



Management of Mucormycosis in Post COVID-19 Patients and Its Outcome in a Tertiary Care Center: Our Experience

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Abstract To assess the common presentation and extent of disease involvement clinically and radiologically and treatment modalities, sequelae of the disease, complications and treatment response. Mucormycosis is a life-threatening infection that most commonly affects immunocompromised individuals and an exponential increase in the incidence of Rhino-orbital-cerebral mucormycosis was witnessed in the second wave of the COVID-19 pandemic, despite aggressive multimodal treatment carries a significant risk of mortality. A high index of suspicion is required in order to begin the appropriate diagnostic workup and treatment. This study is conducted to assess the outcome and management of mucormycosis in post covid 19 patients. The prospective study includes 180 Patients, who are attending to E.N.T. outpatient department, Triage and patients referred from other departments who had suspected/confirmed Rhino-orbital-cerebral mucormycosis/underwent surgery and/or medical treatment or both. In our study mucormycosis predominantly affected age group between 40 and 60 years, more common in males (77.8%) than females (22.2%), 77.8% patients had post covid status. Most common risk factor was diabetes mellitus. 76% patients had undergone endoscopic/open surgery and 24% patients underwent only medical treatment. Among 138 patients operated, 40% had recurrence and mortality was 16.1% (significantly reduced). Early diagnosis and prompt intervention is paramount to reduce morbidity and mortality. Liposomal Amphotericin B is most effective antifungal with manageable side effects. Patients who underwent Radical

debridement either endoscopically or open approach, had better outcome with minimal recurrence rates. Combined medical and surgical treatment has better outcome, lesser recurrence and mortality.

Keywords Mucormycosis · Liposomal Amphotericin B · FESS (Functional endoscopic sinus surgery) · ROCM (Rhino-orbital-cerebral mucormycosis)

Introduction

COVID-19 since beginning showed variation in its presentations, complications and sequelae [1]. Among various complications associated with COVID-19 that are being reported, the fungal infection mucormycosis (known as black fungus) becoming a serious issue in India due to its uncommon surge and high morbidity [2]. Mucormycosis is a fungal infection belonging to the family Mucorales [3]. *Rhizopus oryzae* is the most common organism isolated from mucormycosis patients and is responsible for 70% of all cases [3]. The major risk factors in patients with mucormycosis include uncontrolled diabetes mellitus with or without ketoacidosis and other forms of metabolic acidosis and immunocompromised conditions [3].

Intracranial spread of the fungus is rapid and progressive in nature, occurs either by direct extension across the bones like cribriform plate/ethmoid, walls of the frontal and sphenoid sinuses, or angioinvasion of the walls of the arteries and veins, causing microvascular thrombosis, occlusion and infarction [4].

Mucormycosis in the bone marrow may promote fungal growth by damaging the endothelial lining of vessels, resulting in vascular insufficiency and leading to bony necrosis and fungal osteomyelitis [2].

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Loose teeth, gingival abscess, swelling and vague facial pain are the usual clinical presentation. Due to varied and vague clinical presentation and other post covid 19 morbidities and lack of awareness among patients and clinicians, there is usual delay in diagnosis, which leads to patient running from pillar to post. Hence patient presented with delayed complications of this disease. Earliest sign of blackening of the posterior end of the turbinate's seen on diagnostic nasal endoscopy were followed by battery of radiological investigations, microbiological and histopathological sampling to confirm the diagnosis.

The use of high dose liposomal amphotericin B as a first-line treatment is strongly suggested, whereas intravenous Isavuconazole and intravenous or delayed-release oral tablet Posaconazole have also been advocated [2]. However, due to lack of availability and elevated cost also leads to increased morbidity and mortality in the initial phase.

This study was undertaken to assess the common presentation and extent of disease involvement clinically and radiologically and treatment modalities, sequelae of the disease, complications and treatment response.

Materials and Methods

Source of Data

180 patients who attended the department of Otorhinolaryngology OPD/triage/Causality and also referred from other departments for suspicious mucormycosis/skull base osteomyelitis with post covid status. Clinically/radiologically/microbiologically suspected mucormycosis were evaluated and treated.

Among the 180 patients, 100 patients were clinically suspected and were referred from surgical and medical departments, 50 patients from medical awareness/campaign, and 30 patients were of recurrent/incomplete treatment done elsewhere.

We devised a protocol based on the presentation and extent of involvement and were treated according to the following flow chart (Fig. 1).

On clinical suspicion a combination of CT and MRI was done. While CT helped in assessing the extent of bone involvement like orbital wall erosions, palatal erosions, sphenoid bone erosions and other sinuses wall erosions. MRI helped in assessing the soft tissue extensions into the pterygopalatine fossa, orbit, neural invasion, cavernous sinus, infratemporal fossa, orbital apex and brain.

Nasal swab for aseptate fungal spores was only for a provisional diagnosis to start antifungal therapy prior to surgery and also for radical or conservative surgical approach in addition to radiological assessment.

Antifungals mainly liposomal/Lipid complex Amphotericin B and Posaconazole were given, after a test dose and later escalation and titration of doses was done by monitoring of vitals/electrolytes/renal functions. Kidney injury was managed conservatively. Amphotericin was stopped 2–3 days prior to the surgery.

Based on CT/MRI and microbiology swab, surgical approach was planned accordingly. Depending on intraoperative extent of the disease and post operative histopathological confirmation of diagnosis, amphotericin was continued.

Antifungals were started on postoperative day 1 of surgery and were given a maximum cumulative dose up to 3–5 g and patients with CNS involvement were given up

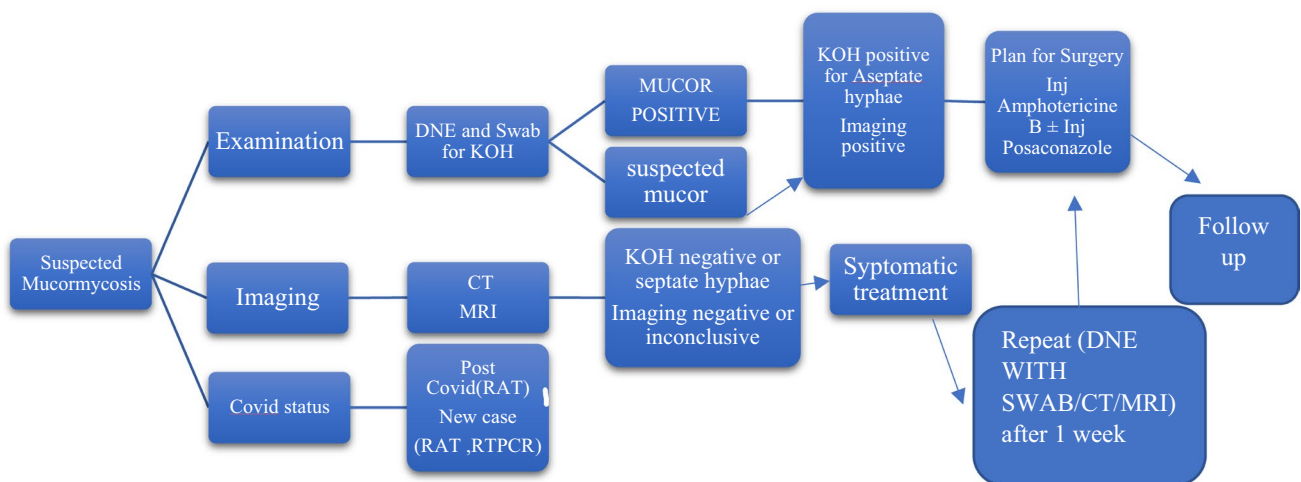


Fig. 1 Protocol

to 5–6 g. To complete the cumulative dose, it took approximately 30–50 days. 11.6% of patients were given retroorbital injection. 1 vial of amphotericin B (50 mg) reconstituted with 10 ml of sterile water, from this 0.8 ml containing 4 mg once daily retrobulbar injection given for 10 days.

Results

After the outbreak of COVID-19 from epicenter China, central city of Wuhan in 2019–2020, three waves were seen. Second wave had surge of mucormycosis, the cause for which is still being investigated but some study showed risk factors like diabetes mellitus, patients who were on aggressive steroid treatment. We being in a tertiary care center, we saw a lot of cases and operated around 138 cases, initially delay in diagnosis due to rarity and lack of education/awareness among patients, general populations and civilians. This unusual surge was investigated and diagnosed provisionally with radiological involvement of osteomyelitic changes respectively in nose / PNS / orbit/ skull base and lungs. Among 180 patients, the following results were obtained.

Our study reveals that mucormycosis predominantly affected age group between 40 and 60 years, more common in males (77.8%) than females (22.2%), 77.8% patients had post covid status, KOH mount was positive for mucormycosis in 75.6% patients, type 2 diabetes mellitus is a common risk factor present in all patients (100%), Diabetic ketoacidosis (DKA) seen in 62.8% patients, Electrolyte Imbalance seen 72.2% patients, hypertension (HT) seen in 71.1%. Other risk factor includes Smoking (72.2%), Alcohol consumption (27.2%), and Anaemia (2.2%) [as showed in Table 1].

In this study patients presented with Fever (72.2%), Nasal obstruction (69.4%), Nasal discharge (71.7%), Headache

(72.2%), Eye edema (71.7%), Loss of vision (70%), EOM fixed (71.7%), Proptosis (72.8%), Cheek swelling (72.2%), Palate involvement (70%), Facial nerve involvement (0.6%) and Trigeminal nerve involvement (0.6%) (Fig. 2).

180 patients received Amphotericin B, majority of patients developed adverse drug reactions (Table 2). The adverse drug reactions observed were fever (83%), chills and rigor (88%), Nausea and Vomiting (70%), Breathlessness (30%), Chest pain (20%), Electrolyte imbalance (72.2%), Anaemia (50%) and thrombophlebitis (78%) (Table 2).

In our study, the approach was according to the above-mentioned chart (Fig. 3). Out of 180 patients, 138 patients underwent surgery, almost all patients underwent FESS with debridement (100%), Medial maxillectomy (30%), Modified Denker’s/Caldwell Luc (21.7%), orbital decompression (69.4%), Clival/Retro sphenoid clival and other skull base approach (1.3%), Infratemporal fossa/ Pterygopalatine fossa (33.3%), Infrastructure maxillectomy (30%), TOTAL maxillectomy (15%), extended maxillectomy (7.24%) and Orbital Exenteration (7.25%) (Table 3). In 138 cases, initially FESS/EXTENDED FESS was done in 3/4th of cases, remaining cases and those who had recurrence of 40% underwent open approach and debridement, which includes different types of maxillectomy and debridement of infratemporal fossa, skull base and so on.

Discussion

Mucormycosis is an uncommon infection, it accounts for 8.3–13% of all fungal infections [5]. Post covid 19 pandemic, prevalence of mucormycosis in India increased

Table 1 Demographic distributions

Sl. No.			Frequency	Percent
1	Age	Range 3–82 years	Most prevalent in 40–60 years	
2	Sex	Female	40	22.2
		Male	140	77.8
3	Post COVID status	Absent	40	22.2
		Present	140	77.8
4	KOH	Absent	44	24.4
		Present	136	75.6
5	DM	Present	180	100
6	DKA	Present	113	62.8
7	Electrolyte imbalance	Present	130	72.2
8	HT	Present	128	71.1
9	Smoker	Present	130	72.2
10	Alcoholic	Present	49	27.2
11	Anaemia	Present	4	2.2

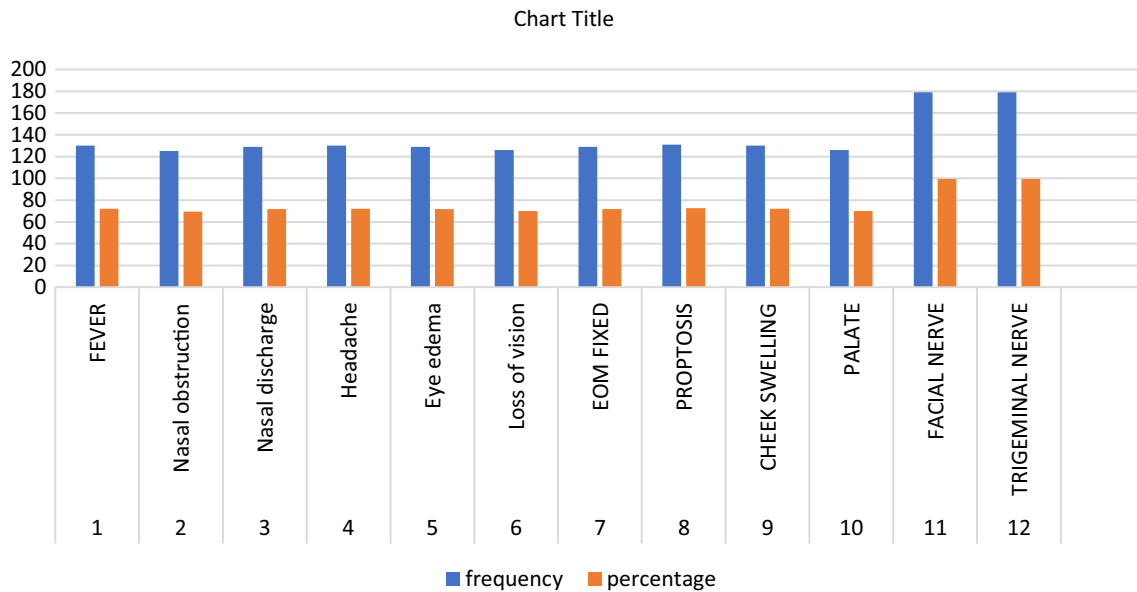


Fig. 2 Clinical features in our study population

nearly 80 times compared to that of previous that is 0.14 per 1000 population [6].

COVID-19-associated mucormycosis is characterised clinically as rhino-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, or other, and includes uncommon, rare manifestations such as endocarditis, osteomyelitis, and peritonitis. The rhino-orbito-cerebral (ROCM) variant is the most common in clinical practice around the world [7].

Depending on the extent of disease clinically, ROCM is classified into 3 stages –

- Stage 1—Rhino-maxillary mucormycosis (RMM).
- Stage 2—Rhino-orbital mucormycosis (ROM).
- Stage 3—Rhino-orbito-cerebral mucormycosis (ROCM).

In the Rhino-maxillary stage, nasal obstruction, nasal discharge is the most common presentation followed by facial pain, paraesthesia, fever, soft tissue swelling of the face and palatal ulcerations. In the rhino-orbital stage eyelid oedema, proptosis, ophthalmoplegia, blurry vision, loss of vision etc. While with intracranial spread (rhino-orbito-cerebral stage), in addition to the above symptom's patients have ophthalmoplegia, diplopia, altered sensorium, hemiplegia, loss of consciousness, fever, headache and vomiting.

Our study reveals that mucormycosis predominantly affected males (77.8%) and with mean age of 48.8 ± 5 , lowest age being 3 years and maximum age of 82 years. In a study by Twinkle Choksi et al. the mean age of patients was 53.5 (12.5 [range, 32–86]) years; 48 patients (66%) were men and 25 (34%) were women. [8]

The preliminary diagnostic tools used are DNE (diagnostic nasal endoscopy) with or without biopsy followed by nasal swab for KOH mount and the radiological investigations included CT scan and MRI.

MRI is the gold standard investigation for the diagnosis of Mucormycosis. It helped us to know the complete extent of the disease, also for earliest detection of soft tissue involvement, like involvement of pterygopalatine fossa, infratemporal fossa, pterygomaxillary fissure, retroorbital area, cavernous sinus and CT was performed in order to assess bony involvement [9]. In spite of the radiological changes being subtle and inconclusive in the early stages, evidence of retro-maxillary fat plane stranding and attenuation of the soft tissue in the CT scan and hyperintense lesion in the retro-maxillary area in an MRI, serve as early radiological pointers towards the diagnosis of mucormycosis.

Some studies states PET-CT is an effective tool for detecting and assessing treatment response [10]. However owing to its false positivity due to inflammation in post operative

Table 2 Adverse reactions to Amphotericin-B

Sl.no	Reactions	Percentage (%)
1	Fever	83
2	Chills and rigor	88
3	Nausea and vomiting	70
4	Breathlessness	30
5	Chest pain	20
6	Electrolyte imbalance	72.2
7	Anaemia	50
8	Thrombophlebitis	78

Fig. 3 Surgical management protocol

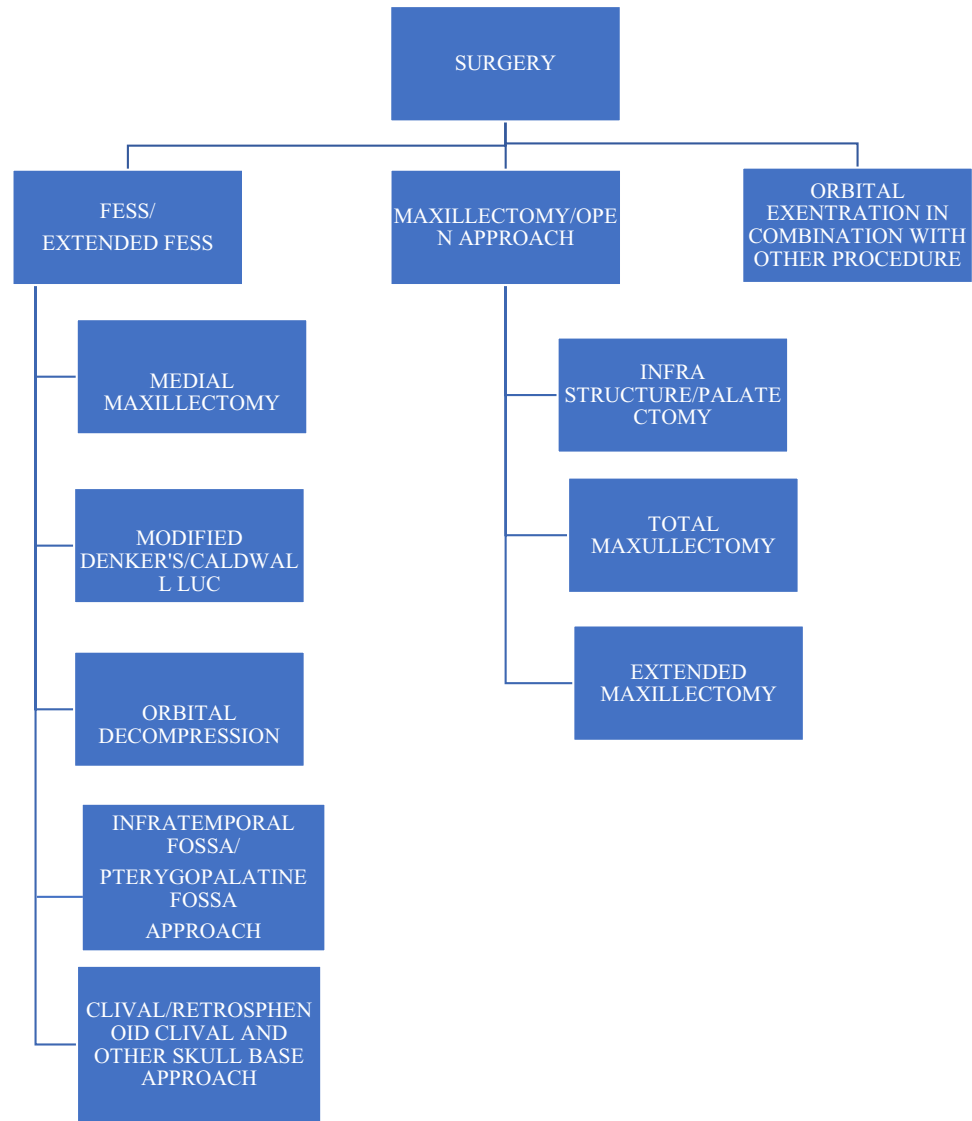


Table 3 Surgical management

Sl. No	Procedure	Frequency	Percentage
1	FESS with debridement	138	76
2	Medial maxillectomy	41	30
3	Modified Denker's/Caldwell Luc	39	21.7
4	Orbital decompression	125	69.4
5	Clival/Retro sphenoid clival and other skull base approach	2	1.3
6	Infratemporal fossa/Pterygopalatine fossa	60	33.3
7	Infrastructure maxillectomy	41	30
8	TOTAL maxillectomy	21	15
9	Extended maxillectomy	10	7.24
10	Orbital Exentration	10	7.25

period in patients and also not a cost-effective tool, it is not considered in our study. Thus, we have considered Diagnostic nasal endoscopy, biopsy, CT and MRI for most of our cases.

In our study maxillary sinus (90.7%) is commonly involved followed by sphenoid sinus (84%) ethmoid sinus (70.3%) and Frontal sinus (60%). Orbital involvement (minimal to gross) was present in 70% cases. Multiple cranial nerve involvement is seen in 4 patients.

The treatment protocol included medical, surgical and combined approaches.

Medical Management

The drug of choice for mucormycosis has always been liposomal amphotericin B but due to sudden surge of cases during the 2nd wave of covid 19 an acute scarcity in the

supplies was noted. Liposomal form being safest among all other forms, due to lack of availability, lipid complex and conventional forms were used initially and with subsequent adequate availability of liposomal form it was switched over to the same.

Antifungals was given after test dose. The escalation dose of antifungals was preferred. It was observed that Injection liposomal Amphotericin B was tolerated up to 300 mg/day in most of the cases, while other forms of Amphotericin B needed titration and intermittent treatment due to its systemic side effects mainly acute kidney injury, electrolyte imbalance and other constitutional symptoms like fever, chills, rigor and breathing difficulty.

Antifungals were started on postoperative day 1 of surgery and were given a maximum cumulative dose up to 3–5 g and patients with CNS involvement were given up to 5–6 g. To complete the cumulative dose, it took approximately 30–50 days.

A study by Laniado-Laborín et al. patients who required higher dose of Amphotericin-B had to undergo dialysis for kidney injury [11]. While in our setup, none of the patients who received high dose of Amphotericin and who had acute kidney injury needed dialysis. They were managed conservatively by titrating the dose and intermittent treatment.

Patients who were intolerant to Inj. Amphotericin-B were treated with Inj. Posaconazole. Some patients who were intolerant to both and postoperative patients who completed cumulative dose of Inj. Amphotericin B, were given Tab Posaconazole 300 mg for up to 3 months.

A study by Safi et al. on effectiveness of retrobulbar injections, showed favorable results 10 while in our study none of the patients showed any signs of improvement [10].

Surgery

The main aim of surgery is radical debridement of Rhino-Orbital-Cerebral mucormycosis (ROCM). But no clear guidelines are present with regard to this.

In our institute, depending on CT/MRI/microbiology swab and involvement of medial and posterior wall of maxilla, palate, orbital walls, sphenoid bone, orbital apex/cavernous sinus, extended FESS via modified denkers approach was done. Thoses patient with gross palatal involvement, masticator space, malar bone, infratemporal fossa, orbital apex, greater wing of sphenoid and skull base were planned for open approach.

During debridement, there was foul smelling discharge, purulent material, unhealthy mucosa, necrotic tissue which was dirty black/greyish white in colour, blackish eschar was noted. In such cases debridement was done up to the point where there was fresh bleeding and healthy mucosa/tissue/ bone seen. In majority of cases fungal debris was noted in

pterygopalatine fossa, even though PNS involvement was not extensive. Thus, all patients irrespective of involvement of PNS, posterior wall of maxillary sinus was opened to look for fungal debris in pterygopalatine fossa. In our observation, mucormycosis was more of peri-sinus disease; so, during surgery, we have to keep an eye on the soft tissue around the sinus rather than only within the sinus itself.

Patients with minimal orbital involvement underwent endoscopic orbital decompression with debridement of orbital tissue. Even in patients with fat stranding in the medial wall of orbit, endoscopic decompression was done, in cases where healthy fat tissue was seen, no further step was taken. In cases of necrosis or fungal debris with preserved vision, extensive but meticulous debridement was done using microdebrider to preserve the orbital structures and muscles (to prevent ophthalmoplegia). Some patients developed medial rectus injury, and recovered over a period of time. Orbital decompression was done in 3/4th of cases (69.4%).

Patients with retro-orbital necrotic tissue/fungal debris, recurrence of disease in the orbit, complete ophthalmoplegia and failed retrobulbar injection cases, all underwent orbital exenteration in subsequent sittings.

Some patients showed posterior extension into the pterygoid plates, basisphenoid and greater wing of sphenoid, required drilling of pterygoid plates and ridge, basisphenoid and greater wing of sphenoid and to debride disease around internal carotid artery and cavernous sinus. 22 patients had extensive involvement of greater wing of sphenoid, debridement and drilling of the same were done. Foramen rotundum and pterygoid canal was drilled till healthy tissue appeared. Necrotic maxillary nerve and nerve to pterygoid canal was noted. In our study, we opened cavernous sinus in two patients and fungal debris was evacuated.

In our study, we have done 30% infra-maxillectomy, 15% total maxillectomy, 7.24% extended maxillectomy. In open approach during maxillectomy, the necrotic bone was easily removed as it was already devitalized and thinned. Preoperatively, a dental impression was taken by dental (Prosthodontist) department for fabricating a temporary obturator, the same was placed during surgery/immediate postoperative day. At the time of discharge, temporary obturator was replaced by permanent obturator.

In our study, histopathological positivity for mucormycosis was seen in 70% of the tissue samples, 20% showed mixed infections (mucormycosis and aspergillosis), 10% showed chronic inflammatory disease.

Follow-up

For Post operative cases weekly once diagnostic nasal endoscopy was done till they were discharged. Once the

patients achieved complete mucosalisation of the cavity and attained a cumulative dose of antifungals, they were discharged. Later patients were reviewed, once a week for 3 weeks, once in 2 weeks for 3 months, later once in a month for 6 months.

During follow up we noticed no recurrence in first 1 month, 40% of patients had recurrence within 3 months. In 60% cases, follow up diagnostic nasal endoscopy showed healthy mucosa, no discharge/necrotic bone/tissue with no orbital involvement whereas in recurrent cases showed necrotic tissue/bone/purulent discharge in the nasal cavity, along with orbital symptoms like gradual loss of vision, ophthalmoplegia, headache and fever. In suspicious of recurrence/residual disease radiological investigation MRI was done. Among these 10.86% patients underwent infrastructure maxillectomy/Palatectomy, Orbital Exenteration (12.31%), total/extended maxillectomy (8%) and Infratemporal fossa/Pterygopalatine fossa (8.69%).

Outcome

Sl. No.			Frequency	Percentage
1	Follow up at 1 month	No recurrence	0	0
2	Follow up at 3 months	Recurrence	55	40
3	Follow up at 6 months	No recurrence	0	0
	Recurrence treatment	infrastructure maxillectomy/Palatectomy	15	10.86
		Orbital Exenteration	17	12.31
		Total/extended maxillectomy	11	8
		Infratemporal fossa/Pterygopalatine fossa	12	8.69
4	Outcome	Death	29	16.1
		Good	151	83.9

Mortality

Prior to Amphotericin, mucor mycosis was uniformly fatal [12]. Presently, with early diagnosis and prompt aggressive intervention the mortality decreased to 50%. With extensive surgical debridement and complete course of injection Amphotericin-B (antifungal treatment), the mortality was around 16.1% in our study, which is quite low.

Most of the patients who succumbed were due to gross involvement of brain and those who had electrolyte imbalance, acute cardiac events, poor cardiac status and one patient had rupture of internal carotid artery intraoperatively and died on 2nd post operative day.

In a study by Mrityika Sen et al. [10] Santosh G Honavar et al., a retrospective study in 2826 patients, ROCM is a rapidly progressive disease, with 30–90% mortality rate in cases with cerebral involvement. For cases associated with COVID-19, the overall mortality has been estimated to be 31% [10].

Jeong et al. [13] study showed overall mortality of 46%, out of which the highest was in disseminated mucormycosis (68%) and least in cutaneous mucormycosis (31%) [13].

Study by Hong et al. [14] Mortality in ROCM (43%) ranged from 34 to 75% with Sino-cerebral having the worst mortality (75%) [14].

Conclusion

In our study, the most common risk factors were post covid status, diabetes mellitus and underlying systemic conditions. The most common type was Rhino-orbital mucormycosis, presented with facial swelling, pain, orbital oedema and nasal discharge. MRI is the gold standard to know the extent of disease and to know the recurrence; CT was done to check for bony involvement. Liposomal Amphotericin B is the most effective antifungal with minimal side effects. Extended FESS with Maxillectomies and thorough debridement had better outcome with minimal recurrence rate. Most of the cases had histopathological confirmation of chronic fungal infection, with aseptate hyphae suggestive of mucormycosis. Combined medical and surgical treatment has better outcome, lesser recurrence and mortality. The main emphasis should be on the prolonged postoperative care and on regular follow up.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest to declare that are relevant to the contents of this article.

Ethical Approval Ethical approval was waived by the Institutional Research Committee VIMS in view of retrospective nature of study and all procedures being performed were part of routine care.

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