

SPECTRUM OF MUCORMYCOSIS CASES ASSOCIATED WITH COVID 19, PRESENTING WITH NEW MANAGEMENT PROTOCOL FROM ORAL & MAXILLOFACIAL SURGICAL UNIT OF A PUBLIC SECTOR TERTIARY CARE HOSPITAL PAKISTAN

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ABSTRACT

**Background:** This original and pioneer national clinical study highlights the surge of COVID-19-associated mucormycosis, a life-threatening fungal infection with high morbidity and mortality, particularly in diabetics and immunocompromised patients. It underscores the critical role of early diagnosis and aggressive surgical intervention in improving patient outcomes. **Objective:** To present the clinical features of Rhino-orbital cerebral mucormycosis (ROCM) cases managed and its association with the COVID-19 Pandemic. **Study Design:** Descriptive cross-sectional. **Duration of Study:** December 2022 to December 2023. **Study Settings:** The study was conducted at the Department of Oral & Maxillofacial Surgery (OMFS), located at SMBBIT and affiliated with DUHS, over one year after Institutional Ethical approval. **Methods:** Patients managed included, both genders with strong clinical suspicion of fungal ROCM infection, whereas Patients with other odontogenic maxillofacial bacterial infections were excluded. Data were collected on demographics, COVID-19, comorbidities, and surgical treatment details with BIPP Dressings. Data was collected and analysed using SPSS version 25 to identify trends and associations. **Results:** Amongst 28 Rhino orbital cerebral mucormycosis (ROCM) cases, nine patients had a positive history of COVID-19. The highest prevalence occurred in the 51–60 age group, male gender was predominant forming 75%. Diabetes mellitus was the leading comorbidity (53.57%). The midface & paranasal anatomical region was the most commonly affected anatomical site (46.42%). The most frequent surgical intervention was partial maxillectomy and BIPP dressings were used for all cases. **Conclusion:** Rhino-orbital cerebral mucormycosis (ROCM) primarily affects COVID-19 patients with underlying comorbidities. Early diagnosis with aggressive surgical intervention is critical, and Bismuth Iodoform Paraffin Paste (BIPP) is essential in controlling local infection and reducing mortality.

**Keywords:** Rhino Orbital Cerebral Mucormycosis (ROCM), Covid-19, Bismuth Iodoform Paraffin Paste (BIPP), Covid Associated Mucormycosis (CAM), Oral & Maxillofacial Surgery (OMFS)

INTRODUCTION

Mucormycosis, referred to as "black fungus" during the COVID-19 pandemic, is a highly aggressive, fatal angioinvasive fungal infection caused by moulds from the order Mucorales and class Zygomycetes. *Rhizopus oryzae* is the most prevalent human infection, forming 60% of mucormycosis cases and 90% of rhino-orbital-cerebral mucormycosis (ROCM) (1). Mucormycetes, commonly found in soil and dust with spores, enter the upper respiratory system through nasal inhalation seeding paranasal sinuses. Fungal spores can also enter through tooth extraction sockets, thus making the significance of oral hygiene critical, especially for patients with comorbidities. These two pathways primarily contribute to developing mid-face, orofacial and ROCM mucormycosis. In addition, spores can also present in other forms, like gastro-intestinal, cutaneous, bone, mediastinal, etc (2). In Pakistan, mucormycosis is documented with unclear prevalence; cases range from 25 to 830 annually. Indian prevalence is 0.14 cases per 1000 population, with a mortality rate of 38%. Pakistan's diabetes mellitus (DM) prevalence rate of 9.8% is a significant risk factor for ROCM, as diabetes is strongly linked to its increased susceptibility (3). Immunocompromised patients, particularly those with diabetic ketoacidosis, are at high risk for mucormycosis infection, especially in the maxillofacial & cerebral regions, contributing to marked mortality (4).

COVID-19 has globally intensified the occurrence of COVID-associated mucormycosis (CAM), especially among people with

diabetes. In COVID-19-positive individuals, hyperglycemia, often exacerbated by corticosteroid treatment, creates an acidic environment favourable for CAM. Concurrently, corticosteroids impair the phagocytic activity of white blood cells (WBCs), diminishing their migration & phagolysosome fusion thereby further weakening immune defence against mucormycosis (5). Other risk factors for mucormycosis include hematologic disorders, malignancies, neutropenia, hepatitis, malnutrition, etc., which further compromise immune functions (6). CAM gained global attention in early 2021, particularly during India's second COVID wave. The overuse of corticosteroids, hyperglycemia, and a high concentration of *Mucorales* spores contributed to a substantial rise in CAM. While mucormycosis is typically rare, with an average incidence of 0.2 per 100,000 people in India, whereas, we feel Pakistan may also have similar rates, a majority of cases likely go undocumented, undiagnosed, and unmanaged, contributing to unrecognized fatalities (7, 8).

Clinical manifestations of CAM are diverse and include grey-black discoloured hard palatal tissue, putrid smell, mobile teeth, ulcerations, headache, drowsiness, fever, facial swelling, orbital cellulitis, chemosis, cranial nerve palsy, etc. Amongst its features, necrosis of the maxilla and hard palate, blood in sputum, and respiratory issues are also found (9).

Our study patients predominantly presented with palatal soft tissue discoloration, mobile teeth, putrid smell, drowsiness, lethargy and fever. In maxillofacial surgical practice, mucormycosis, pansinusitis or the involvement of multiple sinuses is typical and progresses

rapidly to involve adjacent anatomical facial regions. Computed tomography (CT) imaging shows air-fluid levels, mucosal thickening and bone erosion, making CAM diagnosis difficult from maxillary malignancies (10). Early diagnosis is crucial for ROCM patient survival and requires clinical acumen and diagnostic tests, like microbiological cultures, fungal smears, histopathological staining, etc. ROCM is primarily diagnosed clinically based on the patient's history and the above-stated clinical presentations. An aggressive surgical intervention is essential to prevent local and systemic progression. Routine management outline includes hospitalisation, early surgical intervention, and antifungal therapy to correct underlying health conditions (11,12). The Shaheed Mohtarma Benazir Bhutto Institute of Trauma (SMBBIT), Karachi, is a 500 bedded level 1 centre & is one of the largest public-sector tertiary Health care centres in Sindh province, playing a pivotal role in addressing maxillofacial emergencies, ranging from traumatology, oncology domains to serious ROCM, cervicofacial necrotizing fasciitis & odontogenic infection, it also serves as a referral centre for other Medical profession Surgical specialties [13]. This is not a local data-based review study, but Pakistan's pioneer and largest ROCM clinical study, wherein BIPP (Bismuth Iodoform Paraffin Paste) has also been used for management for the first time. Our study objective is to investigate CAM-associated characteristics of ROCM patients, raise awareness for early clinical diagnosis, promote early-aggressive surgical intervention & use BIPP to reduce mortality. Furthermore, we also share a new ROCM management protocol to augment the literature on this underreported & neglected research area from Pakistan.

## METHODOLOGY

A descriptive cross-sectional study conducted at the Department of Oral & Maxillofacial Surgery (OMFS) SMBBIT, affiliated with Dow Dental College, DUHS Karachi, from December 2022 to December 2023 after Institutional Ethical approval (ERC-000057/SMBBIT/Approval/2022) on dated 29th December 2022. A non-probability consecutive sampling technique was employed. The sample size was calculated using OpenEpi, version 3, based on the frequency of mucormycosis in COVID-19 patients ( $1.8\% \pm 5\%$ ) and a 95% confidence level with a 5% margin of error. The estimated sample size was 28.

Our inclusion criteria included All adult patients of both genders presenting with clinical features of CAM infection. Exclusion criteria included patients of all odontogenic bacterial facial space infections, cervicofacial necrotising fasciitis & ROCM cases refusing surgery or leaving against medical advice. The study was approved by the SMBBIT Research Ethics Committee (ERC-000057/SMBBIT/Approval/2022). A detailed history was taken & clinical and radiographic examinations were performed CT scans of the face with 3D reconstruction were performed. Data was recorded on a pre-designed proforma. All study patients were admitted for aggressive and immediate surgical intervention, BIPP dressing was used for all cases & underlying comorbidities were corrected. Each patient is surgically managed under a single general anaesthesia. High-risk consent is taken from patients and attendants & multi-disciplinary team (MDT) approach is used in a few cases. Data was analysed using SPSS software version 25. Descriptive statistics were employed to summarise the findings. Frequency percentage calculated for categorical variables. All results are presented as tables, charts, and graphs.

## RESULTS

Graph 1 illustrates the age-wise distribution of patients, with the majority falling into the 51-60 age group (53.58%), followed by the 41-50 age group (21.42%); the age range of patients was between 31 and 60 years. A higher proportion of male patients ( $n=21$ , 75%) were observed than females ( $n=7$ , 25%) in ratio 3: 1.

The Study Age Groups, Gender and Management outcomes, showing high survival rates, are self-explanatory from Graph 1, Chart 1 and Chart 2.

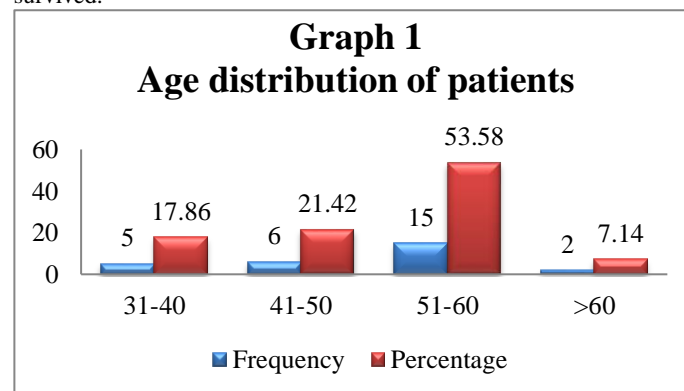
Table 1 Represents the co-morbidities, COVID-19 status & profession of patients. The most common co-morbidity was diabetes mellitus ( $n=15$ , 53.57%), followed by patients with no known co-morbidities (NKCM) ( $n=6$ , 21.42%). The majority of patients were non-vaccinated ( $n=21$ , 75%). Regarding COVID-19 status, 09 patients (32.14%) were COVID-19 positive, 12 patients (42.86%) were COVID-19 negative, and seven patients (25%) had recovered from COVID-19. The most common profession among the patients was farming (35.71%).

Table 2 displays the past treatment history of the patients. Steroids were used in 11 cases (39.28%), followed by antiviral drugs (25.00%) & broad-spectrum antibiotics (21.42%)

Table 3 shows the surgical treatments administered to ROCM cases. The majority of patients underwent partial maxillectomy with palatal resection ( $n=12$ , 42.85%), followed by total maxillectomy ( $n=7$ , 25%), unilateral rhino maxillectomy ( $n=5$ , 17.85%), unilateral rhinorbitomaxillectomy ( $n=3$ , 10.71%), and bilateral rhino maxillectomy ( $n=1$ , 3.57%).

Table 4: Illustrates the presentation sites of mucormycosis cases. The paranasal region was the most commonly affected site (46.42%), followed by the maxilla (25%), palate (14.28%), and sino-orbital area (14.28%)

Table 5: Represents systemic and local side effects of Bismuth Iodoform Paraffin Paste ( BIPP ) dressings used. BIPP is being used in ROCM for the first time and the majority of patients tolerated & survived.



Graph 1: Age distribution of the study population

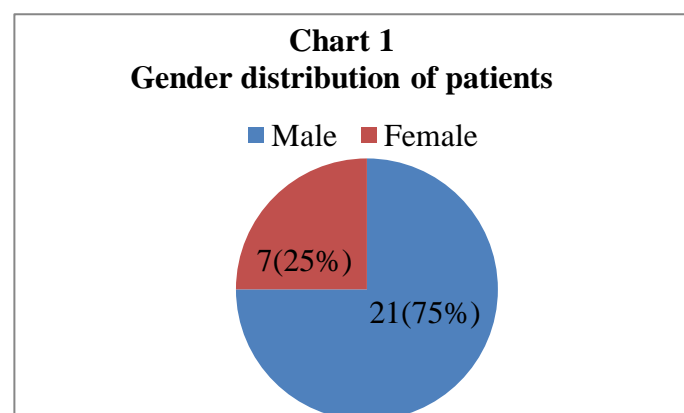


Chart 1: Gender distribution of patients

**Table 1: Co-morbidities , COVID-19 & Profession Status of patients**

Co-morbidities	Cases	Percentage (%)
Diabetes mellitus	15	53.57
Healthy (NKCM)	06	21.42
Hypertension	03	10.71
Ischemic heart disease	02	7.14
Renal & hepatic diseases	02	7.14
<b>COVID-19 Vaccination status</b>		
Non-Vaccinated	21	75.00
Vaccinated	07	25.00
<b>COVID-19 status</b>		
Negative	12	42.86
Positive	9	32.14
Recovered	7	25.00
<b>Profession</b>		
Farmer	10	35.71
Soil worker	8	28.57
Labour	5	17.85
Miner/Coal worker	3	10.71
Office workers	2	7.14

**Table 2: Past Treatment history of patients**

Treatment	Cases	Percentage (%)
Steroids	11	39.28
Remdesivir (Anti-viral)	07	25.00
Broad spectrum antibiotics	06	21.42

Oxygen support	02	07.14
Mechanical ventilation	02	07.14

**Table 3: Surgical Treatment of ROCM Cases**

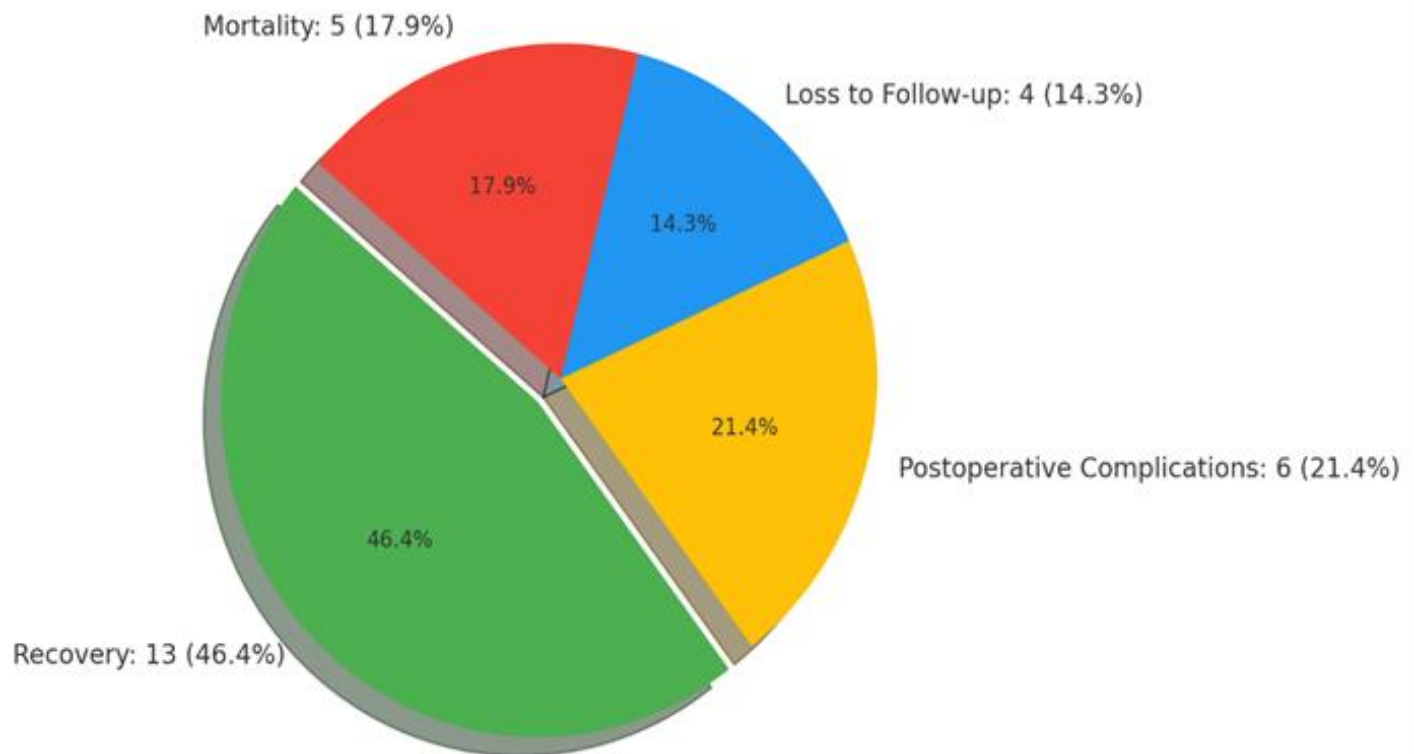
Type of Surgical treatment	Cases	Percentage (%)
Partial Maxillectomy + palatal resection	12	42.85
Total Maxillectomy	07	25.00
Rhinomaxillectomy unilateral	05	17.85
Rhinorbitomaxillectomy unilateral	03	10.71
Rhinomaxillectomy bilateral	01	03.57

**Table 4: Presentation site of ROCM cases**

Anatomical Site	Cases	Percentage (%)
Paranasal	13	46.42
Maxilla	07	25.00
Hard Palate	04	14.28
Sino orbital	04	14.28

**Table 5: BIPP DRESSING RESULTS**

BIPP USED	SYSTEMIC EFFECTS	LOCAL SIDE EFFECTS		
Total Study Cases: 28	Nausea/Vomiting /Gastric upset	Neuropathy	Allergic rashes	Total Absence of complication
	02	02	04	20

**Chart 2: Represents Surgical Management outcomes**





**From the ROCM study patients shared 01 clinical cases: surgically managed, BIPP dressings done and shared with informed consent from the patient and his attendant.**

**CASE#1:** A 47Y/M known diabetic presented with a necrotic left orofacial wound, unresponsive to previous medical treatment for two months, accompanied by pain, swelling, and total left eye vision impairment. Preoperative clinical (fig. A, B) & CT scans (fig C, D) revealed suspected extensive fungal infection involving the maxilla, nasal bone and orbit. He underwent left rhino-orbito-maxillectomy for complete excision of the necrotic hard and soft tissues. Extractions of all compromised teeth & left eye exenteration under Nasal intubation (fig; E, F). BIPP dressings are periodically done, showing progressive healing phases with granulation tissues and highlighting the patient's successful post-operative recovery (fig; G, H, I).

## DISCUSSION

A global and general observation complemented via research from healthcare physicians shows that the incidences of mucormycosis among COVID-19 patients were frightening. The majority of our study patients had diabetes and received steroid treatment for SARS-CoV-2 infection, making them further susceptible to opportunistic infections. Mucormycosis caused by mucormycetes moulds has five forms based on the spread site: paranasal sinuses, orbital and brain (rhino-orbito-cerebral), pulmonary, gastrointestinal, cutaneous and disseminated (14).

The fungus hyphae are angioinvasive pathogens, causing infarction and death of the host tissues. The first case series with COVID-associated mucormycosis (CAM) in India gathered clinical data in 2020 and suggested; "mucormycosis and COVID-19 may be interconnected". Other findings by Mehta S and Saidha PK et al. (14, 15) describe glucocorticoid treatment's effect on COVID-19 and its connections. Diabetic ketoacidosis causes macrophage dysfunction and is the most frequent risk factor for fungal sinusitis and ROCM. In addition to hyperglycemia, an alteration of iron metabolism occurs in

severe COVID-19. Severe COVID-19 is also a hyperferritinemic syndrome, but whether high ferritin is a marker of a severe systemic disease versus a modulator of pathophysiology is unclear. Irrespective of its role, high ferritin levels lead to excess intracellular iron collection, generating reactive oxygen species resulting in tissue damage. Due to severe infection and DKA, cytokines, significantly IL-6, stimulate ferritin synthesis and downregulate iron export, resulting in intracellular iron overload, further exacerbating the pathophysiological destruction process (15). The increased free iron radicals induce cellular damage, aiding the fungal metabolic process and growth (23). The combination of hyperglycemia, acidosis, and high iron enhances the upregulation of 78-kDa glucose-regulated protein (GRP78) in the endothelial cells. This heat shock protein mediates the binding of fungal hyphae on the laminin and type IV collagen at the endothelial cells' basement membrane, causing angioinvasion and tissue necrosis (24). Thus, hyperferritinemia associated with COVID-19 plays an integral part in the pathogenesis and progression of mucormycosis (25). Different theories explain the possible role of Covid-19 in the Pathogenesis of mucormycosis. According to Janjua et al. (16), SARS-CoV-2 opens the ground for opportunistic infections by impairing cell-mediated immunity by significantly reducing T-lymphocytes (CD4+ and CD8+). Pandiar et

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al. (17) explained the multisystem tropism of the virus due to its high affinity for the angiotensin-converting enzyme 2 (ACE-2) receptors. This exclusive pioneer 28 ROCM Pakistani study shows 21 (75%) males as the majority and 07 (25%) as females and is comparable to Katari SK et al. & Priyanka and Jignasa et al. findings (18,19). The Age-wise distribution of mucormycosis-positive cases revealed the highest incidence (53.58%) in the 51–60 age group, compared with Katari SK et al. (18), showing its highest incidence of 27.6% in the same age group. Diabetes was noted as the most common comorbidity in our study (53.57%), and steroid usage was observed (64.28%). In contrast, compared to this study, a survey by Afzal S Nasir M (20,21) reports that diabetes was noted in 35 cases out of 48 (72.91%) history of steroid use was present in 45.83% of patients.

Most of the cases which were positive for mucormycosis had diabetes mellitus and had received supplemental oxygen and steroids during treatment of COVID-19. This is comparable to findings by Sharma S et al., which show similar findings (22). It must also be noted that the COVID-19 pandemic has affected humanity globally. A vast majority remained negative for diagnosis but showed its clinical presentations, & Our 06 study patients formed the second largest group with 21% grouped as no known comorbidities (NKCM). Thus, our results further support that the COVID-19 pandemic significantly compromised people's immune status and made them vulnerable to opportunistic fungal infections, including our study patients who had no known comorbidities but presented with features of CAM.

In rare cases of mucormycosis, such as the one reported by Abdulaziz A. Bakathir, antifungal therapy was not delivered (26). In most cases, we also followed the same protocols and relied more on our clinical on-the-spot surgical findings. We felt, we were able to eradicate 90% of fungal-infected tissues & thus avoided antifungal drugs to prevent all its associated systemic toxicities. However, only a few cases received antifungal drugs under guidance from infectious diseases specialists, for a minimal time, but were again stopped due to complications. Empirical antibiotics and analgesics were given as needed (27). Some COVID-19-positive Patients were operated on as per the prevalent PPE Policy at the designated Operation Theatre.

Bismuth Iodoform Paraffin Paste (BIPP) has three key components: Bismuth subnitrate, iodoform, and sterile liquid paraffin. The Bismuth subnitrate has radiopaque and astringent properties and releases nitric acid upon hydrolysis as antiseptic qualities. Iodoform serves as an antiseptic and also imparts a distinct odour and taste, which is also helpful in monitoring the dressing's effectiveness. The sterile liquid paraffin lubricates the dressing, making it easier to remove from the wound site without causing further tissue damage and pain. These components contribute to BIPP's utility in managing all types of maxillofacial wound infections by promoting a combined moist healing environment, preventing bacterial growth and avoiding trauma to the surrounding tissues (28). While BIPP has no documented direct antifungal activity & we believe it's being used for

the first time in our country to successfully manage ROCM cases. We suggest that the drying effect of Bismuth subnitrate on blood vessels reduces the hemorrhagic supply to the fungal hyphae, thereby potentially limiting their rapid growth with other unknown mechanisms needing exploration. This local environment may help control the spread of mucormycosis and other infections (29). One advantage of BIPP use over other antiseptic dressings is its long-lasting presence inside the wound site. This varies from a few to fourteen days, and it can also be changed regularly in open wounds only when the dressing loses its strong colour, or smell, dries out, or becomes soaked with pus, fluids, etc. However, prolonged use can lead to discomfort, including pain, skin erythema, and local irritation (28). BIPP dressings usage is a routine protocol at our OMFS unit for almost all types of simple to complex oral & maxillofacial surgery patients and is used in infected wounds as per need in; traumatology, firearm injuries, oncology, cervicofacial necrotizing fasciitis and other odontogenic infections also. This active BIPP usage is initiated and promoted by our Head of department due to his personal positive clinical experiences of over two decades (13, 28, 29).

It is well-known that "Oral health is essential for general health", which also dramatically influences the overall quality of life (30). Therefore, oral health maintenance is paramount to prevent opportunistic fungal and other infections from becoming debilitating. Our article is also a wake-up call for all concerned medical-surgical healthcare professionals to prioritise maintaining an oral health environment for all associated matters, as shared in this study.

From 28 patients of this pioneer Pakistani original ROCM study treated for COVID-19-associated mucormycosis, the following outcomes were observed: Thirteen patients (46.43%) achieved full recovery following surgical intervention and supportive care, highlighting the potential efficacy of early aggressive surgical management with BIPP dressings in improving survival outcomes. Six patients (21.43%) experienced postoperative complications, including infection, delayed healing, electrolyte imbalance and bed sores. These complications required additional supportive care and closed monitoring, underscoring the importance of comprehensive postoperative care in managing this high-risk patient population. Four patients (14.28%) did not return for follow-up. Thus limiting the assessment of long-term outcomes for these cases. Five patients (17.86%) succumbed to the infection & died showing morbidity, despite aggressive and timely surgical treatment efforts, reflecting the global high risks associated with mucormycosis in patients with COVID-19 and the role of associated comorbidities. Due to Fungal spores being mostly found in soil, most of our CAM patients were associated with the farming profession, supporting the aetiology of spores. For this pioneer Pakistani ROCM study, our Surgical Management practices performed under the guidance of the Team Lead are shared as, a new Strategic Protocol called "Prof S Katpar et al, Mucormycosis Management Protocol 2025". It is based on 07/ Seven identified Critical Parameters, shared as follows:

Critical Parameters	Strategic ROCM Management Protocol Strengths
<b>1. Prompt &amp; Extensive Aggressive Surgical Intervention</b>	Immediately remove / aggressive debridement of the source of infections, all radiographically and clinically visible orofacial necrotic soft and hard tissues with at least extra 0.5cm healthy tissue margins, wherever possible, if needed including orbital procedures like; enucleation or exenteration etc. The entire hard Palatal maxillary flap must be raised; and exposed for assessment of fungal infection. Palate bone colour and tap sounds play a major role in assessment. Afterwards, the entire Palatal soft tissue flap must be curated and sutured with the existing healthy maxillary buccal mucosa. All hidden and visible greenish-black fungal colonies must be eradicated. Furthermore, must avoid overtight closure of all oral wounds and as per clinical condition, intra-extra oral surgery must be done.
<b>2. Elimination of Primary &amp; Contributing local Odontogenic Infection Foci</b>	Comprehensive extractions with curettage of all visible compromised teeth from either side of the maxilla be done. In combination, must also extract all other vulnerable infected teeth from both, the healthy maxilla and Mandible. This is to effectively remove the primary and all contributing potential odontogenic infection foci from both jaws and prevent recurrent infection.

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<b>3. Selective Use of Antifungal Therapy</b>	Antifungal therapy was avoided in majority of cases to prioritize surgical outcomes and minimizing drug-related complications but symptomatic antibiotics continued. Pus was sent for culture & sensitivity and antibiotics changed as per results. Furthermore, we relied more on-the-spot clinical findings and subsequent decisions to do aggressive debridement of infected mucor tissues.
<b>4. Application of BIPP Dressings</b>	BIPP is used in Pakistan for the first time in ROCM cases at surgical operated sites and periodically changed under copious irrigation, to ensure optimal wound hygiene and promote healing. We strongly discourage anaerobic/closed wound dressings and strongly promote an aerobic-open BIPP dressing environment with tagging sutures. Regularly Change BIPP in the first 3 - 5 days and continue changing for at least 14 to 21 days, till healthy granulation tissues form.
<b>5. Optimization of Comorbidities</b>	Rigorous assessment, monitoring and management of all comorbidities to strengthen immunity and also support holistic patient recovery. Optimize patients to the fullest. Control Glycemic levels, Anemia and other underlying systemic factors as per the patient's medical status.
<b>6. Integrative Faith and Spiritual Wellness Surgical Practices</b>	Praying internally and asking for guidance from Allah, Almighty Creator of the Universe as per religious Ideology has been followed by our Team lead surgeon for two decades. Incorporation of this faith-driven surgical practices at no point overcomes skilled surgical care at all, but only compliments surgical care delivered. This leads to fostering; positive faith, strong confidence, and psychological and spiritual wellness. We also guided all complex patients and their attendants to offer prayers, not only for themselves but also for our surgical team. We believe this aspect practice aspect contributes to overall safe recovery and better survival, as very challenging ROCM cases with very poor prognosis successfully survived.
<b>7. Single-Stage General Anesthesia Surgical Approach</b>	We adopted a single-stage surgical procedure to minimize all health-related risks associated with multiple general anaesthesia exposures. We also encouraged nasal intubation with support from a skilled and motivated Anesthesiologist. This nasal intubation is most important to provide greater surgical access to eradicate mucormycosis infection from the mid-face, nose, orbit, zygomatic bones and skull base. Furthermore, it greatly also aids in the extraction of teeth from both jaws.

Clinical Outcomes: All the above-stated 07 management pillars complement each other. The implementation of this above-stated strategic protocol has only one major objective, "to save a human life" and that, reconstruction can only be done, if the ROCM patient survives! This pioneer study is pivotal in achieving a notably high patient survival rate of 46.43%, with each parameter contributing significantly to effectively managing in recovery of complex cases. Faith-based, spiritual practices have shown a positive impact on patient outcomes, promoting resilience and aiding recovery, as supported by emerging evidence and practised by our team lead. This aspect only complements and does not replace good surgical practices (31,32).

The mortality rate from our study (17.86%) is comparatively lower than several international studies, as Singh et al. (5) reported a 38% mortality rate in COVID-19-associated mucormycosis cases. At the same time, Prakash & Chakrabarti (4) highlighted a generally high mortality rate for mucormycosis worldwide. In addition, studies from Pakistan, Nasir et al. (21) & India, and Moorthy et al. (9) have shown even higher mortality, particularly in uncontrolled diabetic patients receiving corticosteroids. Our positive findings suggest that early aggressive surgical intervention and using BIPP dressings have positively contributed to improving survival rates, and our findings show a substantial 46% Survival rate. This is greater than many international studies, and we hardly find any studies wherein teeth have been extracted to remove as a major contributing cause for ROCM. Studies are mostly documented by a non-maxillofacial specialist, who has a poor understanding of oral health ecology and its clinical dynamics (1,4,8,9,23). This aspect further compliments the significance of MDT and the importance of maintaining Oral Health for patients with underlying systemic health issues.

Absence to remove teeth, etc., can be a primary contributing factor for patient survival & allow residual mucormycosis infection to persist in oral tissues, thus requiring repeated surgeries. This critical aspect

appears to be overlooked in various national and international studies about mucormycosis management but does not emphasize dental extractions as part of surgical treatment, as can be seen from studies by (Singh et al. (5); Prakash & Chakrabarti (4); Rudramurthy et al. (7); Nasir et al. (8); Moorthy et al. (9)). Therefore, all our study patients underwent tooth extractions and were operated under single general anaesthesia to reduce anaesthesia related complications under high-risk consent and detailed counselling (33). Reconstruction of surgical defects was avoided during the initial surgery as the objective was, to save a life as ROCM is known for high mortality. Instead, some patients received obturator prostheses, under prosthodontist care to cover the surgical defects and provide immediate functional and aesthetic benefits (34). Reconstruction was planned later, onwards, followed by clinical and radiological resolution of the dreadful disease after safe recovery (35).

The above-stated gaps shared, further promote the significance of MDT / Teamwork, as we included ENT, Neurosurgery, Infectious Disease Specialists and Ophthalmology Clinicians for backup support in a few cases, whereas, we managed the vast majority of cases. It is generally sensed amongst the Oral & Maxillofacial Surgical (OMFS) fraternity in Pakistan, that, we get neglected by other Medical Health Care Professionals for all clinical pathology-surgical cases related to mouth and facial regions. This, inter Health Care Professional gap should be decreased now by all colleagues who may also be indirectly involved in managing these patients, but show reluctance to include OMFS Specialty. Due to the scope of dynamic and complex OMFS Specialty surgical work domains, it forms the best Professional bridge between Dentistry and Medical Health Care Profession (13). Therefore, to promote MDT and collaborative research culture, above stated gaps should be reduced to deliver positive patient management outcomes. This study is also a wake-up call for all concerned Medical-Surgical Health Care professionals managing mucormycosis Patients, to prioritize maintaining an oral health environment and promote referral culture. Also note that, currently we continue to operate newer ROCM cases based on our above-stated new management protocol.

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Only limited international studies support BIPP as one Iraqi study shows 27 diagnosed ROCM Patients managed (27). Our study strengths shared via this original clinical study with 28 patients show the maximum patient population, as compared to the other National database and international studies (3,16, 20, 21, 27). Therefore, with 28 cases we state with confidence that our Maxillofacial SMBBIT/ DUHS Surgical Unit is the largest referral Centre in Sindh Province and our country for managing ROCM infection cases and is also the largest study reported on BIPP usage from Pakistan. We also recommended BIPP usage for Odontogenic and cervicofacial necrotizing fasciitis infections. Our study limitations include the absence of checking Ferritin levels due to high cost and unavailability. Also, data for amphotericin antifungal drugs used for only a few ROCM patients is insufficient as it was immediately stopped due to complications and the long-term follow-up of our survival patients is inadequate.

## CONCLUSION

This is a pioneer, original clinical study from Pakistan, wherein BIPP is used on opportunistic lethal ROCM patients for the first time. It is also vital for all concerned healthcare professionals involved in its management to remain vigilant for a new post-COVID surge of ROCM cases. Furthermore, to decrease Dentistry and Surgical Professional Gaps, we encourage OMFS Patient referral and a collaborative research culture. Above stated complex clinical pictures case presented is self-explanatory for “Prof S Katpar et al Mucormycosis Management Protocol”. We further recommend this new protocol implementation, research and who knows, what lies in deep waters, beneath the amazing mustard-coloured BIPP iceberg?

## DEDICATION:

Prof. J Rutherford Morison introduced BIPP during the 1<sup>st</sup> World War, initially used as a Sepsis antidote and we remain indebted to his great contribution to Humanity. Prof. Mervyn M Hosein showed BIPP usage as a Fellowship Supervisor, to his trainee Prof. Shahjahan Katpar, who is an ardent advocate supporting the healing miracles of this wonder drug! We dedicate this exclusive study to Prof. J Rutherford Morison and Prof. Mervyn M Hosein for their respective positive contributions rendered to BIPP usage in Surgical Practice.

## DECLARATIONS

### Data Availability statement

All data generated or analysed during the study are included in the manuscript.

### Ethics approval and consent to participate

Approved by the department concerned. (ERC-000057/SMBBIT/Approval/2022)

### Consent for publication

Approved

### Funding

Not applicable

## CONFLICT OF INTEREST

The authors declared the absence of a conflict of interest.

## AUTHOR CONTRIBUTION

### SUNNY KUMAR (Resident Oral & Maxillofacial Surgery)

Collecting data, Compiled Results, Critical input, study design, Review of Literature, drafting articles & correspondence with the Journal.

### SHAHJAHAN KATPAR (Professor & Head of Department)

Overall Conception of the entire Study, critical input & final approval of the manuscript draft.

### MUNAWAR DIN LARIK (FELLOW)

Contributed to manuscript writing & Review of Literature.

### DR TEHREEM UN NISA (SENIOR DENTAL SURGEON)

Manuscript revisions & data analysis.

### DR TEHREEM KHAN (FELLOW)

Contributed to data Entry, data analysis & collecting references.

### DR MUNIR HUSSAIN (Lecturer)

Data analysis, collecting references, & Coordination of collaborative efforts.

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