Original Research Article

Mucormycosis in COVID-19 pandemic: Study involving tertiary hospitals in Aurangabad District

Abstract

Introduction-Throughout the second wave of COVID-19, cases of mucormycosis were increased suddenly during this period in India. A collective study was conducted in tertiary care hospitals in Aurangabad.

Materials and methods - A retrospective descriptive study was carried out in Aurangabad (Maharashtra), in association with the Aurangabad Municipal Corporation (AMC), oralcare.co.in and SNDH Hospital, Aurangabad. Data was collected by AMC from 3 major tertiary hospitals present in Aurangabad where treatment of mucormycosis was done from May 2021 to July 2021. The data of total 135 patients with mucormycosis was received by the AMC were included in the study. It included demographics of the patients, medical and clinical history, history of COVID 19, treatment of COVID 19 (use of steroids in COVID-19 treatment, use of immunosuppressant drugs, oxygen therapy), type of mucormycosis, treatment and outcomes of mucormycosis.

Results- In the present study, 74.7% of mucormycosis patients were males. 77.4% of mucormycosis patients were above 50 years of age. Diabetes mellitus was the most common risk factor seen in 67% of patients with mucormycosis. About 87.4% of patients with mucormycosis had a history of COVID-19. Majority of the patients in the study population were diagnosed with the rhino-maxillary-orbital type of mucormycosis which is 39%, followed by the rhino-cerebral type-25%. Only 1% patients showed rhiono-nasal -orbital type of mucormycosis. 30% patients were not categorised into any type. All the patients in the study population received amphotericin B and surgical treatment. About 84.4% patients were discharged after the mucormycosis treatment. 15.6% patients died during or after the treatment.

Conclusion-Mucormycosis was predominantly seen in male above the age of 50 years, COVID-19 infection and diabetes mellitus was common risk factor for mucormycosis.

Keywords- COVID-19 · Mucormycosis · Rhino-cerebroorbital · Diabetes, etc

Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS COV 2) has created mayhem all over the world [1]. The association of SARS COV 2 with a gamut of opportunistic of fungal and bacterial infections made it more overwhelming for the health care systems globally, especially in the developing countries [2]. During the second wave of SARS COV2 the surge of covid 19 associated mucormycosis in India was unanticipated and devastating due to its rapid spread, high morbidity and mortality rates and the limitation of antifungal drugs [3]. In the peak months of mucormycosis in india (May to July 2021), more than 47,000 cases were reported and the actual figures certainly will be higher [2].

The term 'Mucormycosis' was coined by Dr. R. D. Baker, an American pathologist [4]. Mucormycosis is also known as zygomycosis and amongst the lay people it is popular as black fungus. Mucormycosis is an opportunistic fungal infection caused by the organisms, Mucorales, who are active in instigation and speeding the decay of organic materials [5]. It was an infection which was once very rare and affected the immunocompromised individuals. The incidence mucormycosis varies in the range of 0.003 – 0.005– 1.7 million of the population [4,6,7] But the picture changed spontaneously during the second wave of COVID 19 in India. In India, mucormycosis was seen in 0.14 per 1000 population, which was about 80 times higher as compared to developed countries [8].

Mucormycosis presents itself in varuios forms based on the anatomical site of involvement. It can be classified into rhino-orbito-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal, disseminated and other miscellaneous forms, which include infection of bones, heart, ear, parotid gland, uterus, urinary bladder and lymph [9,10]. It was observed that rhino-orbital cerebral mucormycosis was the most frequent disease seen in the post COVID mucormycosis patients in India, alos accounting for the highest mortality[11]. The hallmark of mucormycosis is tissue necrosis resulting from angioinvasion and thrombosis [4]. The common symptoms seen in the post COVID mucormycosis patients were headache, fever, facial swelling(unilateral), orbital cellulitis, palpebral edema, ptosis, chemosis and ophthalmoplegia [12].

It has been noted that in the developing counteries, especially in india the most common predisposing factors were Diabetes mellitus which is contrasting the haematological malignancies and history of transplants in the developing countries[13,14]. Three important case series from India stated diabetes as a

risk factor over 50% cases with mucormycosis [15]. Although aggressive surgery was done in all patients of mucormycosis, the death rate in mucormycosis remained high.

The present study aimed to study the association between COVID 19 and mucormycosis, risk factors associated with mucormycosis and the outcomes of the treatment of mucormycosis.

Materials and methods

A retrospective descriptive study was carried out in Aurangabad (Maharashtra), in association with the Aurangabad Municipal Corporation, oralcare.co.in and SNDH Hospital, Aurangabad. Data was collected by AMC from all the tertiary hospitals present in Aurangabad where treatment of mucormycosis was done from May 2021 to July 2021. The study was approved by the Instituional Ethical Committee of SNDH. The data of total 135 patients with mucormycosis was received by the AMCwere included in the study. All patients included in the present study were microbiology and or histopathology confirmed cases of mucormycosis. All mucormycosis patients regardless of COVID-19 status were included in the study. The data provided by the hospital was sent in a predefined format provided by AMC for uniform data entery. It included demographics of the patients, medical and clinical history, history of COVID 19, use of steroids in COVID-19 treatment, use of immunosuppressant drugs, oxygen therapy,type of mucormycosis, treatment of mucormycosis. Diagnostic endoscopy was done in all patients and KOH testing was done and an RT-PCR for COVID 19 infection confirmation. All patients had a CT, CBCT or MRI of PNS and brain depending on the presentation of the patient. All patients were done all routine blood investigations.

The data of all the patients was not completely filled in all the areas, for such patients the missing data was directly taken from the records of the respective hospitals after the list was received.

Results

1. Gender distribution

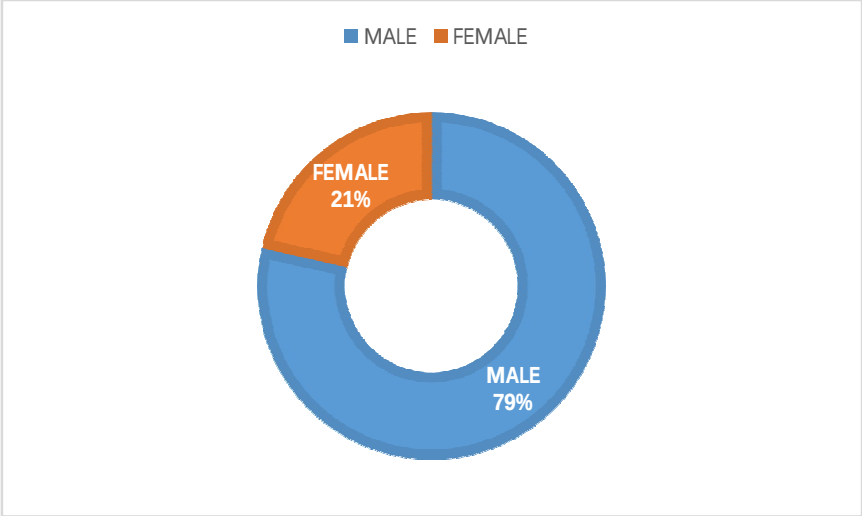

Fig 1. Sex distibution in study population

2. Age distribution in the study population

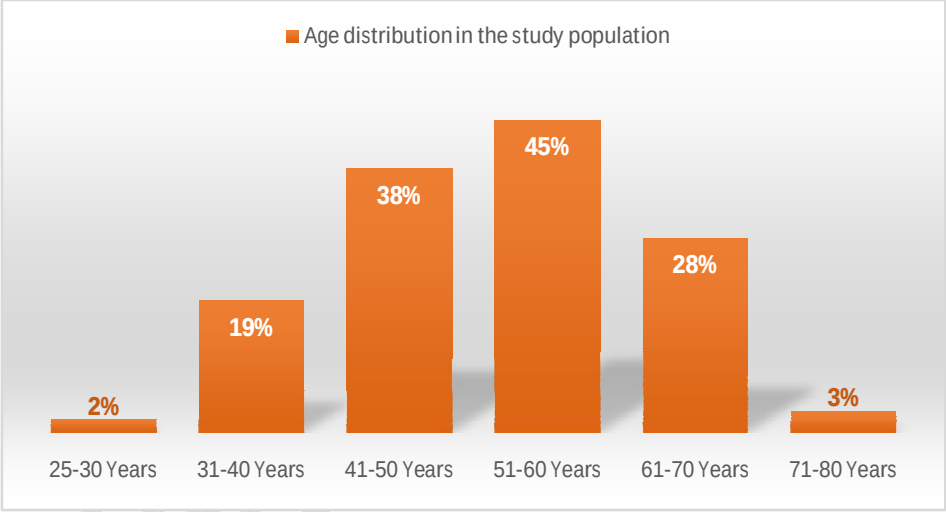

Fig 2. Age distribution in the study population

3. Comorbidities in the study population

Table 1. Comorbidities in the study population

COMORBIDITY	**No of patients N= 135**	**Percentage (%)**

DM	72	53
HTN	16	12
DM AND HTN	19	14
MORE THAN 2	7	5
OTHER	8	6
NONE	13	10

Table 2. COVID-19 status in mucormycosis patient

Mucormycosis patients	**No. of patients (N= 135)**	**Percentage (%)**
H/o COVID-19-positive	118	87.4%
***No** H/O COVID-19-positive*	17	12.6%

Table 3. COVID-19 vaccination status in mucormycosis patient

Mucormycosis patients	**No. of patients (N= 135)**	**Percentage (%)**
Vaccinated	6	4.4%
***No**n vaccinated*	129	85.6%

Table 4. COVID-19 treatment history

COVID treatment	**No of patients N= 118**	**Percentage (%)**
O2 AND STEROID	76	64.4
ONLY O2 and ICU	14	11.8
ONLY STEROID	12	10.2
NOT KNOWN	16	13.6

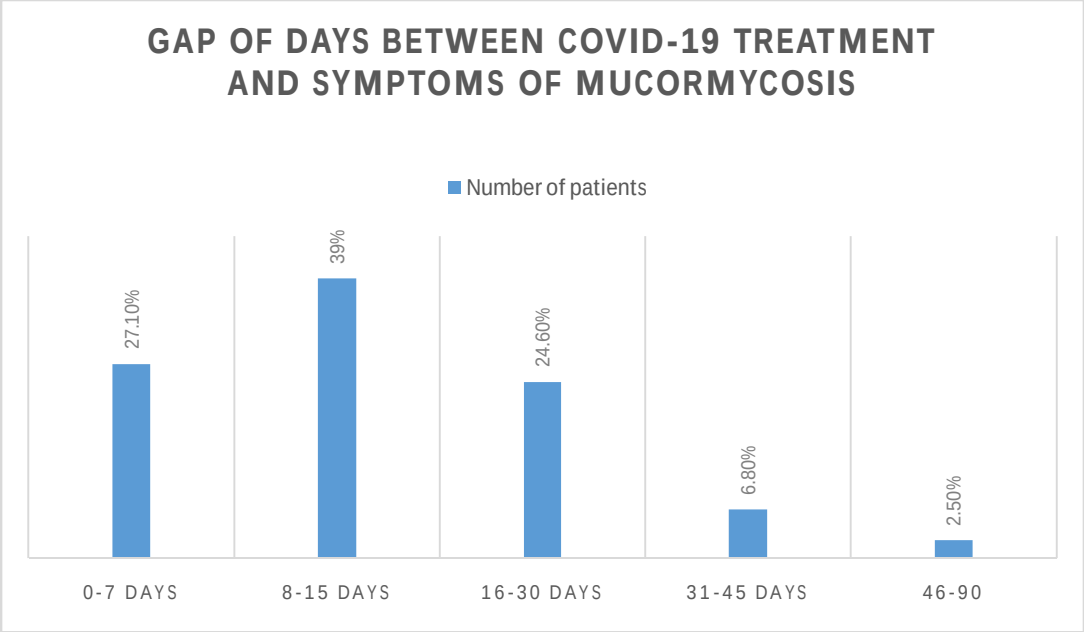

Fig 3. Gap between COVID-19 treatment and symptoms of mucormycosis

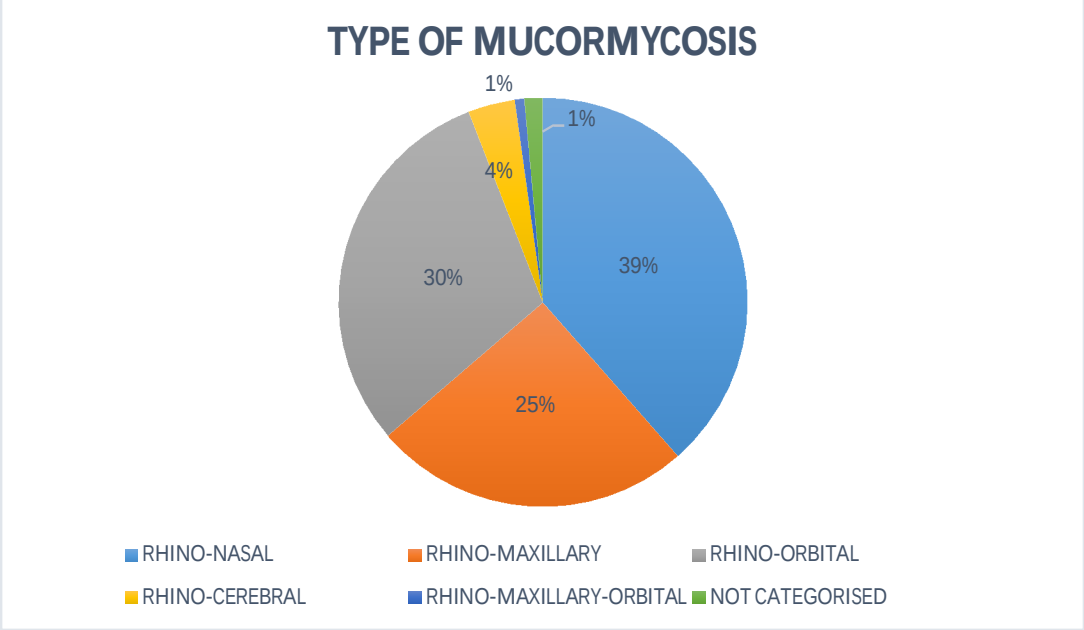

Fig 4. **Type of Mucormycosis seen in the study population**

Table 5. OUTCOMES OF MUCORMYCOSIS PATIENTS

Outcomes of mucormycosis treatment	**N= 135**	**Percentage**
Discharged	114	84.4
Death	21	15.6

Table 6. Prognosis of mucormycosis patients

Mucormycosis patients	**No of patients recovered**	**No of patients dead**	**Total**
Diabetic patients	76	21	97
Vaccinated patients	5	1	6
Recurrence	1	0	1
Discharged against medical advice	5	0	5

Age and sex distribution in the study population

In the present study, 74.7% of mucormycosis patients were males and 66% of mucormycosis patients were females (Fig. 1). 77.4% of mucormycosis patients were above 50 years of age and no patient was under 25 years of age. The youngest patient was 27 years old while the oldest was 73 years of age.(Fig. 2).

Risk factors associated with mucormycosis

In the present study, diabetes mellitus was the most common risk factor seen in 67% of patients with mucormycosis. 53% were having only diabetes mellitus, 12% were having only hypertension and in 14% both diabetes and hypertension was seen. Patients with more than 2 comorbidities contributed to 5 % of total population. While 6 % patients reported other comorbidities like chronic kidney disease, hypothyroidism, CVSD. About 24% patients reported to have no any co morbidity.

COVID 19 infection and mucormycosis

In the present study, 87.4% of patients with mucormycosis had a COVID-19 infection while 12.6% patients had no any record of COVID 19 infection. Looking at the treatment of COVID 19, 64.4% patients received oxygen therapy as well as steroids. 13.6% patients had no record of the type of COVID 19 treatment.

In the present study, 80% of patients were present during COVID-19 treatment and within 15 days of COVID-19 infection. No patient with mucormycosis was presented after 3 months of COVID-19 infection.

Type of mucormycosis

The majority of the patients in the study population were diagnosed with the rhino-maxillary-orbital type -39%, followed by the rhino-cerebral type-25%. Only 1% patients showed only rhiono-nasal and only rhino-orbital type. 30% patients were not categorised into any type.

Outcomes of mucormycosis treatment

All the patients in the study population received amphotericin B and surgical treatment. Multiple surgeries were done to remove all necrotic areas from nose, sinuses, palate, maxilla, pterygopalatine fossa, infratemporal fossa and mandible including orbital externeration and in case of cerebral involvement, extensive areas were involved.

About 84.4% patients were discharged after the mucormycosis treatment. 15.6% patients died during or after the treatment. About 28.8% patients underwent maxillectomy, 35.3% patients underwent orbital externeration and 6% patients were treated by cerebral surgery.

Out of 15.6% deaths all the patients were diabetics and had extensive involvement including the orbits and cerebral. One patient who was vaccinated died during the treatment. One patient was re-admitted due to complications. 5 patients were discharged against medical advice.

Discussion

Mucormycosis is an uncommon but fatal fungal infection caused by a group of molds collectively called mucormycetes. The mold fungi belong to Rhizopus, Mucor, Rhizomucor, Cunninghamella, and Absidia [17].

This fungus shows the ability to impair the internal lamina of blood vessels, predominantly the arteries, lymphatics, and veins by toxic and mechanical modes. The spores in the beginning enters the sinuses and starts germinating into various hyphae in the immunocompromised patients. It is assumed that the pterygopalatine fossa is the biggest reservoir of the fungal hyphae [17,18].Later there is spread of the fungus, causing thrombosis and nerve dysfunction. The pathological manifestation involves blood vessels, cartilage, bone, neural and perineural areas, and often meninges. There is formation of palatine eschars and damages the nasal turbinates due to necrosis. The infection from the sinuses spreads causing osteolysis which consecutively invades the orbital structures. Subsequently the infection spreads to ethmoid sinusescausing involvement of the brain through the retro-orbital path or frontal lobes. As the

infection spreads along the regions of the sphenoid sinuses to the neighbouring cavernous sinus, it may cause cranial nerve palsies. The extensive involvement and spread in juglar veins, the cavernous sinus, and the carotid artery may further cause worsening of the patient's state. [19,20].

There has been a sudden outburst of mucormycosis cases in India in the second wave of COVID 19. Many researchers called this as post COVID mucormycosis[2,16,17]. In the present study a whooping number of 135 patients were operated for mucormycosis in just one city of India, in just 3 months' duration. 84.4% had a history of COVID 19 infection.

It was observed in several reports that india was in forefront in the world for the cases of post COVID mucormycosis[21-23]. Many studies reported that India has been accounted for by 45,435 cases of mucormycosis till September of 2021[24]. The black fungus cases are on the higher side in Gujarat and Maharashtra with around 7109 and 10,139 cases respectively [24].

Age and Gender-According to the study conducted by Hoenigl, majority of patients were male (78%) and the median age was 55 years (range 10–86) [25]. Priya, P the most commonly affected age-group was that between 41 and 60 year in a Tertiary Care Center in South India [26].

Rao VU in 2021 reported mucormycosis patients with a mean age of 49.1 years while 71% were aged between 41 and 60 years and most patients were male. Wasiq, Mohammed et al reported that the mean age of the his covid 19 associated mucormycosis study group was 51.16 years with males (69%) and females (31.0) [28].

Accorving to Chavhan et al,, 74.7% of mucormycosis patients were males and 77.4% of mucormycosis patients were above 40 years of age and male were on the higher side. [8]

Moorthy A et al, in 2021 reported that the incidence of mucormycosis is not age or gender dependent, and the significantly higher number of males in this study may be a reflection of higher Covid-19 prevalence of males in India. [29]

In the present study, 79% of mucormycosis patients were males and 77.4% of mucormycosis patients were above 50 years of age and no patient was under 25 years of age. In the present study, age and sex distribution among mucormycosis patients was similar to previous studies done except the upper and lower limits of ages of patients, in the present study the age range was(27-73 years).

Risk factors and type including COVID 19 infection

The most common type of risk factor in the mucormycosis patients was uncontrolled diabetes mellitus along with hematologic disorders, steroid therapy and malnourishment [30]. Other risk factors include deferoxamine therapy, overload of iron, and in some cases of drug abuse, stem cell transplants or organ transplant [17].

Patients who use corticosteroids, tocilizumab and iatrogenic immunosuppression [31] may also develop mucormycosis. There are other conditions that may increase the risk of developing mucormycosis, such as renal insufficiency, presenting with HIV or AIDS [32]. Extreme malnutrition, the use of illegal drugs that involve needles, as well as hepatitis or cirrhosis have all been associated with mucormycosis [30].

As discussed previously, in the present condition there are multiple possible contributing factors for the development of mucormycosis among patients with COVID-19 and these include diabetes mellitus, obesity, use of corticosteroid, and the development of cytokine storms (16). The triad of SARS-CoV-2, steroid and uncontrolled diabetes mellitus have contributed towards a significant increase in the incidence of angioinvasive maxillofacial mucormycosis [33]. However, the presence of spores and other factors might play a role as well [34].

In a study conducted by Rao VU et al it was found that middle-aged COVID-19 patients who were treated with steroids for diabetes mellitus were prone to mucormycosis [27]. Pathological changes in the pancreas were observed in patients with severe COVID-19, indicating that SARS-CoV-2 can cause pancreatic injury and this could be one of the reasons why COVID-19 patients with no history of diabetes have high blood glucose levels.[35] Diabetes mellitus, when combined with the SARS-CoV-2 virus and steroid therapy, appears to cause a vicious cycle of hyperglycaemia and immunosuppression, which can lead to severe fungal colonisation such as mucormycosis [36].
Another possible explanation for the association between COVID-19 and MCR is the “endothelialitis” observed in severe COVID-19. Autopsy series have shown more severe pulmonary vascular endothelial injury and new vessel growth in patients who died of COVID-19 than patients who died of influenza A (H1N1) [37,38]

According to the study by John, T.M 98% patients had dibetes melltus as risk factors for severe COVID-19 of the 35 patients in the study with information on glycemic status, 33 (33/35, 94%) had DM, with a mean HbA1C of 10 (in patients who had an HbA1c value available) [38]

In a systematic review by singh et al it was found that hyperglycemia was the single most important risk factor observed in 83.3% of the patients with mucormycosis and COVID-19, pre-existing Diabetes mellitus in 80% and concomitant ketoacidosis in 15%.[39]

In the present study, diabetes mellitus was the most common risk factor seen in 67% of patients with mucormycosis. 53% were having only diabetes mellitus, 12% were having only hypertension and in 14% both diabetes and hypertension was seen.

According to Muthu et al., diagnosis of mucormycosis was after a mean of 19.5 days from the diagnosis of COVID-19 [40]. 25% of mucormycosis cases were early COVID-19 active mucormycosis, diagnosed

within 7 days of COVID-19 diagnosis. Most of the mucormycosis cases in India were late COVID-19 active mucormycosis cases [40].

Mucormycosis was seen in 59.4% active COVID-19-positive cases and 40.6% in post-COVID-19 cases [41]. According to Patel et al., most cases of mucormycosis were diagnosed 8 or more days after COVID-19 diagnosis [41].

According to Mehta et al., 2–5 weeks gap was seen between recovery from COVID-19 and onset of symptoms of mucormycosis. According to Gerg et al., mucormycosis usually developed 10–14 days after hospitalization [42].

In the present study, 87.4% of patients with mucormycosis had a COVID-19 infection while 12.6% patients had no any record of COVID 19 infection. Looking at the treatment of COVID 19, 64.4% patients received oxygen therapy as well as steroids. 13.6% patients had no record of the type of COVID 19 treatment.

In the present study, 80% of patients were present during COVID-19 treatment and within 15 days of COVID-19 infection. No patient with mucormycosis was presented after 3 months of COVID-19 infection.

Type of mucormycosis

In the present study majority of the patients in the study population were diagnosed with the rhino-maxillary-orbital type -39%, followed by the rhino-cerebral type-25%. Only 1% patients showed only rhiono-nasal and only rhino-orbital type. 30% patients were not categorised into any type.

According to Sarkar et al. [41], nose and sinus were the most common site (88.9%), followed by rhino-orbital (56.7%) and ROCM type (22.2%). According to Mehta et al., ROCM type is more common in India [42].

According to Muthu et al., rhino-orbital (ROM) and rhino-orbito-cerebral mucormycosis (ROCM) were seen in 89% of cases in India and globally seen in 64% cases of mucormycosis [40]. According to Pal et al., rhino-orbital mucormycosis was seen in 42%, rhinoorbito-cerebral mucormycosis was seen in 24% and pulmonary mucormycosis was seen in 10% [43].

Outcome

The survival rate for rhino-orbito-cerebral disease in patients without any systemic disease is about 75%; with other diseases is about 20%; and in pulmonary disease is considered to be fatal. Data collected by Suganya et al. (2019) described the survival rate in diferent forms of Mucormycosis that varies with foci

of the infection: rhino-orbito-cerebral Mucormycosis – 45%, focal cerebral Mucormycosis – 33%, pulmonary Mucormycosis – 36%, sinusitis without cerebral involvement – 87%, cutaneous isolated – 90%, disseminated disease – 16%, and involvement of gastro intestinal form – 10% [44]. Unfortunately, the mortality rate is high which makes Mucormycosis a devastating disease. In a recent study conducted in India by Prakash and Chakrabarti (2021) in gastro intestinal form showed highest mortality rate of 66.7%, followed by disseminated (61.5%), pulmonary (61.3%), cutaneous (57.1%), renal (50%) and rhino-orbitocerebral (48.6%) [45]. The mortality can soon reach 100% if not diagnosed and treated timely. Though Mucormycosis is globally distributed, certain risk factors and clinical forms contribute to its estimated prevalence to around 70 times higher in India than that in global data [46]. In the world, India is the most afected country with 44.3% immunocompetent patients infected with Mucormycosis, followed by USA (19.8%) and Australia (5.7%) [46].

In the present study it was found that about 84.4% patients were discharged after the mucormycosis treatment. 15.6% patients died during or after the treatment. About 28.8% patients underwent maxillectomy, 35.3% patients underwent orbital externeration and 6% patients were treated by cerebral surgery

Conclusion

Similar to the reports in India and other countries, COVID 19 associated mucormycosis cases reported in this study were diagnosed in individuals with diabetes, hyperglycaemic status and with history of previous use of corticosteroids. Identifying these individuals at risk can help the early identification of mucormycosis. In addition, strict glycaemic control and avoidance of unnecessary corticosteroid in non-severe COVID-19 cases could help in preventing this complicated fungal infection.

References

1. . Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;6736:1– 9. https://doi.org/10.1016/S0140-6736(20)30566-3.
2. Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and pathophysiology of COVID-19-associated mucormycosis: India versus the rest of the world. Mycopathologia. 2021 Dec;186(6):739-54. https://doi.org/10.1007/s11046-021-00584-8
3. Patel A, Agarwal R, Rudramurthy S, Shevkani M, Xess I, Sharma R, et al. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis. India Emerg Infect Dis. 2021. https://doi.org/10.3201/Eid2709. 210934.
4. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. J Fungi 2020;6:E265https://doi.org/10.3390/ jof6040265

5. Suganya R, Malathi N, Karthikeyan V, Janagaraj VD (2019) Mucormycosis: a brief review. J Pure Appl Microbiol 13:161–165.https://doi.org/10.22207/JPAM.13.1.16
6. Chander J, Kaur M, Singla N, Punia RPS, Singhal SK, Attri AK, et al. Mucormycosis: battle with the deadly enemy over a five-year period in India. J Fungi 2018;4:E46https://doi.org/10.3390/jof4020046
7. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi 2019;5:E26https://doi.org/10.3390/jof5010026
8. Chavan RP, Ingole SM, Nazir HA, Desai WV, Kanchewad GS. Mucormycosis in COVID-19 pandemic: study at tertiary hospital in India. European Archives of Oto-Rhino-Laryngology. 2022 Feb 5:1-0.
9. Roden M.M., Zaoutis T.E., Buchanan W.L., Knudsen T.A., Sarkisova T.A., Schaufele R.L., Sein M., Sein T., Chiou C.C., Chu J.H., et al. Epidemiology and outcome of zygomycosis: A review of 929 reported cases. *Clin. Infect. Dis.* 2005;41:634–653. doi: 10.1086/432579. [PubMed] [CrossRef] [Google Scholar]
10. 4. Jeong W., Keighley C., Wolfe R., Lee W.L., Slavin M.A., Kong D.C.M., Chen S.C.A. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. *Clin. Microbiol. Infect.* 2019;25:26–34. doi: 10.1016/j.cmi.2018.07.011. [PubMed] [CrossRef] [Google Scholar]
11. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, Nasir N, Bonifaz A, Araiza J, Klimko N, Serris A. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. The Lancet Microbe. 2022 Jan 25.
12. *John, T.M.; Jacob, C.N.;Kontoyiannis, D.P. When Uncontrolled Diabetes Mellitus and Severe COVID-19 Converge: The Perfect Storm for Mucormycosis. J.Fungi* ***2021****, 7, 298. https:// doi.org/10.3390/jof7040298*
13. Chakrabarti, A.; Das, A.; Sharma, A.; Panda, N.; Das, S.; Gupta, K.L.; Sakhuja, V. Ten Years' Experience in Zygomycosis at a Tertiary Care Centre in India. J. Infect. 2001, 42, 261–266.
14. Chakrabarti, A.; Chatterjee, S.S.; Das, A.; Panda, N.; Shivaprakash, M.R.; Kaur, A.; Varma, S.C.; Singhi, S.; Bhansali, A.; Sakhuja, V. Invasive zygomycosis in India: Experience in a tertiary care hospital. Postgrad. Med. J. 2009, 85, 573–581.
15. Chakrabarti A., Das A., Mandal J., Shivaprakash M.R., George V.K., Tarai B., Rao P., Panda N., Verma S.C., Sakhuja V. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. *Med. Mycol.* 2006;44:335–342. doi: 10.1080/13693780500464930. [PubMed] [CrossRef] [Google Scholar]
16. Al-Tawfiq, Jaffar A et al. "COVID-19 and mucormycosis superinfection: the perfect storm." *Infection* vol. 49,5 (2021): 833-853. doi:10.1007/s15010-021-01670-1

17. Azhar, Asim et al. “Mucormycosis and COVID-19 pandemic: Clinical and diagnostic approach.” *Journal of infection and public health* vol. 15,4 (2022): 466-479. doi:10.1016/j.jiph.2022.02.007

18. Hosseini SMS, Borghei P. Rhinocerebral mucormycosis: pathways of spread. Eur Arch Oto Rhino Laryngol J Eur Fed Oto Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto Rhino Laryngol Head Neck Surg 2005;262:932–8. https://doi.org/10.1007/ s00405-005-0919-0

19. [76] Therakathu J, Prabhu S, Irodi A, Sudhakar SV, Yadav VK, Rupa V. Imaging features of rhinocerebral mucormycosis: a study of 43 patients. Egypt J Radio Nucl Med 2018;49:447–52. https://doi.org/10.1016/j.ejrnm.2018.01.001

20. [77] Petrikkos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis Publ Infect Dis Soc Am 2012;54(Suppl 1):S23–34. https://doi.org/10.1093/cid/cir866

21. 0 Alekseyev K, Didenko L, Chaudhry B. Rhinocerebral mucormycosis and COVID-19 pneumonia. J Med Cases. 2021;12(3):85–89. https://doi.org/10.14740/jmc3637.

22. 21 Sahoo JP, Mishra AP, Pradhan P, Samal KC. Misfortune never comes alone - the new “black fungus” accompanying COVID-19 wave. Biotica Res Today. 2021;3(5): 318–320.

23. 22 Singh AK, Singh R, Joshi SR, Mishra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes, Metab Syndrome: Clin Res Rev. Published online 2021:1-7. doi:10.1016/j.dsx.2021.05.019

24. Ghosh D, Dey S, Chakraborty H, Mukherjee S, Halder A, Sarkar A, Chakraborty P, Ghosh R, Sarkar J. Mucormycosis: A new threat to Coronavirus disease 2019 with special emphasis on India. Clinical Epidemiology and Global Health. 2022 Mar 19:101013.

25. Hoenigl M, Seidel D, Carvalho A, Rudramurthy SM, Arastehfar A, Gangneux JP, Nasir N, Bonifaz A, Araiza J, Klimko N, Serris A. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. The Lancet Microbe. 2022 Jan 25.

26. Priya, P., Ganesan, V., Rajendran, T., & Geni, V. G. (2020). Mucormycosis in a Tertiary Care Center in South India: A 4-Year Experience. *Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine*, *24*(3), 168–171. https://doi.org/10.5005/jp-journals-10071-23387

27. Rao VU, Arakeri G, Madikeri G, Shah A, Oeppen RS, Brennan PA. COVID-19 associated mucormycosis (CAM) in India: a formidable challenge. British Journal of Oral and Maxillofacial Surgery. 2021 Nov 1;59(9):1095-8.

28. Wasiq, Mohammed et al. “Coronavirus disease-associated mucormycosis (CAM): A case control study during the outbreak in India.” *The Journal of the Association of Physicians of India* vol.

70,4 (2022): 11-12.

29. Moorthy A et al (2021) SARS-CoV-2, uncontrolled diabetis and corticosteroids –an Unholy Trinity in invasive fungal infections of maxillofacial region? A retrospective, multicentric analysis. J Maxillofac Oral Surg 6:1–8. https://doi.org/10.1007/ s12663-021-01532-1

30. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis Publ Infect Dis Soc Am 2005;41:634–53. https://doi.org/10. 1086/432579

31. Group WHOREaFC-TW, Sterne JAC, Murthy S et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 324(13), 1330–1341 (2020).

32. Badali H, Canete-Gibas C, Mccarthy D ˜ et al. Epidemiology and antifungal susceptibilities of Mucoralean fungi in clinical samples from the United States. J. Clin. Microbiol. 59(9), e01230–e01221 (2021).

33. Garg D, Muthu V, Sehgal IS, Ramachandran R, Kaur H, Bhalla A, et al. Coronavirus disease (Covid-19) associated mucormycosis (CAM): case report and systematic review of literature. Mycopathologia. 2021;186:289–98. https://doi.org/10.1007/ s11046-021-00528-2.

34. Maini A, Tomar G, Khanna D, Kini Y, Mehta H, Bhagyasree V. Sino-orbital mucormycosis in a COVID-19 patient: a case report. Int J Surg Case Rep. 2021. https://doi.org/10.1016/j.ijscr.2021. 105957.

35. Montefusco L,Ben Nasr M, D'Addio F, et al. Acute and long-termdisruption of glycometabolic control after SARS-CoV-2 infection. Nat Metab 2021;3:774–85.

36. Chen J, Wu C, Wang X, et al. The impact of COVID-19 on blood glucose: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2020;11:574541.

37. Ackermann, M.; Verleden, S.E.; Kuehnel, M.; Haverich, A.; Welte, T.; Laenger, F.; Vanstapel, A.; Werlein, C.; Stark, H.; Tzankov, A.; et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N. Engl. J. Med. 2020, 383, 120–128.

38. John, T.M., Jacob, C.N. and Kontoyiannis, D.P., 2021. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. *Journal of Fungi*, *7*(4), p.298.

39. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr Clin Res Rev.* 2021 doi: 10.1016/j.dsx.2021.05.019. [CrossRef] [Google Scholar]

40. Muthu V, Rudramurthy SM, Chakrabarti A et al (2021) Epidemiology and pathophysiology of COVID-19-associated mucormycosis: India versus the rest of the world. Mycopathologia 186:739–754. https://doi.org/10.1007/s11046-021-00584-8

41. . Sarkar S, Gokhale T, Choudhury SS, Deb AK (2021) COVID-19 and orbital mucormycosis. Indian J Ophthalmol 69(4):1002–1004. https://doi.org/10.4103/ijo.IJO_3763_20

42. Mehta S, Pandey A (2020) Rhino-orbital mucormycosis associated with COVID-19. Cureus 12(9):e10726

43. Pal R, Singh B, Bhadada SK, Banerjee M, Bhogal RS, Hage N et al (2021) COVID-19-associated mucormycosis: an updated systematic review of literature. Mycoses 64(12):1452–1459.

44. Suganya R, Malathi N, Karthikeyan V, Janagaraj VD (2019) Mucormycosis: a brief review. J Pure Appl Microbiol 13:161–165. https://doi.org/10.22207/JPAM.13.1.16

45. Prakash H, Chakrabarti A (2021) Epidemiology of mucormycosis in India. Microorganisms 9:1–12. https://doi.org/10.3390/micro organisms9030523

46. - Monika, P., & Chandraprabha, M. N. (2022). Risks of mucormycosis in the current Covid-19 pandemic: a clinical challenge in both immunocompromised and immunocompetent patients. *Molecular Biology Reports*, 1-12.