase; WBC, white blood cell.

Bold values indicate increased risk of mortality due to Mucormycosis.

in 5 (8.5%) patients. Eight patients (13.6%) required invasive mechanical ventilation while 18 (30.5%) required ICU admission for CAM.

Fever with chills (78%), thrombophlebitis (59.3%), hypokalaemia (88.1%), anaemia (57.6%) and nephrotoxicity (50.8%) were the most common complications observed in patients during hospital admission for CAM (Supplementary file). Central nervous system (CNS) complications (stroke/cerebritis/brain abscess) developing during hospital admission, were seen in 25.4% patients. There were 14 deaths (23.7%) in our cohort during first hospital admission. On Relative risk analysis, CT severity index during COVID-19 admission ≥18 ($p = .017$), presence of symptoms like eye swelling ($p = .002$), loss of vision ($p < .0001$), ptosis ($p = .005$) and limb weakness ($p = .001$), presence of diabetic ketoacidosis ($p = .011$), cerebral involvement by Mucorales ($p = .0004$) and development of CNS complications like stroke ($p < .0001$) were associated with increased risk of death (Table 6, Figure 1). All patients who were discharged from hospital were followed up for a minimum period of 6 weeks to look for late complications. Three patients needed re-admission, 48, 54 and

TABLE 5 Treatment regimens used in CAM

Treatment regimen for CAM	Total patients (*n* = 59) *n* (%)	Discharged (*n* = 44) *n* (%)	Death (*n* = 15) *n* (%)	*p*-value
Anti-fungal therapy administered				
Liposomal Amphotericin B	53 (89.8)	42 (95.5)	11 (73.3)	**.032**
Amphotericin B lipid complex/ emulsion	17 (28.8)	17 (38.6)	0 (0.0)	**.003**
Amphotericin B de-oxycholate	27 (45.8)	22 (50)	5 (33.3)	.263
Total Amphotericin B days				
Not given	5 (8.5)	1 (2.3)	4 (26.7)	**.015**
<21 days	30 (50.8)	20 (45.5)	10 (66.7)	
≥21 days	24 (40.7)	23 (52.3)	1 (6.7)	
Median (IQR)	21 (14, 27)	22 (15, 28)	10 (6, 21)	**.004**
Posaconazole	58 (98.3)	44 (100)	14 (93.3)	.254
Isavuconazole	5 (8.5)	5 (11.4)	0 (0.0)	.315
Antibiotics given	55 (93.2)	40 (90.9)	15 (100.0)	.564
Surgical procedures				
FESS	56 (94.9)	42(95.4)	14(93.3)	.781
Orbital decompression	10 (16.9)	10 (22.7)	0 (0.0)	.052
Palatal clearance	1 (1.7)	1 (2.3)	0 (0.0)	>.999
Exenteration	13 (22)	6 (13.6)	7 (46.7)	**.008**
Maxillectomy	9 (15.3)	9 (20.5)	0 (0.0)	.095
Neurosurgery	5 (8.5)	3 (6.8)	2 (13.3)	.593
Oxygenation and ventilation data				
Nasal oxygen by prongs	1 (1.7)	0 (0.0)	1 (6.7)	.254
Nasal oxygen by face mask	0 (0.0)	0 (0.0)	0 (0.0)	
Nasal oxygen by NRBM	5 (8.5)	4 (9.1)	1 (6.7)	>.999
NRBM (days) Median (IQR)	13 (12, 14)	13 (12, 14)	ND	
HFNO	0 (0.0)	0 (0.0)	0 (0.0)	
NIV	2 (3.4)	0 (0.0)	2 (13.3)	.061
NIV (days) Median (IQR)	2 (1, 2)	0 (0, 0)	2 (1, 2)	**.015**
Invasive mechanical ventilation (IMV)	8 (13.6)	1 (2.3)	7 (46.7)	**<.0001**
IMV (days) Median (IQR)	3 (2, 4)	3 (3, 3)	3 (2, 4)	**<.0001**
ICU admissions				
Required ICU	18 (30.5)	8 (18.2)	10 (66.7)	**<.0001**
ICU stay (days) Median (IQR)	3 (3, 6)	3 (2, 7)	4 (3, 5)	**<.0001**

Abbreviations: CAM, COVID-19 associated mucormycosis; FESS, functional endoscopic sinus surgery; HFNO, high flow nasal oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; NIV, non-invasive ventilation; NRBM, non re-breathing mask.
Bold values indicate increased risk of mortality due to Mucormycosis.

37 days after first discharge in view of re-appearance of symptoms and/or imaging evidence of progression of disease. All 3 patients needed repeat surgical debridement and additional Amphotericin B treatment. They were successfully discharged the second time. Two patients also needed re-admission for osteomyelitis of maxilla and alveolar arch. It needed partial maxillectomy and placement of dental prosthesis. One patient who had undergone exenteration of eye was readmitted 90 days later for insertion of orbital prosthesis. One patient who had been treated for cerebral mucormycosis (bilateral complete vision loss and multiple cerebral infarcts) with 42 days of high dose Liposomal Amphotericin B and Posaconazole was re-admitted with aspiration pneumonia 12 days later and died. Cause of death was respiratory failure due to aspiration pneumonia and acute respiratory distress syndrome (ARDS, Total deaths in cohort - 15, 25.4%).

TABLE 6 Relative risk of death in CAM

Factors	Relative risk (95% CI)	*p*-value
Age >60 years (Ref: ≤60 years)	2.162 (0.9300, 5.0251)	.098
Male (Ref: Female)	0.702 (0.2708, 1.8205)	.506
Diabetes Mellitus (Ref: Diabetic)		
Newly diagnosed/ pre-diabetic	0.353 (0.0887, 1.4048)	.052
COVID-19 related factors		
HRCT score ≥18 (Ref: <18)	3.438 (1.6153, 7.3155)	**.017**
Irrational use of steroids (Ref: Rational use)	0.689 (0.2875, 1.6530)	.407
Not vaccinated against COVID-19 (Ref: vaccinated)	1.130 (0.3743, 3.4139)	.822
Duration between 1st COVID-19 test and CAM diagnosis ≥15 days (Ref: <15 days)	0.892 (0.3670, 2.1676)	.803
Duration between COVID-19 discharge and CAM admission ≥15 days (Ref: <15 days)	0.671 (0.1764, 2.5556)	.544
Type of CAM (Ref: Paranasal sinus only)		
Paranasal sinus +Orbital	0.455 (0.0690, 3.0048)	.259
Paranasal sinus +Orbital + Cerebral	5.440 (1.7140, 17.2662)	**.0004**
Symptoms of Mucormycosis (Ref: No symptom)		
Facial pain	0.810 (0.3246, 2.0187)	.663
Facial swelling	2.167 (0.7794, 6.0234)	.098
Headache	1.023 (0.3802, 2.7539)	.964
Eye swelling	5.121 (1.2665, 20.7087)	**.002**
Eye pain	4.138 (1.3003, 13.1684)	**.003**
Loss of vision	7.238 (2.2978, 22.8006)	**<.0001**
Ptosis	3.619 (1.4252, 9.1899)	**.005**
Deviation of angle of mouth	1.662 (0.5140, 5.3715)	.482
Nasal discharge	0.451 (0.1148, 1.7733)	.146
Limb weakness	3.927 (1.9784, 7.7961)	**.001**
Toothache	0.296 (0.0932, 0.9422)	**.012**
Investigations in CAM		
Diabetic Ketoacidosis (Ref: No)	3.267 (1.5012, 7.1085)	**.011**
Blood urea level	1.023 (1.0013, 1.0452)	**.0002**
ALC ≥1000 (Ref: <1000)	0.379 (0.1531, 0.9422)	.065
Procalcitonin >2 (Ref: ≤2)	1.507 (0.5467, 4.1513)	.460
C-reactive Protein ≥50 (Ref: <50)	3.438 (0.4949, 23.8759)	.063
Ferritin >1000 (Ref: ≤1000)	2.436 (0.7011, 8.4634)	.153
D-Dimer >252 (Ref: ≤252)	1.286 (0.3315, 4.9860)	.697
Treatment days in CAM (Ref: ≤21 days)		
Total Amphotericin days ≥21 days	0.125 (0.0172, 0.9093)	**.002**
Posaconazole >21 days	0.364 (0.1293, 1.0228)	.055
Complications in CAM (Ref: No complication)		
Hepatitis	2.229 (0.9437, 5.2628)	.079
Thrombophlebitis	0.457 (0.1872, 1.1164)	.083
Anemia	2.941 (0.9267, 9.3351)	.067
Thrombocytopenia	3.674 (1.6211, 8.3244)	**.004**
Stroke/Cerebritis	19.067 (4.8522, 74.9224)	**<.0001**

Abbreviations: ALC, absolute lymphocyte count; CAM, COVID-19 associated mucormycosis; HRCT, high resolution computerized tomography scan.
Bold values indicate increased risk of mortality due to Mucormycosis.

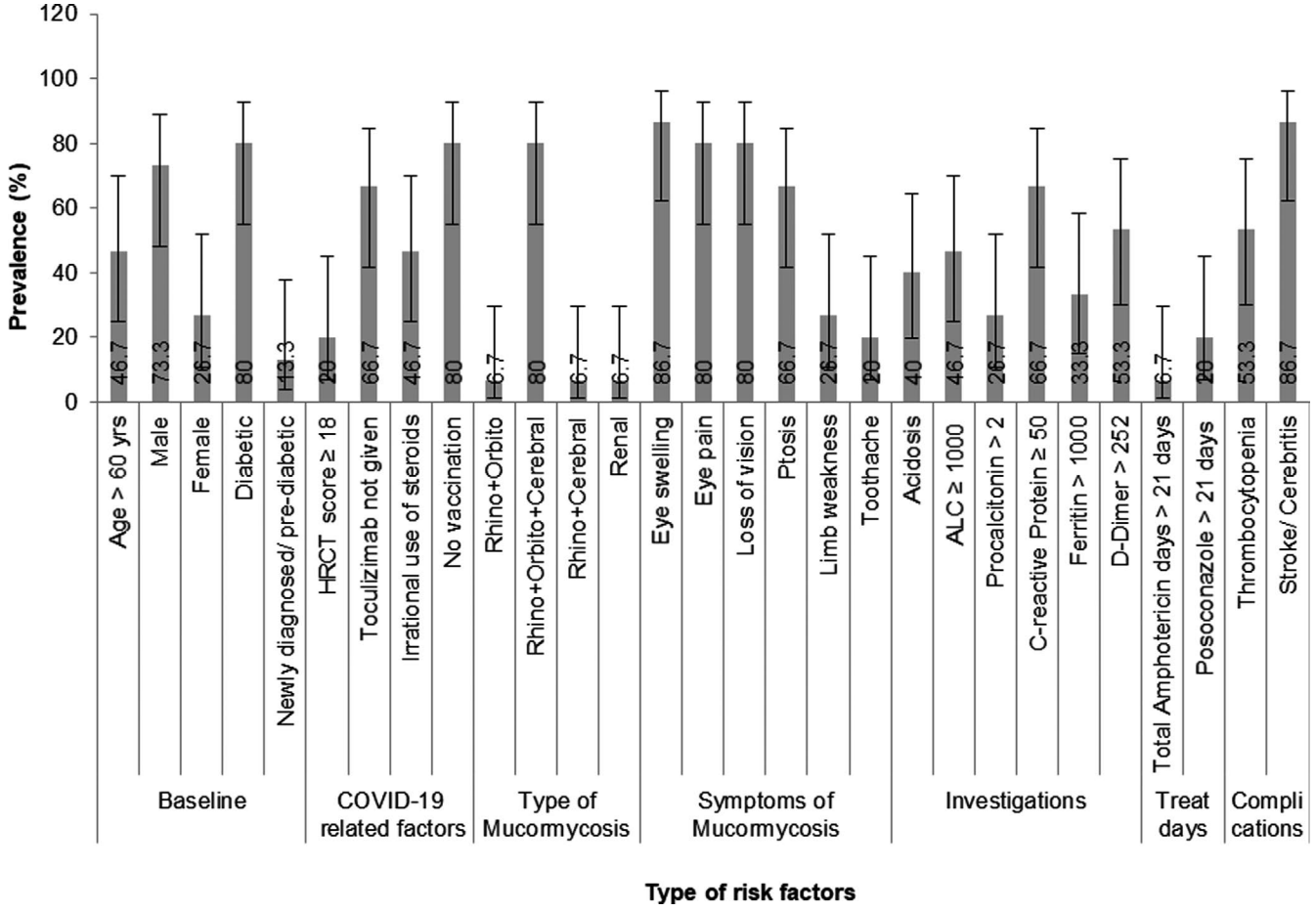

FIGURE 1 Prevalence of risk factors in CAM patients who died

4 | DISCUSSION

We conducted a single-centre, retrospective cohort study of 59 patients with CAM who were admitted at a tertiary level private hospital in Pune, India in the last 15 months. Lack of imaging modalities in rural areas, inability to identify early symptoms by general practitioners, shortage of anti-fungal therapy (especially Liposomal Amphotericin B) during second COVID-19 wave and inadequate number of specialists to perform complex endoscopic, orbital and skull base surgeries posed a serious challenge in tackling rising ROCM cases in India.[7,10] However, in our cohort, majority of patients ended up getting multi-disciplinary treatment for CAM. As a result, 74.6% patients were successfully discharged after control of disease. Mortality rate in our cohort at 6 weeks follow-up was 25.4%.

Majority of the patients in our study were middle-aged (median age: 52 years), of which nearly two-thirds were male. Case series on CAM by Sharma et al, described diabetes as a risk factor in 90% cases, of which 52% had uncontrolled disease.[33] A systematic review of 101 cases of CAM by Singh et al also noted that more than 80% cases had either pre-existing or new onset hyperglycaemia as a risk factor.[43] Our study has demonstrated similar findings, in that 90% of included patients were diabetic with almost 30% being newly diagnosed with DM at the time of admission for COVID-19. Of the 56 patients who had HbA1c value available, 50 had uncontrolled DM (HbA1c > 7%). Median HbA1c in our cohort was 9.3% while it was 9.6% in the study by Sen et al[40] Tight control of blood sugar level among patients with Diabetes Mellitus/ COVID-19 co-infection could help in reducing incidence of ROCM.

Both the RECOVERY trial[15] and World health organization (WHO) COVID-19[53] guidelines clearly recommend against usage of Corticosteroids in COVID-19 patients not requiring oxygen (absence of hypoxia). Despite that, indiscriminate use of steroids in mild COVID-19 continues in India. The underlying reasons include the sudden surge of cases during second COVID-19 wave leading to panic among general practitioners, inadequate time for triaging patients in busy outpatient clinics, non-evidence-based clinical practice, availability of over-the-counter steroids, shortage of hospital beds and inadequate monitoring of patients taking steroids. The improper use of corticosteroids has been identified as an independent risk factor for CAM by the MucoCovi network.[7] In their retrospective analysis of 187 Indian CAM patients, they found that 78% (150/187) had received steroid therapy but only 33% patients had received steroids at appropriate dosages. In 33% patients (50/150), steroids were not indicated while among 30% (45/150) patients, steroids were indicated but were prescribed in inappropriately high dose.[7] In comparison, in our cohort, 56% patients were prescribed

steroids for non-hypoxemic, mild to moderate COVID illness (irrational steroid therapy) while in 8.5% patients steroids were indicated, but were prescribed in inappropriately high dose. Thus, there is an urgent need to stop prescription of steroids in non-hypoxemic COVID-19 patients and to limit the dose and duration of steroids in hypoxic patients.

In our cohort, patients were treated with a combination of surgical debridement (94%), intravenous Amphotericin B (91%) and concomitant oral Posaconazole therapy (98%). Mortality rate at 6 weeks follow-up was 25.4% which is lower than what is reported by Pal et al[42] and Patel et al (MucoCovi network - 6 week mortality rate of 38.3% and 12 week mortality of 45.7%).[7] Reasons for lower mortality in our cohort as compared to the MucoCovi network could be relatively younger population (median age 52 years versus 56.9 years), lower prevalence of hypoxia during COVID-19 (44% versus 56%), lower pulmonary involvement (0% versus 8.6%), increased use of combination anti-fungal therapy (91% versus 50%) and higher use of combined surgical and medical approach (91% versus 71%).[7] However, presence of diabetic ketoacidosis (10.9% versus 8.6%) and prevalence of cerebral involvement (44% versus 23%) was higher in our cohort than the MucoCovi study.[7] Both the factors, presence of diabetic ketoacidosis ($p = .011$) and cerebral involvement ($p = .0004$) were associated with increased mortality on Relative risk analysis. In CAM patients with cerebral involvement, mortality rate was 50%, which is 5 times higher than among patients without cerebral involvement. Our findings are consistent with studies of mucormycosis in patients not having prior COVID-19 infection.[54,55] In these studies, presence of disseminated infection was associated with increased mortality while complete surgical removal of infected tissue and treatment with Amphotericin B was associated with improved survival.[54,55] Development of ROCM while the patient is still under active treatment for moderate or severe COVID-19 may pose significant challenges in the management—specifically termination of corticosteroids and surgery under general anaesthesia. This was reflected in the CT severity index ≥18 (depicting severe COVID pneumonia) being a significant risk factor for increased risk of death due to CAM ($p = .017$). Patients with ROCM also remain at risk for delayed complications and may need re-admission with further surgical and anti-fungal treatment to resolve them.

4.1 | Limitations

Our study has several limitations. First, this is only a descriptive cohort. As there is no control group (COVID-19 patients without mucormycosis), risk factors for mucormycosis cannot be evaluated. Second, as it is not a randomized controlled trial, unmeasured confounding cannot be ruled out. Third, as for all retrospective studies, some individuals diagnosed with mucormycosis may be unreported leading to measurement bias and underestimation of mortality due to CAM. Fourth, we collected data from a single centre in India unlike other multicentre cohort studies.[7,37,39,40,42] Fifth, an overwhelmed health care system, inadequate workforce and lack of exhaustive reporting due to surge of cases during second COVID-19 wave could be responsible for underestimation of co-morbidities, presenting symptoms and complications amongst patients in our cohort. Sixth, inflammatory markers such as ferritin, CRP and D-dimer were not available for all patients in the cohort. Seventh, we did not look for environmental factors causing healthcare-associated mucormycosis such as contaminated ventilation systems, air conditioners and ongoing construction in our hospital. We did not estimate the burden of Mucorales spores in our hospital environment. We also did not investigate the link between risk factors like use of industrial oxygen, contaminated nebulizer fluids or inline humidifier tubing used in ventilator circuits and contaminated oxygen delivery systems with increased incidence of CAM in our cohort.[10] Eighth, other unexplored factors, including genetic predisposition were not identified.

Despite these limitations, this retrospective cohort study adds to the growing body of literature on epidemiology, clinical features, anatomic site of involvement, management strategies, outcomes and long-term complications due to COVID-19 associated mucormycosis (CAM).

5 | CONCLUSIONS

CAM is a rapidly progressive, angio-invasive, opportunistic fungal infection which is fatal if left untreated. The most common form of CAM seen in our cohort was the Rhino-orbito-cerebral (ROCM) one. Clinicians should have a high index of suspicion for ROCM in patients recovering from COVID-19, especially among patients with new or previously diagnosed diabetes mellitus and clinical manifestations of headache, facial or orbital pain. Combination of surgical debridement, intravenous Liposomal Amphotericin B and oral Posaconazole therapy leads to clinical and radiologic improvement in majority of cases. Cerebral involvement by Mucorales is associated with higher mortality.

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AUTHOR CONTRIBUTION

Ameet Dravid: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Project administration (equal); Validation (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Reema Kashiva:** Conceptualization (equal); Supervision (equal). **Zafer Khan:** Conceptualization (equal); Project administration (equal);

Supervision (equal). **Balasaheb Bande:** Conceptualization (equal); Project administration (equal); Supervision (equal). **Danish Memon:** Conceptualization (equal); Project administration (equal); Supervision (equal). **Aparna Kodre:** Conceptualization (equal); Project administration (equal); Supervision (equal). **Milind Mane:** Conceptualization (equal); Project administration (equal); Supervision (equal); Validation (equal). **Vishal Pawar:** Data curation (equal); Project administration (equal); Supervision (equal); Validation (equal); Visualization (equal). **Dattatraya Patil:** Data curation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal). **Suraj Kalyani:** Data curation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal). **Prathamesh Raut:** Data curation (equal); Methodology (equal); Supervision (equal); Validation (equal); Visualization (equal). **Madhura Bapte:** Data curation (equal); Project administration (equal); Validation (equal). **Charlotte Saldanha:** Data curation (equal); Methodology (equal); Resources (equal); Validation (equal); Visualization (equal). **Dinesh Chandak:** Data curation (equal); Methodology (equal); Resources (equal); Supervision (equal); Validation (equal). **Teerthgouda Patil:** Data curation (equal); Supervision (equal). **Sateesh Reddy:** Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Validation (equal). **Krushnadas Bhayani:** Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal). **Laxmi Suresh:** Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal). **Vishnu Dillibabu:** Data curation (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal). **Shipra Srivastava:** Data curation (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Supervision (equal); Validation (equal). **Shubham Khandelwal:** Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Validation (equal). **Sailee More:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Validation (equal). **Atif Shakeel:** Data curation (equal). **Mohit Pawar:** Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Software (equal). **Pranava Nande:** Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal). **Amol Harshe:** Data curation (equal). **Sagar Kadam:** Data curation (equal); Investigation (equal). **Sudhir Halikar:** Conceptualization (equal); Data curation (equal); Investigation (equal); Writing – original draft (equal). **Nudrat Kamal:** Data curation (equal); Investigation (equal); Supervision (equal). **Danish Andrabi:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal). **Sachin Bodhale:** Data curation (equal); Investigation (equal). **Akshay Raut:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal). **Sangeeta Chandrashekhar:** Data curation (equal); Investigation (equal). **Chandrashekhar Raman:** Data curation (equal); Investigation (equal); Methodology (equal). **Uma Mahajan:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Writing – original draft (equal). **Gaurav Joshi:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Writing – original draft (equal). **Dileep Mane:** Conceptualization (equal); Data curation (equal); Project administration (equal); Supervision (equal); Validation (equal); Writing – original draft (equal).

ORCID

Ameet Dravid https://orcid.org/0000-0002-1909-7530

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