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Covid-19 Associated Mucormycosis and Its Surgical Sequelae: A Systematic Review of the Literature

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Abstract

Background: The aim of this systematic review of literature is to know the characteristics of the patients with Covid-19 related mucormycosis, associated comorbidities as well as the use of steroids in people with Covid-19, the site of mucormycosis, the size and location of substance loss caused by surgical debridement, the contribution of maxillofacial rehabilitation in survivors. **Methods:** Using keywords, studies were selected from the following databases: MEDLINE (via PubMed), Science Direct and Google Scholar, including publications from 2019 until February 2022. They were filtered by title, abstract, and full text. **Results:** Among the 706 records identified from the databases, 28 publications were considered relevant and met the eligibility criteria, including 21 case reports and 7 case series. These studies included 69 patients with a mean age of 50.4 years, from different countries. **Conclusions:** Despite the the limitations of our review, we can conclude that mucormycosis is an opportunistic and deadly fungal illness in uncontrolled diabetes individuals who are immunocompromised. Physicians should be conscious of red flags such as previous Covid-19 infection, particularly in those who were hospitalized and given high-flow oxygen therapy as well as high-dose long-term steroids; metabolic diseases.

Subject Areas

Oral Dentistry, Maxillofacial Prosthesis

Keywords

Mucormycosis, Zygomycosis, Phycomycosis, Covid-19, SARS-Cov-2, Maxillofacial Prosthesis, Palatal Obturators

1. Introduction

Coronavirus disease 2019 (Covid-19) is an acute viral illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The novel virus was first identified from an outbreak in the Chinese city of Wuhan in December 2019, and has been spreading in whole China and the world. As of 13 March 2022, over 455 million confirmed cases and over 6 million deaths have been reported globally [1]. The increased case reports of opportunistic infections in Covid-19 patients raise an important concern, especially for patients with underlying diseases and who received immunosuppressive therapy [2]. Among all these opportunistic infections, mucormycosis has become a matter of concern with its rapid increase of cases with rapid spread as compared to the pre-Covid-19 era [3]. It has been reported in patients with severe Covid-19 or those recovering from the disease and has been associated with severe illness and death. It has been first described as phacomycosis or zygomycosis in 1885 by Palatauf, then Baker developed the name mucormycosis in 1957 [4]. It is caused by the fungi belonging to the order Mucorales [5], most commonly Rhizopus and Mucor species [6]. These fungi are ubiquitously found everywhere, and transmission occurs through inhalation, inoculation, or ingestion of spores from the environment. They can be inhaled and subsequently spread to the lungs, sinuses, brain, and eyes. Less often, infection may develop when the spores enter the body through a cut or an open wound [7]. The incidence rate of mucormycosis globally varies from 0.005 to 1.7 per million population in developed countries [5], but the rise is very high especially in India among patients with uncontrolled diabetes mellitus [8], where the prevalence of the invasive fungal infection is estimated as 140 per million populations, which is about 80 times higher than the prevalence in developed countries [9]. Mucormycosis is mainly seen in immunocompromised patients or in patients with underlying diseases, for example diabetes with or without diabetic ketoacidosis, solid organ transplantation, neutropenia, long-term systemic corticosteroid use, and iron overload [10]. Diabetes mellitus, however, remains the major risk factor for mucormycosis worldwide, with a 46% overall death rate [5]. Clinically, the disease is characterized in susceptible patients by direct invasion with considerable tissue necrosis of nearby structures, followed by rapid development 6 and angioinvasion from the nasal and sinus mucosa into the orbit and brain. Its management includes aggressive surgical debridement of the underlying disease, and systemic and local antifungal therapy [11]. Though, the surgical debridement results in the creation of a loss of maxillary substance, hence dentists and oral-maxillofacial surgeons' role can be related to important points: First, identification and early diagnosis as affection of the palate and maxilla may be the first sign of the disease, improving the prognosis and avoiding significant mortality and morbidity. Second, the management of the loss of substance created by surgical debridement causes a degradation of quality of life of the patients. An increasing number of patients with Covid-19-associated mucormycosis (CAM) have been reported worldwide

recently. The association of these two critical infectious diseases is challenging for the whole world. The objective of this thesis is three-fold: First to discuss the characteristics of Covid-19-associated Mucormycosis. Second, to determine the most encountered comorbidities in CAM patients. Finally, to assess the contribution of maxillofacial rehabilitation in improving the quality of life of survivors, it rarely reported in existing systematic reviews.

2. Materials and Methods

2.1. Materials: Databases and Keywords

An extensive literature search was performed following PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Selected clinical studies were collected from the following databases: MEDLINE (via PubMed), Science Direct and Google Scholar, including publications from 2019 until February 2022. Searches were conducted using relevant predefined keywords and MeSH terms such as "mucormycosis", "Covid-19", "Maxillofacial Prosthesis" and "Palatal Obturators".

2.2. Methods: Search Strategy

These keywords were used in multiple combinations and equations using Boolean operators "AND", "OR".

2.3. Methods: Inclusion Criteria

Inclusion criteria were the following: Case reports and cases series of rhino-orbito-cerebral mucormycosis; articles published in English and French, between 2019 and 2022.

3. Results

3.1. Study Selection Process and Flow Chart

The exhaustive search yielded 541 potentially relevant articles. Filtering screened out 472 publications based on titles and abstracts and after elimination of duplicates. Full-text analysis of the remaining 69 articles led to the exclusion of an additional 41 publications. Thus, 28 articles met the eligibility criteria. **Figure 1** below shows the sequence of the literature search on the PubMed, Science Direct and Google Scholar databases using the different keywords and Boolean equations mentioned above, according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart.

3.2. Analysis of Selected Articles

A total of 28 articles [12]-[39] consisting of 69 patients were included in this review. Out of these studies, 21 were individual case reports, while 7 were case series reporting 13, 16, 2, 2, 8, 2, and 5 cases respectively. A total of 69 cases of confirmed mucormycosis in people with confirmed Covid-19 (RT-PCR diagnosis for 28 patients (40%), Computerized Tomography Scan for 4 patients (5.7%),

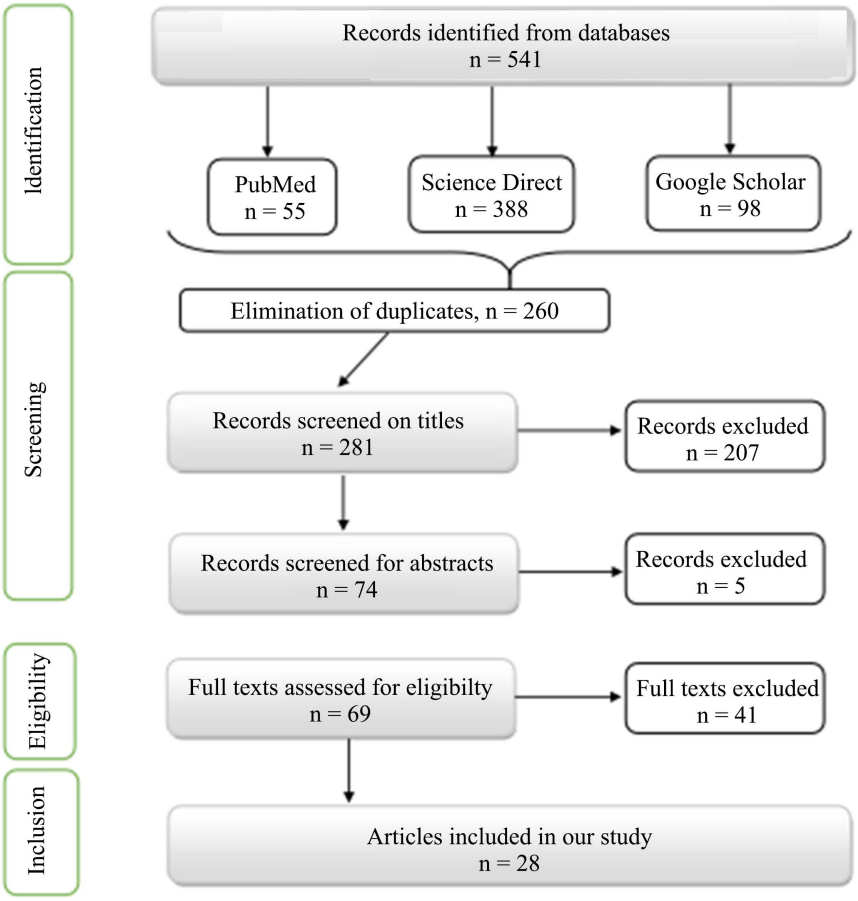

Figure 1. Flow chart as per PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Chest X-Ray for 1 patient (1.4%), Reactive SARS Cov-2 IgG antibody test for 1 patient (1.4%) and Rapid antigen Covid-19 test for 1 patient (1.4%)) were retrieved. Largely, 49 cases (71%) of mucormycosis in patients with Covid-19 were reported from India, followed by 9 cases (13%) from Egypt and 4 cases (5.7%) from Iran. Only 8 (11.2%) cases were reported from other parts of the world; USA, Turkey, UK, Spain, Pakistan, Iraq, Cambodia and Nepal, counting 1 (1.4%) case per country.

Pooled data from this study showed mucormycosis was predominantly seen in males (68.1%), mainly after recovering from Covid-19 (85%). Recovered Covid-19 was defined as those who were discharged from hospital. The most commonly seen comorbidities were diabetes mellitus (n = 54, 78.2%), with 8 patients with ketoacidosis (11.6%), followed by hypertension (n = 12, 17.4%), and chronic kidney disease (n = 5, 7.2%). Only 4 patients (5.8%) did not have any comorbidity.

Corticosteroid intake for treatment of Covid-19 was not defined for 13 patients (18.8%); not used for 26 patients (37.7%), and was used for 30 patients (43.5%). The dose and duration of the corticoid therapy were not reported in all the included studies, therefore, they could not be analyzed. Antibiotic data were

available for 14 cases: they were given broad-spectrum antibiotics as Meropenem and Ceftriaxone, and in 6 cases, the type of antibiotic was not mentioned. Remdesivir was used for 10 patients (14.5%), and Tolicizumab was used in 2 cases (2.9%).

Patients included in our study most commonly presented clinical characteristics and symptoms as unilateral facial swelling, pain, ptosis, proptosis, nasal blockage, ophtalmoplegia, headache, fever, blurry vision and loss of vision.

In this review, we found that the most frequent involvement sites of mucormycosis were rhino-orbital in 35 cases (50.7%), rhino-orbito-cerebral in 14 cases (20.3%), rhino-sinusal in 8 cases (11.6%), and rhino-cerebral in 6 cases (8.6%). Figure 5 reports results found about location sites of mucormycosis.

Although 13 (46.4%) articles have not provided the details of fungal agent causing mucormycosis, Rhizopus species was the most commonly encountered pathogen causing Covid-19 associated mucormycosis (21/69, 30.4%).

Surgical intervention was performed in majority of cases (62/69, 89.9%). Specific antifungal monotherapy was prescribed to 37 patients out of 69 (53.6%). Moreover, combined antifungal therapy with antibiotics was reported in 26 cases (37.7%). Mortality rate among patients was 34.8% (24/69), 42 patients were still alive (60.9%), and 3 (4.3%) lost follow-up.

In our review, only two studies reported maxillo-facial reconstruction in survivors; in case report presented in Deek *et al.* [13] review, free chimeric anterolateral myocutaneous flap was preconized. The patient survived the surgical intervention with no post-operative complications after full recovery (2 months). The patient was healthy and had baseline mental status. Aesthetic rectifications were possible 3 to 6 months post-operatory if needed.

The case presented in Saad et Mobarak [17] report was not favorable for an immediate obturator neither intra-operatively nor in the post-operative healing phase. That was due to the large amount of tissue excised. Anterolateral thigh flap was planned in the reconstructive surgery management plan, but the patient deceased 5 days after surgery.

4. Discussion

4.1. Pathogenesis, Host Defence against Mucormycosis and Host-Pathogen Interaction

Mucormycosis, also known as Zygomycosis or "Black Fungus", is a deadly fungal infection caused by Mucorales and zygomycotic species [39]. Mucorales can enter the body via ingestion, inhalation, or skin lesions. Inhaled or inoculated Mucorales spores cause a significant inflammatory reaction in healthy hosts. Depending on the entry point, spores inoculate into the host tissue. After surviving from the first line of immune defence (resident mononuclear and polymorphonuclear phagocytes), they germinate into hyphae, the fungus's angioinvasive form. They transformate using the condition of the host like iron overloads or ketoacidosis, then disseminate to other organs causing infections in

multiple systems such as the rhino-orbito-cerebral, pulmonary, gastrointestinal, or cutaneous systems. This causes necrosis of tissue, thrombus formation or hemorrhage [40]. Mucorales have multiple known characteristics that contribute to the disease's aggressiveness, including innate thermotolerance, capacity to bind to endothelial cell membrane, rapid growth, capacity to acquire iron from the host organism, downregulation of host-defense genes involved in pathogen recognition, immune response, and tissue healing [41]. In Covid-19 context, additional conditions help create a favorable environment to fungus invasion, proliferation, and pathogenic development inside the body, as the viral pneumonia has been linked to increased body temperature, breathlessness, osmolarity and hypoxic conditions during and post-SARS-CoV-2 infection [42].

4.2. Common Risk Factors and Comorbidities for Mucormycosis

Mucormycosis is usually an opportunistic infection, with specific risk factors occurring in patients with impairments in host defence and/or increased available serum iron; nevertheless, a small percentage of infections occur in healthy individuals [43]. Many people recovering from Covid-19 had lately been infected by the disease since they are immunocompromised, making them more susceptible. Awadhesh Kumar Singh, reported in a systematic review a total of 101 cases of mucormycosis in people with Covid-19, of which 82 cases were from India among which 18 (out of total 31) expired because of several associated comorbidities [44].

According to studies, the most recurring and common predisposing risk factors were diabetes mellitus, hypertension, corticosteroid use and immunosuppression, immunodeficiency, malignancies, and cell/tissue/organ transplants.

- **Diabetes mellitus**

Elevated blood sugar allows Rhizopus to grow efficiently. To survive in the acidic environment of Diabetic Ketoacidosis (DKA), the fungus uses its ketone reductase system. Acidosis aids in the dissociation of iron, resulting in the sequestration of proteins in the serum, which enhance fungus virulence and survival [45]. The presence of diabetes mellitus is a major predisposing factor for mucormycosis as described in a meta-analysis among patients included in 23 studies with Rhino-orbito-cerebral mucormycosis (ROCM) [3]. The presence of diabetes mellitus among patients with Covid-19 associated mucormycosis was estimated to be 66.4% in one study including 144 total cases of CAM (Covid-19 associated mucormycosis) [46] and 83% in another study that included 80 cases of CAM [47]. In our review, we found that diabetes mellitus was the most predominant associated factor in CAM patients included. The prevalence of DM among the patients was about 76%. That is due to the presence of favorable conditions, as low oxygen conditions, favorable acidic medium, high glucose levels, and low phagocytic activity due to immunosuppression (SARS-CoV-2 mediated). In these conditions, Mucorales spores germinate rapidly in patients with CAM, along with several other risk factors such as background comorbidities

and prolonged hospitalization. In Covid-19, the number of people with DM (Diabetes Mellitus) affected seemed to be increased, explained by the following reasons [48]:

- Mucorales spores grow in low pH environments, such as those caused by diabetic ketoacidosis (DKA).
- Excellent resources for mucormycosis are created in hyperglycemia, as free iron level increased by glycosylation of transferrin, ferritin, and reduced iron binding capacity.
- The cytokine storm caused by Covid-19, particularly interleukin-6, raises free iron by raising ferritin levels due to reduced iron transport.
- Rhizopus species have an active ketone reductase system, which aids Rhizopus growth in the acidic/glucose-rich environment found in diabetic ketoacidosis [48].

- **Use of steroids**

The immune dysfunction and hyperglycemic state induced by glucocorticoids explains the predisposition for invasive fungal infections caused by Mucorales moulds [49]. According to a Systematic Review, Meta-Analysis, and Meta-Regression Analysis by Bhattacharyya, increased corticosteroid usage as part of the Covid-19 therapy protocol exacerbated glucose homeostasis, putting patients at risk for opportunistic fungal infection [3]. In our study and as shown in Table VI, a high percentage of patients were found to have received corticosteroid therapy a part of the protocol of management of Covid-19 illness, *i.e.* 43%. Glucocorticoids, principally dexamethasone or prednisolone, are given indiscriminately to patients hospitalized for Covid-19 [50]. In the post-COVID time, the systematic review by Singh *et al.* consisting of 101 cases of Covid-19 with mucormycosis co-infection reported corticosteroid intake in 76.3% of cases [44]. Similarly, in another systematic review by John *et al.*, corticosteroid intake was present in 88% of cases [51]. These findings are consistent with our results, as corticosteroid use was present in most included studies. Corticosteroid use is frequently associated with uncontrolled hyperglycemia and the development of DKA. Acidosis caused by low pH, is ideal for mucor spores to grow. Furthermore, steroid usage decreases white blood cells phagocytic activity, impairs bronchoalveolar macrophage migration, ingestion, and phagolysosome fusion, and makes a diabetic patient more likely to be affected by mucormycosis [44].

5. Clinical Manifestations of Mucormycosis

Mucormycosis has different clinical manifestations depending on the location of the infection. Infection usually begins in the mouth or nose, as in sinusitis or periorbital cellulitis, and spreads via the eyes to the central nervous system. As in our study, most commonly presented clinical characteristics and symptoms are unilateral facial swelling, pain, ptosis, proptosis, nasal blockage, ophtalmoplegia, headache, fever, blurry vision and loss of vision. One side of the face may appear larger, with "black lesions" appearing rapidly on the palate or nose. If not

treated, pyrexia, chest pain, cough, dyspnea, and hemoptysis can all occur when the lungs are affected. Symptoms such as bloating, gas, and constipation can occur when the gastrointestinal tract is impacted. The damaged skin may appear as a darker red sensitive area with a deepening center due to tissue loss. There could be an ulcer, which can be very painful.

Because of the absence of vascular supply, invasion into blood vessels can result in thrombosis and eventually death of adjacent tissue. Because disseminated mucormycosis frequently occurs in people who already have medical issues, determining which symptoms are caused by mucormycosis can be difficult. Patients with a disseminated mucormycosis in the brain may develop mental problems or go into a coma [39]. Multiple mobile teeth with gingival erythema and pus-draining sinuses might be one of the first symptoms of ROCM. These symptoms can be mistaken for odontogenic infection, leading to misdiagnosis by general dentists unfamiliar with the disease's clinical presentation. It has been discovered that general dental practitioners who work with patients on a regular basis, who had low sense of suspicion for mucormycosis, wasted valuable time attempting root canal treatments and extracting these mobile teeth, delaying the start of definitive mucormycosis therapy and thereby resulting in a poor/fatal prognosis for the patient.

Similarly to our study, a review by Hussain *et al.* describing the clinical presentation, treatment modalities, and patient outcomes of Covid-19 associated mucormycosis, described facial discomfort, ptosis, proptosis, visual acuity, and vision loss as the most prevalent complaints identified [52].

6. Mucormycosis Diagnosis

Early detection and treatment of mucormycosis are crucial for a favorable outcome and prognosis before angioinvasion and necrosis spread, resulting in dissemination. Mucormycosis is diagnosed by a careful examination of clinical manifestations and laboratory investigations. Lab testing includes tissue biopsy, and depending on where the infection is suspected, it may include a CT scan of the lungs, sinuses, or other regions of the body. Furthermore, diagnostic methods including computed tomography and serum polymerase chain reaction (PCR) (which finds Mucorales DNA in the serum at an early stage) are effective in diagnosing the infection.

- **Histopathology**

Histological tests are the most important part of mucormycosis diagnosis. A tissue section is used to diagnose mucormycosis. Hyphae are commonly 6 to 30 μm in diameter, broad, non-septate. Fixed tissue stains with haematoxylin and eosin (H & E) or specialized fungal stains like Grocott Methenamine-silver (GMS) or periodic acid-Schiff (PAS) reveal broad-based, ribbon-like non-septate hyphae with wide-angle branching (about 90˚). Except one patient, histological evaluation was performed in all patients n = 68 (98.5%). Broad aseptate hyphae was the most commonly found.

- **Culture**

Mucorales grow quickly, with mycelial elements covering the entire plate in one to seven days [53]. They are saprophytic bacteria that live in soil and decompose organic waste. Mucorales in clinical specimens grow at 37˚C [54], generating fluffy white, grey, or brownish colonies that rapidly fill the Petri dish in one to seven days. Culture was performed in 52% of cases included in our study. Despite the fact that fungal cultures were only positive in 50% of cases, recent studies have showed a significant increase in culture positivity from 72% to 89% [55]. A variety of procedures can be used for direct microscopic detection of Mucorales. On microscopy, Mucorales are known for having broad, ribbon-like aseptate hyphae with right-angle branching, but there can be variations making it difficult to distinguish Aspergillus hyphae from Mucorales hyphae in direct microscopic identification [56].

- **Imaging**

CT (Computed Tomography) has made it possible to detect pulmonary or sinus abnormalities earlier than with traditional sinus and chest radiography. Nodules, halo signs, reverse halo signs, cavities, wedge-shaped infiltrates, and pleural effusions coupled with pleuritic discomfort are examples of such lesions (56). Fungal invasion of the vasculature and other tissues can be detected using both CT and MRI [57]. Soft tissue involvement, mucosal thickening, bone erosion, necrosis, cerebral and cavernous sinus involvement are all revealed on CT. The blood vascular involvement and intracranial extension of the infection can be better defined with an MRI. With a proton density-weighted MRI scan, infiltration of the orbital fat and regions of cellulitis on the eyelids can be seen more clearly [58].

- **Molecular Diagnosis**

The most extensively sequenced portion of fungal DNA is the internal transcribed spacer (ITS), which is used as a first-line tool for Mucorales species identification as used in the report included in our study by Tabarsi *et al.* [22], in complementary identification (in adjunction to culture and histological examination) of the responsible species. Molecular-based approaches have gained acceptance for confirming infection when employed on tissues. Methods for detecting or identifying Mucorales DNA in blood have shown good results in terms of detecting the disease earlier and more effectively [59]. According to a study conducted by Skiada *et al.* [60], these methods include conventional polymerase chain reaction (PCR), restriction fragment length polymorphism analyses (RFLP), DNA sequencing of defined gene regions, and melt curve analysis of PCR products. Currently, diagnosis based on molecular assays can be interesting as a complementary add on tool to the conventional diagnostic procedures.

7. Management of Covid-19-Associated-Mucormycosis

The effective and complete management of mucormycosis starts with immediate diagnosis, followed by urgent administration of antifungal therapy, treatment of

underlying disease or essential predisposing factors, surgical debridement of necrotic areas, and adjunct therapy if necessary [43].

- **Immediate diagnosis**

Delay in diagnosis has been linked to a much worse outcome. Previous studies have demonstrated the importance of early management of the disease in improving the survival rate of the patients [61]. Culture allows to grow and identify species responsible for mucormycosis. It is confirmed by histological examinations as presented in our study in almost all cases. Quantitative polymerase chain reaction systems could lead to faster diagnosis. While CT scan results show signs of sinusitis, MRIs detect infection in the orbital or central nervous system [62].

- **Urgent start of antifungal therapy**

In our systematic review, a part from a patient where the intake of antifungal therapy was not specified, all patients received Amphotericin B, in adjunction or not to other antifungal medication. In recent studies, the drug of choice for treatment of mucormycosis was Liposomal Amphotericin B when the patients have good renal function. As an alternative for patients with renal disease, Posaconasole was used due to the nephrotoxicity of Amphotericin B. A recent study suggests that 5 - 7.5 mg/kg/d of liposomal Amphotericin B are enough for most cases of mucormycosis [62]. Second-line suggests combined antifungal therapy. Results in a cohort study demonstrated that the combination of amphotericin B with posaconazole showed a remarkable degree of synergism against Rhizopus isolates [63]. Although, monotherapy and combined therapy show no difference in mortality rates in our study.

- **Reversal of essential predisposing factors**

It is critical to reverse or prevent underlying defects in host defense while managing patients with mucormycosis. According to a review by Azhar *et al.*, every patient under immunosuppressive therapy, as steroids and corticosteroids, should be monitored and checked every 12 h [45]. The use of corticosteroids should be dose reduced or stopped if possible, if no sign of improvement was recorded during the follow-up. Management of DKA in diabetic patients is primordial in treating mucormysosis, by restoring euglycemia and normal acid-base status. In our review, a few studies mentioned the management of associated comorbidities and reversal of predisposing factors, especially diabetes mellitus and/or ketoacidosis, in addition to administration of multivitamin complex to improve immunity in ill patients. Noting that the administration of iron, blood transfusion, and desferrioxamine should be carefully regulated, as it is demonstrated that it exacerbates the severity of infection [62].

- **Surgical intervention**

Mucormycosis commonly progresses quickly, and antifungal medication alone is frequently not enough to manage the illness. The huge quantity of tissue necrosis that occurs during mucormycosis necessitates surgery. Surgical debridement of infected and necrotic tissue should be done urgently. In our systematic review of literature, a high percentage of patients underwent surgical de-

bridement, *i.e.* 89.9%., improving the global outcome of the disease. Early surgical excision of the infected sinuses and adequate debridement of the retroorbital space can often prevent the infection from spreading into the eye, avoiding the need for enucleation and resulting in interesting cure rates (85%) [51]. Repeated surgical exploration of the sinuses and orbit may be necessary to ensure that all necrotic tissue has been debrided and the infection has not progressed, as shown in the study conducted by Arana *et al.* [33] included in our review; where the 62 years old male patient was subject to surgical debridement 7 times, showing positive outcome after the study. An Updated Evidence Mapping conducted by Hussain *et al.* showed a higher survival percentage in patients who underwent both medical and surgical therapy (64.96%) [52]. Depending on infected site and extension of infected area, surgical treatment may become challenging especially in cases of disseminated mucormycosis or the absence of removal of infected focus.

- **Adjunct therapy**

Patients with elevated serum iron levels are more susceptible to mucormycosis infection as the Mucorales are able to use host iron as a critical factor of virulence. Iron metabolism plays a significant role in spreading infection with Mucorales, being a crucial element playing its role in the growth of cells and development. Iron chelators find an effective role as an adjunct therapy to control mucormycosis [64]. Some of the iron chelators approved by the FDA (Food and Drug Administration) are deferiprone, injectable desferrioxamine, deferasirox [65]. In vitro and in vivo antifungal efficacy of iron chelators against Mucorales has been reported, therefore they can be used as effective iron chelators in clinical therapy [64]. As a result, iron chelators could be used as an additional therapy to help manage iron levels in the body. So far, iron chelators have not been used on a regular basis to manage CAM.

8. Benefit of Maxillofacial Rehabilitation in Survivors

Surgical excision and debridement of the necrosed areas might result in significant maxillary defects after the maxilla has been implicated. If there is a palatal deformity, post-operative consequences may include difficulties in mastication, deglutition and speech. Blindness could be a post-operative consequence if the resection includes ocular exenteration. Facial, nasal, and oral deformities are known complications of the surgical management of ROCM, and that is often leading to a lower quality of life. These resultant defects require reconstruction in the form of flaps with or without prosthesis for dental and palatal defects [66], restoring both function and patient's appearance. The rehabilitation management is started after complete recovery from infection. The prosthesis is designed differently depending on the nature and extent of the defect. Many classifications of maxillofacial defects have been proposed to determine the most appropriate form to manage the loss of substance resulting in the surgical treatment of mucormycosis [67]. Durrani *et al.* classification of maxillary abnormalities, published in 2013, appears to be suitable for correlating clinical stages of

mucormycosis. Their classification is as follows [68]:

1) Alveolectomy: These defects involve the alveolar bone alone.

2) Sub-total Maxillectomy: These defects cause oro-nasal or oro-antral fistula but do not disturb the orbital wall of maxilla.

3) Total Maxillectomy: These defects are characterized by absence of complete maxilla including orbital floor but the orbital contents remain intact.

4) Radical Maxillectomy: These defects are characterized by absence of orbital contents along with the maxilla.

5) Composite Maxillectomy: These defects involve resection of facial skin, soft palate, and any other part of the oral cavity.

All these defects can be further classified into Unilateral and Bilateral defects.

According to a recent review conducted by Kumar *et al.* about Prosthodontic Perspectives in Mucormycosis [67], prosthodontic management of the surgical defect resulting in maxillary resection is done with an obturator prosthesis in three steps, that helps the patients through various stages of recovery: an immediate surgical obturation, an interim obturation, and a definitive one after complete healing of surgical site. The immediate surgical obturator is placed the day after surgery, temporarily, to restore the continuity of the hard palate and reduce the psychological impact [69]. It can also be used as in interim obturator in some cases until the definitive prosthesis is confected. In cases where the defects are large, and the function is still altered, it is recommended to confect an independent interim obturator [70]. One the site is healed, dimensionally stable and the patient's systemic condition becomes stable, fabrication and insertion of definitive obturator can be considered. Oppositely and according to our review, immediate and interim obturators don't always find their indication, especially when the extent of the defect is large; therefore the definitive prosthesis is confected directly after healing of the site. The definitive prosthesis guarantees better retention and stability, hence needs fastidious planning in order to be used in the long-term. Mani *et al.* suggest in a report the rehabilitation of the loss of the substance caused by maxillectomy due to mucormycosis, a modified and easy technique of an obturator that was more lightweight and more retentive, allowing the patient to have normal functional movements [71]. Quality of life is important to consider in mucormycosis since, in addition to the disease's high deadly potential, it has major functional and aesthetic effects for patients. As a result, quality of life, like survival, is considered an outcome in clinical trials [72].

9. Conclusion

In this systematic review, we studied 69 cases that showed mucormycosis in COVID-19. Some conclusions have been drawn through our work: Covid-19 is a virus that spreads quickly and widely, causing mild to severe symptoms. The majority of the patients are reported from India. The disease is an opportunistic and deadly fungal illness in uncontrolled diabetes individuals who are immunocompromised. In Covid-19, supportive care, corticosteroids, and remedial medi-

cines are all potential therapy choices. These patients, on the other hand, may be susceptible to invasive mold infections as a result of their usage of steroids. Diabetes mellitus complicates the management of Covid-19 infection. Injections of liposomal amphotericin B are indicated as the first line of treatment for mucormycosis. Azole drugs such as Posaconazole and Isavuconazole can be used if the patient's treatment regimen is intolerable or if the patient is generally weak. Studies show that glucose control, timely treatment with liposomal amphotericin B, and surgical debridement are effective in the management of mucormycosis. The disease's prognosis is determined by factors such as early detection and treatment to prevent infection from spreading into the cerebral space. Patients with CAM had a significant death rate, despite the fact that adjunct surgery, in addition to antifungal medication, was linked to better clinical results, thus, improving the conditions that facilitate the emergence of mucormycosis among Covid-19 patients requires a comprehensive approach. Obturators benefit the patient in terms of function, aesthetics, phonation, and psychological well-being. It is critical to predict and treat the causes of ROCM in order to obtain a good outcomeif detected early on, resulting in a better prognosis. Physicians should be conscious of red flags such as previous Covid-19 infection, particularly in those who were hospitalized and given high-flow oxygen therapy as well as high-dose long-term steroids; metabolic diseases, particularly if uncontrolled diabetes; patients receiving immunosuppressive treatment for any reason; or patients who may be immunosuppressed in any other way.

Conflicts of Interest

The authors declare no conflicts of interest.

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