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**Original Research Article**

# Per-operative evaluation of destructive pattern of COVID associated rhinocerebral mucormycosis

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## ABSTRACT

**Background:** The rapid global spread of Coronavirus disease led to declaration of COVID-19 as a pandemic on March 11,2020. Secondary infections are reportedly common in hospitalized, severely ill COVID-19 patients, encompassing between 10 and 30% of cases, fungal being 10 times more common. Mucormycosis is amongst the most fulminant form of zygomycosis caused by mucorales species of the phylum zygomycota and currently referred as COVID associated mucormycosis (CAM). The aim of this study is to evaluate the extend and pattern of destruction in nose, paranasal sinus and orbit found during the surgical debridement of post COVID hyperglycemic patients of mucormycosis.
**Methods:** This prospective observational study was done on a random sample of 86 patients who came to ENT OPD of a tertiary care centre of middle India with clinical, radiological or histological findings suggestive of CAM. These patients underwent aggressive surgical debridement followed by antifungals and strict control of diabetic mellitus. The extend and pattern of destruction caused by CAM in nose, paranasal sinus and orbit noticed peroperatively were analysed.
**Results:** Out of the 86 patients who got operated, there are 62 males and 24 females patients aged from 28 to 86 years. The left side was involved in 41 patients, and the right side in 66 patients. Among the nasal involvement, middle turbinate (56) was maximally involved followed by inferior turbinate (52), superior turbinate (1), septum (17) with posterior septum mostly involved, floor of nose was involved in (4) patients. The orbit was involved in 28 cases in which lamina papyracea was eroded in all cases followed by inferior orbital wall, orbital muscles, optic nerve. Cribriform plate was eroded in 3 patients. The overall extent of involvement of mucormycosis is as follows maxilla (86), ethmoid (71), frontal (29), sphenoid (30), septum (17), orbit (28), alveolus (5), palate (10), intracranial (9), subcutaneous phycomycosis (10).
**Conclusions:** Management of CAM is really challenging which needs a multidisciplinary approach that includes aggressive surgical debridement, aggressive medical therapy with Amphotericin B and correction of the predisposing factors primarily diabetics mellitus

**Keywords:** COVID associated mucormycosis, Surgical debridement, Amphotericin B, Recurrence

## INTRODUCTION

The rapid global spread of the Coronavirus disease led to the declaration of COVID-19 as a pandemic on March 11, 2020 (Organization, 2020). As India continues to achieve stability over the existing situation, another imminent threat has emerged as a challenge to India in the form of coronavirus disease-associated mucormycosis. Mucormycosis called black fungus is caused by fungus of the order Mucorales and is one of the most rapidly fatal fungal infections known. These infections are opportunistic that they occur when

organisms to which we are frequently exposed gain entry into the body due to decreased host defenses or through an invasive portal, such as dental extraction. The incidence of mucormycosis has risen more rapidly during the second wave as compared to the first wave of COVID-19. Drugs like corticosteroids i.e., methylprednisolone and dexamethasone are believed to modulate inflammation mediated lung injury and thereby reduce progression of respiratory failure in COVID-19.[1] But their inadvertent use leads to increased incidence of side effects like secondary infections, diabetics mellitus etc in post COVID patients. High incidence of mucormycosis is seen in uncontrolled diabetic patients, because they produce the enzyme ketoreductase, which allows them to utilize the patient's ketone bodies. It is also likely that the hyperglycemia stimulates fungal growth and the reduced chemotaxis and phagocytic efficiency permit innocuous organisms to proliferate.[2] Mucormycosis usually occurs in one of the following four clinical forms-rhinocerebral, pulmonary, gastrointestinal, or disseminated. Rhinocerebral form is further subdivided into rhino-orbito-cerebral form which is invasive and may involve the ophthalmic and internal carotid arteries and rhino-maxillary form which involves the sphenopalatine and greater palatine arteries, resulting in thrombosis of the turbinate and necrosis of the palate.[3,4] Nearly 40-70% of all reported cases manifest signs and symptoms involving facial and oral tissues. A black necrotic eschar is the most characteristic and pathognomonic lesion. Other sites of oral lesions include gingiva, lips, alveolar ridge, palate, cheeks, tongue, and mandible. Necrosis of the maxilla is usually rare due to its rich vascularity.[5,6] Early aggressive surgical debridement is important for successful management of CAM which can be done endoscopically or through an open approach. The goal is to remove all the necrotic tissue until fresh bleeding is encountered facilitating the penetration of antifungals. Repeated debridement may be needed until clinical improvement is established.

## METHODS

### *Study area and target population*

This prospective observational study was done on 86 patients who got operated for COVID associated mucormycosis in a tertiary care centre of middle India (NSCB MCH, Jabalpur) between May 2021 to June 2021.

### *Study design*

This is a prospective observational study.

### *Inclusion criteria*

Patients given consent for the study, patients clinically, radiologically or histologically suggestive of mucormycosis and patients undergone surgery for CAM in the present institution during the time period

### *Exclusion criteria*

Patients who denied surgery, patients in inoperable stage and patients who had been operated from other institution.

### *Data collection*

Patients with clinical, radiological or histological findings suspicious of CAM posted for surgical debridement were included in the study. Detailed history regarding the COVID infection, symptoms, hospitalisation, predisposing risk factors for mucormycosis and the medication details were taken. Diagnostic nasal endoscopy performed in all cases which showed details of nasal cavity and nasopharynx and smear taken for microbiological evaluation. Ophthalmological consultation was done in all cases to find loss of vision and fundus examination. Computed tomography (CT) scan of the nose and paranasal sinuses and T2 weighted fat supressed gadolinium enhanced MRI was done to evaluate the extent of disease. CBCT done to evaluate the status of maxilla and mandible. All had undergone radical debridement via endoscopic sinus surgery alone or in combination with traditional open procedures. In patients with intracranial involvement, after nasal debridement, the patients transferred to neurosurgery department for neurosurgical clearance. Suspicious tissue had been sent for histopathology, KOH mount, fungal culture and pus for culture and sensitivity. Liposomal amphotericin B had been administered to the patient and the Dose calculated as per the weight of patient, the extent of disease and renal parameters of the patient. The patients had been kept on frequent follow up.

The preoperative findings in nose, paranasal sinus and orbit along with the details of operative procedures performed were entered in Microsoft excel and analysed. Analysed data was presented in the form of frequency and percentage shown by pie and bar chart.

### *Ethical approval*

Ethical approval for this was obtained from the institutional ethics committee

### *Statistical analysis*

The data collected was entered in Microsoft excel and analysed. Analyzed data was presented in the form of frequency and percentage shown by pie and the bar chart.

## RESULTS

Out of the 86 patients got operated, there are 62 male and 24 female patients (Figure 1), aged from 28 to 86 years. The mean age of the patients in this study was 45.5 years (Figure 2).

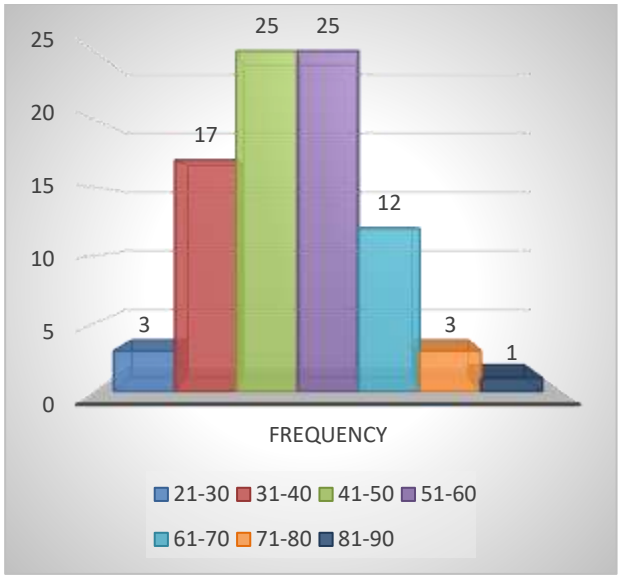


**Figure 1: Age wise distribution of post COVID mucorpatients.**

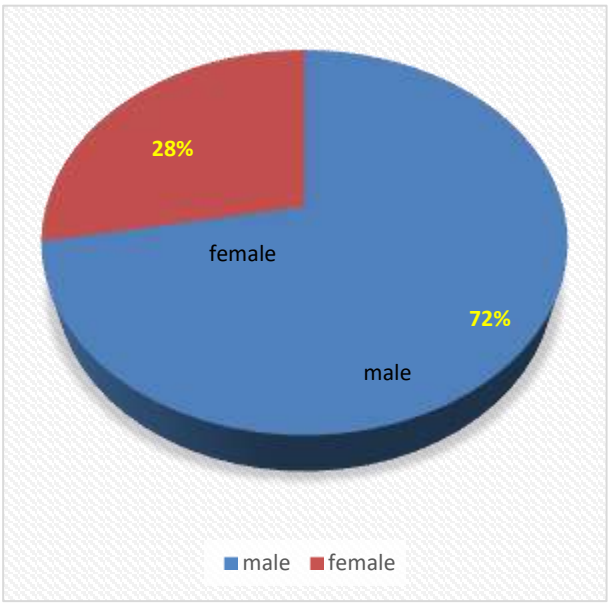


**Figure 2: Sex wise distribution of post COVID mucormycosis.**

Out of 86 cases, unilateral disease was found in 60 cases and bilateral disease in 26 cases. The left side was involved in 41 patients, and the right side was involved in 66 patients (Figure 3). There were 58 patients with Stage 1 disease, 19 patients with stage 2 and stage 3 disease in 9 patients. During the initial evaluation, sinonasal symptoms were present in all patients. These included facial numbness, palatal ulceration, bloody rhinorrhea, loosening of teeth, anosmia etc. the 28 patients had orbital problems, such as ptosis, proptosis, fixed eye, or loss of vision. Regarding predisposing factors, all patients were diabetic and post COVID. Among the nasal structures middle turbinate was involved in (56) cases followed by inferior turbinate (52), superior turbinate (1) and septum (17) with posterior septum mostly involved, floor of the nose was involved in 4 cases (Figure 4).

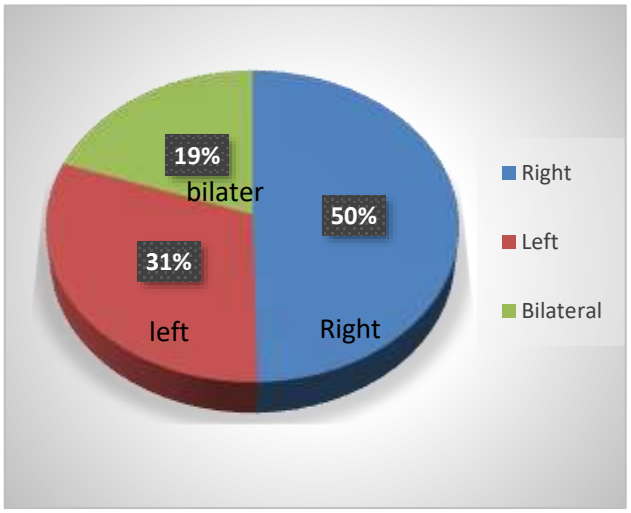


**Figure 3: Laterality of involvement of post COVID. mucormycosis.**

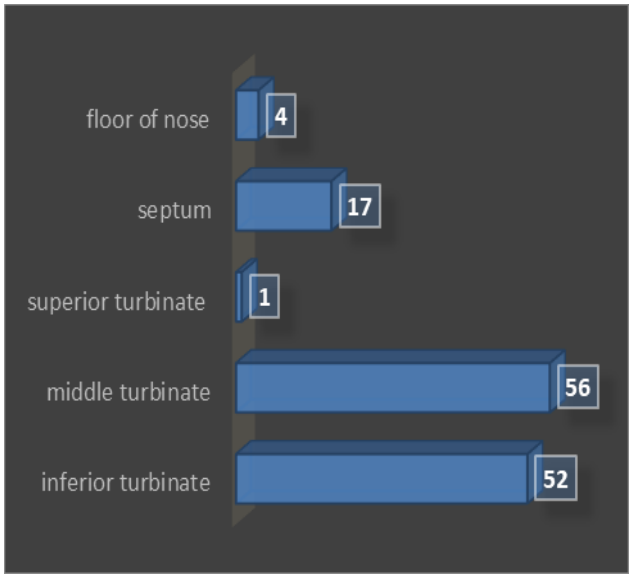


**Figure 4: Nasal involvement of post COVID mucormycosis.**

Among the paranasal sinus involvement, right maxillary sinus was involved in 60 patients and left in 26 patients, bilateral involvement in 19 patients, dead mycotic debris was seen in antrum around 80% cases. The antrum, anterior and medial wall of maxillary sinus was involved in most cases. Anterior ethmoid was involved in (71 patients) with bilateral involvement in 10 patients. Posterior ethmoid was involved in (62) patients with bilateral involvement in 8 patients. Frontal sinus was diseased in (29 patients) and sphenoid sinus in (30 patients). Out of 86 patients, pterygopalatine fossa was involved in (18) patients and infratemporal fossa in (12) patients. Pterygoid plate was diseased in 24 patients (Figure 5).

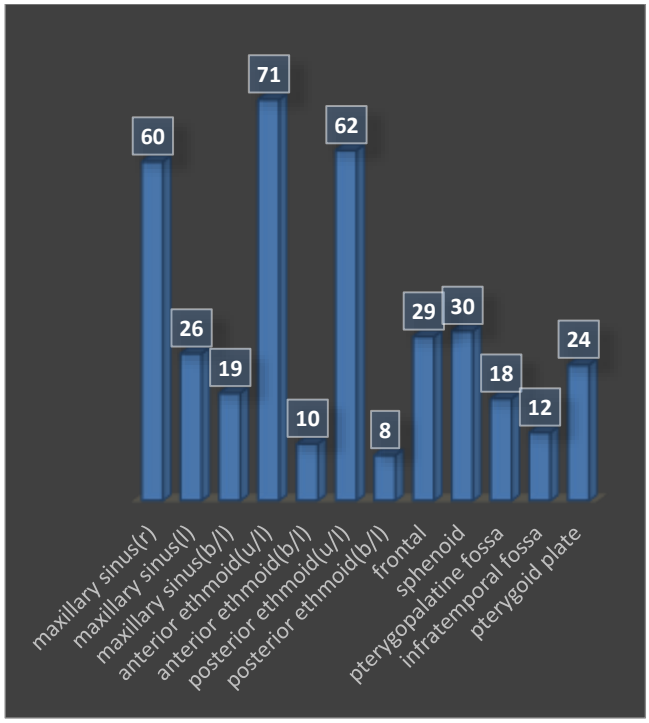


**Figure 5: Paranasal sinus involvement in post COVID mucormycosis.**

Out of the 28 patients with orbital involvement, medial orbital wall or lamina papyracea was eroded in all patients, orbital floor was involved in (20 patients) and orbital muscles in (9) patients in which inferior and medial rectus were mostly involved, optic nerve up to the extent of orbital apex engulfed with mycotic tissue in 7 patients and the cribriform plate was eroded in 3 patients. Infraorbital nerve was the commonest route of spread of infection to the orbit (Figure 6). Pus was seen behind the periorbita in around 6 cases. Foramen rotundum and vidian canal was involved in 6 patients.

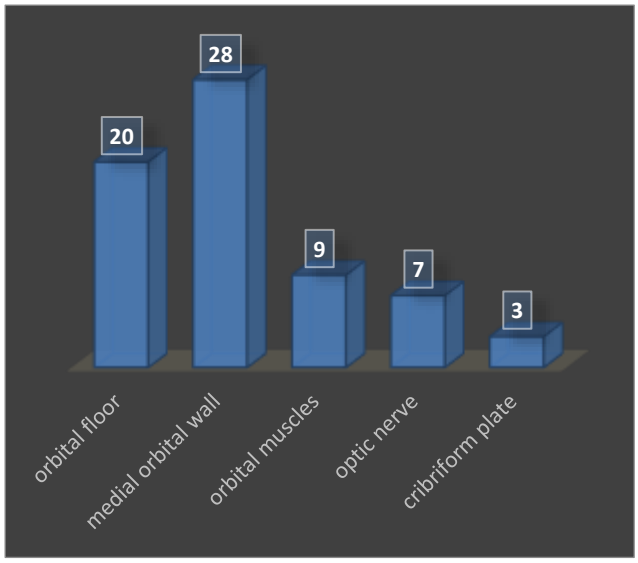


**Figure 6: Orbital involvement in post COVID mucormycosis.**

The overall extent of destruction of mucormycosis is as follows maxilla (86), ethmoid (71), frontal (29), sphenoid (30), septum (17), orbit (28), alveolus (5), palate (10), intracranial (9), subcutaneous phycomycosis (10).

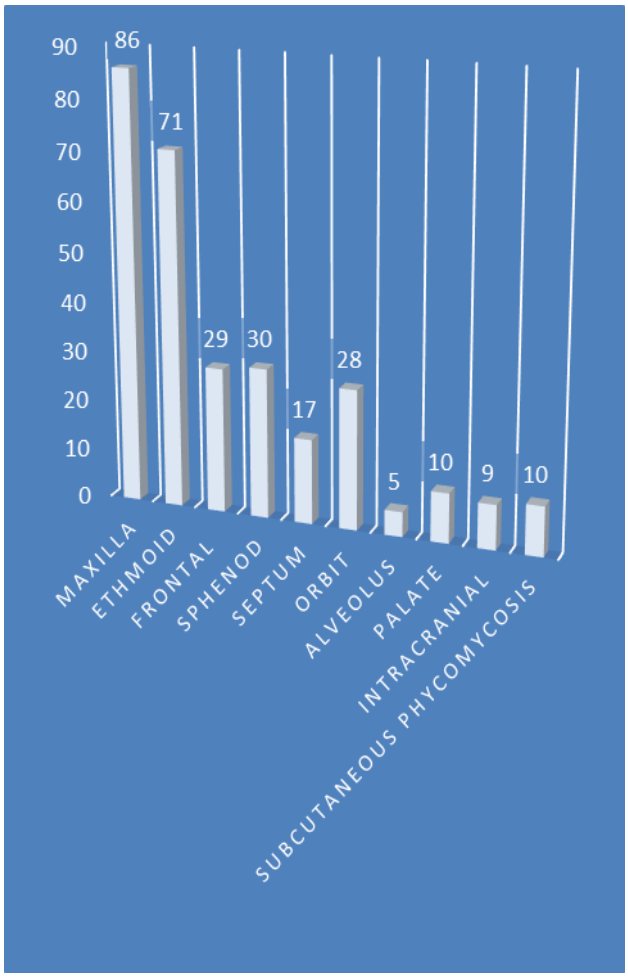


**Figure 7: Extent of involvement of post COVID mucormycosis.**

Endoscopic sinus surgery alone or in combination with other open surgeries performed for the complete debridement of the disease. Caldwell luc surgery combined with endoscopic nasal debridement performed in 61 patients. Uncinectomy done in 28 patients. Septectomy (21), turbinectomy (59), anterior ethmoidectomy (74), posterior ethmoidectomy (63), medial maxillectomy (36), inferomedial maxillectomy (7), alveolectomy (5), palatal curettage or resection done in (10) patients, orbital decompression in 20 patients (Figure 8). Out of 3 patients with cribriform plate erosion,2 cases were locally repaired with fat by ENT while the third one with large defect required neurosurgical repair. Around 3 patients developed temporal lobe abscess and had been successfully drained by neurosurgical department. The 12 patients had recurrence and had undergone revision surgery. The most common sites of recurrence were palate, alveolus, pterygopalatine fossa and zygoma.

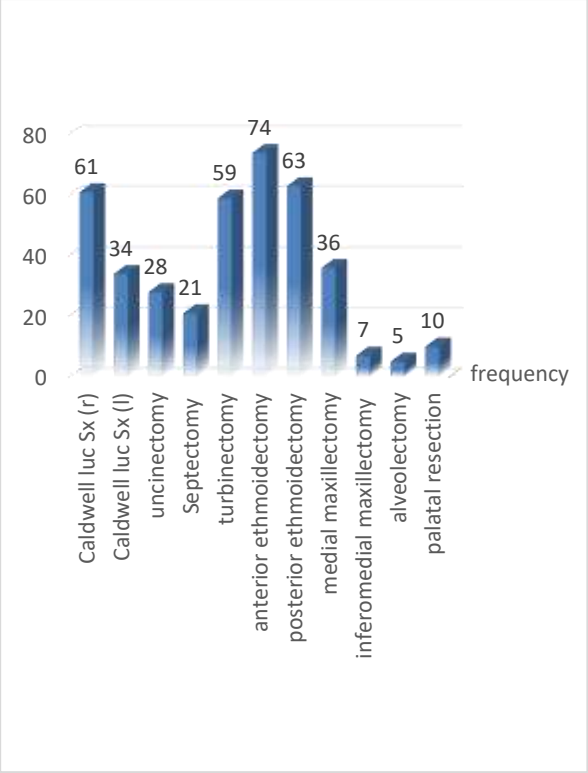


**Figure 8: Operative procedures in mucormycosis.**

## DISCUSSION

Infection with zygomycetes can be acquired by inhalation, ingestion or the deposition of spores in wounds. Under metabolic hypoxic state as often found in patients with mucormycosis associated with diabetes mellitus, polymorphonuclear cells are less effective at removing the hyphae, thereby abetting establishment of the infection. The fungus has a propensity to grow along the elastic lamina of the blood vessels, dissecting the lamina away from the media. This direct invasion and dissection by the fungus causes extensive endothelial damage, resulting in thrombus formation and ischaemia to the surrounding tissues. The infarcted tissue creates an environment that promotes fungal proliferation and the resultant poor vascular supply prevents systemic medical therapy from eradicating the fungus.

The incidence of mucormycosis in head-and-neck region is not related to sex or age generally.[7] But in our study male:female ratio is 2.6:1 with mean age is 45.5 years. As the age advances the increased incidence of diabetics and weaker immune system might have contributed to it.

In rhinocerebral mucormycosis the infection typically starts in the nasal or maxillary sinus and spreads to the sphenoid or ethmoid sinus frontal sinus seldom involved.[8] An area of ulceration or an extraction socket in the mouth can be a port of entry for mucormycosis into the maxillofacial region, particularly when the patient is immunocompromised. The fungus forms a layer on the surface of paranasal sinus walls (hollow air spaces), it doesn't go into the tissues directly. It first grows in the walls of the sinuses and from there it starts taking nutrition from the walls of sinuses and begins invading the blood vessels, causing blockage in blood vessels and thereby causing ischemic necrosis of distal area. This is also the reason why the drugs given or even injected intravenously do not reach the body of the fungus and thus, surgical debridement is needed. The vessels mostly involved are internal maxillary arteries, sphenopalatine and greater palatine artery. The sphenopalatine artery divides in two branches: "nasopalatine artery," which supplies the nasal septum and "posterior nasal artery," supplying the turbinates. This account for the involvement of turbinates and septum in CAM. Hard palate is usually affected because of its proximity to the infection of the nasal cavity, paranasal sinuses and due to involvement of greater palatine artery which is a branch of internal maxillary artery. Isolated intraoral involvement is extremely rare.[9] In the present study turbinates were mostly involved followed by septum and floor of nose.

Orbital extension of mucor was observed in 28 cases. Fungus can invade the orbit either through the ethmoid foramina, nasolacrimal duct or via dehiscence of the lamina papyracea.[10] Upon invasion the fungus can affect the orbital muscles, optic nerve and orbital apex structures causing opthalmoplegia, conjunctival chemosis, proptosis and diplopia. In the present study lamina papyracea was eroded in all cases and infraorbital nerve was observed as the commonest route of spread of infection to the orbit. Among the orbital muscles medial rectus and inferior rectus were commonly involved. In the present study in 6 cases, foramen rotundum and vidian canal was filled with mycotic tissue. Due to the angio-invasive property of fungus, it can invade central retinal artery or ophthalmic artery leading to central retinal aryery occlusion or ophthalmic artery occlusion leading to blindness. Once inside the orbit infection can spread to the brain via Superior orbital fissure or via orbital apex or orbital veins, causing cavernous sinus thrombosis, carotid cavernous sinus fistula, temporal/frontal lobe abscess, local multiple occlusive strokes or carotid artery thrombosis. Once brain involvement occurs, the prognosis of the patient is extremely poor. In the present study cribriform plate was eroded in 3 patients and temporal lobe abscess developed in 10 patients.

Aggressive surgical debridement has been the classic treatment for rhinocerebral mucormycosis.[11] It is feasible to use ESS to debride the diseased tissue in most cases completely, especially early cases. Endoscopic endonasal medial maxillectomy was performed in patients with initial stage disease confined to the lateral wall of nose, maxillary antrum, medial orbital wall, ethmoid, frontal and sphenoid sinus. In patients with extensive involvement of medial orbital wall, anterior and lateral wall of maxillary sinus, endoscopic procedure was supplemented with Caldwell luc/ denkers approach. In patients with pterygopalatine fossa and pterygoid plate

involvement, the area was exposed via endoscopic medial maxillectomy or wide middle meatal antrostomy. Few cases with extensive involvement of pterygopalatine and infratemporal fossa involvement, sublabial approach was made. Perineural spread along the maxillary division of trigeminal nerve was observed in 10 cases which was partially resected by clearing around the foramen rotundum.

Orbital involvement was seen in 28 cases in which lacrimal sac was diseased in around 12 cases. Lamina papyracea was eroded in 20 cases which was flaked off with frees elevator and orbital periosteum was palpated. Pus was seen behind the periorbita in 6 cases which was drained by making multiple incisions over the periorbita and thus medial orbital decompression done. Orbital floor was involved in 20 patients and the lateral wall of the orbit seemed diseased in 1 recurrent case which was cleared via subciliary/ weber ferguson approach. Fungal debris encircling the optic nerve posterior to globe was seen in 7 patients which was removed with cold instruments. The 3 patients having extensive orbital involvement with pus around the optic nerve and periorbita, with no vision were transferred to ophthalmology department for orbital exenteration.

In patients with extensive involvement of maxilla, zygoma and orbital floor had undergone total maxillectomy which was done in three recurrent cases. Alveolar process of maxilla and palate was involved in few cases where inferior maxillectomy was done via sublabial and palatine incision. When there was bilateral involvement midfacial the de-glowing approach is the made.

Cribriform palate was eroded in 3 cases. Two cases with smaller defect was repaired with fat and nasal mucosa from the turbinate. The other case with larger defect was repaired by neurosurgeon with fascia lata and overlaid with fat and secured with fibrin glue, supported by folleys catheter with bulb inflated *in situ*. Temporal lobe abscess developed in 3 cases. After clearing the nas-orbital part, the patients had been transferred to neurosurgical department for abscess drainage.

Decisions about the timing and extent of debridement are often made at the bedside. Although radical surgical debridement of infected tissues usually results in higher rates of survival, the value of such surgery in the treatment of intracranial disease remains questionable. The intracranial surgery may cause loss of vision in the non-involved eye, and the surgery that is necessary to treat CROM remains generally disfiguring and may have severe psychological ramifications for the patient. However, reconstructive surgery following the complete resolution of the infection (which may be performed in several steps) and other restorative measures may offer some solace to the patient.

***Limitations***

Since it is a short duration study, the long term sequalae following the surgical debridement of CAM and the recurrence pattern were not evaluated.

## CONCLUSION

Management of CAM is really challenging. After the surgical debridement, controlling the underlying metabolic disorder, in most of our patients it is diabetics mellitus was a big challenge, followed by recurrence which was observed in 12 cases. Most commonly recurrence was found in palate and alveolus. In the present study the destructive pattern was observed more in nose and paranasal sinus followed by orbit, palate and intracranial. A multidisciplinary approach with aggressive surgical debridement, aggressive antifungal therapy, correction of the predisposing factors primarily diabetics mellitus and close follow up of the patients are equally important. This fungal infection is characterized by a rapid progression to disseminated infection and a high mortality rate, which is why early diagnosis and timely intervention lead to a better outcome.

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*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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