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COVID-19 Associated Mucormycosis

A Case series of Risks, Clinical features and Outcomes from Maharashtra, India

Abstract
This case series explores Covid-19 associated Mucormycosis (CAM), its risk factors, clinical features and outcomes from a tertiary centre in Maharashtra, India, during the second wave of COVID-19.
Methods: A retrospective, observational case series of 104 consecutive patients admitted to the hospital at various stages of complications of CAM, during the second wave of COVID-19 pandemic (Jan'21-Apr'21). Diagnosis was confirmed using Potassium hydroxide wet mount (KOH), histopathology, fungal culture, and Cone-Beam Computed Tomography(CBCT).
Results: There were 81% men, mean age 49 ± 12.4 years, and all patients had a history of corticosteroids usage, 82% had a prior diagnosis of diabetes mellitus (DM) and the rest were newly diagnosed. Diagnosis of mucormycosis was confirmed on 2 modalities in 71%; KOH and histopathology in 31 (30%), fungal culture with KOH and histopathology together detected 25 (24%). 9% were diagnosed exclusively with CBCT. Patients with prior DM had higher morbidity OR 8.30 [95% CI: 2.12, 32.5; p=0.002] and mortality OR 13.23 [95% CI: 1.67, 104.7; p=0.014] than non- DM patients. Mortality was higher in patients with rhino + orbital involvement than patients with rhino + maxillary involvement [OR 8.37 [95% CI: 1.52, 46.09; p=0.014].
Conclusion: Diabetes remained the highest risk factor for development of CAM in patients with COVID-19 on corticosteroids, with high mortality and morbidity. Timely medical and surgical interventions and multi-disciplinary approaches could potentially reduce mucormycosis-associated mortality. Among the diagnostic modalities, detection using CBCT may increase the diagnostic yield in patients not detected in other modalities.

Keywords: Mucormycosis, Corticosteroids, Covid-19, Rhino Orbital Cerebral mucormycosis, COVID-19 associated mucormycosis

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Introduction

COVID-19 is an infectious condition caused by the virus SARS-CoV-2, which mainly affects the human respiratory tract (lungs, nose, and sinuses). [1] The symptoms mainly included fever, cough, fatigue shortness of breath, loss of taste or smell, in some cases asymptomatic. symptoms. [2]

COVID-19–associated rhino-orbital-cerebral mucormycosis (CAROCM) is the most common type observed during the current epidemic, followed by the pulmonary form. [3] [4] Before the COVID-19 pandemic, the mortality associated with mucormycosis was 50%. However, during the COVID-19 pandemic in India, it had increased to 85%, due to the unavailability of healthcare resources, overburdened healthcare workers, and poor diagnostic quality. [5]

Mucormycosis, is a non-contagious infection, caused by a group of filamentous moulds of the order Mucorales[1]. The most common CAROCM symptoms observed in that study included orbital/facial pain and oedema, vision loss, ptosis, and nasal congestion, the primary signs included periocular/facial oedema, vision loss, proptosis, and nasal discharge. [6] Pulmonary mucormycosis mimics the symptoms of COVID-19, such as pyrexia, cough, and dyspnoea. [5]

Uncontrolled hyperglycaemia is an significant risk factor that predisposes to mucormycosis. Patients with diabetic ketoacidosis, a serious complication of diabetes, are the greatest at risk. Along with the potential consequences of steroid-induced hyperglycaemia, COVID-19 patients with uncontrolled diabetes, who are also receiving corticosteroids or other immunosuppressants, seem to be highly vulnerable to the development of mucormycosis. Innate immunity is altered in the diabetic population, as reflected by polymorphonuclear (PMN) dysfunction [7]. Reduced PMN chemotaxis, impaired transmigration through vascular endothelium, and reduced superoxide production are the three major components of PMN dysfunction [8]. Adaptive immunity is also impaired, though less well-studied. It is known, for example, that in type-1 diabetics there is poor metabolic control, inflammatory cytokine production, including interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-and interferon (IFN) are reduced.

Although with the extensive vaccination drive, the COVID-19 surge and its complications are reducing, there is the lingering threat of mucormycosis in any new incidence of probable infections. Considering the significant morbidity and mortality associated with mucormycosis, it is highly pertinent to document the experience of management in the affected population. COVID-19 deteriorates the immune status of patients, paves the way for opportunistic and secondary infections, and worsens pre-existing clinical conditions. [9] [10]

Aim

Given this, in our tertiary care centre, we have retrospectively evaluated the history of patients post-COVID-19 and the outcome of patients diagnosed with mucormycosis. The study focuses on the clinical, radiological, and microscopic profile of mucormycosis patients, who have a prior history of COVID-19, and their diagnostic and management modalities, and aims at quantifying the association of various risk factors.

Materials and methods

This is a retrospective observational study on patients with post-COVID mucormycosis, admitted to a single tertiary care hospital centre in Nagpur, India, from January 2021 – to December 2021. Details of 104 patients were complete and accessible and hence were included in the study. Earlier, these patients were either hospitalized in different centres for COVID-19 treatment or home-quarantined. Accordingly, all the previous COVID-19 diagnoses and treatment details were obtained based on the available records. Further, the data on the diagnosis of mucormycosis along with the presenting signs and symptoms of these patients were also available. This study was carried out after obtaining approval from the institutional ethical committee and written informed consent from the patients.

The guidelines were developed using the evidence criteria, which were set forth by the American Infectious Diseases Society and Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, India, and the key recommendations in the absence of validated biomarkers (mannan, galactomannan, beta-glucan).

The diagnosis of mucormycosis relies on histology and/or detection of the organism by culture from involved sites with identification of

the isolate at the species level (no grading). The three modalities used were the KOH (potassium hydroxide) test, histopathology of nasal endoscopy biopsy, and its fungal culture. KOH staining revealed broad, ribbon-like aseptate hyphae when examined under a fluorescence microscope. Fungal cultures of the biopsied tissue were grown and recorded over 7, 14, and 21 days. In most cases of mucormycosis, as a radiological tool, computed tomography (CT) was used to diagnose the extension of the lesion in the rhinomaxillary region. Recently, Cone-Beam Computed Tomography (CBCT) with 10 times lesser radiation dose has replaced conventional CT. Additionally, CBCT is highly accurate and pictures 3-dimensional imaging with volumetric data in sagittal, coronal, and axial planes. CBCT provides higher quality diagnostic images with submillimetre resolution and also with shorter scanning times (< 60s).

Biochemical investigations like complete blood count (CBC), serum electrolyte, creatinine, HbA1c, and C-reactive protein (CRP) were done at the presentation. Patients have been treated medically with therapeutic doses of injection Liposomal Amphotericin or a conventional form of Amphotericin and antifungals like Isavuconazole and Posaconazole, along with early surgical interventions, which include endoscopic debridement of the infected sinus and surrounding tissues with unilateral or bilateral maxillectomy, orbital enucleation, and decompressive craniotomy.

The patients' outcome was categorized into three viz., recovery, and recovery with morbidity and mortality. The status of each patient till the end of August 2021 was sought either through telephonic follow-up or through direct interaction when they attended the hospital for follow-up. All the data related to mucormycosis were obtained from the hospital's electronic medical records (EMR) system as well as patient files (hard copies) and collated for statistical analysis.

Statistical methods

The demographic, clinical signs, and investigational parameters, measured on a continuous scale, were summarized in terms of mean and standard deviation, while categorical parameters were expressed in terms of numbers and percentages. A Venn diagram was used to depict the number of patients diagnosed with three different modalities. Patients' outcome was classified into recovery, recovery with morbidity, and mortality. The risk of morbidity and mortality concerning recovery was estimated corresponding to the levels of different factors using multinomial logistic regression. The unadjusted and adjusted risk estimates were obtained for each factor suggesting the likelihood of outcome corresponding to each factor level. All the analyses were carried out using SPSS ver 20.0 (IBM Corp. the USA) software and the statistical significance was evaluated at a 5% level.

Results

The study population included 104 patients with mucormycosis with a mean age of 49.23 ± 12.38 years (Table 1). The majority (80.8%) were male. All patients tested positive for COVID-19 either on RT- PCR (95.2%) or had a positive CT score. More than half of the patient's required hospitalization with a mean duration of hospital stay was 11.63 ± 6.33 days. Regarding COVID-19 treatment, steroids were administered to 75 (72.1%) patients, oxygen was required for 48 (46.2%) and antibiotic were used in 60 (57.7%) patients. There were only 9 (8.7%) patients on antifungal treatment. About 85 (81.7%) patients had a history of diabetes before presentation, and 19 patients were newly diagnosed with DM. The majority of the patients were on insulin or oral combination (81.2%) therapy. The mean duration of DM was 5.2 ± 6.8 years.

Table 2 provides the clinical signs and symptoms observed in mucormycosis patients at presentation. Majorly, of the patients had normal vital signs. There were 49% and 39.4% cases of eye ptosis and proptosis, respectively. Eyeball movement restriction was observed in 32 (30.8%) patients, 53 (51%) patients had facial discoloration, and 31 (29.8%) patients had pallor. As regards symptoms, the majority i.e., 82 (78.8%) patients had facial numbness, followed by 73 (70.2%) with facial swelling. Dental pain was observed in 35 (33.6%) patients, while 32 (30.8%) had blurred vision. Headache was present in 77 (74%) patients.

Table 3 provides the descriptive statistics for investigational parameters in mucormycosis patients at presentation. While hematological parameters were normal within the respective recommended ranges, the mean hemoglobin levels were lower. The mean blood urea level remained elevated.

Diagnosis of mucormycosis

KOH and histopathology techniques could detect mucormycosis in 29.8% of patients. KOH, histopathology, and fungal culture together were useful in the diagnosis of nearly one-fourth of the cases (Table 4). Overall, 74 (71.1%) patients were diagnosed positively on at least two modalities. CT/CBCT could exclusively detect the 8.6% of cases that remained undetected on any or all of the three methods.

Radiological and microscopic findings

Table 4 provides the radiological profile of patients on CT and CBCT. On CT-based classification of patients according to the number of sinuses involved, 63.5% had three or more sinuses involved. 38.5% Of the CBCT evaluations (Table 4) that could be performed on 53 patients, haziness, osteolytic changes, and bone loss were observed in maximum i.e., 16 (30.2%) patients Mucor involvement was mostly either rhino + maxillary or rhino + orbital (Table 4). There were 8 (7.7%) cases of rhino + maxillary + orbital + cerebral (ROCM) involvement. Nearly cultures from 43.3% of individuals displayed fungal growth comprising Rhizopus species, Mucoromycetes, Rhizopus arrhizus, Aspergillus fumigatus, Zygomycetes, and Fusarium species.

Risk evaluation

The risks of morbidity and mortality associated with different factors were obtained as shown in Table 5. The adjusted risk estimates indicated that in patients with DM had significantly higher odds of morbidity 8.30 [95% CI: 2.12, 32.5; p=0.002] and mortality 13.23 [95% CI: 1.67, 104.7; p=0.014] than non- DM patients. The risk of morbidity due to multiple sinus involvement observed on CT was more than twice compared to single sinus involvement; however, the finding remains statistically insignificant. CT findings indicated that the adjusted odds of mortality outcome were significantly lower i.e., 0.16 [95% CI: 0.03, 0.90; p=0.038] for patients with age < 50 years as compared to age ≥ 50 years. As regards mucor involvement, the risk of mortality was 8.37 [95% CI: 1.52, 46.09; p=0.014] times higher in patients with rhino + orbital involvement than patients with rhino + maxillary involvement.

Discussion

Mucormycosis is one of the most serious post-COVID-19 complications that have emerged in certain parts of India, particularly in Central India. [11] Our study findings demonstrate that diabetes mellitus is one of the major risk factors for mucormycosis. In our study, a total of 104 patients were admitted to the hospital with COVID-19-associated mucormycosis. A meta-analysis of 600 articles in non-COVID has shown diabetes mellitus as the most common predisposition and an independent risk factor for rhino-orbital-cerebral mucormycosis. [12]

COVID-19 is the primary infection. Mucormycosis is a secondary infection. Delta Variant of COVID-19 causes coagulopathies. [13] COVID-19 targets the beta cells of the pancreas and the beta cells are destroyed. [14] This results in glucose imbalance in the body which results in hyperglycaemia, along with low immunity of the patient due to cytokine storms from COVID-19 infection. [15] Patients are observed with sudden rise and fall of cytokine storm which may last for a period of 48hrs. this cytokine storm goes to peak levels and affects most of the anti-inflammatory regions causing a decrease in immunity and causing hypercoagulopathies. [16]

Hyperglycaemia stimulates fungal proliferation and also causes a decrease in chemotaxis and phagocytic efficiency which permits otherwise innocuous organisms to thrive in acid-rich environments. The hyperglycaemic state leads to the immunosuppression of these patients. [17] The altered phagocytic pathways in individuals with diabetes impair the ability to phagocytize fungal spores. [14] The mean Hb_{A1c} in our study was 9.88±2.51%, which shows that most of the patients had uncontrolled diabetes mellitus, which is a major independent risk factor contributing to Mucormycosis. There is an associated significantly high mortality (OR-8.3) and morbidity (OR-13.2) among diabetic patients compared to individuals without diabetes. Among our patient population with diabetes, a significant proportion (34%) were newly diagnosed with their diabetes post-COVID-19 infection.

Diabetes, when coupled with COVID-19–induced systemic immune change, results in decreased immunity and an increased risk of secondary infections. [18] [19] A recent systematic review of 15 studies confirmed the role of diabetes in CAM. Managing diabetes is thus crucial for controlling both COVID-19 and CAM. [20] [21]

In some patients, the newly diagnosed diabetes status could also be due to the destruction of insulin-producing beta cells of the pancreas by

SARS-COV-2. We believe that some of our newly diagnosed diabetic patients had been in a hyperglycaemic state for a long time to develop an immunosuppressive stage where fungal spores could flourish as soon as an infectious disease such as COVID-19 appeared. [22]

During the treatment of COVID-19 and its complications, the use of corticosteroids caused a decrease in lung inflammation, cytokine storm, and fever. [23] [24] These studies however neither confirm that corticosteroids are the sole independent risk factor nor eliminate them as a risk factor. Diagnostic confirmation can be obtained by (a) direct microscopy with slides mounted with potassium hydroxide, particularly when it is necessary to start therapy immediately; (b) fungal culture; (c) biopsy of the affected lesions with adequate precaution; (d) radiological (computed tomography of osteomeatal complex and magnetic resonance imaging with contrast) examinations. [25] [26]

This study shows the involvement of eye symptoms like proptosis, and ptosis, along with fixation of eye movements, and has also shown that these symptoms are more prevalent as the number of sinus involvement increases. The orbital apex syndrome leads to the worst prognosis and also causes advanced invasion in mucormycosis and represents a surgical emergency that usually warrants orbital exenteration. As the orbital apex syndrome involves infarcted neurovascular tissue and threatens extension into the cavernous sinus, urgent surgical intervention is needed. Orbital apex syndrome is described as the loss of vision from optic neuropathy and ophthalmoplegia because of the involvement of oculomotor nerves in the orbital apex, which causes signs and symptoms that are derived from the involvement of structures inside the orbital apex, superior orbital fissure, or the cavernous sinus. [27]

Patients with invasive brain involvement had higher morbidity and higher mortality. In our study, the spread of mucor had 50 (48.1%) rhinomaxillary, followed by 44 (42.3%) with rhino orbital. Fungal culture evaluations showed growth in 45 (43.3%) patients, which mainly comprised of Rhizopus species, Mucoromycetes, Rhizopus arrhizus, Aspergillus fumigatus, Zygomycetes, and Fusarium species.

Diagnosis based on at least two modalities of fungal culture, KOH, and histopathology could detect 74 (71.1%) patients. Nine of the patients who could not be diagnosed based on the above three modalities could be diagnosed based on CBCT findings. CBCT has been considered one of the best choices of examination for detecting Mucormycosis since it gives high-resolution imaging, diagnostic consistency, and risk-benefit assessment. [28] In our study, this was done in nearly half (50-65%) of the patients. CBCT have high sensitivity for detecting condylar osseous defects overall. [29] Therefore it is suggested that erosion of the condylar surface may be easier to detect from CBCT images than other morphologic changes. Using a higher scan resolution (0.2-mm voxel size), the defects, regardless of size, were detected with >80% sensitivity.[30]

A study that compared conventional tomography, CT and CBCT with micro-CT and microscopic observations and concluded that CBCT most accurately depicted erosive changes of the bone cortex of the mandibular condyle. The high detectability of CBCT images on bone morphology of mandibular condyles was confirmed. CBCT images most accurately depicted erosive change of the bone cortex of the mandibular condyle. [31]

Pneumatization of the temporal bone may be a tough diagnostic challenge for the assessment of cortical erosions in the articular eminence if it advances the articular surface, and CBCT is a much superior method to depict such anatomic variations [32]. Thereby early detection of bone degeneration can help in early removal to prevent an infection on avascularised tissue. For example, degeneration was found in the maxilla, maxillectomy was done. This avascular necrosis is caused in this case by Coagulopathies by Delta Variant COVID-19 infections. [33]

CBCT Scan helped in the early detection and diagnosis of mucormycosis thereby decreasing the mortality and morbidity significantly in our study. Early detection resulted in medical and minimal surgical interventions. CBCT showed osteolytic findings of mucormycosis has been highlighted in 16 (30.2%) patients, followed by haziness and osteolytic changes in 10 (18.9%) cases, and 9 (16.9%) patients showed osteolytic changes and haziness and bone loss each.

Out of 104 patients, mortality was seen in 17 (16.34%) patients, 64 (61.53%) patients with

morbidity, and 23 (22.11%) patients who recovered. Our study findings indicate an increased incidence and risk of morbidity in the younger population (<50 years) of infected individuals. One possible reason is due to delayed referral to our centre that the patients presented with advanced stages of the disease on presentation.

Studies suggest that patients with disseminated mucormycosis (68 %) have the highest case fatality and it is least in cutaneous mucormycosis (31%). [34] Disseminated mucormycosis tends to occur in people already sick from other medical conditions, making it difficult to identify the symptoms related to mucormycosis. Patients with disseminated infection in the brain develops mental status changes or coma. Cutaneous lesions resemble blisters or ulcers, which turn the infected area black with other symptoms like pain, warmth, excessive redness, or swelling around the wound.

Our study guides the early diagnostic assessment and timely administration of antifungal therapy in COVID-19 patients, who were at risk of developing rhino-orbital-cerebral mucormycosis. The medical treatment includes the use of Amphotericin – liposomal and conventional form of it. Before the advent of Amphotericin B, mortality rates associated with mucormycosis were as high as 90 percent. The disease continued to have high mortality rates, ranging between 50 to 80 percent. [35]

In our study, due to the sudden rise in several cases of mucormycosis and lack of availability of the liposomal form of Amphotericin, the patients were treated with combination therapy of liposomal and conventional forms of amphotericin as with other antifungals.

The role of amphotericin B is useful only when the necrosis has an aggressive infection from mucormycosis as per the Global guideline for the diagnosis and management of mucormycosis of 2021 [36] First-line treatment with liposomal amphotericin B 5–10 mg/kg per day is strongly supported across all patterns of organ involvement. If substantial renal toxicity develops, the dose can be reduced as necessary, but doses below 5 mg/kg per day are recommended with marginal strength only. [37]

Doses should not be slowly increased over several days; rather, the full daily dose should be given from the first treatment day. Amphotericin B lipid complex 5 mg/kg per day is recommended with moderate strength for patients without CNS involvement. [38] The use of amphotericin B deoxycholate is discouraged whenever alternatives are available. Isavuconazole is recommended with moderate strength for the first-line treatment of mucormycosis. The group marginally supports the use of posaconazole oral suspension, and moderately supports posaconazole delayed-release tablets and infusion for first-line treatment.

Isavuconazole is strongly supported as a salvage treatment. Posaconazole delayed-release tablets or infusions are strongly supported for salvage treatment, and when available should be preferred over posaconazole oral suspension, which in turn is marginally supported for salvage treatment. [36] If there is an indolent mucormycosis infection we use other antibacterial or antifungal drugs. Amphotericin B has predominantly used in the acute, invasive, and aggressive spread of necrosis in short duration and when the central nervous system and the sinuses are involved. Amphotericin B is not given for any chronic infections. [39]

Our study shows less mortality as compared to other studies, due to early diagnosis and a multidisciplinary approach (including an oral and maxillofacial surgeon, otorhinolaryngologist, ophthalmologist, infectious disease, physician, endocrinologist, intensive care team, and other specialties) towards the disease. The management also advocates using diagnostic imaging as a guide for both initial diagnoses and as a tool to delimit the infected zone and plan the boundaries of surgery. Thus, a multidisciplinary medical and surgical approach is needed for the successful management of mucormycosis. Perioperative and intraoperative direct examination, KOH smear, and cytology performed during the surgery accelerate the diagnosis and early treatment.

Conclusion

In summary, Rhino Orbital Cerebral (ROC) mucormycosis in the population with diabetes mellitus is still the most frequently reported clinical presentation of this infection. Diabetes mellitus is an independent risk factor for mucormycosis. The usage of corticosteroids to treat COVID-19 and its complications has possibly increased in mucormycosis cases. A multidisciplinary approach with the use of medical and surgical management improves the outcome of mucormycosis. Early clinical

diagnosis, specialized training in laboratory diagnostic mycology, multidisciplinary management, and timely antifungal therapy are important for the successful management of mucormycosis. Being a retrospective observational study, COVID-19 strains could not be evaluated which needs further research.

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Tables and Figures

Table 1: Descriptive statistics for general characteristics of mucormycosis patients

Characteristics	**Statistics**
N	104
Age in years [Mean ± SD]	49.23 ± 12.38
Sex [Male / Female] [No. (%)]	84 (80.8) / 20 (19.2)
History of diabetes [No. (%)]	85 (81.7)
Duration of DM in months [Mean ± SD]	62.72 ± 81.15
HbA1c* (%)	9.88 ± 2.51
Treatment	
Oral	16 (18.8)
Insulin and Oral	69 (81.2)
COVID-19 status of patients	
RT PCR positive‡ [No. (%)]	99 (95.2)
Hospitalization [No. (%)]	60 (57.7)
Days of hospitalization [Mean ± SD]	11.63 ± 6.33
Steroid intake [No. (%)]	75 (72.1)
O2 requirement [No. (%)]	48 (46.2)
Antibiotic intake [No. (%)]	60 (57.7)
Antifungal intake [No, (%)]	9 (8.7)

*At admission to hospital for mucormycosis; ‡5 patients were diagnosed as positive based on CT score.

Table 2: Clinical signs and symptoms in mucormycosis patients at presentation

Clinical signs		**Statistic**
Temperature (°F) [Mean ± SD]		98.10 ± 1.17
Respiratory rate (/min) [Mean (SD)]		22.13 ± 2.99
Pulse (/min) [Mean (SD)]		92.28 ± 13.42
Systolic BP (mmHg) [Mean (SD)]		129.44 ± 15.89
Diastolic BP (mmHg) [Mean (SD)]		82.03 ± 11.19
Eye ptosis [No. (%)]		51 (49.0)
Proptosis [No. (%)]		41 (39.4)
Eyeball movement restriction [No. (%)]		32 (30.8)
Maxillary sinus swelling [No. (%)]		18 (17.3)
Nasal discharge [No. (%)]		11 (10.6)
Facial discoloration [No. (%)]		53 (51.0)
Pallor [No. (%)]		31 (29.8)
Palatal discoloration [No. (%)]		12 (11.5)
Palatal necrosis [No. (%)]		8 (7.7)
RS [No. (%)]		1 (0.9)
Symptoms		
Facial		
	Numbness	82 (78.8)
	Swelling	73 (70.2)
Dental		
	Pain	35 (33.6)
	Loosening of teeth	18 (17.3)
	Bleeding gums	7 (6.7)
	Tooth loss	5 (4.8)
Ophthalmic		
	Blurred vision	32 (30.8)
	Loss of vision	11 (10.6)
	Diplopia	7 (6.7)
Others		
	Headache	77 (74.0)
	Stuffy nose	26 (25.0)
	Nasal discharge	7 (6.7)
	Loss of smell	6 (5.8)

Table 3: Descriptive statistics for investigational parameters at presentation

Parameters		**Statistics**
Haemoglobin (g/dl) [Mean ± SD]		
Male		11.39 ± 2.28
Female		9.74 ± 1.78
Total leukocyte count (cells/mm^3) [Mean ± SD]		11674.74 ± 5114.5
Platelet count ($10^3/mm^3$) [Mean ± SD]		280.65 ± 124.27
Serum creatinine (mg/dl) [Mean ± SD]		1.21 ± 1.16
Blood urea (mg/dl) [Mean ± SD]		34.86 ± 25.83
eGFR [No. (%)]	< 60	24* (23.1)
	> 60	80 (76.9)
Na (mmol/lt) [Mean ± SD]		135.41 ± 5.31
K (mmol/lt) [Mean ± SD]		3.90 ± 0.82
SGOT (U/L) [Mean ± SD]		29.28 ± 30.71
SGPT (U/L) [Mean ± SD]		30.11 ± 23.23

*eGFR < 15%: **3**; 15-29%: **3**; 30-59%: **18**

Table 4: Radiological and histopathological findings on patients at presentation

CT findings	No. (%)
Sinus involvement	
<=1	18 (17.3)
2	20 (19.2)
3	26 (25.0)
4	40 (38.5)
CBCT findings	
Haziness	7 (13.2)
Osteolytic change	9 (16.9)
Haziness + Osteolytic change	10 (18.9)
Haziness + Bone loss	9 (16.9)
Osteolytic change + Bone loss	2 (3.8)
Haziness + Osteolytic change + Bone loss	16 (30.2)
Mucor involvement	
Rhino + Maxillary	50 (48.1)
Rhino + Orbit	44 (42.3)
Rhino + Maxillary + Orbit	1 (0.9)
Rhino + Maxillary + Orbit + Cerebral	8 (7.7)
Pulmonary	1 (0.9)
Fungal culture	
*Fungal growth**	45 (43.3)
No growth	59 (56.7)

*Majorly includes *Rhizopus species*, *Mucormycocetes*, *Rhizopus arrhizus*, *Aspergillus fumigatus*, *Zygomytes* and *Fusarium* species

Table 5: Unadjusted and adjusted risk associated with different factors

Factor	Level	Unadjusted risk [95% CI; P-value]		Adjusted risk‡ [95% CI; P-value]	
		Recovered with morbidity	Mortality	Recovered with morbidity	Mortality
Age (years)	*<= 50*	Ref	Ref	Ref	Ref
	> 50	NS	NS	NS	0.16 [0.03, 0.9; **0.038**]
Sex	*Female*	Ref	Ref	Ref	Ref
	Male	NS	NS	NS	NS
Diabetes Mellitus	*No*	Ref	Ref	Ref	Ref
	Yes	5.26 [1.85, 14.93; **0.002**]	8.19 [1.51, 44.26; **0.014**]	8.30 [2.12, 32.5; **0.002**]	13.23 [1.67, 104.7; **0.014**]
Steroid intake	*No*	Ref	Ref	Ref	Ref
	Yes	NS	NS	NS	NS
O_2 requirement	*No*	Ref	Ref	Ref	Ref
	Yes	NS	NS	NS	NS
Mucor involvement	*Rhino + Maxillary*	Ref	Ref	Ref	Ref
	*Rhino + Orbital**	NS	8.75 [1.92, 39.78; **0.005**]	NS	8.37 [1.52, 46.09; **0.014**]
eGFR	*> 60*	Ref	Ref	Ref	Ref
	< 60	NS	NS	NS	NS
CT (Sinus involvement)	*None or 1*	Ref	Ref	Ref	Ref
	2	NS	NS	NS	NS
	3	NS	NS	NS	NS
	4	NS	NS	NS	NS

*Includes cases with maxillary and cerebral involvement; ‡All factors included in the *multinomial logistic regression* model

Figure 1: Diagnosis of mucormycosis patients