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RESEARCH ARTICLE

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Baseline findings of a multicentric ambispective cohort study (2021–2022) among hospitalised mucormycosis patients in India

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ABSTRACT

In India, the incidence of mucormycosis reached high levels during 2021–2022, coinciding with the COVID-19 pandemic. In response to this, we established a multicentric ambispective cohort of patients hospitalised with mucormycosis across India. In this paper, we report their baseline profile, clinical characteristics and outcomes at discharge. Patients hospitalized for mucormycosis during March–July 2021 were included. Mucormycosis was diagnosed based on mycological confirmation on direct microscopy (KOH/Calcofluor white stain), culture, histopathology, or supportive evidence from endoscopy or imaging. After consent, trained data collectors used medical records and telephonic interviews to capture data in a pre-tested structured questionnaire. At baseline, we recruited 686 patients from 26 study hospitals, of whom 72.3% were males, 78% had a prior history of diabetes, 53.2% had a history of corticosteroid treatment, and 80% were associated with COVID-19. Pain, numbness or swelling of the face were the commonest symptoms (73.3%). Liposomal Amphotericin B was the commonest drug formulation used (67.1%), and endoscopic sinus surgery was the most common surgical procedure (73.6%). At discharge, the disease was stable in 43.3%, in regression for 29.9% but 9.6% died during hospitalization. Among survivors, commonly reported disabilities included facial disfigurement (18.4%) and difficulties in chewing/swallowing (17.8%). Though the risk of mortality was only 1 in 10, the disability due to the disease was very high. This cohort study could enhance our understanding of the disease's clinical progression and help frame standard treatment guidelines.

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1. Introduction

Mucormycosis is a relatively uncommon, angio-invasive fungal infection increasingly recognised for its poor prognosis and high mortality (Peterson et al. 1997; Roden et al. 2005; Sridhara et al. 2005; Petrikkos et al. 2012; Jeong et al. 2015; Jeong et al. 2019a, 2019b; Reid et al. 2020). Diabetes mellitus is the leading risk factor for the disease, with an overall associated mortality of about 46% (Skiada et al. 2020). Most human infections result from direct inhalation of the sporangiospores released in the air or inoculation via skin or mucosa (Roden et al. 2005). The reported global annual incidence of the disease ranges from 0.005 to 1.7 per million population. Although the disease is more prevalent in subtropical countries, there has been an increasing trend in disease occurrence in many Western countries (Skiada et al. 2020; World Health Organization 2023).

India has the highest reported burden of mucormycosis globally, which is about 80 times more than the prevalence reported in the developed world (Prakash et al. 2019; Prakash and Chakrabarti 2019, 2021; Patel et al. 2021; Satish et al. 2021; Sen et al. 2021). This high burden gained greater significance during the COVID-19 pandemic, with increasing case reports of rhino-orbital mucormycosis among COVID-19 patients and a high overall mortality of 30.7% (Prakash and Chakrabarti 2019; Singh AK et al. 2021). Low oxygen, high glucose, acidic medium, high iron levels and reduced phagocytic activity of white blood cells provide a suitable environment for fungal growth (Patel et al. 2021; Sen et al. 2021; Singh AK et al. 2021). The creation of such an environment could be mediated by either COVID-19 or corticosteroids used for treatment, both, or other comorbidities like diabetes mellitus (Patel et al. 2021; Singh AK et al. 2021; Ponnaiah et al. 2022; Muthu et al. 2023). The inappropriate use of glucocorticoids during COVID-19 management, i.e. the use of steroids in the absence of hypoxaemia, has been identified as an additional risk factor for CAM (Patel et al. 2021; Muthu et al. 2023). It was also reported that after adjusting for gender, comorbidities and COVID-19-related hypoxaemia, increasing age and intracranial involvement affected the survival of patients (Muthu et al. 2023). Hyperglycaemia, regardless of diabetes mellitus, steroid use and hospitalisation status, was also reported to be associated with an increased risk of rhino-orbital-cerebral mucormycosis (Ponnaiah et al. 2022).

Despite aggressive therapy, the high reported overall mortality from the infection has remained a concern, emphasising the need to develop a greater understanding of disease progression. In the wake of COVID-19, many case-control studies and systematic reviews were published on the risk factors of disease development. Still, there is a need for well-designed longitudinal studies that could shed more light on the factors determining the prognosis and survival of patients, especially among hospitalised patients (Chander et al. 2018; Manesh et al.

2019; Maini et al. 2021). Hence, we established a multicentric ambispective cohort of patients hospitalised for mucormycosis across India.

In this paper, we describe (primary objective) the baseline characteristics of this cohort in terms of sociodemographic background, personal behaviours, clinical features, extent of the disease at diagnosis, disease progression, comorbidity profile, investigations conducted, treatment received and outcomes at discharge.

2. Methods

2.1. Study design and setting

In this multicentric ambispective cohort study, patients hospitalised with mucormycosis admitted to 26 selected government and private tertiary care hospitals and medical colleges that provide multidisciplinary treatment for mucormycosis across India were established. The process of establishing the cohort and the follow-up plan are described in Figure 1. Enrolment of participants was done from the hospital admission records, and baseline information was collected retrospectively. In addition to the patients already treated and discharged, patients prospectively diagnosed during the study period were also eligible for inclusion. The study protocol was approved by the Institutional Human Ethics Committee (IHEC) of the coordinating centre (NIE/IHEC/202107-02) and the IHECs of all the collaborating hospitals. Informed consent was taken from either the patient or a legally acceptable representative who is a close family member or caregiver in the case of a deceased/seriously ill person.

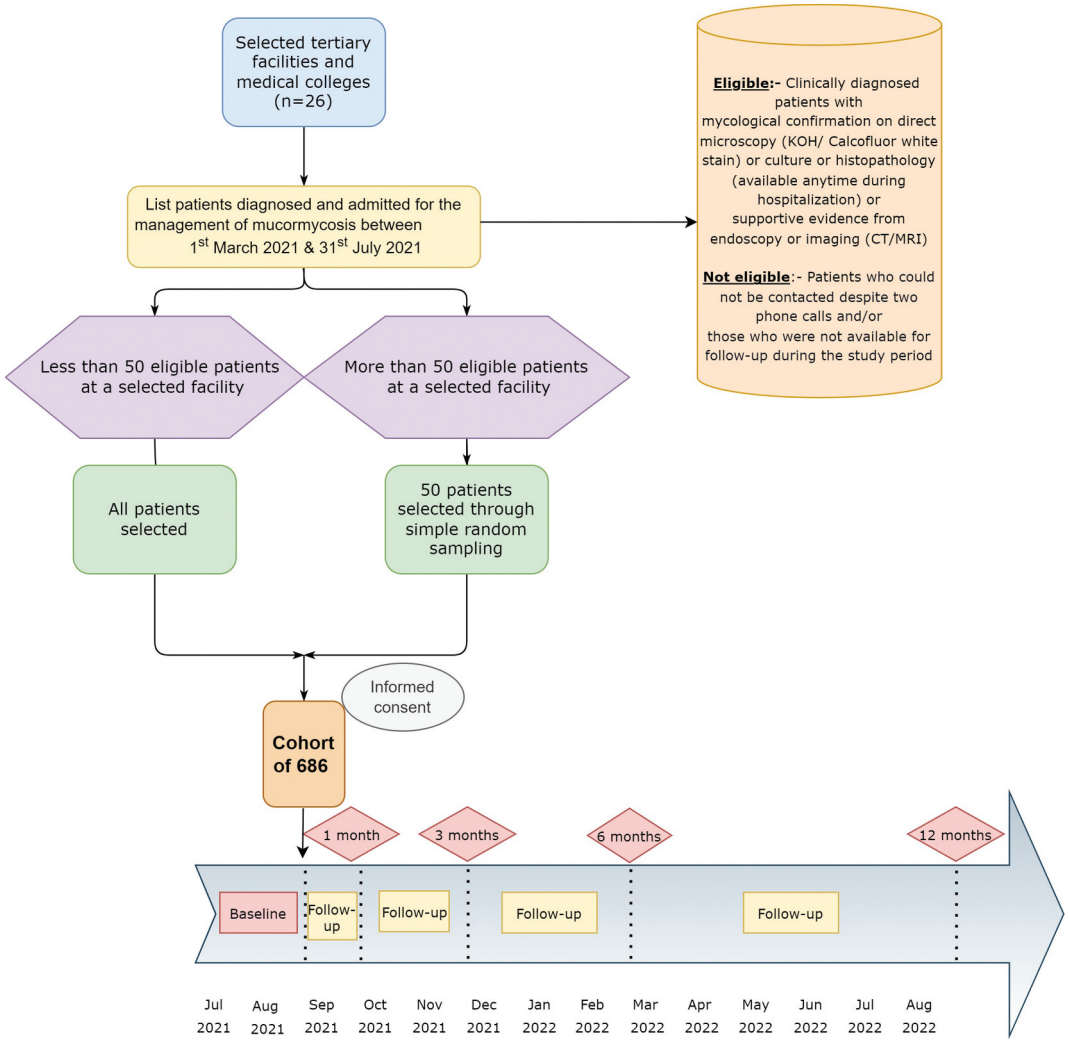

Figure 1. Flowchart depicting participant selection process and establishment of the cohort of hospitalised mucormycosis patients, India, 2021.

2.2. Study participants

Participants were selected from the list of patients admitted for mucormycosis in the study hospitals. Patients hospitalised between 1 March and 31 July 2021 were eligible for inclusion. Patients who were initially managed outside the study hospital, those who could not be contacted despite two phone calls and those not available for follow-up during the study period were excluded.

The collaborating hospitals were required to upload a list containing the unique identification numbers of all patients meeting the eligibility criteria into a web application developed by the ICMR-National Institute of Epidemiology (ICMR-NIE) for the purposes of this study. When more than 50 cases were uploaded, the web application randomly selected 50 cases from the list, and the output was downloaded by the study hospitals for recruitment (Figure 1).

2.3. Sources and methods of data collection

ICMR-NIE trained all the investigators and data collectors from the collaborating hospitals on data collection and management. For patients who were currently hospitalised, data were collected at the time of discharge from the hospital to capture the complete hospitalisation-related information through patient interviews and medical records. For patients already discharged from the study hospital, baseline forms were filled following recruitment into the study through hospital records and telephonic interviews.

The completed forms were uploaded and synced to the MUCOR Cohort Study Group cloud by the site investigators, which were then checked for completeness prior to data entry by trained data entry operators at the coordinating centre. An online data capture module was developed using Research Electronic Data Capture (REDCap), a secure web application for building and managing online surveys and databases.

2.4. Study variables

We developed the data collection instrument based on a detailed review of available literature, through which we identified the potential risk factors associated with mortality among mucormycosis patients (Figure 2).

Information pertaining to the following variables was collected from hospitalised mucormycosis patients:

(i) Socio-demographic and behavioural characteristics.

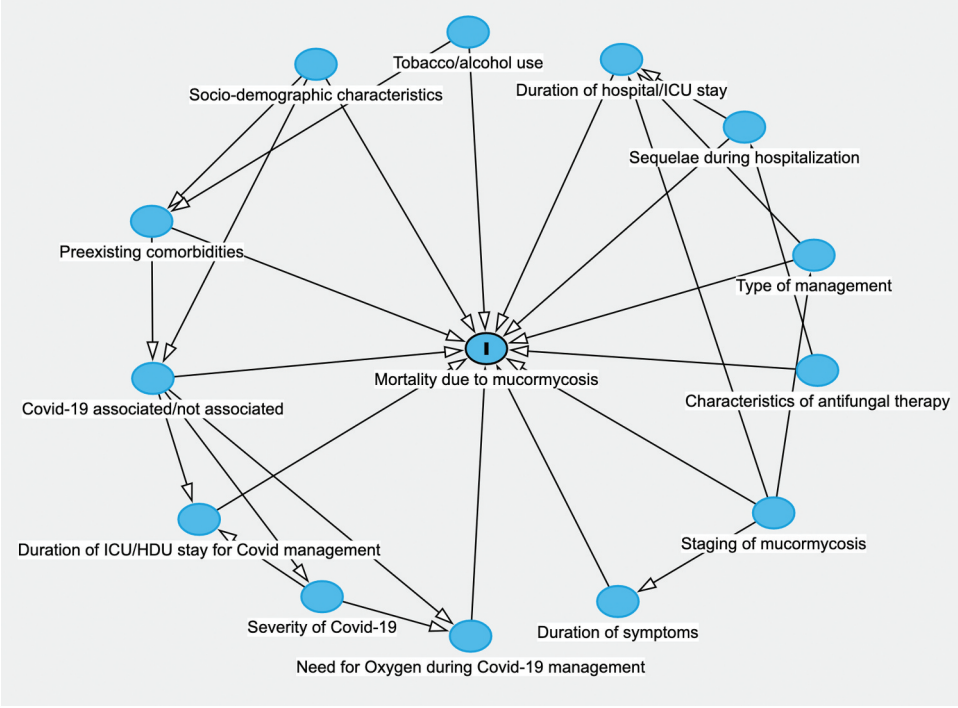

Figure 2. Directed acyclic graph demonstrating the relationship between potential risk factors of mortality due to mucormycosis.

(ii) Clinical, radiographic and histopathological characteristics.
(iii) Laboratory parameters – blood haemoglobin level, blood glucose, HbA1c, serum ferritin, and cell counts.
(iv) Diagnosis of mucormycosis was based on mycological confirmation on direct microscopy (KOH/Calcofluor white stain), culture, histopathology (available anytime during hospitalisation), supportive evidence from endoscopy or imaging (such as Computerized Tomography-CT or Magnetic Resonance Imaging-MRI).
(v) COVID-19 status of patients was assessed using RT-PCR, GeneXpert, Rapid Antigen Test-RAT or CT (CORAD-5).
(vi) Information about comorbidities such as cardiovascular diseases, stroke, kidney diseases, liver diseases, hypertension, diabetes mellitus, organ transplant, current or previous malignancies, HIV/AIDS, current or previous tuberculosis, asthma, sinus infections, and other comorbidities and the treatment.
(vii) Treatment details including type, dosage, and duration of antifungal drug therapy and surgery.

We defined COVID-19 Associated Mucormycosis (CAM) as mucormycosis detected after/concurrent with laboratory confirmed COVID-19. The diagnoses of COVID-19 and mucormycosis were based on the diagnostic methods described above. We estimated the interval between the diagnosis of COVID-19 and mucormycosis in the median and inter-quartile range (IQR).

2.5. Sample size

We used the proportion of deaths among hospitalised mucormycosis patients at the end of 90 days (proportion of the expected outcome, $p = 52\%$) from a previous study for sample size estimation (Patel et al. 2020). Considering an alpha error of 5%, and absolute precision of 5% (d), the sample size was estimated as 384 eligible mucormycosis patients using the formula $n = 1.96*p*(1-p)/(d*d)$. The calculated sample size was adjusted for 20% non-response rate to get the final sample size of 480 patients. The cohort was established during the second wave of the COVID-19 pandemic, which was characterised by heightened transmissibility of infection and high mortality in India (Samarasekera 2021). Although the estimated sample size was only 480, we included as many patients as possible from the participating sites to account for the anticipated high rates of mortality.

2.6. Statistical methods

We performed descriptive analysis for all the baseline variables. We provided frequencies and percentages for categorical variables and median and IQR for continuous variables. We described the socio-demographic characteristics, personal behaviours, comorbidity profile, clinical features, investigations carried out, disease progression, and sequelae and COVID-19 related features for the entire cohort. We also provided a comparison of the proportions of selected characteristics between Covid-associated mucormycosis (CAM) and non-CAM patients. We provided a comparison of important clinical features and outcomes by site of involvement. We provided figures to highlight the distribution of comorbidities, the dose ranges of different formulations of Amphotericin B, and the distribution of different surgical techniques among the cohort. All analyses were conducted in R version 4.2.2 and Stata version 17.

3. Results

We recruited a total of 686 patients who fulfilled the eligibility criteria. In the following section, we describe the baseline characteristics of the cohort in terms of their socio-demographic, behavioural and clinical characteristics, symptoms and stages of mucormycosis, investigations and management, disease progression, clinical sequelae, and CAM.

3.1. Socio-demographic, behavioural and clinical characteristics

The majority of the participants were males (72.3%) and resided in urban areas (57.7%). The majority were formally educated (81.7%), and over half had a regular income (58.2%). About 7% of them currently used smoked/smokeless tobacco or consumed alcohol (7.6%) (Table 1).

Table 1. Socio-demographic characteristics of the cohort of hospitalised mucormycosis patients, India, 2021 (N = 686).

Characteristics	n (%)
Age in years, *Mean (SD)*	51 (12)
Gender	
Male	496 (72.3)
Female	190 (27.7)
Place of residence	
City/town	396 (57.7)
Village	290 (42.3)
Location of residence	
Within same district as the study hospital	323 (47.1)
Within same state but different district	311 (45.3)
Different state	52 (7.6)
Income status	
Regular income	398 (58.2)
Irregular/seasonal income	234 (34.2)
No income	52 (7.6)
Level of education	
Illiterate/no formal schooling	125 (18.3)
Primary education	229 (33.5)
Secondary education	208 (30.4)
Degree & above	122 (17.8)
Use of smoked/smokeless tobacco	
Never used	397 (57.9)
Former user (not used in the last 1 year)	95 (13.8)
Current user	47 (6.9)
No response	147 (21.4)
Alcohol consumption	
Never used	414 (60.3)
Former user (not used in the last 1 year)	80 (11.7)
Current user	52 (7.6)
No response	140 (20.4)

SD – standard deviation; sum of frequencies under each variable may not add up to total N due to missing data.

Table 2. Profile of current comorbidities reported by the cohort of hospitalised mucormycosis patients, India, 2021 (N = 686).

Comorbidities (multiple responses)	Currently under treatment n (%)	Currently not under treatment n (%)	Total n (%)
Diabetes mellitus	522 (76.1)	13 (1.9)	535 (78.0)
Hypertension	194 (28.3)	10 (1.5)	204 (29.7)
Any disease of the heart	45 (6.6)	2 (0.3)	47 (6.9)
Any disease of the kidneys	19 (2.8)	3 (0.4)	22 (3.2)
Stroke	14 (2.0)	1 (0.1)	15 (2.1)
Any disease of the sinuses	6 (0.9)	5 (0.7)	11 (1.6)
Fungal infection	7 (1.0)	1 (0.1)	8 (1.1)
Asthma	4 (0.6)	1 (0.1)	5 (0.7)
HIV/AIDS	2 (0.3)	1 (0.1)	3 (0.5)
Cancer	3 (0.4)	0	3 (0.4)
Any disease of the liver	2 (0.3)	0	2 (0.3)
Tuberculosis	1 (0.1)	0	1 (0.1)
Other comorbidities	75 (10.9)	13 (1.9)	88 (12.8)

The majority of the participants had a prior history of diabetes mellitus (78%) and were currently on treatment (76.1%). Among those with no prior history of diabetes, 63.8% (46 out of 72) were newly diagnosed with diabetes mellitus during hospitalisation for mucormycosis. The commonest treatment among those who reported diabetes mellitus was oral hypoglycaemic drugs (81.4%), while almost a fourth were on insulin therapy (26.6%). The majority of the participants did not report any interruption in treatment for diabetes (79.1%). The other major morbidities reported by the participants include hypertension (28.3%) and cardiovascular disease (6.6%) (Table 2). Diabetes mellitus and hypertension coexisted in a quarter of patients (24.5%), followed by a combination of diabetes mellitus, cardiovascular disease and hypertension (7.8%) (Figure 3).

About 3.4% of the participants presented with diabetic ketoacidosis. The majority of the participants had serum Ferritin values exceeding the normal range (93.3% of males had >300 ng/mL, and 92.6% of females had >200 ng/mL).

3.2. Symptoms and clinical presentation of mucormycosis

Pain, numbness, or swelling on one or both sides of the face was the most common symptom among patients (73.3%), followed by severe headache (64.6%), one/both sided stuffy or blocked nose (43.7%), pain in the eye (42.4%), red-eye, double vision, or blurred vision (37.6%) and tooth pain (33.4%) (Table 3). Drooping of eyelids (23.9%), brown or black or blood-tinged discharge from the nose (22.5%), mouth sores/loose tooth/recent loss of teeth (22.1%), black lesions on the nasal bridge or upper inside of the mouth (17.2%) and foul-smelling discharge from the nose (17.0%) were also reported. At the time of diagnosis, a major proportion of the participants had involvement of orbit (43.4%), followed by involvement of paranasal sinuses (25.9%), brain (10.1%), nasal mucosa (2.3%), lungs (1.2%), and other organs (3.8%) (Table 3). The median (IQR) period from the onset of symptoms to diagnosis of the disease was eight days (5–15) (Table 4).

3.3. Investigations and management

Microscopy of tissue samples was the most common investigation done (83.5%), followed by nasal endoscopy (71.0%), MRI – head and neck (68.4%), and

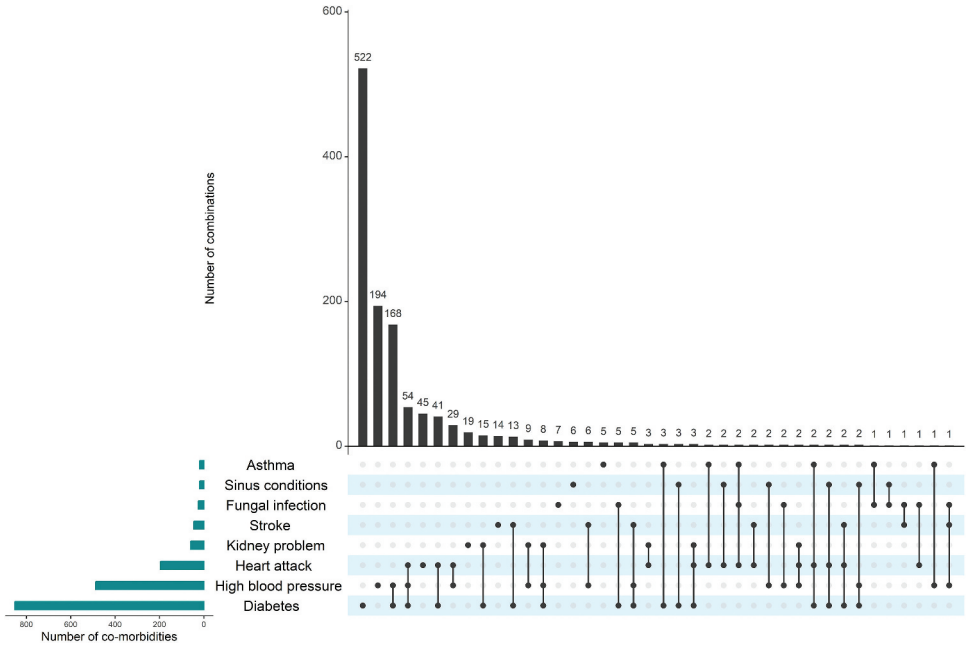

Figure 3. Distribution of multi-comorbidity profile in the cohort of hospitalised mucormycosis patients, India, 2021.

rhinoscopy (64.7%). Chest X-ray (57.9%), CT – head and neck (56.4%), and fungal culture (55.1%) were the other major investigations. Histopathological examination of pre-operative biopsy specimens was done in about two-thirds of the patients (39.7%).

The microscopy findings were positive for mucormycosis among 68.1% of the patients. MRI-head and neck was suggestive among 66.9% patients, followed by nasal endoscopy, which was suggestive of the infection in 65% patients. Fungal culture was suggestive of mucormycosis among 42.4% (Table 5).

Liposomal Amphotericin B (L-Amp B) (67.1%) was the commonest drug formulation used for treatment, followed by Posaconazole (59.8%) and conventional Amphotericin B (36.0%). The median dosages of the commonest formulations of Amphotericin-B and the interquartile ranges are presented in Figure 4. Intra-orbital Amphotericin-B was also given to a relatively lower proportion of patients (10.1%). The most common side effect reported for Amphotericin therapy was kidney damage (19.6%). A large proportion of participants received some form of intervention or surgery along with drug therapy (n = 678, 98.8%), with the highest proportion being endoscopic sinus surgery (n = 505, 73.6%), followed by total maxillectomy (n = 161, 23.5%) and radical debridement (n = 151, 22.0%) (Figure 5). The median (IQR) number of surgeries conducted per patient was one (1–2), and the median number of days of hospitalisation was 19 (9–33).

3.4. Disease progression and clinical sequelae

About 10% of the patients died in the hospital during the baseline data collection period and 3.6% of the patients left the hospital against medical advice. A majority (87%) of the participants were discharged from the hospital after completion of treatment. The infection was either stable (43.3%) or in regression (29.9%) in the majority of the patients. The disease was progressing (12.4%) in a relatively low proportion of patients, while the status of progression could not be assessed due to the unavailability of MRI reports in about 14.4%. The major clinical sequelae included facial disfigurement (18.4%), disabilities related to chewing and swallowing (17.8%) and difficulties in speech and articulation (14.7%). Blindness (9.8%) and decreased vision (10.8%) were also common (Table 6).

3.5. COVID-19 associated mucormycosis (CAM)

CAM constituted the majority of the cohort (80%), and most of the patients were diagnosed with COVID-19 before the diagnosis of mucormycosis (76.5%) with a median duration of 23 days (IQR of 13–41 days) (Tables 3 & 4). The majority of the CAM patients

Table 3. Comparison of selected exposures and outcomes between Covid-associated mucormycosis (CAM) and non-CAM patients in the cohort of hospitalised mucormycosis patients, India, 2021.

Characteristics	COVID-19 associated mucormycosis N = 549 n (%)	Non-COVID-19 associated mucormycosis N = 137 n (%)
Mean age (SD)	51 (12)	51 (13)
Gender		
Male	396 (72.1)	100 (73)
Female	153 (27.9)	37 (27)
Comorbidities		
Any comorbidity	461 (84.0)	117 (85.4)
History of diabetes mellitus	428 (78.0)	107 (78.1)
History of diabetic ketoacidosis	17 (3.1)	6 (4.4)
Symptoms		
Pain, numbness, or swelling on one or both sides of the face	399 (72.6)	106 (77.4)
Severe headache	343 (62.5)	102 (74.5)
Red-eye, double vision, or blurred vision	188 (34.2)	70 (51.1)
Drooping of eyelids	122 (22.2)	42 (30.7)
Pain in the eye	217 (39.5)	74 (54.0)
One/both sided stuffy or blocked nose	230 (42.0)	70 (51.1)
Tooth pain	173 (31.5)	56 (40.9)
Sites involved at diagnosis		
Rhino-orbital	192 (35.1)	55 (40.1)
Rhino-orbito-cerebral	55 (10)	14 (10.2)
Pulmonary	7 (1.3)	1 (0.7)
Any other organ involvement	23 (4.2)	3 (2.2)
Stages of organ involvement in rhino-orbito-cerebral mucormycosis		
Nasal mucosa	13 (2.9)	3 (2.6)
Orbit	240 (53.9)	58 (50)
Paranasal sinuses	137 (30.8)	41 (35.3)
CNS	55 (12.4)	14 (12.1)
Supportive histopathological and radiological findings		
Microscopy findings positive in KOH	361 (66)	97 (70.8)
Microscopy findings positive in Calcoflour	6 (1.1)	1 (0.7)
Positive fungal culture	226 (41.3)	65 (47.4)
Positive findings in MRI scan (both head and neck and chest/abdomen)	375 (68.4)	84 (61.8)
Positive findings in CT scan findings (both head and neck and chest/abdomen)	324 (59.3)	70 (51.5)
Treatment		
Lipid-based Amphotericin-B	354 (64.6)	106 (77.4)
Posaconazole	341 (62.2)	69 (50.4)
Endoscopic sinus surgery	409 (74.5)	96 (70.1)
Total maxillectomy	139 (25.3)	22 (16.1)
Radical debridement	118 (21.5)	33 (24.1)
Combination of antifungal therapy	536 (97.6)	131 (95.6)
Outcome variables		
Status during discharge		
Discharged alive	477 (86.9)	119 (86.9)
Died during hospitalisation	52 (9.5)	13 (9.5)
Absconded/left against medical advice	20 (3.6)	5 (3.7)
Presence of any disability	233 (42.4)	66 (48.2)
Disease progression		
Stable disease	238 (43.4)	59 (43.1)
In regression	170 (31.0)	35 (25.5)
Progressive disease	62 (11.3)	23 (16.8)
Unknown	79 (14.4)	20 (14.6)

SD – standard deviation.

Table 4. Duration between diagnosis of COVID-19 and mucormycosis among Covid-associated mucormycosis (CAM) in the cohort of hospitalised mucormycosis patients, India, 2021.

Sequence of diagnosis of COVID-19 and mucormycosis	Median number of days (inter quartile range)
Duration between COVID-19 diagnosis and mucormycosis diagnosis regardless of the sequence	22 (11–41)
COVID-19 diagnosed before mucormycosis	23 (13–41)
COVID-19 diagnosed concurrently with mucormycosis	2.5 (0–27)
Duration between onset of symptoms to diagnosis of mucormycosis	8 (5–15)

Table 5. Distribution of investigations conducted in the cohort of hospitalised mucormycosis patients, India, 2021 (N = 686).

Investigations	Conducted n (%)	Suggestive findings n (%)
Rhinoscopy	444 (64.7)	365 (53.2)
Nasal endoscopy	487 (71.0)	446 (65.0)
GI endoscopy	7 (1.0)	3 (0.4)
Microscopy	571 (83.5)	467 (68.1)
Fungal culture	378 (55.1)	291 (42.4)
Histopathology (only pre-operative biopsy)	272 (39.7)	250 (36.5)
Chest X-ray	397 (57.9)	56 (8.2)
CT – Head & neck	387 (56.4)	354 (51.6)
CT – Chest & abdomen	112 (16.3)	62 (9.1)
MRI – Head & neck	469 (68.4)	458 (66.9)
MRI – Chest & abdomen	9 (1.3)	3 (0.4)

CT – computed tomography, MRI – magnetic resonance imaging.

were hospitalised (76.9%) for their Covid-related illness. About half of the patients required oxygen as part of COVID-19 management (47.2%) and the commonest mode of supplementation was through masks or prongs (47.0%), followed by non-invasive positive pressure ventilation/high flow Oxygen (5.1%) and intubation (1.5%). Almost two-thirds of the patients had received corticosteroids as part of COVID-19 management (66.5%) and 40.4% received Remdesivir (Table 7).

There was no notable difference in the mean age, gender composition or proportion with comorbidities including diabetes mellitus between CAM and non-CAM patients. However, the proportion of those with symptoms such as pain, numbness or swelling on sides of the face, headache, red eye, double vision or blurred vision, drooping of eyelids, pain in the eye, stuffy/blocked nose, and toothache was higher among the non-CAM patients. The majority of the patients in both CAM and non-CAM groups presented with Rhino-Orbital Mucormycosis (ROM), while the proportion with orbital involvement was slightly higher in the non-CAM group. The proportion with pulmonary mucormycosis or involvement of any other organs was low in both groups. There was no notable difference in the management modalities between the CAM and non-CAM groups. However, Posaconazole (62.2% in CAM versus 50.4% in non-CAM) and total maxillectomy (25.3% in CAM versus 16.1% in non-CAM) were more common in the CAM group. We did not find any notable difference in the proportion of outcomes – death or disability – between the two groups. However, the proportion of disease in progression was higher in the non-CAM group (16.8%) compared to the CAM group (11.3%) (Table 3).

We compared outcomes between those patients who only had a nasal mucosa/paranasal sinus involvement and those who had sinus/orbit/CNS involvement. Disability (29.4% vs. 58%) and mortality (4.1% vs. 15.2%) were higher among the second group. While disease progression was higher in the second group (17%), PNS only group had a higher level of stable disease (48.3%) (Table 8).

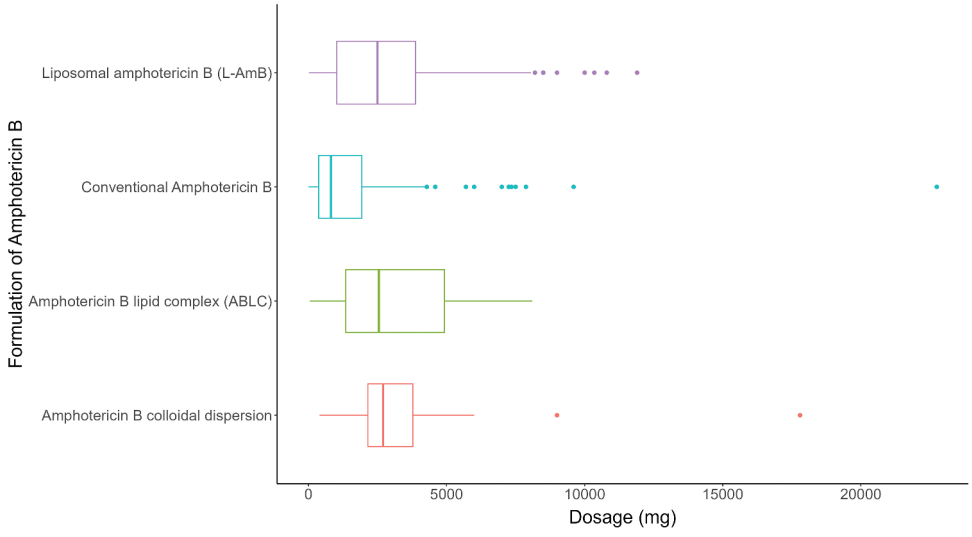

Figure 4. Distribution of dosage of various formulations of Amphotericin-B in the cohort of hospitalised mucormycosis patients, India, 2021.

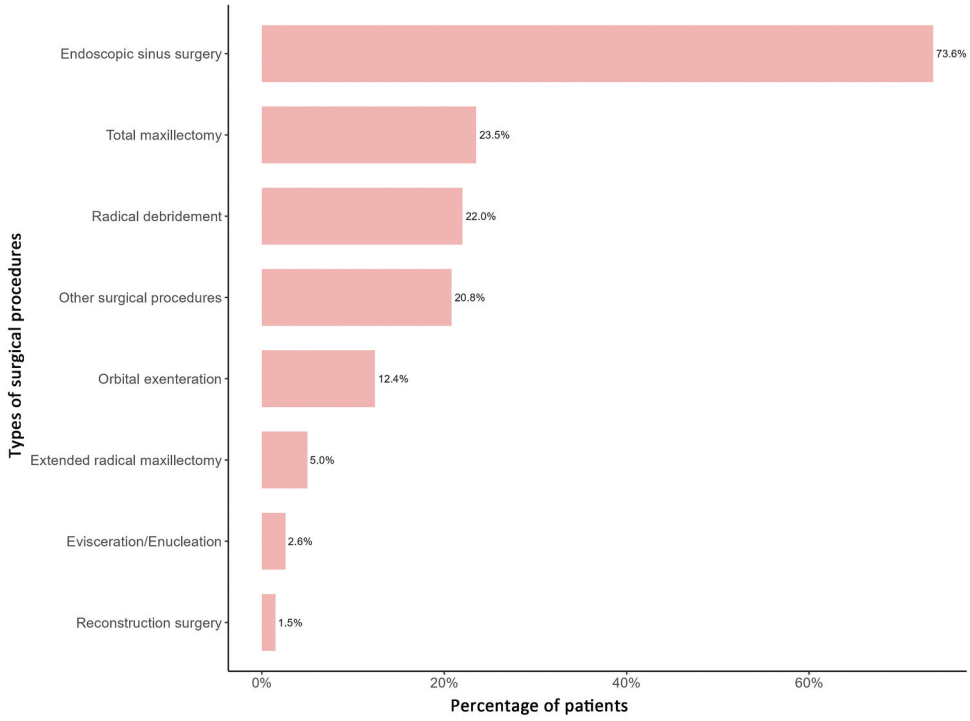

Figure 5. Major surgical procedures are undertaken in the cohort of hospitalised mucormycosis patients, India, 2021.

Table 6. Disease progression and clinical sequelae in the cohort of hospitalised mucormycosis patients, India, 2021.

Characteristics	n (%)
Status of patients at discharge	
Discharged alive	596 (86.8)
Died during hospitalisation	65 (9.5)
Left hospital against medical advice	25 (3.6)
Disease progression (based on MRI findings)	
Stable	297 (43.3)
Regressing	205 (29.9)
Progressing	85 (12.4)
Unknown	99 (14.4)
Clinical sequelae	
Facial disfigurement	126 (18.4)
Chewing and swallowing disability	122 (17.8)
Difficulty in speech and articulation	101 (14.7)
Decreased vision in one eye	74 (10.8)
Blindness in one eye	67 (9.8)
Deviation of mouth to one side/paralysis of face	37 (5.4)
Breathing difficulty	31 (4.5)
Decreased hearing	26 (3.8)
Others	22 (3.2)
Weakness on one side of the body/limbs	17 (2.5)
Paralysis of one side of the body/one limb	16 (2.3)
Coma	14 (2.0)
Decreased vision in both eyes	11 (1.6)
Difficulty in digestion/altered bowel habits	11 (1.6)
Weakness/paralysis of any part of the body	7 (1.0)
Blindness in both eyes	5 (0.7)

MRI – magnetic resonance imaging.

Table 7. COVID-19 positivity, symptoms and management in the cohort of hospitalised mucormycosis patients, India, 2021 (N = 549).

Characteristics	n (%)
Positive for COVID-19 symptoms	389 (70.9)
Place of management of COVID-19	
Hospitals	422 (76.9)
Covid care centres	25 (4.6)
Home isolation	74 (13.5)
Admitted in intensive care units/high dependency units	92 (16.8)
Received oxygen supplementation	259 (47.2)
Drugs received (multiple responses possible)	
Corticosteroids	365 (66.5)
Remdesivir	222 (40.4)
Tocilizumab	5 (0.9)

4. Discussions

This is one of the first and largest cohorts to be established for hospitalised mucormycosis patients in India. The high prevalence of mucormycosis reported in India before the pandemic, the excessive mortality reported among hospitalised mucormycosis patients during the pandemic, and the burden of diabetes mellitus increase its significance in the Indian context. The multicentric nature of this study, which involves both government and private healthcare facilities from varied geographic settings, accounts for a better representation of the heterogeneity of the Indian populace, allowing for greater generalisability of the findings. The results of this inquiry could guide clinicians in devising

Table 8. Comparison of selected exposures and outcomes by levels of involvement in the cohort of hospitalised mucormycosis patients, India, 2021.

Characteristics	Nasal mucosa and PNS only (N = 344)	Others (N = 336)
Mean age (SD)	51.3 (12.1)	51.3 (12.6)
Gender		
Male	252 (73.3)	240 (71.4)
Female	92 (26.7)	96 (28.6)
Comorbidities		
History of any comorbidity	284 (82.6)	289 (86.0)
Diabetes Mellitus	255 (74.1)	275 (81.9)
Treatment		
Lipid-based Amphotericin-B	226 (65.7)	230 (68.5)
Posaconazole	208 (60.5)	199 (59.2)
Endoscopic sinus surgery	269 (78.2)	231 (68.8)
Total maxillectomy	92 (26.7)	67 (19.9)
Radical debridement	53 (15.4)	95 (28.3)
Combination of antifungal therapy	336 (97.7)	326 (97.0)
Outcome variables		
Status during discharge		
Discharged alive	321 (93.3)	269 (80.1)
Died during hospitalisation	14 (4.1)	51 (15.2)
Absconded/left against medical advice	9 (2.6)	16 (4.8)
Presence of any disability	101 (29.4)	195 (58.0)
Disease progression		
Stable disease	166 (48.3)	127 (37.8)
In regression	109 (31.7)	95 (28.3)
Progressive disease	28 (8.1)	57 (17.0)
Unknown	41 (11.9)	57 (17.0)

PNS – paranasal sinuses; SD – standard deviation.

optimal treatment strategies that will minimise adverse outcomes following treatment through characterisation of disease progression under treatment and identification of factors associated with mortality. The baseline data collection for this study was undertaken during the peak of the pandemic with restricted resources, and it was anticipated that this could have implications for the completeness of the data. The potential for attrition was expected to be high, and this was accounted for during the study protocol development.

The cohort has a greater proportion of males, a high proportion of patients with pre-existing diabetes mellitus who presented with hyperglycaemia and a treatment history of COVID-19 that involved corticosteroid usage. The baseline findings, including the overwhelmingly high proportion of CAM, are consistent with the socio-demographic and behavioural characteristics, underlying comorbidities, symptoms and clinical presentation of mucormycosis patients from the studies recently reported from India and the world over, during this period (Prakash et al. 2019; Skiada et al. 2020; Patel et al. 2021; Prakash and Chakrabarti 2021; Satish et al. 2021; Sen et al. 2021; Ponnaiah et al. 2022; Muthu et al. 2023). The occurrence of invasive fungal sinusitis due to mucormycosis and its links to COVID-19 and its management and/or hyperglycaemia, which has been suggested in the more recent literature, has been demonstrated in our baseline findings too.

In our study, we found that the proportion of non-CAM mucormycosis was 20%. This was lower than what was reported (34.8%) in another multicentric India study conducted during September – December 2020 (Patel et al. 2021). The high proportion of non-CAM mucormycosis found in these studies may be due to the following reasons. India is known to be endemic for mucormycosis, and it has been a significant problem in certain parts of the country even before the COVID-19 pandemic (Prakash et al. 2019; Prakash and Chakrabarti 2019, 2021; Patel et al. 2021; Satish et al. 2021; Sen et al. 2021). The prevalence of diabetes, which is known to be a risk factor for mucormycosis (Skiada et al. 2020), irrespective of the presence of COVID-19 was relatively high in the study population (~78%). The Reverse Transcription – Polymerase Chain Reaction (RT-PCR) test used for COVID-19 diagnosis is known to have a sensitivity ranging from 73% to 94%, depending on the kit used (Singh J et al. 2021). This could have led to missed diagnosis of many COVID-19 positive mucormycosis patients. Lastly, apart from apparent clinical disease, COVID-19 is also known to cause sub-clinical infections without signs and symptoms in 16%–20% of individuals (Sah et al. 2021).

According to the previously published literature, rhino-orbital mucormycosis constituted the most common site of involvement followed by pulmonary and other sites (Maini et al. 2021; Patel et al. 2021; Sharma et al. 2021; Ponnaiah et al. 2022; Muthu et al. 2023). The proportion of patients with CNS and lung involvement

was lower in our study compared to others, especially those based on the data from the first wave of the pandemic (Patel et al. 2021; Sen et al. 2021). A multicentric case-control study conducted during the second wave of the pandemic proposed several potential reasons to explain their relatively lower mortality rates including the lower CNS and brain involvement, higher visibility, and awareness among the medical and general community regarding the disease and its association with potential implications such as early diagnosis and institution of prompt treatment modalities including surgical interventions and combination of medical and surgical modalities. The study also suggested the role of reversible risk factors of CAM, including hyperglycaemia and glucocorticoid use, which constituted the majority of the cases reported during this period (Muthu et al. 2023). This could also explain the lower proportion of mortality in our study, especially when compared to the proportions (28%–52%) reported from the literature in India (Patel et al. 2021; Prakash and Chakrabarti 2021). This is also in concordance with the rationale that mortality rates are lower in patients treated with a combination of surgical debridement and Amphotericin B, when compared to those treated with the drug monotherapy (Jeong et al. 2019a). Almost two in three patients from our study were treated using Posaconazole and the proportion of use of Posaconazole was higher in the CAM group. This is in alignment with the existing literature (Patel et al. 2021). A study which assessed the efficacy and safety of Posaconazole among 12 consecutive adult patients admitted with Rhino-Orbito-Cerebral mucormycosis in a tertiary care setting in south India reported complete resolution among the majority of patients and no mortality in a study which followed the patients in a range of 2–24 months (Manesh et al. 2016). The effectiveness of these therapeutic measures, along with the long-term survival of patients, disease progression and clinical sequelae of the disease would emerge through the analysis of the follow-up data. A small proportion of the patients (3.6%) were lost at the baseline as they had left the hospital against medical advice. All the remaining cases either achieved the primary outcome (death) or were available for subsequent follow-ups. The proportion lost to follow-up would affect the calculation of the survival time at one year.

The Indian studies conducted during the second wave of the pandemic focused on the risk factors of the occurrence of CAM (Ponnaiah et al. 2022; Muthu et al. 2023). Although one study did explore the factors associated with mortality from CAM, the follow-up was restricted to 12 weeks (Muthu et al. 2023). The long-time mortality and survival among the patients can be estimated only after the completion of treatment which typically extends up to 6–9 months. We intend to publish these results after the completion of the follow-up.

During the second wave, the disruption of supply and manufacturing chains and shortage of the drug formulation of choice – liposomal Amphotericin B – and the absence of interdisciplinary management guidelines further hindered the availability of prompt treatment among patients (Arun et al. 2022). To avoid such a situation in future, there needs to come about a recognition of the public health significance of this disease, the institution of stringent state monitoring and policy prescriptions for its management.

5. Conclusions and recommendations

Mucormycosis is a very heterogenous disease in terms of clinical presentation and mainly affects those with deranged glucose metabolism. Management of the disease in terms of the investigations performed, drugs prescribed and surgeries performed varied from centre to centre. Although the case fatality was about 10%, there was a high burden of disability among survivors. The study enhances our understanding of the disease, which could be applied to draw greater policy attention to the problem and develop effective public health strategies. The findings of this inquiry could guide clinicians in devising standard treatment protocols and strategies and identification of risk factors for mortality.

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