ONLINE JOURNAL OF BIOLOGICAL SCIENCES

CASE SERIES

# Surge of Mucormycosis in the Jaws Among COVID-19 Patients: A Case Series Highlighting the Role of Diabetes and Immunosuppression

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**Abstract:** Mucormycosis is a life-threatening fungal infection caused by Mucorales species, frequently occurring in immunocompromised patients. This case series investigates the alarming rise in maxillary mucormycosis among post-COVID-19 patients in India and explores its correlation with uncontrolled diabetes and immunosuppressive conditions. This case series analyzed 52 patients, primarily with maxillary infections, to identify the association between COVID-19 and mucormycosis. Diagnostic methods included CT, MRI, and fungal cultures. Despite a low culture positivity rate, these combined methods were critical in assessing the infection and managing treatment. The study highlighted challenges in distinguishing infected tissues from healthy ones during surgical procedures. The study found that mucormycosis in COVID-19 patients led to severe complications, including sepsis and meningitis, often resulting in fatalities. Effective treatment strategies involved surgical debridement, antifungal therapy, and strict diabetes control. Early diagnosis and management were critical in reducing the risks of fatal outcomes. This study underscores a significant correlation between post-COVID-19 mucormycosis and pre-existing comorbidities, particularly diabetes mellitus. Early intervention combining radiological imaging, surgical debridement, and antifungal therapy is critical to improving clinical outcomes. The findings warrant further prospective studies to establish targeted prevention and treatment protocols.

**Keywords:** Mucormycosis, COVID-19, Maxillary Infections, Fungal Infections, Diabetes and Immunosuppression

**Received:** 02-06-2025 | **Revised:** 15-08-2025 | **Accepted:** 07-11-2025 | **DOI:** 10.3844/ojbsci.2026.26.01.025

## Introduction

The rare fungal infection known as mucormycosis is caused by coming into contact with mucor mold, which is found in many places, including soil, decomposing organic matter, and even healthy people's nasal mucosa. This pathogen primarily targets the sinuses, brain, and lungs, posing a significant risk, especially for those with diabetes or a compromised immune system [1,2]. The year 2020 marked a challenging period for global health due to the rapid spread of a novel virus, highlighting the vulnerabilities within healthcare systems worldwide. Amidst the ongoing battle against COVID-19, health authorities globally faced hurdles in delivering essential services while attempting to vaccinate populations against the virus and its emerging variants. Laxing attitudes toward preventive measures such as social distancing and mask-wearing have become more noticeable. Despite a decreasing trend in COVID-19 cases in India, a fierce second wave led to daily cases exceeding 300,000. By June 7, 2021, India reported 28,252 mucormycosis cases, with a significant number linked to COVID-19 and diabetes, recording the highest single-day spike of 6,329 cases [3]. Despite previous high infection rates, the rapid virus spread in India has surprised scientists, with daily cases soaring since early March 2021. Other countries, including France, Germany, Brazil, and the United States, are also experiencing significant outbreaks [4]. The increase in the number of cases in India has significantly contributed to global COVID-19 statistics, with nearly half of the recent cases worldwide and a quarter of the deaths reported from the country [4]. The global incidence of COVID-19 remains at its peak, with over 175 million new cases reported weekly [5]. Currently, the WHO is monitoring four variants of concern, namely, B.1.1.7 (first identified in the United Kingdom), B.1.351 (first identified in South Africa), P.1 (first identified in Japan), and B.1.617 (first identified in India), which contain mutations associated with increased spread and resistance to immune responses and are now detected in several other countries [6].The surge in mucormycosis cases among COVID-19 patients, particularly those with diabetes treated with steroids, is alarming. Such treatments can suppress the immune system and elevate blood sugar levels, creating favorable conditions for mucormycosis. Patients with weakened immune defenses, including those undergoing bone marrow transplants, are at heightened risk for this infection [7-11]. This review underscores the importance of understanding mucormycosis, its association with various health conditions, and the additional risks posed by COVID-19 [12]. This study aimed to guide healthcare providers toward optimal treatment strategies and preventive measures amidst the increased strain on healthcare systems during the pandemic.

**Table 1. Overview of clinical signs, diagnostic tests, patient history, and treatment administered.**

| Ref. | Symptoms | Treatment | Key Findings |
|---|---|---|---|
| 14 | Upper jaw toothache, headache, proptosis, vision loss | Not specified | Neuroaxis involvement was significant in mucormycosis post-COVID, with complications like stroke. |
| 15 | Tooth mobility, abscess, pus discharge | Surgical debridement, prosthetic rehabilitation | Highlighted extensive osteomyelitis in the maxilla post-COVID-19, emphasizing surgical and post-surgical management. |
| 16 | Oral symptoms detected early by dentists | Prosthetic rehabilitation post-surgery | Dentists play a crucial role in early detection and management of mucormycosis in the head and neck. |
| 17 | Jaw osteomyelitis | Early diagnosis and treatment | Emphasized early recognition for reducing mortality and morbidity in post-COVID mucormycosis cases. |
| 18 | Pain in temporal and orbital regions, tooth mobility | Antifungal drugs, surgical debridement | Early treatment with antifungals and surgery is crucial for survival. |
| 19 | Rhino-orbital symptoms | Not specified | Early recognition vital for optimal treatment and outcomes. |
| 20 | Various, including sinus and rhino-orbital involvement | Not specified | Systematic review highlights global surge in mucormycosis cases linked to COVID-19, especially in India. |
| 21 | Sudden tooth mobility, toothache, jaw pain | Not specified | Oral involvement frequent in post-COVID mucormycosis, with diabetes and steroid use as likely contributing factors. |
| 22 | Symptoms in orofacial structures | Surgical debridement, antifungal drugs | Stresses the importance of rapid diagnosis and multidisciplinary treatment. |
| 23 | Involvement of maxillary sinus, teeth | Not specified | Scoping review identifies increased risk and emphasizes need for early detection and comprehensive care. |

The surge in mucormycosis cases during the COVID-19 pandemic has presented unique diagnostic and management challenges, particularly in immunocompromised patients, such as those with diabetes. Oral and maxillofacial manifestations of mucormycosis have been notably aggressive, often requiring a multidisciplinary approach for effective diagnosis and treatment [13]. Clinical features, including facial swelling, pain, tooth mobility, and non-healing wounds, are common in the affected population. Advanced imaging techniques like CT and MRI, alongside histopathological examination, are crucial in confirming the diagnosis, although low culture positivity remains a diagnostic challenge. Table 1 provides a comprehensive overview of the key clinical symptoms, diagnostic tests, treatment modalities, and notable findings from previous studies on COVID-19-associated mucormycosis.

In the context of the COVID-19 pandemic, a stark increase in mucormycosis cases, particularly affecting the jaws, has been observed. The patients' details are given in Table 2.

## Methodology

### Study Design and Setting

This case series was conducted at a tertiary care center in Mangalore, India, between May 2021 and December 2022, during the second wave of the COVID-19 pandemic. Ethical approval for this study was granted by the institutional ethics committee (Approval No. TMC/EC/E/2022/015). Informed consent was obtained from all participants prior to inclusion.

### Study Population

The study included 52 patients diagnosed with mucormycosis involving the maxilla, all with a confirmed history of COVID-19 infection. Inclusion criteria were: Age ≥ 18 years, Radiological or clinical evidence of mucormycosis involving the maxillary region, History of COVID-19 infection within the last 3 months, no prior antifungal treatment before hospital admission, Patients with incomplete medical records or those lost to follow-up were excluded from the study.

### Clinical Evaluation and Data Collection

Comprehensive demographic and clinical data were collected that included, age, sex, comorbidities (especially diabetes mellitus), History of COVID-19 infection and steroid use, presenting symptoms (e.g., facial pain, gingival swelling, tooth mobility), Site of mucormycosis involvement (unilateral or bilateral maxilla). Each patient underwent a thorough extraoral and intraoral examination by oral and maxillofacial surgeons. Data were compiled from patient charts and surgical reports.

### Diagnostic Investigations

All patients underwent radiological imaging for diagnosis like Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) were used to evaluate the extent of infection, bony destruction, and soft tissue involvement. Fungal culture and KOH staining were performed on debrided tissue samples. Histopathological examination was used to confirm fungal invasion. Despite the low culture positivity rate, imaging combined with histopathology ensured diagnostic accuracy.

### Treatment Protocol

Treatment involved a multidisciplinary approach that included surgical debridement or maxillectomy depending on the extent of disease. Infra-sequestrectomy of the maxilla and Functional Endoscopic Sinus Surgery (FESS) were the most common procedures. Antifungal therapy primarily with liposomal amphotericin B at 5-10 mg/kg/day, adjusted based on renal function. In cases where liposomal formulations were unavailable, amphotericin B deoxycholate was administered. Step-down therapy included posaconazole or isavuconazole where appropriate.

### Prosthetic Rehabilitation

Patients with extensive maxillary resection received temporary obturators during the early healing phase definitive prostheses once the disease was controlled and soft tissue healing was adequate

### Data Analysis

Descriptive statistics were used to summarize patient demographics, clinical features, treatment details, and outcomes. Distribution tables were created to compare unilateral and bilateral involvement. Graphs were used to represent age distribution and surgical procedures.

## Patient Details

In the context of the COVID-19 pandemic, mucormycosis cases have surged significantly, particularly affecting patients with underlying health conditions such as diabetes. This case series investigates 52 patients who experienced maxillary mucormycosis after COVID-19 infection, highlighting the clinical presentations, diagnostic complexities, and treatment modalities in this cohort (Table 2).

| # | Age/Sex | Immunocompromised | History of Covid | Site of disease | Procedure performed | Complications | Prosthetic rehabilitation | Unilateral/Bilateral |
|---|---|---|---|---|---|---|---|---|
| 1. | 45/F | Diabetes Mellitus | + | Right side maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | Death due to sepsis | | Unilateral |
| 2. | 55/M | Diabetes Mellitus | History of fever | Bilateral maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | Temporary obturator | Bilateral |
| 3. | 56/M | Diabetes Mellitus | + | Right side maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | Temporary obturator | Unilateral |
| 4. | 45/M | Diabetes Mellitus | + | Anterior maxilla | Sequestrectomy | - | Fixed prosthesis | Anterior region of maxilla |
| 5. | 60/M | Diabetes Mellitus | + | Bilateral maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | Oronasal and oroantral fistula | Temporary obturator | Bilateral |
| 6. | 36/M | Diabetes Mellitus | + | Unilateral maxilla | Sequestrectomy and debridement | - | Temporary obturator | Unilateral |
| 7. | 38/F | Diabetes Mellitus | + | Bilateral maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | - | Bilateral |
| 8. | 45/M | Diabetes Mellitus | + | Partial Maxilla | Sequestrectomy and debridement | - | - | Unilateral |
| 9. | 55/m | Diabetes Mellitus | | Partial maxilla | Bilateral medial maxillectomy & FESS | - | - | Bilateral |
| 10. | 70/M | Diabetes Mellitus | + | Bilateral maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | Temporary obturator | Bilateral |
| 11. | 59/M | Diabetes Mellitus | + | Bilateral maxilla | Bilateral Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | Temporary obturator | Bilateral |
| 12. | 50/M | Diabetes Mellitus | + | 3/4th maxilla | Right Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | Temporary obturator | Bilateral |
| 13. | 48/M | Diabetes Mellitus | - | 3/4$^{th}$ maxilla | Maxillectomy & FESS | - | - | Bilateral |
| 14. | 58/M | Diabetes Mellitus | + | 3/4$^{th}$ maxilla | Sequestrectomy & debridement? | - | Temporary obturator | Bilatreral chronic |
| 15. | 60/M | Diabetes Mellitus | + | Unilateral maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | - | Unilateral |
| 16. | 55/F | Diabetes Mellitus | + | Sphenoid sinus | Curettage and FESS | - | - | Unilateral |
| 17. | 45/M | Diabetes Mellitus | + | Maxillary sinus | FESS & Medial maxillectomy | - | - | Unilateral |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 18. | 48/F | Diabetes Mellitus | + | Right maxilla | Infra sequestrectomy of maxilla & Functional Endoscopic Sinus Surgery (FESS) | - | - | Unilateral |
| 19. | 56/M | Diabetes Mellitus | + | Left maxilla | FESS & Partial maxillectomy | - | - | Unilateral |
| 20. | 55/F | Diabetes Mellitus | + | Left maxilla | FESS & Inferior alveolectomy wrt medial maxilla | - | Permanent prosthesis | Unilateral |
| 21. | 48/F | Diabetes Mellitus | + | Maxilla | FESS & Medial maxillectomy | - | - | Unilateral |
| 22. | 53/F | Diabetes Mellitus | + | Maxilla | FESS & Medial maxillectomy | - | - | Unilateral |
| 23. | 64/M | Diabetes Mellitus | + | Maxilla | FESS & Infra-sequestrectomy of maxilla? | - | Death | Unilateral |
| 24. | 47/M | Diabetes Mellitus | + | Right maxilla | FESS & Caldwell Luc Procedure | - | - | Unilateral |
| 25. | 49/M | Diabetes Mellitus | + | Maxilla | FESS & Infra sequestrectomy of maxilla? | - | Temporary complete denture | Left side Unilateral |
| 26. | 53/M | Diabetes Mellitus | + | Maxilla | FESS & Infra sequestrectomy of maxilla | - | - | Unilateral |
| 27. | 57/F | Diabetes Mellitus | + | Maxilla | FESS & Infra sequestrectomy of maxilla | - | - | Unilateral |
| 28. | 55/M | Diabetes Mellitus | + | maxilla | FESS & Infra sequestrectomy of maxilla | - | - | Unilateral |
| 29. | 46/F | Diabetes Mellitus | + | Left maxilla | FESS & lateral rhinotomy | - | - | Unilateral |
| 30. | 53/M | Diabetes Mellitus | + | Left maxilla | FESS & External Caldwell luc procedure | - | - | Unilateral |
| 31. | 52/M | Diabetes Mellitus | + | Right side | Partial maxillectomy & FESS | Right side | - | Unilateral |
| 32. | 42/F | Diabetes Mellitus | + | Zygoma, orbit, maxilla | FESS & Inframaxillectomy | - | - | Unilateral |
| 33. | 60/M | Diabetes Mellitus | + | Right side complete maxilla Left side anterior maxilla | Infrasequestrectomy | - | - | Bilateral |
| 34. | 54/F | Diabetes Mellitus | + | Maxilla | FESS & Infra sequestrectomy of maxilla | - | - | Bilateral |
| 35. | 34/M | Diabetes Mellitus | + | Maxilla | FESS & Infra sequestrectomy of maxilla | - | Temporary obturator | Unilateral |
| 36. | 49/M | Diabetes Mellitus | + | Orbit, maxilla | Bilateral FESS & medial maxillectomy | ptosis | - | Bilateral |
| 37. | 43/M | Diabetes Mellitus | + | Left Maxilla | FESS & medial maxillectomy | - | Left side temporary obturator | |
| 38. | 50/M | Diabetes Mellitus | + | Left Maxilla | Infrasequestrectomy of maxilla | - | - | Unilateral |
| 39. | 45/M | Diabetes Mellitus | + | Left Maxilla | FESS & Caldwell luc procedure | - | - | Unilateral |
| 40. | 63/F | Diabetes Mellitus | + | Left Maxilla | FESS & External Caldwell luc procedure | - | - | Unilateral |
| 41. | 41/M | Diabetes Mellitus | + | Left Maxilla | FESS & maxillectomy | - | - | Bilateral |
| 42. | 43/M | Diabetes Mellitus | + | Left Maxilla | FESS & surgical debridement | - | - | Unilateral |
| 43. | 36/M | Diabetes Mellitus | + | Left maxilla and floor of orbit | FESS & medial maxillectomy | paresthesia | - | Unilateral |
| 44. | 41/F | Diabetes Mellitus | + | Maxilla | Surgical debridement | - | - | Unilateral |
| 45. | 54/M | Diabetes Mellitus | + | Maxilla | Surgical debridement | - | - | Unilateral |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 46. | 41/F | Diabetes Mellitus | + | Maxilla | Right side infra sequestrectomy of maxilla | - | Temporary obturator | |
| 47. | 62/M | Diabetes Mellitus | + | Maxilla | FESS & Caldwell luc procedure | - | - | Unilateral |
| 48. | 53/F | Diabetes Mellitus | + | Maxilla | Infra sequestrectomy of maxilla | - | - | Unilateral |

The clinical features presented in the above table provide insight into the aggressive nature of mucormycosis in patients, often resulting in complex surgical interventions and life-threatening complications. Following the clinical data presented in Table 2, an analysis of the patient's demographics and disease characteristics highlights significant trends. The majority of the affected individuals were between 40 and 60 years of age, with a higher incidence observed in males. Moreover, the bilateral involvement of the maxilla was more frequent compared to unilateral cases, indicating a more severe spread in many patients. These findings underscore the aggressive nature of mucormycosis in COVID-19 patients, particularly those with pre-existing conditions like diabetes. Fig. 1 and Fig. 2 further illustrate the age distribution and the extent of maxillary involvement in the study cohort.

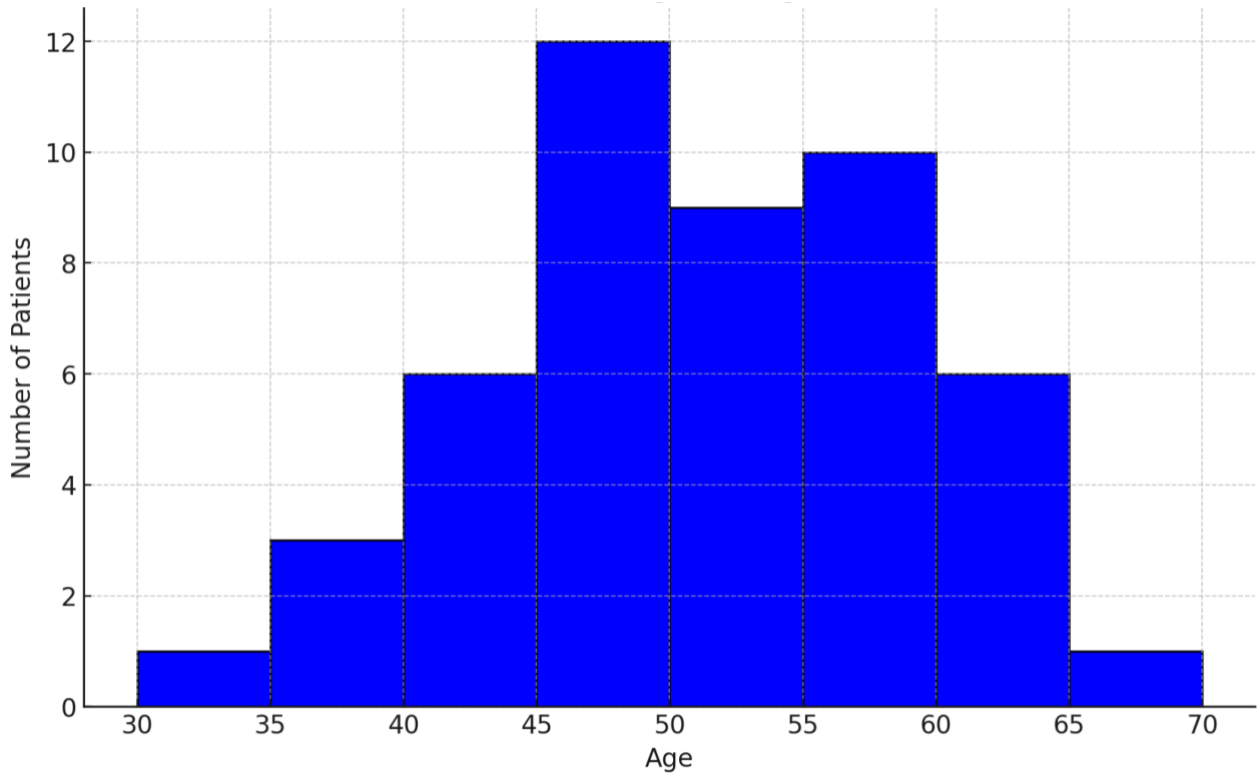


**Figure 1. Distribution of Age among Patients.**

## Clinical Presentation, Diagnostic Challenges, and Treatment of Mucormycosis in COVID-19 Patients

This case series delves into the clinical presentations, diagnostic challenges, treatment modalities, and outcomes of 52 patients, including both male (39 patients) and female (13 patients), with demographic information available across the age group of 40 to 60 years. The clinical spectrum, site of predilection, and bilateral vs. unilateral spread of the disease underscore the severity and complexity of managing mucormycosis in the context of COVID-19. The patients presented with a myriad of symptoms, including multiple pus discharges, exposed bone, mobility of teeth, and a change in resonance, highlighting the aggressive nature of mucormycosis infections. The site of the disease predominantly affected the maxilla, with a peculiarly high incidence of bilateral maxilla involvement in 35 patients and unilateral maxilla involvement in 15 patients. The remaining patients reported involvement on both sides of the anterior maxilla, with a rare presentation on the posterior side of the maxilla

and an even rarer occurrence of one patient in the mandible. This distribution pattern points toward a pronounced susceptibility of the maxillary bone to mucormycosis in COVID-19 patients, a finding that prompted a re-evaluation of the underlying pathophysiological mechanisms linking mucormycosis to COVID-19 (Fig. 5).

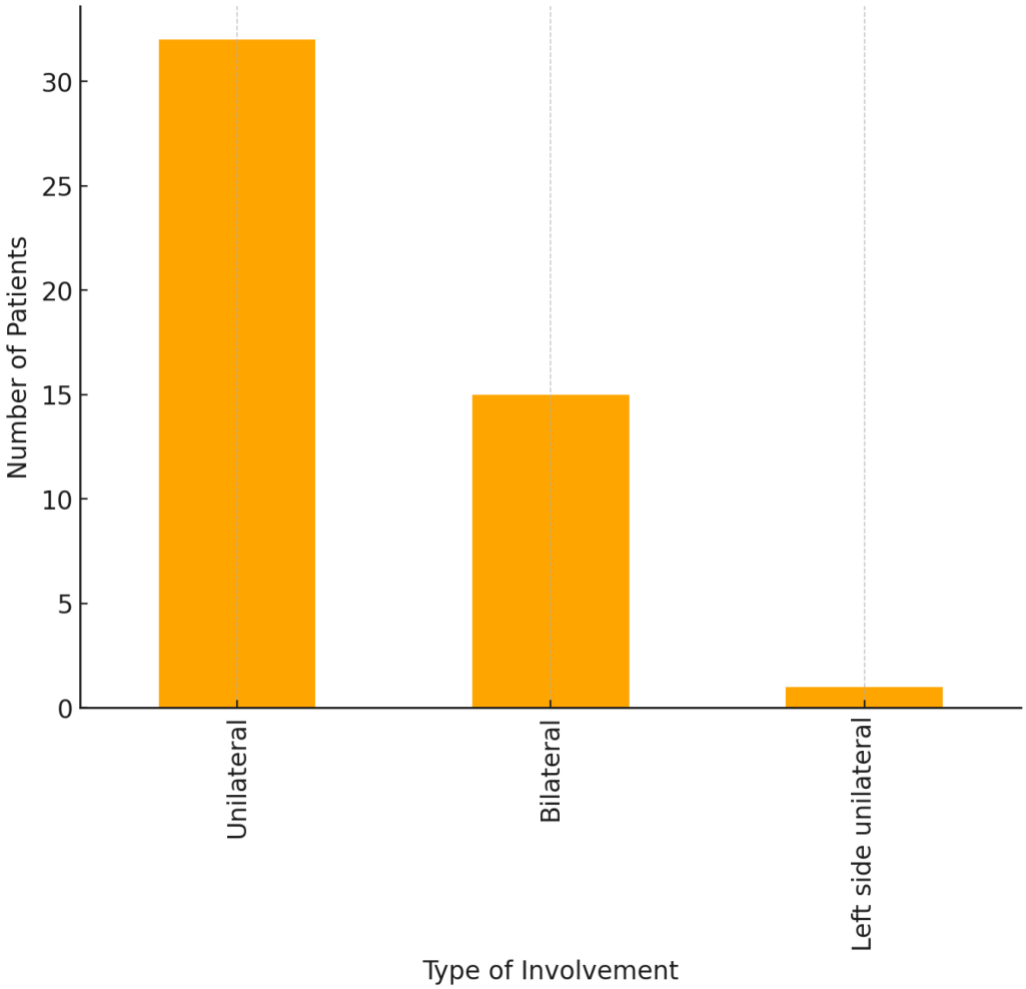


**Figure 2. Unilateral vs. Bilateral Maxilla Involvement.**

Further dissection of the complications arising from mucormycosis in these patients revealed a grim picture, with two deaths attributed to severe complications, one due to meningitis following cranial involvement and another due to sepsis. This finding underscores the potential for mucormycosis to induce life-threatening complications in COVID-19 patients, particularly when it extends beyond the initial site of infection. The involvement of the infratemporal fossa in 10 patients and the floor of the orbit in 7 patients illustrates the propensity of the infection to spread to adjacent structures, further complicating the management and increasing the morbidity associated with the disease. The diagnosis of mucormycosis in these patients was established through a combination of CT and MRI supplemented with fungal culture and staining. This multimodal diagnostic approach is pivotal for delineating the extent of disease and guiding therapeutic interventions. Notably, virtual planning was employed in the management of one patient, highlighting the role of advanced technologies in tailoring individualized treatment plans. However, the management of these patients is fraught with challenges, primarily due to the lack of bleeding during surgical debridement, which is typically a guide for removing infected tissue. Additionally, the absence of a clear demarcation between diseased and non-diseased bone added a layer of complexity to the surgical interventions, necessitating a cautious and conservative approach to minimize the risk of exacerbating the patient's condition (Fig. 3, 4, and 6).

Table 1 provides a detailed summary of the clinical signs, diagnostic tests, patient demographics, and treatment strategies in this cohort. For instance, common symptoms included multiple gingival swellings, pus discharge, and non-healing exposed bone, predominantly in the maxilla (Fig.7). Diagnostic approaches combined CT and MRI with fungal cultures, although low culture positivity presented a challenge in some cases. Treatment modalities included surgical debridement, antifungal therapy, and strict glucose control.

**Table 3. Clinical features, diagnostic approaches, patient demographics, and treatment modalities in patients with mucormycosis associated with COVID-19.**

| Heading | Details |
|---|---|
| **Clinical Signs and Symptoms** | - Multiple gingival swelling and pus discharge sites, non-healing exposed bone in the extraction sites, mobility of teeth, change in voice resonance, and predominant involvement of the maxilla, often bilateral. |
| **Diagnostic Tests** | - Combined use of CT scans and MRI for imaging, Fungal cultures, and histopathological staining; noted challenges with low culture positivity rates, highlighting diagnostic complexities. |
| **Patient History** | - Age range primarily 40 to 60 years, Demographic distribution: 39 males and 13 females, Significant prevalence of diabetes among patients, History of COVID-19 infection, often treated with steroids which exacerbate susceptibility to mucormycosis. |
| **Treatment Administered** | - Surgical debridement to remove infected tissues, Antifungal therapy, predominantly with liposomal Amphotericin B, Rigorous glucose control for diabetic patients; challenges included lack of bleeding during surgery, complicating the distinction between infected and healthy tissues, use of removable obturators for rehabilitation in some cases. |

The predominance of diabetes among the patients in this series is a notable finding, reflecting the well-documented correlation between diabetes and an increased risk of mucormycosis. This correlation emphasizes how important it is for COVID-19 patients to have strict glucose control, particularly if they have mucormycosis or are at risk for it. In this cohort, the mucormycosis treatment was multimodal, focusing on disease control as the mainstay of care. A coordinated effort was made to manage the disease and lessen its impact on the patient's quality of life, and surgical debridement, antifungal therapy, and, in certain cases, the provision of removable obturators for rehabilitation were used. The lack of bleeding and the difficulty in differentiating between healthy and infected tissue are two of the therapeutic challenges in this series that emphasize the need for novel surgical methods and diagnostic instruments in the treatment of mucormycosis. Due to the high prevalence of diabetes among patients, managing the condition becomes increasingly difficult, calling for a comprehensive strategy that takes care of the underlying metabolic disorder as well as the infectious disease[24-26].

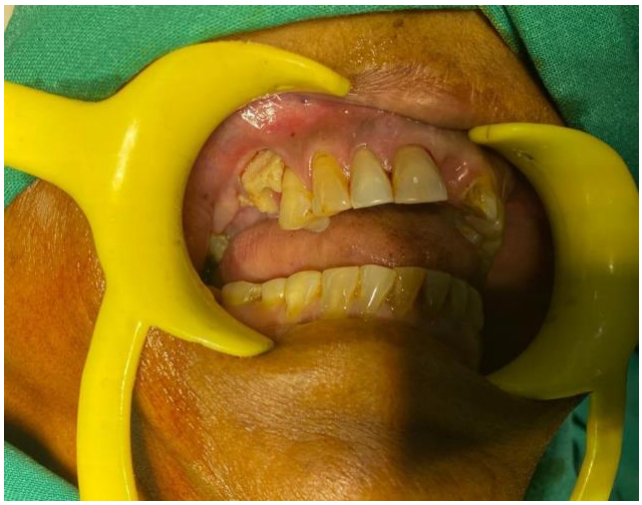

**Fig. 3 Exposed, unhealthy bone in extraction sockets**

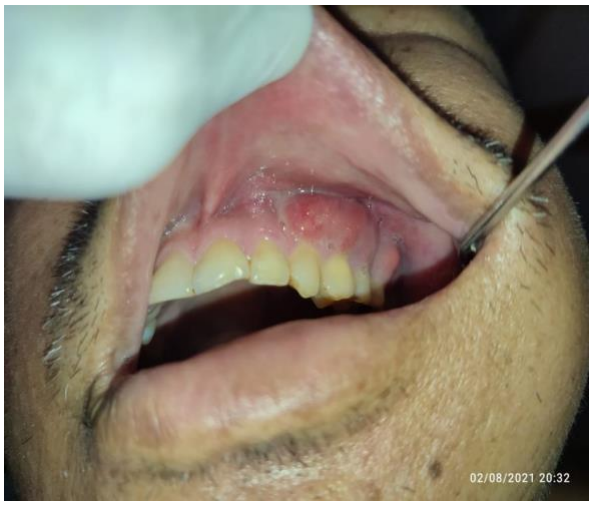


**Fig. 4 Inflamed gingiva with pus drainage**

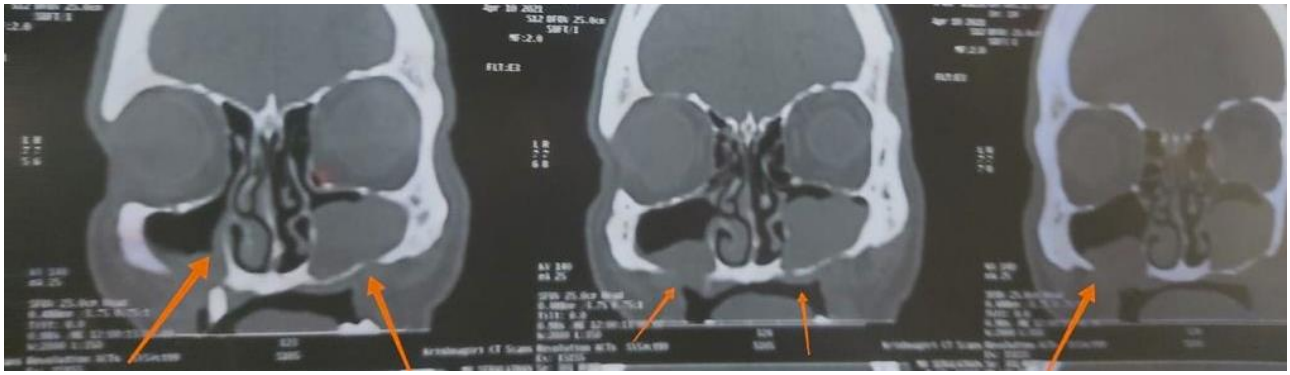

**Fig. 5 CT images showing the involvement of the maxillary sinus reaching the orbital floor**

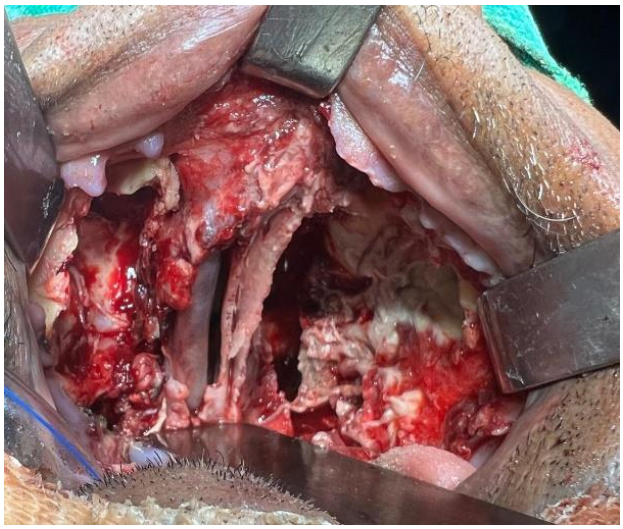

**Fig. 6 Resected specimen of the diseased bone**

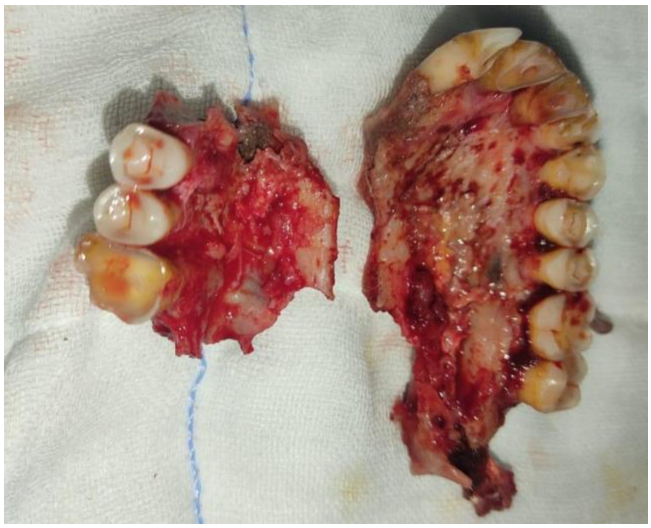

**Fig. 7 Involved, necrotic maxillary bone**

## Discussion

The cases presented encompass a diverse range of maxillofacial surgeries performed on patients with diabetes mellitus. These interventions, ranging from infra sequestrectomies to functional endoscopic sinus surgeries (FESS) and maxillectomies, are aimed at addressing various complications, including chronic infections and oroantral fistulas. Despite the use of meticulous surgical approaches, some patients experience severe outcomes, such as sepsis-related fatalities, highlighting the heightened risks in diabetic patients. Prosthetic rehabilitation, ranging from temporary obturators to permanent prostheses, plays a pivotal role in restoring oral function and aesthetics. Furthermore, the classification of patients into unilateral and bilateral procedures underscores the complexity of surgical interventions and their impact on patient outcomes [27].

Mucormycosis frequently occurs as an invasive fungal infection among individuals with hematological conditions, those who have undergone allogeneic stem cell transplants, and patients with diabetes [23]. Contrary to traditional risk factors, HIV infection does not lead to an increased risk of mucormycosis unless it is accompanied by factors such as the use of illicit intravenous drugs, neutropenia, diabetes mellitus, or the use of corticosteroids, resulting in a mortality rate of approximately 52.2%. This is corroborated by the work who examined 1630 autopsies of patients who succumbed to AIDS, finding mucormycosis in only two cases [28]. Rhino-orbits-cerebral mucormycosis (ROCM) is predominantly observed in individuals with uncontrolled diabetes, with Rhizopus oryzae accounting for almost 90% of these cases and a mortality rate exceeding 50% [29]. The prevalence of mucormycosis has notably increased during the COVID-19 pandemic, especially in South Asian countries, which is largely attributed to the administration of corticosteroids. Among patients with COVID-19, the sinuses emerged as the most frequent site for mucormycosis infections, accounting for 79.4% of cases, particularly affecting the maxillary sinus in nearly half of these patients. The average time from COVID-19 diagnosis to the onset of mucormycosis was

approximately 16.15 days, with a range from 2 to 90 days. However, mucormycosis remains uncommon in Malaysia, with only a single case reported [30, 31]. The outcome of mucormycosis can differ greatly depending on the location and severity of the infection. Vaughan and colleagues have shown that the overall survival rate reaches 59.5% with treatment but drops to 21% without intervention [32]. Fortunately, this patient showed no signs of intracranial or orbital complications, which might have adversely affected his prognosis. He achieved a positive response to the surgical removal of the infected tissue and the administration of suitable antifungal treatment [33-35].

Microscopic examination (either direct or via histopathology) and the culture of clinical samples are fundamental to the diagnosis of mucormycosis. Nonetheless, it has been observed that merely one-third of positive microscopic samples also yield positive cultures. This discrepancy in culture results can be ascribed to various factors, including the methods of sample collection, storage, and processing, which could compromise the survival of Mucorales fungi [36]. In a study focusing on cases of pulmonary mucormycosis in cancer patients, it was noted that, although not statistically significant, patients with positive cultures tended to show a greater degree of necrosis and fungal hyphae but a lower rate of vascular invasion than those with negative cultures [37]. Clinically, those with positive cultures more frequently had hematological cancers, had undergone hematopoietic cell transplants, and showed signs of severe lymphopenia (absolute lymphocyte count ≤ 500/μL) and monocytopenia (absolute monocyte count ≤100/μL). In cases where cultures do not yield positive results, molecular diagnostics such as conventional polymerase chain reaction (PCR) could serve as valuable supplementary tools to enable faster diagnosis [38].

## Conclusion

In summary, within the framework of the ongoing pandemic, this case series on mucormycosis of the jaw in COVID-19 patients clarifies the clinical characteristics, diagnostic difficulties, and management complexities of this uncommon but serious fungal infection. In order to reduce the morbidity and mortality linked to mucormycosis in COVID-19 patients, these findings highlight the significance of early diagnosis, aggressive disease management, and stringent glucose control. In addition, this series emphasizes how important it is to continue studying the pathophysiology of mucormycosis in order to create more potent therapeutic and preventive measures, especially given its link to diabetes and COVID-19. The potential for secondary infections like mucormycosis, which can exacerbate the clinical course and outcome of COVID-19 patients, must be closely monitored by the medical community as the pandemic progresses. Intense antifungal therapy, correction of any underlying risk factors, and surgical intervention when practical are the three main components of managing mucormycosis. According to international standards, 5-10 mg/kg of liposomal amphotericin B (AmpB) should be used daily. Before beginning amphotericin B therapy, evaluations of renal function must be performed. The use of AmpB deoxycholate is advised only in scenarios where alternative antifungal treatments are unavailable due to its potential for more severe systemic side effects, including reactions related to infusion and nephrotoxicity [39]. In many of the patients we studied, AmpB deoxycholate was the primary treatment option because other antifungal medications were not available at our facility. However, a retrospective study suggested that AMPB deoxycholate remains a viable option for mucormycosis treatment in settings limited by resources. Treatment with AmpB should be maintained until there is evident clinical improvement, typically spanning several weeks. To date, the efficacy of combination therapy remains unproven, and thus, it is not endorsed by leading treatment protocols. For those showing a positive response to liposomal AmpB, the transition to oral posaconazole or isavuconazole as a step-down therapy is an option. Isavuconazole has demonstrated comparable effectiveness to liposomal AmpB in treating mucormycosis [40]. The duration of the treatment should persist until clinical and radiographic evidence indicates the resolution of the infection. Ideally, treatment should also continue until the underlying causes of immunosuppression have been addressed. The duration of therapy can increase for several months, and in cases where immunosuppression is irreversible, some patients may require ongoing treatment indefinitely [29]. Additionally, herbal medicine has been explored as a complementary approach in managing COVID-19 and associated secondary infections like mucormycosis. Certain plant-derived compounds, such as curcumin, andrographolide, and allicin, exhibit antiviral and antifungal properties, potentially aiding in immune modulation and reducing inflammation. Some studies suggest that extracts from Tinospora cordifolia and Nigella sativa may support immune function and enhance antifungal activity when used alongside conventional treatments. Maintaining periodontal health is crucial in preventing opportunistic infections, particularly in immunocompromised individuals recovering from COVID-19. Regular professional dental cleanings, proper oral hygiene practices, and the use of antimicrobial mouth rinses can reduce the risk of periodontal disease, which may otherwise create an entry point for fungal infections. Furthermore, protecting enamel through fluoride treatments, remineralizing agents, and a balanced diet can help maintain overall oral health and prevent bacterial and fungal colonization in vulnerable patients.

## Acknowledgments

The authors have no acknowledgments to declare.

## Funding Information

The authors received no specific funding for this work.

## Competing interests

The corresponding author states that there is no Competing interest.

## Data availability

Article includes all available data, and as such, it does not contain any primary data that is unrevealed.

## Ethical approval

This study was conducted in accordance with the ethical guidelines and principles of the Declaration of Helsinki. Ethical approval for this study was obtained from the Ethics Committee of Tanvi Medical Centre, Mangalore, India under the approval number TMC/EC/E/2022/015

Informed consent was obtained from all participants before their inclusion in the study. No identifiable patient data has been disclosed in this study.

## Consent for publications

We confirm that this work is original and is not under consideration for publication elsewhere.

## Authors Contribution

Rammohan: Investigation, data curation, resources, visualization, writing-original draft (cases).
Dharnappa Poojary: Conceptualization, methodology, supervision, project administration, writing-review & editing;
Sreehari Sreedhar: Investigation, methodology, validation, visualization, writing-review & editing.
Grisilda Vidya Bernhardt: Formal analysis, methodology, writing-original draft, writing-review & editing.
Rashmi K. S.: Data curation, formal analysis, validation, writing-review & editing.
Janita R. T. Pinto: Resources, investigation, p, writing-review & editing.
Pooja Shivappa: Literature review, visualization, writing-original draft (review) and editing.
Pratik Kumar Chatterjee: Methodology, validation, writing-review & editing. All authors approved the final version and are accountable for the work.

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