

Original Research Article

Study of the association of COVID-19 infection in the treatment outcomes in patients of rhino orbital Mucormycosis presenting to a tertiary care center

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Abstract: Background: During the second wave of COVID-19 starting in January 2021, an increase in Mucormycosis infection was recorded in various Indian states. With the aim of identifying the contribution or relationship of covid 19 infection in the incidence, severity and treatment outcomes of Mucormycosis during the pandemic, this retrospective observational research study was conducted.

Method: 113 people with rhino orbital Mucormycosis were included in the retrospective observational investigation. Based off the past medical records, basic demographic information was gathered. In order to evaluate the association between covid 19 infection and Mucormycosis, patient histories of COVID infection, steroid usage during therapy, and oxygen consumption were collected. Positive RTPCR and/or Positive Rapid antigen tests were used to diagnose active covid positive status. Using a nasal swab/tissue KOH mount, nasal endoscopy with biopsy, and radiographic tests to determine the extent, the diagnosis of Mucormycosis infection was established. A multidisciplinary strategy was used to handle the patients in collaboration with the departments of medicine, ophthalmology, neurosurgery, and OMFS. Individuals with uncontrolled diabetes received insulin and/or oral medications, and BSL was aggressively managed. Each patient received 3 to 5 mg/kg body weight/day of intravenous amphotericin B, adjusted according to renal function, medication availability, and the severity of the illness. Individuals who underwent endoscopic debridement using a modified Denker's technique or medial maxillectomy had disease that was restricted to the nose and paranasal sinuses but did not affect the palate or orbit. Whole maxillectomy was performed on patients who had palatal involvement. Most individuals with orbital involvement underwent a limited procedure for orbital decompression or rarely an exenteration/evisceration procedure.

Results: Out of 113 patients, 26 (23%) had a Covid positive status at the point they were initially assessed, 56 (49.55%) had confirmed prior h/o covid infection, 31 (27.4%) had no proven h/o covid 19 infection, and 62 (54%) had h/o usage of steroids to treat their covid infection. Of the 113 patients, 90 patients underwent combination medicinal and surgical therapy, which comprised of administering injectable Amphotericin B and performing endoscopic endonasal debridement of the afflicted areas. 23 patients (20%) were left unoperated, largely as a result of problems arising from active COVID-19 infection (15 patients, 13%) or severe cerebral involvement (6 patients), as well as the refusal of two patients undergo surgery. Out of the 113 patients who received treatment, 24 (21.23%) died from the disease, leaving 89 (78.76%) surviving. Of the survivors, 27 (23.89%) had some form of disability at the end of the treatment period (in form of cranial nerve palsies, permanent loss of vision, palatal perforations and in 1 case a patient had an open left maxillary and nasal cavity which was referred to plastic surgeon for revision surgery and rehabilitation and 62 patients (54.86%) healed fully without any sequelae. Those who received combination therapy, which included both surgery and IV amphotericin, fared far better (84 in 90 survived 93%) than those who had only IV amphotericin B therapy (5 in 23 survived 22%).

Conclusion: Covid positive status was linked to higher disease severity, increased morbidity, and increased mortality after therapy. There were several individuals with Mucormycosis who had no prior history of COVID. Increased mortality was linked to uncontrolled diabetes, Rhino orbital cerebral expansion, and concurrent covid positive status. Our study shows that invasive Mucormycosis can have a positive clinical result with immediate vigorous surgical debridement and antifungal drug administration.

Keywords: COVID; Cranial nerve palsies; Amphotericin B.

1. Introduction

In terms of health, mortality, and the global economy, the pandemic coronavirus disease 2019 (COVID-19) brought on by the brand-new SARS-CoV-2 had a catastrophic impact. Globally, it is acknowledged that systemic glucocorticoids can increase survival in mild to severe COVID-19 infections. But there was a significant danger of secondary bacterial or fungal infections due to its extensive usage [1,2].

Given that Mucormycosis was previously associated with an already high mortality (45% - 90%) in low- and middle-income countries, including India, the exceptional spike in reporting of Mucormycosis infection in these instances posed a serious issue [3–7]. The population of India was more susceptible to Mucormycosis since it had the second-largest population of diabetics in the world. During the second wave of COVID-19, Mucormycosis cases rose, making the situation in hospitals worse. There were 14,872 Mucormycosis cases recorded in India as of May 28th, 2021. With 3726 instances, Gujarat had the most, followed by Maharashtra. Moreover, the states of Rajasthan, Andhra Pradesh, Karnataka, Haryana, Madhya Pradesh, Uttarakhand, and Delhi reported an increased number of Mucormycosis cases. As stated by the previous health minister of India, Mr. Harsh Vardhan, there have been over 40,000 cases of Mucormycosis registered as of June 28, 2021. In a number of Indian states, Mucormycosis was declared an epidemic and has been classified as a notifiable disease.

The severe problem posed by the COVID-19 pandemic was made more difficult by the quick spread and high death rate of Mucormycosis [8]. In an immunocompromised host, this rare but lethal fungal infection first affects the nasal cavity and paranasal sinuses (presenting with symptoms similar to acute sinusitis), but it has a tendency to progress quickly to the orbit and intracranial locations [9–11] with a correspondingly steadily deteriorating clinical result. Hence, for these patients to have a satisfactory result, a high index of clinical suspicion with the goal of early diagnosis and vigorous care is of the paramount significance.

Following the pandemic, several papers describing various manifestations of Mucormycosis in COVID-19 patients have appeared in the medical literature [8,12–15]. Here, we describe our nine-month experience treating Mucormycosis during the second wave of covid 19 pandemic at our tertiary care facility March 2021–November 2021. We also assess whether individuals with Mucormycosis who get combination surgical and medical therapies have better results.

2. Materials and methods

Patient selection and characteristics: This retrospective study received permission from the institutional ethics committee (IEC). Between March 2021 and November 2021, all patients with invasive fungal illness of the paranasal sinuses were enrolled in the trial, regardless of whether they tested positive for COVID-19, had recovered from COVID-19 infection (past covid), or had no prior history of COVID-19 infection. Additionally, patient records were further examined in subgroups of cases with positive (rhino-orbital-cerebral COVID-19-associated Mucormycosis, or ROCCAM) and cases with negative (rhino-orbital-cerebral Mucormycosis, or ROCM) results based on real-time reverse transcriptase polymerase chain reaction (RT-PCR). In accordance with our hospital's policy, all patients received appropriate medical and surgical care when feasible.

Management Protocol at our tertiary care hospital: Step by step, we adhered to our institution's policy in an effort to address the situation quickly and aggressively. Following all COVID-19 precautionary measures, we first carried out a thorough preliminary evaluation (wearing full protective gears). The probability of the former was constantly kept in mind, and patients were appropriately checked, given that literature had shown an increase in instances of Mucormycosis among COVID -19 patients. For KOH (potassium hydroxide) staining, fluorescence brightening microscopy, specific stains (Periodic acide Schiff), and bacteriological culture, an aseptically harvested medial meatal nose swab or representative tissue was supplied. On admission, samples for pertinent haematological and biochemical tests, such as glycosylated haemoglobin (HbA1c) and RT-PCR for COVID-19, were also collected. Imaging (CT or MRI) was done on the nasal cavity, paranasal sinuses, orbit, and intracranial structures to confirm or refute the diagnosis and gauge the extent of

the disease. As the first imaging modality, gadolinium contrast enhanced MRI was used to define the spread of the disease and determine an effective surgical course.

3. Treatment

The patients were treated by a multidisciplinary team with the goal of managing the comorbid illnesses and invasive Mucormycosis urgently. Patients were admitted to a dedicated Mucormycosis ward where a large team, including the departments of medicine, otorhinolaryngology, and ophthalmology, visited and tracked the development of the patients. When Mucormycosis was confirmed, amphotericin was started intravenously. Based on clinical observations and studies, amphotericin was given to all patients at a dose of 3-5 mg/kg/day (over a period of 3-4 weeks) for a desired cumulative dose of 4.5 gm. These patients' serum electrolytes and renal function tests were regularly checked, and the dosage was adjusted as necessary. According to the severity of the illness, maxillectomy, orbital decompression, orbital exenteration, and maxillectomy were among the surgical procedures performed on maximal patients with the goal of total or near total surgical debridement. An intraoperative specimen was sent for histology, sensitivity testing, and confirmation of diagnosis. Regular post operative DNE and local debridement was done in the post operative period. On the fourteenth postoperative day, a radiological study (post-operative CT PNS with Orbit or MRI PNS with Orbit scan) was performed to look for disease expansion or recurrence. Patients were discharged on oral posaconazole daily (300 mg in once daily dose) with intent of continuing the same till clinically stable (usually a period of 45 days).

4. Results

As shown in Table 1 and Figure 1, 26 of the 113 patients that were examined at the time of presentation were covid positive (≤ 14 days between covid positivity and Mucormycosis diagnosis), 56 had history of covid positive status (>14 days between covid positivity and Mucormycosis diagnosis), and 31 were non covid positive (27% of all Mucormycosis positive cases). Among the Covid linked groups (covid positive patients + h/o covid positive status), the mean interval between Covid positivity and Mucormycosis diagnosis was 23 days. Whenever possible, patients received surgical debridement of the affected regions in addition to IV amphotericin B treatment. In this, 89 out of 113 people (or 76%) survived, which is a respectable survival rate given the characteristics of the disease.

As shown in Table 2, 90 of the 113 patients who were included in the study had combination medicinal and surgical therapy, which comprised the above-described injection of Amphotericin B and endoscopic surgical debridement of the afflicted regions. 23 patients (20%) were left unoperated largely as a result of problems from active COVID-19 infection (13 patients, 56.52%) severe cerebral involvement (8 patients, 34.78%) as well as the refusal of two patients to have surgery.

90 patients underwent surgery, of whom 6 underwent a second surgery because of active post-operative disease as seen in post-operative MRI scans. Of these, 42 underwent FESS (using Denker's approach) with clearance of the paranasal sinuses, 21 underwent endonasal debridement in addition to retro maxillary/infratemporal fossa clearance, 27 underwent medial orbital wall decompression in addition to endonasal debridement, and 6 underwent orbital exenteration/evisceration (in combination with FESS).

As seen in Table 3, During the treatment anaemia in 42 (37%) patients, deranged RFT in 64 (57%) patients, hyponatremia in 37 (33%) patients and hypokalemia in 58 (51%) patients were commonly seen with no significant variations across the three groups corrective measures were taken for all derangements which included dose adjustment of the IV amphotericin dosage in patients with significant renal function derangement.

Out of the 113 patients who received treatment, 24 (21.23%) succumbed to the illness, leaving 89 (78.76%) alive. Of the survivors, 27 (23.89%) had some form of disability at the end of the treatment period (in form of cranial nerve palsies, permanent loss of vision, palatal perforations and in 1 case a patient had an open left maxillary and nasal cavity which was referred to plastic surgeon for staged surgery and rehabilitation.) and 62 patients (54.86%) completely recovered without any residual effects.

Significant post-operative disability was evident in a total of 27 patients following the end of treatment period, in these, 4 patients (15%) were among the patients with concurrent covid positive status (n=26), 15

patients (27%) were among the patients with prior h/o covid positivity (n=56), and 8 patients (25%) among the patients without any h/o covid (n=31), as seen in Figure 3.

Only 10 (38%) of the Mucormycosis patients with concurrent covid positivity survived due to the significant challenges associated with dealing with these patients, which were primarily related to surgical fitness due to the severity of covid 19 infection in these patients. Significantly better outcomes were observed in the post covid and non covid groups, with 50 patients out of 56 (89%) and 29 out of 31 (93%) patients surviving, respectively, as particularly in comparison to the covid positive group. Significantly better outcomes were noted in the post covid and non covid group with 50 patients out of 56 (89%) and 29 out of 31 (93%) surviving respectively as compared to the covid positive group where only 10 (38%) survived as significant difficulties were associated when dealing with covid positive Mucormycosis patients which were mainly related to surgical fitness because of severity of covid 19 infection in these patients.

We also observed that patients receiving combined therapy (ie surgery + IV amphotericin) fared far better (84 in 90 survived 93%) then those receiving only IV amphotericin B therapy alone (5 in 23 survived 22%) as per Table 4.

Within the covid associated Mucormycosis patients who succumbed, Majority had some form of steroid use in the past and many also had h/o oxygen support while undergoing treatment for covid as seen in Tables 5 and 6.

Table 1. Showing covid status of Mucormycosis diagnosed cases at the time of presentation

COVID Status	n	%
COVID positive on presentation	26	23
Post-COVID	56	49.5
No H/O COVID-19 infection	31	27.5

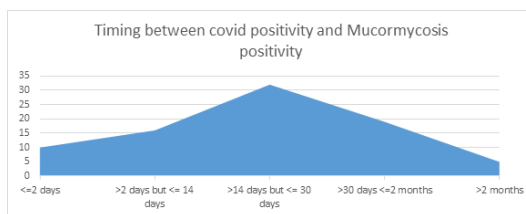


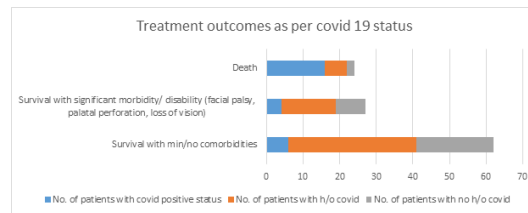
Figure 1. Showing timing between covid positivity and Mucormycosis diagnosis

Table 2. showing the surgical modalities undertaken during the study period. Note that systemic antifungal therapy was started for all patients regardless of surgical modality employed

Treatment modality	n	covid	Post covid	Non covid
A. Only Paranasal sinus clearance	42	3	31	8
B. Only PNS + Retro maxillary clearance/total maxillectomy	21	2	9	11
C. PNS + Retro maxillary clearance/total maxillectomy with medial orbital wall decompression	27	5	12	10
D. Orbital Exenteration	4	3	1	0
E. Orbital Evisceration	2	2	0	0
F. Only conservative management with systemic anti-fungals	23	16	5	2
a. Due to Intracranial involvement	8	5	2	1
b. Unfit for surgery	13	10	3	0
c. refusal to undergo surgery	2	1		1

Table 3. Showing derangement of various biochemical parameters at the start and at the end of treatment period

Dranged Parameters at the presentation	Total n,(%)	Covid positive n,(%)	Past covid n,(%)	Non-covid n,(%)
Anaemia	11 (10%)	3 (12%)	5 (9%)	3 (10%)
Deranged RFT	15 (13%)	4 (15%)	10 (18%)	3 (10%)
hyponatremia	6 (5%)	3 (12%)	2 (4%)	1 (3%)
kypokalemia	6 (5%)	3 (12%)	2 (4%)	1 (3%)
Deranged parameters at the end of treatment period	Total	Covid positive n,(%)	Past covid n,(%)	Non-covid n,(%)
Anaemia	42 (37%)	11 (42%)	21 (38%)	10 (32%)
Deranged RFT	64 (57%)	15 (58%)	33 (59%)	16 (51%)
hyponatremia	37 (33%)	10 (38%)	18 (32%)	9 (29%)
hypokalemia	58 (51%)	12 (46%)	31 (55%)	15 (48%)

**Figure 2.** showing treatment outcomes based on covid status of the patients**Table 4.** Showing treatment outcomes as per the treatment modalities employed

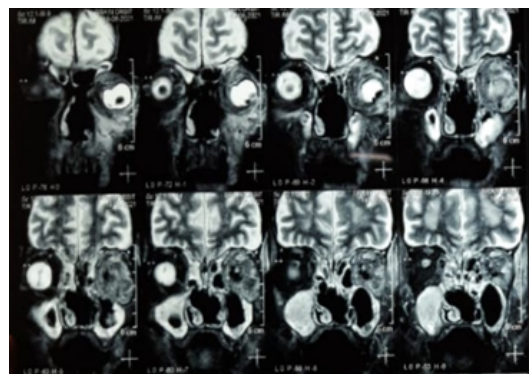
Surgical modality		survival	Death
Only Paranasal sinus clearance	42	41	1
Only PNS + Retro maxillary clearance/total maxillectomy	48	45	3
Orbital exentration/ evisceration	6	4	2
Only systemic antifungals	23	5	18

Table 5. showing mortality rate in association with prior oxygen use

Total deaths in Mucormycosis patients associated with covid	h/o Oxygen use	No h/o oxygen use
Covid positive (16)	10	6
Post covid (6)	3	3

Table 6. showing mortality rate as per prior steroid use

Total deaths in Mucormycosis patients associated with covid	h/o Steroid use	No H/o steroid use
Covid positive (16)	16	0
Post covid (6)	5	1

**Figure 3.** MRI PNS and orbit with gadolinium contrast showing salt and pepper appearance of the left periorbital region

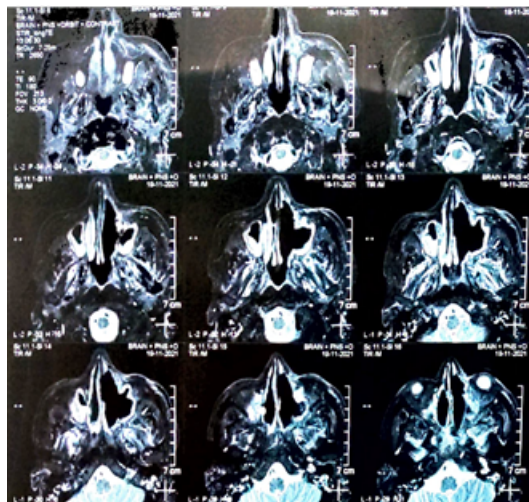


Figure 4. 14th day Post operative MRI with PNS with Orbit with contrast in a patient who had undergone B/L FESS with medial maxillectomy on the left side showing active disease in the right maxillary sinus

5. Discussion

The Mucorales fungus that causes Mucormycosis is aggressively virulent and typically found as a commensal in normal nasal mucosa. It typically manifests itself as an angioinvasive disease in the context of an underlying immunocompromised condition [16].

Often occurring risk factors for Mucormycosis include diabetes mellitus, diabetic ketoacidosis (DKA), solid organ or hematological cancers, neutropenia, high dosage corticosteroids, and the state following organ transplantation [17]. The etiology of Mucormycosis is primarily characterized by the presence of hyperglycemia, acidosis, elevated ketones, and free iron in combination with impaired phagocytic activity. Because to the reduced CD4 and CD8 cells, higher inflammatory cytokines, and frequent use of steroids, COVID-19 infection results in a compromised immune system [18–20].

Mucormycosis can be divided into ROCM, pulmonary, cutaneous, gastrointestinal, and diffuse varieties according on the affected anatomical region. Most instances are of the ROCM and secondly of pulmonary varieties; the former includes a range of restricted sino-nasal illness, limited rhino-orbital disease, and rhino-orbital-cerebral disease (ROCD) [2,19–23].

In comparison to CT, MRI offers a better assessment of intracranial and soft tissue extension. The criteria for Mucormycosis clinical diagnosis were first reported by Smith et al. in 1950 [24] is still regarded as the gold standard and includes characteristics such as black, necrotic turbinates, ipsilateral facial pain, peri-orbital or peri-nasal swelling with discoloration and induration, ptosis with proptosis of the eyeball and complete ophthalmoplegia, as well as numerous cranial nerve palsies unlinked to recorded lesions. There are published studies that show people with untreated diabetes had a significant risk of Mucormycosis even before the COVID-19 pandemic [23,25,26].

The early symptoms of Mucormycosis are similar to those of COVID-19: headache, fever, and nasal congestion [27]. Also, earlier ocular manifestation of Mucormycosis mimic the ocular manifestations of COVID-19 such as conjunctivitis, eye redness and excessive tearing which might have caused the delay in seeking further treatment in many of these cases, in fact many of these patients happened to present to us after they had already lost vision in one of their eyes [28,29]. Due to the close proximity and thin bones that separates the paranasal sinuses from the neighboring tissues (orbit and intracranial), after entering the nasal or oral cavity in this group of individuals, the fungal spores can readily enter these structures (cribriform plate and lateral lamella) [21,22]. Permanent blindness is seen when the Mucormycosis infection has advanced to the point where it affects the medial rectus muscle, optic nerve, and orbital apex tissues [30].

In our study, blindness was observed in 37 patients (32.74%). 27 patients with covid associated Mucormycosis developed blindness (32.92%) and 10 patients with no history of covid (32.2%).

Among patients with COVID-19, Song et al., Sen et al., and Sharma et al. found an elevated risk of Mucormycosis [2,13,15]. According to the large multicenter study of 2285 patients by Sen et al., [31] invasive fungal sinusitis can develop both concurrently with COVID-19 and after recovery. In this study 56% of

patients experienced Mucormycosis symptoms within 14 days of receiving a COVID-19 diagnosis. While 44% of patients had signs of Mucormycosis after recovering from COVID-19, further rises were observed on Days 15 and 20 with 10% and 7% of patients, respectively. Seven individuals were found to have delayed Mucormycosis three months after COVID-19.

Among the 82 patients with covid associated Mucormycosis in our investigation, the mean time between a COVID-19 positive RT-PCR and symptoms suggestive of onset of invasive fungal sinusitis was 23.7 days (range: 2-154). In our study, signs and symptoms appeared in 12.20% of patients within 2 days of RTPCR positivity, between 3 and 14 days in 19.51% of patients, between 15 and 30 days in 39% of the patients, and in 29.26% beyond 30 days following the diagnosis of COVID-19. Results showed that sinusitis, particularly in high-risk individuals, was a warning indicator in the immediate post-COVID-19 period. While 92% of patients had symptoms within three months of recovering from COVID-19, this study suggested the necessity for early ENT assessment and placed an emphasis on educating patients and family about the signs of invasive fungal sinusitis. Patients with early diagnosis and restricted illness progression had the greatest prognosis with the least amount of morbidity and death, according to observations [31]. In our own investigation, comparable results were seen. Also, there were major treatment issues for patients who tested positive at the time of diagnosis, including stopping steroids, getting fit for surgery, and undergoing surgery while donning a PPE outfit.

We had a 21.23% 30-day death rate (24/113 individuals). Those who underwent simultaneous medical and surgical treatment ($p < 0.001$) as well as those without concurrent covid positive status ($p > 0.05$) showed a greater rate of survival. Several Mucormycosis endoscopic findings in COVID-19 patients are shown in Figure 4. The surgical specimen that had been necrotic and debrided and that had been sent for histology and fungal staining showed broad-based irregular aseptate fungal hyphae with right-angled branching that resembled Mucormycosis. All patients received intravenous Amphotericin-B (3-5 mg/kg) after consulting with the department of medicine.

Of the 24 patients (21.23%) patients who succumbed to illness (despite immediate and intensive care), One patient had severe maxillary and orbital involvement (underwent orbital exenteration with maxillectomy), two patients had disease restricted to the paranasal sinuses, and eight patients had rhino-orbito-cerebral involvement. Due to significant post-COVID lung fibrosis, the later patients underwent endoscopic debridement and passed away on postoperative day 5, and day 7 respectively. 21 of 24 individuals who passed away from the condition had severe COVID 19 pneumonia and/or post covid pulmonary fibrosis, inadequate glycemic management, and prior history of steroid use.

In this study by, Skiada et al. it was found that the length of time that patients had been experiencing symptoms prior to being admitted, the location of the infection (rhino-orbital Mucormycosis with cranial extension) and concurrent covid 19 positive status have all been linked to higher mortality. On the other hand, prolonged antifungal medication and combination surgical and medicinal therapy were both independently related to improved survival [32]. Antifungal medications presumably penetrate necrosed tissue more effectively after surgical debridement, leading to improved results. Tragically, not all patients were fit to undergo major surgery for rhino-orbital illness. Patients with intracranial extension had a much higher mortality rate, and the majority couldn't be operated on. Mortality was high among patients who were unable to have surgery despite receiving proper antifungal medication, indicating the need for early identification and improved therapeutic approaches.

Even with rigorous debridement and intravenous antifungal medications, the prognosis for invasive fungal sinusitis is dismal, with documented fatality rates ranging from 33.3% to almost 100% in disseminated infections [9,33].

A study by Turner et al. showed a mortality rate of 50.3% in non-COVID-19 invasive fungal sinusitis. In the covid 19 pandemic scenario, multicenter studies performed by Singh et al. and Sen et al. show mortalities of 31% and 14%, respectively, in COVID-19-associated invasive fungal sinusitis. There is an increased risk of morbidity and death with intracranial and orbital expansion [31].

Poorer prognosis is directly correlated with delaying the start of Mucormycosis therapy [34]. According to prior research, individuals who begin therapy within six days after the beginning of symptoms have a survival percentage of 76%-81%, whereas those who wait longer than 12 days to seek medical attention have a lower survival rate of 36%-42% [35].

Hence, a higher index of suspicion in post-COVID-19 patients, early diagnosis, vigorous surgical debridement, and the administration of antifungals all contribute to a higher survival probability. The immune system, which, when severely damaged by COVID-19, needs to be salvaged. During the start of the pandemic we undertook FESS with denker's approach for most of the patients, as our experience with these patients increased we understood the need of aggressive debridement with exploration of areas around the the paranasal sinuses (retromaxillary/infratemporal, periorbital and premaxillary region) to be of vital importance in adequately managing the disease and improving survival outcomes. Another of point of note was the debilitating effect of orbital exenteration/evisceration operations, wherein in our study such was done only in 6 patients, 2 of whom did not survive in the post op period.

The strengths of our study include relatively large sample size for this rare but devastating disease, adherence to institutional protocol, histopathological confirmation in all cases.

6. Conclusion

The unexpected increase in Mucormycosis infections among COVID-19-infected individuals has been a big burden as well as a learning experience. Morbidity and death from MUCORMYCOSIS can be significantly decreased with early detection and treatment.

We found that the death rate and post treatment disability was considerably greater in MUCORMYCOSIS complicated COVID-19 cases compared to non-COVID-19 cases. A combination surgical and medicinal approach produced superior results. It is advisable to start a unified strategy as soon as feasible.

When required, corticosteroids should only be used sparingly and rigorous glycemic management is required due to the substantial correlation between hyperglycemia and steroid consumption and the development of Mucormycosis in both active and recovered COVID-19 patients Ultimately, doctors should work to abide by national and international regulations for their usage, and the over-the-counter selling of these medications should be outlawed.

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Conflicts of Interest: "Authors declare no conflict of interests."

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