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**Original Research Article**

# A Retrospective Study on Mucormycosis and Other Fungal Infections Associated With COVID-19

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## Abstract

A drastic increase in mucormycosis and other opportunistic infections was observed during the Covid-19 pandemic owing to multisystem involvement and related Immunosuppression. This retrospective study was carried out among SARS-COV-2 infected patients having invasive fungal infections [IFI] admitted to a tertiary care hospital in the southern part of India, for one year from August 2020. Among a total of 115 suspected cases, 54 patients were diagnosed to have IFI, during or immediately after Covid 19 disease. The most common fungal pathogens isolated were *Mucorales* (57.4%) followed by *Aspergillus* spp. (20.3%), *Candida* spp. (9.2%) and mixed infections (13.1%). Important predisposing factors identified were diabetes mellitus (70.7%), prolonged use of corticosteroids (85%), and administration of broad-spectrum antibiotics (90%). The predominant species identified among the diagnosed mucormycosis cases were *Rhizopus* spp. (54%) and *Mucor* spp. (25%); the site of involvement was paranasal sinus (70.1%), and rhino-orbital in 48.7% of the cases. Increased incidence of invasive *Aspergillus* infection in COVID-19 was seen mainly among ICU patients on ventilators, with Covid-19 induced lung damage. Common presentations were Chronic Pulmonary Aspergillosis, Rhino sinusitis, and Asthma. Of the total IFI, 9.2 % were caused by *Candida* spp. Of which 75% were due to Non- albicans candida species. Candidemia was the major presentation observed (90%). Of the patients with IFI, 90 % of them recovered, and the rest of them (7.4%) succumbed to infection. Of the patients with rhino-orbital mucormycosis who survived, 10 (39 %) had facial disfigurement and 11 (45 %) had a loss of vision.

**Keywords:** Mucormycosis, Covid -19, Invasive Fungal Infection, Immunosuppression, Rhinosinusitis.



## INTRODUCTION

Management of COVID-19 and associated complications has become a huge challenge to our healthcare system. Immunosuppression caused by SARS-CoV-2 per se and due to immune modulators like Corticosteroids, Tocilizumab, and JAK inhibitors along with broad-spectrum antibiotics may predispose to opportunistic fungal infections during or after Covid-19 infection [1]. *Mucorales*, *Aspergillus* spp., and *Candida* spp. has emerged as the major agents causing COVID-19 associated IFI. Mucormycosis was referred to as "black fungus" by vernacular media because of the characteristic blackening of the affected tissue due to necrosis and angio-invasion [2]. Mucormycota was ubiquitously present in the environment; the spores generated from various species may infect humans mainly via inhalation, inoculation, and rarely by ingestion. *Rhizopus arrhizus*, *Mucor* spp., and *Apophysomyces* are commonly isolated Mucorales from clinical samples [3]. Uncontrolled diabetes mellitus, ketoacidosis, renal failure, use of iron therapy, etc. predispose to mucormycosis. In patients with diabetic ketoacidosis, phagocytes become dysfunctional due to low pH; coupled with this, impaired chemotaxis and defective intracellular killing will predispose to infection [4]. Rhino-orbital mucormycosis is the most common clinical presentation followed by pulmonary, cutaneous, renal, gastrointestinal, and disseminated infections.

Several studies have reported higher rates of *Aspergillus* infection in COVID patients; mainly by the

species, *Aspergillus flavus and Aspergillus fumigatus* [5]. Paranasal sinuses and lungs are the primary sites affected. Usual clinical presentations of pulmonary aspergillosis are invasive pulmonary aspergillosis, chronic pulmonary aspergillosis, allergic broncho-pulmonary aspergillosis, chronic rhinosinusitis, and fungal asthma. Co morbidities like COPD, diabetes and factors like prolonged ventilation, Corticosteroid therapy, and ICU stays without proper infection control measures can predispose to IFI. Among Mucorales *Rhizopus* spp., *Cunninghamella* spp., *Saksenaena vasiformis* etc. Have higher angio-invasiveness and can lead to disseminated fungal infections as compared to other species which are mainly observed in immunocompromised and neutropenic patients [6, 7]. Invasive Zygomycete infections manifest as multiple cutaneous lesions, intracranial lesions, and pulmonary, or bloodstream infections because of the rapid progression of infection with angio-invasion, early prompt diagnosis and timely initiation of treatment are critical in these cases, which help in bringing down the mortality and complications associated with the disease.

## MATERIALS & METHODS

Covid 19 positive (by RT-PCR) or three months following COVID-19 infection with clinical features of IFI, admitted to the department of ENT and infectious diseases for one year from August 2020 were enrolled for the study. Detailed history, risk factors, and clinical manifestations of probable patients were captured from the case records according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC MSG CRITERIA) [8].

Samples received from probable IFI cases were biopsy specimens by FESS (Functional Endoscopic Sinus Surgery) and DNE (Direct Nasal Endoscopy), nasal crust, ear discharge, endotracheal aspirate, broncho-alveolar lavage, and blood samples depending on the clinical presentation. Specimens except blood samples were examined by direct microscopy using 10 % KOH and inoculated in Sabouraud Dextrose Agar (Micro expressLOT No: SDA 1304) in sterile tubes for culture (two sets each with and without Cycloheximide) followed by incubation at 22ºC and 37ºC for a period of one month.

The presence of fungal growth was monitored daily for up to one week, then twice weekly for up to one month. Lactophenol Cotton Blue (LPCB) staining of positive cultures (Figure 1, A-D) was carried out for identification. For visualizing better morphology, microculture techniques were employed under sterile conditions. In culture-confirmed cases, the clinical relevance of the isolate was ascertained by clinical and radiological correlation.

## RESULTS

This study reflects the clinical-mycological profile, morbidity, mortality, and risk factors related to various IFIs in patients with SARS-CoV2 infection. Of the total 115 suspected cases, 54(47%) of them were confirmed to have IFI during or after Covid-19 infection according to EORTC MSG Criteria. Among culture-positive cases, the majority were males (70%), and 68.2% of them belonged to the age group 60-80 years reflecting the overall age group which got affected by severe COVID-19. Paranasal sinus involvement [maxillary/ethmoid/frontal sinus] was present in more than 76% and orbital extension was found in 48 % of the cases. *Rhizopus spp*. (31.4%) *Mucor* spp. (14.8%*)*, *Aspergillus* spp. (9.2%), and *Candida* spp. (9.2%) were the major isolates, followed by *Rhizomucor* spp. *(*3.7%), *Cunninghamella* spp. (3.7%) and *Syncephalastrum* spp. (3.7%) mixed infection with Mucorales and *Aspergillus* spp. was noted in 24.3 % of the cases. In rhino-orbital mucormycosis, enucleation and repeated surgical debridement were indispensable in 47% of cases. Postoperatively, these cases ended up with facial disfigurement (39%) and loss of vision (45%) as sequelae.

In our study group, 70 % of patients were diabetic, and among them, more than 85% had uncontrolled blood glucose levels. Covid-19 related illness and sequelae led to prolongation of inpatient stay for an average of more than 20 days in more than 90% of the study population. Use of corticosteroids like methylprednisolone/dexamethasone, for more than two weeks, was noted in 90% of the patients, and most of them (82.7%) received broad-spectrum antibiotics during the treatment period. Chronic kidney disease was observed in 20 % of patients. *Rhizopus* spp. followed by *Candida* spp. were the agents noted in this group with mortality of more than 90%.

The disease showed various presentations including headache, unilateral facial pain (60%), decreased vision (30%), and facial palsy (5%). KOH mount performed on various samples showed 68% positivity for fungal elements. All mucormycosis cases were managed by Liposomal Amphotericin B (5mg/kg/day for 3-6 weeks, in cases of intracranial involvement a higher dose of 10 mg/kg/day was preferred). The majority showed improvement with LAMB; after reaching a cumulative dose of 3-5 gm, consolidation therapy was initiated with Posaconazole (Posaconazole 300 mg BD followed by 300 mg OD). CAPA (Covid Associated Pulmonary Aspergillosis) cases, positive for Aspergillus by culture, were managed by Voriconazole; and cases positive for both Aspergillus and Mucorales (probable co-infection) were administered LAMB. Acute Invasive Fungal Sinusitis (AIFS) cases with marked mucosal thickening and nasal cavity opacification (as radiological findings) were managed by sinus surgery, and debridement coupled

with antifungal therapy. About 90% of candida infections were treated with fluconazole alone, and two cases required caspofungin therapy. Lack of species identification and antifungal susceptibility testing was a major limiting factor. Even with early diagnosis and proper management, four deaths were reported due to IFI, mainly by the agents *Rhizopus* spp. (75%) and *Candida* spp. (25%).

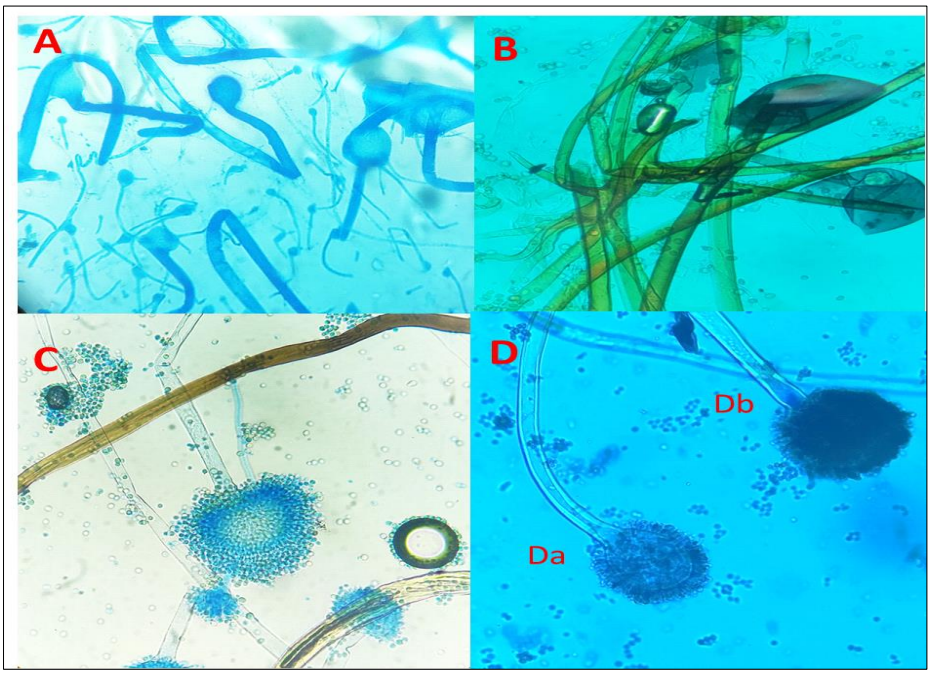


**Fig. 1: Lacto phenol cotton blue (LPCB) staining of the fugal pathogens obtained. A, B, C, D (Da), (Db).**

A: LPCB of fungal growth from nasal scrapings- showing wide ribbon-like twisted hyphae without rhizoids, sporangiophore, and oval sporangia- *Mucor* spp. B: LPCB showing wide hyphae, and rhizoids beneath the sporangiophore- *Rhizopus* spp.C: Fungal growth from DNE specimen showing ribbon-like twisted hyphae and merosporangia –*Syncephalastrum* spp. D: Mixed fungal infections from FESS specimen showing *A.flavus and A.niger.* Da: LPCB showing hyaline septate hyphae with subglobose vesicle, biseriate phialides, radiate over most of the vesicles -suggestive of *Aspergillus flavus.* Db: LPCB showing hyaline septate hyphae with globose vesicle, biseriate phialide, and black echinulate conidia -suggestive of *Aspergillus niger.*

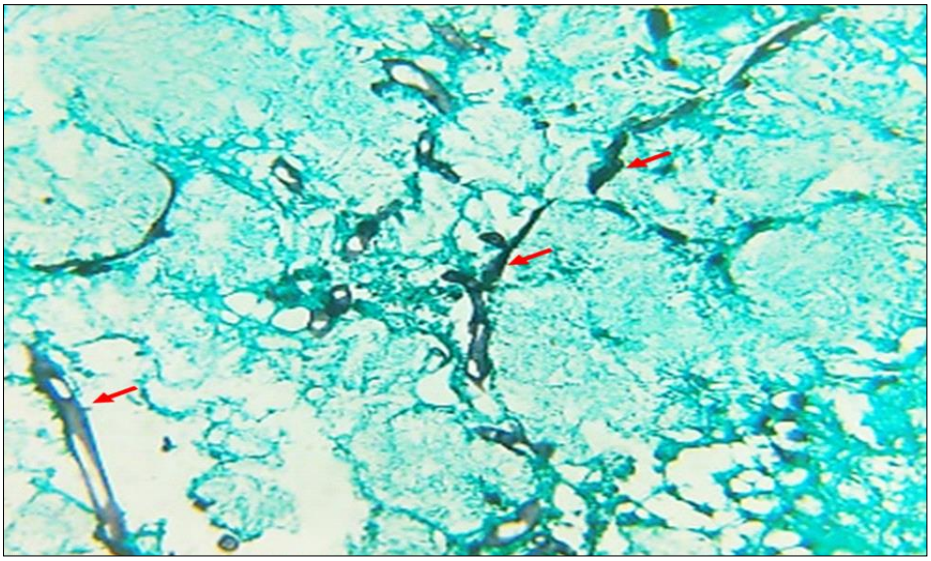

**Fig. 2: Gomori Methenamine silver staining of FESS specimen showing broad non-parallel hyphae- suggestive of Zygomycetes**

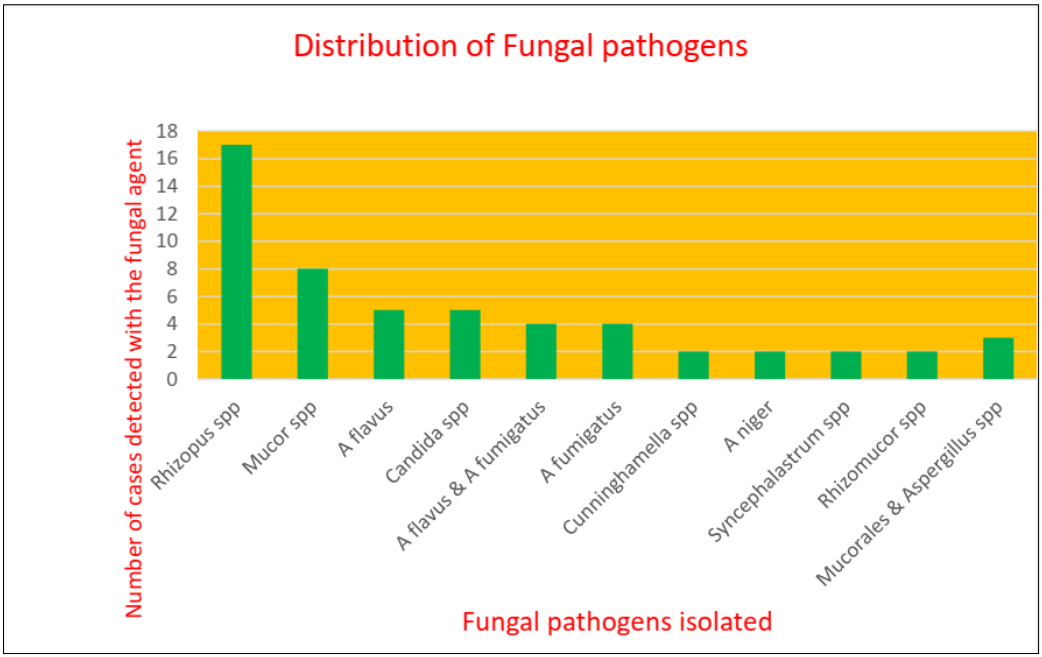


**Fig. 3: Shows the distribution of various fungal pathogens in Covid 19 disease during or after the illness**

**Table 1: Various risk factors and sites of involvement In *Aspergillus* infections**

| Agent | Percentage of isolates | Site involved | Duration of hospital stay more than 2 weeks | Use of Oxygen mask and ventilator | Uncontrolled DM |
|---|---|---|---|---|---|
| *A. flavus* | 9.20% | PNS (80%) +LRT (30%) | >90% of cases | >82% of cases | 89% cases |
| *A.niger* | 3.70% | PNS (>85%) | >85% cases | >80ases | 86% cases |
| *A.flavus& A. fumigatus* | 7.40% | PNS (85%) + EYE(67%) | >90% of cases | >87% of cases | 90% cases |
| *Mucorales& Aspergillus* co infection | 5.50% | PNS (88%) +EYE (65%) + LRT (57%) | >97% of cases | >80% of cases | 84% cases |

## DISCUSSION

Opportunistic fungal infections especially mucormycosis have increasingly been reported from India during Covid 19 pandemic. The study conducted by AK Singh *et al.*, in May 2021 depicts the increased incidence of opportunistic fungal infections mainly by Mucorales in SARS-CoV-2 infection [1]. We made the same observation in our system with Covid positive patients. Along with the aggressive virus, uncontrolled diabetes mellitus, chronic steroid therapy, use of broad-spectrum antibiotics, ventilator support, nasal oxygenation, chronic kidney disease, etc. help the fungal agents to invade the host easily. Rhino orbital involvement was the common manifestation observed, which correlates with the study conducted by Nehra H R *et al.*, in the north-western part of India [2].

### Risk Factors

38 patients (70%) of the group were having diabetes mellitus, among them, more than 85 % reported having uncontrolled blood glucose levels even after insulin therapy and oral hypoglycaemic agents. We analyzed other risk factors, chronic kidney disease (20%), prolonged steroid therapy (80%), history of usage of broad-spectrum antibiotics (90%), and an increased hospital stay of more than 15 days played a major role in the development of Covid related fungal infections. Severe and Critical Covid cases were affected more than mild and moderate cases, 42% of patients developed symptoms within three weeks of covid infection. Analysis of events during covid treatment revealed that more than 40 % needed ICU to stay, 15 % had undergone invasive procedures, and more than 45% were on nasal cannulation. These findings are closely related to the study conducted by Mishra N *et al.*, In their study, they found that there was an increase in the incidence of mucormycosis following post-COVID-19 infection. On retrospective analysis of the patient's records, they found that 60% of patients had received steroids and the majority had co-morbidities. They concluded that patients with COVID-19 infection are susceptible to mucormycosis because of impairment of barrier defense, dysfunction of phagocytes, lymphocytes and the use of immunosuppressive medications such as steroids and Tocilizumab [4].

**Clinical Features**

In a study by Ritu Arora, out of 60 patients, 35 patients (58%) had ocular/orbital involvement at presentation. In the affected eye, 10 had no perception of light and the rest of the patients had diminished visual acuity. Ocular manifestations were ptosis (29), ophthalmoplegia (23), periocular tenderness /edema (33), proptosis (14), black discoloration of eyelids (3), facial palsy (3), endophthalmitis (4), retinal artery occlusion (8), disc edema (4) and disc pallor (5) [5]. These findings of the study closely resemble our results. More than 70 % of patients had facial pain; other presentations were loss of vision (24%), facial palsy (5%), redness over the face (35%), nasal crusts, blackening of the palate, etc. Paranasal sinuses and eyes were involved more as compared to other sites. (Fig 4&5)

The majority of fungal lower respiratory infections in Covid were attributed to *Aspergillus spp*, particularly in patients with a history of long-term ICU stay and/or use of oxygen masks/ventilators. *Aspergillus* is an indoor as well as outdoor mold and is present in humid environments. Increased incidence of CAPA is sometimes missed, as the clinical as well as radiological findings resemble Covid-related changes [9].

**Etiological Agents Involved**

In this study, the common etiological agents (Figure 3) were *Mucorales* followed by *Aspergillus* spp. and *Candida* spp. Among Mucorales, *Rhizopus spp*. Was the most common type and was associated with severe infections implicating the virulence and pathogenicity of this species. A study conducted by Valliappan Muthu *et al*., showed Covid Associated Mucormycosis (CAM) is reported more in India as compared to the rest of the world and the most common species obtained was *Rhizopus arrhizus* [10].

In CKD patients also, *Rhizopus* spp. was identified as the common agent and increased mortality was observed in these cases also. *Rhizopus arrizhus* is the common agent diagnosed in CAM in various studies [9]. Usually, *Syncephalasrum* spp. is a laboratory contaminant; however, this fungus was isolated from two of our cases satisfying the diagnostic criteria. In these cases, repeated culture from lesions together with clinical as well as radiological correlation proved the etiology. These patients showed better responses to treatment when compared to others.

CAPA was an alarming disease during the second wave of Covid -19 pandemic in India. Unsanitary vents, tubing, humidifiers, and oxygen masks, might have led to direct spread through inhalation of conidia of *Aspergillus* spp. resulting in co-infection in Covid -19 [10, 11]. In this study, 25% of the cases were diagnosed to have an infection by *Aspergillus* spp. Table 1 depicts the various *Aspergillus* spp. involved, site of involvement, and risk factors associated. Prolonged hospital stays (> 2 weeks), and use of oxygen masks and ventilators (>80% cases) resulted in an increased incidence of CAPA. Clinical and radiological changes in Covid- 19 infection are similar to the manifestation of CAPA. So proper diagnosis of CAPA and other *Aspergillus* infections is a big challenge for treating [11]. The use of galactomannan assay to detect invasive aspergillosis in CAPA helps to tackle the situation [12].

Although *Candida albicans* remains the most common agent of superficial and deep fungal infections, an increasing incidence of non-albicans candida species like *C.tropicalis*, *C.krusei*, *C.glabrata*, *and C parapsilosis*is is seen, and tend to be less susceptible to azoles mainly fluconazole. *Candida auris* has emerged as an important nosocomial pathogen with clonal inter and intra-hospital transmission. In our study, 9.2% of patients were diagnosed to have an infection with *Candida* spp. and we lost one patient due to candidemia even after early therapy with caspofungin.

**Radiological Findings**

Radiological findings on CT/MRI of the paranasal sinus and brain, help to study the extent of the disease as well as the degree of involvement of IFI. On CT, bone erosion or mucosal thickening may be subtle. The finding of extra sinus extension is described as an early and characteristic finding suggestive of AIFS (Acute Invasive Fungal Sinusitis). The commonest early CT finding of sinus and nasal cavity involvement is marked mucosal thickening and nasal cavity opacification. These findings appear earlier than osseous erosion or extra sinus extension. "Black turbinate sign "on post-contrast MRI – a non-enhancing devitalized tissue contrasting with the typical mucosal enhancement is seen in mucormycosis [13]. CT of paranasal sinus of ROM cases showed bony erosion, while MRI provides a better view of sinus opacification, tissue infiltration (> 95% cases) orbital and intracranial involvement. (Figure 4&5) Early orbital changes include inflammatory changes in orbit fat and extraocular muscles and resulting proptosis, which can be better identified radiologically. It is important to rule out cerebral infarction or subarachnoid hemorrhage due to thrombosis of the carotid artery or a mycotic aneurysm in AIFR. All patients with features of IFI with sinus and rhino orbital involvement had undergone CT/MRI on the day of admission and repeated worsening of symptoms to rule out the extension of disease after clinical cure.

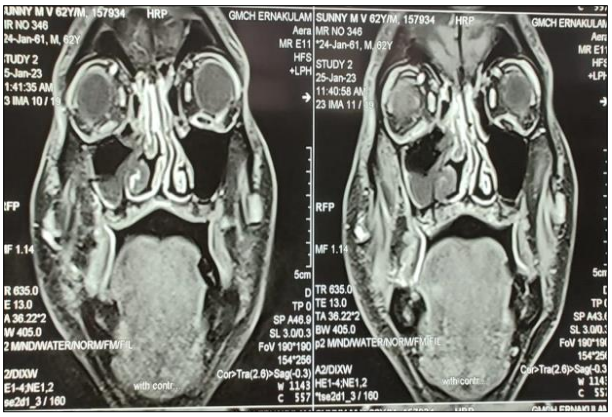

**Fig. 4: MRI (Nose, PNS & Orbit) T1W1+Contrast: Lack of enhancement of right inferior and middle turbinate (Black Turbinate sign)**

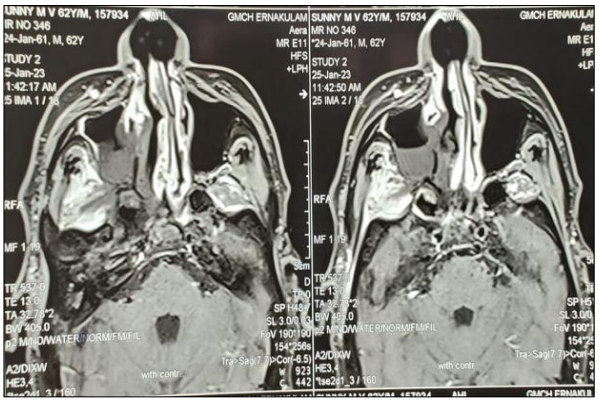

**Fig. 5: MRI TIWI+ Contrast (Axial and Coronal sections): ill defined non- enhancing soft tissue posteriorly obliterating retro-antral fat right extending to pterygopalatine fossa and infratemporal fossa**

**Treatment**

The mainstay of treatment of IFI is reverting the underlying immunosuppression (ketoacidosis, neutropenia, etc), along with surgical debridement and appropriate antifungal therapy. Proper glycaemic control is needed throughout the therapy. Surgical correction, either endoscopic or open, aims to confirm the diagnosis and remove non-viable tissue. In a study conducted by Turner *et al.*, patients who underwent endoscopic surgery had improved survival as compared to open surgery in orbital exenteration and are advisable only for a completely non-functioning eye [15]. In our study more than 70% cases were managed surgically to remove devitalized tissue by endoscopic approach (DNE, FESS). In cases with orbital involvement and complete loss of vision, enucleation was done, and 25-30% of cases were managed by maxillectomy followed by reconstruction surgeries.

Broad-spectrum antifungal agents should be started as early as diagnosis of AIFR is suspected. Amphotericin B, a polyene antifungal, is used as the mainstay of treatment before the identification of fungal agents which covers mucormycosis as well as aspergillosis. Liposomal preparations (LAMB) are preferred due to lesser nephrotoxicity and can be used at higher concentrations for longer.

Almost all cases of suspected mucormycosis were managed by intravenous LAMB and switched to oral Posaconazole (300 mg BD for one day followed by 300mg OD for 3-6 months) after clinical and radiological improvement. Proper surgical debridement and antifungal therapy play a major role in the management of mucormycosis. In a study conducted by skiada *et al.*, in laiko hospital Greece, where they treated the patients with LAMB along with Posaconazole and Isavuconazole; and observed better effects. But when we go through our cases, it is evident that proper surgical debridement along with LAMB followed by consolidation therapy with Posaconazole is enough for CAM [14, 15].

Non-invasive infections by *Aspergillus* spp. Were managed by suction clearance and FESS. IFI with *Aspergillus* spp.was tackled by intravenous voriconazole (6mg/kg IV for 2 doses, followed by 4 mg/kg IV 12 hourly) later deescalated to oral voriconazole. It is now recommended as the treatment for invasive aspergillosis of sinuses by IDSA. Co-infection with *Mucorales* and *Aspergillus* spp. was managed by proper surgical correction and LAMB. A randomized trial showed voriconazole led to improved survival in invasive aspergillosis as compared to liposomal Amphotericin B [16].

As per IDSA guidelines, suspected invasive *Candida* infections should be empirically managed with intravenous caspofungin 70 mg loading dose, followed by 50 mg I.V QID or Anidulafungin 200 mg IV loading dose followed by 100 mg IV (QID). After species identification, for less resistant species like *C. albicans, C. parapsilosis, C. tropicalis etc*, therapy can be stepped down to Fluconazole. In our center, Invasive *Candida* infections were managed by intravenous fluconazole, and only two cases required caspofungin therapy.

**Morbidity and Related Mortality**

Even with the prompt diagnosis and the management mortality rate was 7.4% even after management with enucleation, extensive maxillectomy, and LAMB, among that, two were CKD patients.A study conducted by *Velliappan muthu et.al* .showed fatality rate of cases reported from India (36.5%) was less than the globally reported cases (61.9%) [17]. Haemodialysis and the multiorgan damage in CKD play a vital role in the pathogenesis of opportunistic infections. Invasive fungal infections in immunocompromised have more mortality and morbidity as compared to healthy individuals. Glycemic control, proper surgical debridement, adequate choice, and duration of antifungal therapy decide the outcome of IFI.

## CONCLUSION

Opportunistic fungal infections in COVID-19 disease have higher morbidity and mortality. Proper management during Covid infections and the judicious use of antibiotics and steroids will help to reduce the number of cases. Early diagnosis and management of IFI are necessary to prevent the disease sequelae. The number of opportunistic infections during the COVID-19 pandemic strongly suggests the need for rapid diagnostic kits to diagnose the agents and the importance of antifungal susceptibility testing in our laboratories. The virulence and pathogenicity of various agents should be studied in detail to access the genetic changes that occurred in the agent in near future. Point-of-care test with good sensitivity is much needed to combat these terrible bugs.

### Limitations

We didn't differentiate patients based on the treatment they received during admission for COVID-19. Other limitations were the retrospective nature of the study, lack of identification of *Candida* species, absence of long-term follow-up of infective cases. We couldn't analyze the variation in the type of amphotericin received among various patients. Antifungal susceptibility of the isolates and therapeutic drug monitoring for Voriconazole or Posaconazole levels were not done in the study.

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**Conflict of Interest:** Nil

## REFERENCES

1. Singh, A. K., Singh, R., Joshi, S. R., & Misra, A. (2021). Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *15*(4), 102146.
2. Nehara, H. R., Puri, I., Singhal, V., Sunil, I. H., Bishnoi, B. R., & Sirohi, P. (2021). Rhinocerebral mucormycosis in COVID-19 patient with diabetes a deadly trio: Case series from the north-western part of India. *Indian Journal of Medical Microbiology*, *39*(3), 380-383.
3. Yu, J., Walther, G., Van Diepeningen, A. D., Gerrits Van Den Ende, A. H. G., Li, R. Y., Moussa, T. A. A., ... & De Hoog, G. S. (2014). DNA barcoding of clinically relevant Cunninghamella species. *Sabouraudia*, *53*(2), 99-106.
4. Mishra, N., Mutya, V. S. S., Thomas, A., Rai, G., Reddy, B., Mohanan, A. A., ... & Hegde, R. (2021). A case series of invasive mucormycosis in patients with COVID-19 infection. *Int J Otorhinolaryngol Head Neck Surg*, *7*(5), 867-870.
5. Arora, R., Goel, R., Khanam, S., Kumar, S., Shah, S., Singh, S., ... & Pant, R. (2021). Rhino-orbito-cerebral-mucormycosis during the COVID-19 second wave in 2021–a preliminary report from a single hospital. *Clinical Ophthalmology*, 3505-3514.
6. Jeong, W., Keighley, C., Wolfe, R., Lee, W. L., Slavin, M. A., Kong, D. C. M., & Chen, S. A. (2019). The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clinical microbiology and infection*, *25*(1), 26-34.
7. Gomes, M. Z., Lewis, R. E., & Kontoyiannis, D. P. (2011). Mucormycosis caused by unusual mucormycetes, non-Rhizopus,-Mucor, and-Lichtheimia species. *Clinical Microbiology Reviews*, *24*(2), 411-445.
8. Donnelly, J. P., Chen, S. C., Kauffman, C. A., Steinbach, W. J., Baddley, J. W., Verweij, P. E., ... & Pappas, P. G. (2020). Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clinical Infectious Diseases*, *71*(6), 1367-1376.
9. Ghazi, B. K., Rackimuthu, S., Wara, U. U., Mohan, A., Khawaja, U. A., Ahmad, S., ... & Essar, M. Y. (2021). Rampant increase in cases of mucormycosis in India and Pakistan: a serious cause for concern during the ongoing COVID-19 pandemic. *The American Journal of Tropical Medicine and Hygiene*, *105*(5), 1144.
10. Muthu, V., Rudramurthy, S. M., Chakrabarti, A., & Agarwal, R. (2021). Epidemiology and pathophysiology of COVID-19-associated mucormycosis: India versus the rest of the world. *Mycopathologia*, *186*(6), 739-754.
11. Lei, Y, J. (2020). MicrobiolImmunol Infect, S1684-1182(20)30124-9.
12. Rackimuthu, S., Khan, H., Mohan, A., Hunain, R., Ghazi, B. K., Hasan, M. M., ... & Essar, M. Y. (2021). Emergence of a medley of invasive fungal infections amidst the coronavirus disease 2019 (COVID-19) pandemic in India. *Antimicrobial Stewardship & Healthcare Epidemiology*, *1*(1), e40.
13. DelGaudio, J. M., Swain, R. E., Muller, S., & Hudgins, P. A. (2003). Computed tomographic findings in patients with invasive fungal sinusitis. *Archives of Otolaryngology–Head & Neck Surgery*, *129*(2), 236-240.
14. Skiada, A., Lass-Floerl, C., Klimko, N., Ibrahim, A., Roilides, E., & Petrikkos, G. (2018). Challenges in

the diagnosis and treatment of mucormycosis. *Medical mycology*, *56*(suppl_1), S93-S101.

15. https://dhs.kerala.gov.in/wp-content/uploads/2021/05/Guidelines-Mucormycosis-management.pdf
16. Donnelly, J. P., Chen, S. C., Kauffman, C. A., Steinbach, W. J., Baddley, J. W., Verweij, P. E., ... & Pappas, P. G. (2020). Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clinical Infectious Diseases*, *71*(6), 1367-1376.
17. Herbrecht, R., Denning, D. W., Patterson, T. F., Bennett, J. E., Greene, R. E., Oestmann, J. W., ... & De Pauw, B. (2002). Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *New England Journal of Medicine*, *347*(6), 408-415.