Original Research Article

Analysis of Risk Factors for Mucormycosis in Covid-19 Patients Admitted in Tertiary Care Hospital Aurangabad.

Abstract:
Introduction: Mucormycosis is manifested by a variety of different syndromes in humans, particularly in immunocompromised patients and those with diabetes mellitus. Recently, several cases of mucormycosis in people with COVID19 have been increasingly reported worldwide, in particular from India. This prompted us to conduct a study in mucormycosis patients with COVID-19, to know its clinical profile of the COVID-19 patients with mucormycosis and identify of various risk factors in mucormycosis patients with COVID-19 infection.
Material &Methods: This Cross sectional Descriptive study was conducted in Department of Medicine, MGM Medical College and Hospital, Aurangabad [Maharashtra]. A total of 100 patients admitted from April 2021 to August 2021 were enrolled as study participants. All covid-19 patients admitted in MGM who are diagnosed with mucormycosis by microbiologicaly (KOH mount) or radiologicaly (CT/MRI)or by histopathology.
Observations & Results: The mean age of patients was 59.72±12.47 years. The male 73 (73.0%) predomiance than female 27(27.0%). 88(88.0%) of patients were having Diabetic Mellitus and 31(31.0%) of patients were having hypertension. All the patients were given Antibiotic & steroids during treatment of COVID-19 at hospitalisation. 15(15.0%) of patients were addmitted in ICU during treatment of COVID-19. 76(76.0%) patients were required Oxygen, 03(3.0%) were on NIV/Ventilator and 08 (8.0%) patients were on HFOT during treatment of COVID-19. Overall (97.0%) of patients were recoved.
Conclusion: Dabetes mellitus is identified as the leading underlying comorbidity in cases diagnosed with mucormycosis in post COVID-19 patients. Also use of steroid, duration of use of steroid, and oxygen therapy during the treatment of COVID-19 were risk factors observed in the patients with mucormycosis.

Keywords: *Mucormycosis, Steroid in COVID-19,* post-COVID-19.

Introduction:-

Mucormycosis is manifested by a variety of different syndromes in humans, particularly in immunocompromised patients and those with diabetes mellitus. Devastating rhino-orbital-cerebral and pulmonary infections are the most common syndromes caused by these fungi.
Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) has been associated with a wide range of opportunistic bacterial and fungal infection [1]. Both Aspergillosis and candida have been reported as the main fungal pathogens for co-infection in people with COVID-19[2]. Recently, several cases of mucormycosis in people with COVID19 have been increasingly reported worldwide,in particular from India. The primary reason that appears to be facilitating mucorales spores to germinate in people with covid-19 is an ideal environment of low oxygen (hypoxia), high glucose(diabetes, new onset hyperglycemia, steroid induced hyperglycemia), acidic medium(metabolic acidosis,diabetic ketoacidosis[DKA]),high iron levels(increased ferritins) and decreased phagocytic activity of WBC due to immune suppression (SARS CoV-2 mediated, steroid mediated or background comorbidities) coupled with several other shared risk factors including prolonged hospitalization with or without mechanical ventilators.
The genera in the order mucorales cause most human infection. These organisms are ubiquitous in nature and can be found on decaying vegetations and in the soil. These fungi grow rapidly and release large numbers of spores that can become air borne. Because the agents of mucormycosis are common in the environment,they are relatively frequent contaminants in the clinical microbiology laboratory; all

humans have ample exposure to these fungi during day to day activities. The fact that mucormycosis is a rare human infection reflects the effectiveness of the intact human immune system. This is further supported by the finding that almost all human infections due to the agents of mucormycosis occur in the presence of some underlying compromising condition [2].

The genera most commonly found in human infections are *Rhizopus*, *Mucor* and *Rhizomucor*;*Cunninghamella*,*AbsidiaSaksenaea*,and*Apophysomyces*are genera that are less commonly implicated in infection.*Rhizopusoryzae* is most common type and responsible for nearly 60% of mucormycosis cases in humans and also accounts for 90% of Rhino-orbital –cerebral (ROCM) form [3].

Globally, the prevalence of mucormycosis varied from 0.005-1.7 per million population, while its prevalence is nearly 80 times higher (0.14 per 1000)in India compared to developed countries,in a recent estimate of year 2019-20[4,5,6] in other words, India has highest cases of mucormycosis in the world. Notwithstanding, India is already having second largest population with diabetes mellitus (DM) and was the diabetes capital of the world, until recently. Importantly, DM has been the most common risk factor linked with mucormycosis in India, although hematological malignancies and organ transplant takes the lead in Europe and USA [7].

While long term use of corticosteroids has often been associated with several opportunistic fungal infections including aspergillosis and mucormycosis, even a short course of corticosteroids has recently been reported to link with mucormycosis especially in people with DM. a cumulative prednisolone dose of more than 600mg or total methyl prednisolone dose of 2-7gm given during the month before, predisposes immunocompromised people to mucormycosis [8]. There are few case reports of mucormycosis resulting from even a short course (5-14 days) of steroid therapy, especially in people with DM [9]. Surprisingly 46% of the patients had received corticosteroids within the month before the diagnosis of mucormycosis in the European Confederation of Medical Mycology study [10].

These findings need a relook in the context of COVID-19 pandemic where corticosteroids are often being used. There has been a steep rise in case reports/series of mucormycosis patients with COVID-19 especially in India. Similarly, several case reports are being reported from other parts of globe. Several anecdotal cases are being reported in grey literature such as the print and electronic media. These findings are unprecedented and carry an immense public health importance especially because fatality rate with mucormycosis is high. Especially the intracranial involvement of mucormycosis increases the fatality rate to as high as 90%[11]. Moreover, rapidity of dissemination of mucormycosis is an extraordinary phenomenon and even a delay of 12 hours in the diagnosis could be fatal, the reason 50% of cases of mucormycosis have been historically diagnosed only in the post-mortem autopsy series. This prompted us to conduct a study in mucormycosis patients with COVID-19, to know its clinical profile of the COVID-19 patients with mucormycosis and identify of various risk factors in mucormycosis patients with COVID-19 infection.

Aim &Objectives:

- To study the clinical profile of the COVID-19 patients with mucormycosis
- To identify of various risk factors in mucormycosis patients with COVID-19 infection.
- To study the outcome of mucormycosis patients in COVID-19 infection.

Material and Methods:

Study Design: Cross sectional Descriptive study.

Study Area- Department of Medicine, MGM Medical College and Hospital, Aurangabad [Maharashtra], India.

Sample Size- 100mucormycosispatients

Study Duration: A total of 100 patients admitted from April 2021 to August 2021 were enrolled as study participants.

Ethical Approval-Thestudy is subjected for approval to "Ethical Committee" of MGM Medical College & Hospital Aurangabad [MH], India.

Inclusion Criteria: All covid-19 patients admitted in MGM who are diagnosed with mucormycosis by microbiologicaly (KOH mount) or radiologicaly (CT/MRI)or by histopathology.

Exclusion Criteria:

- COVID-19 patients with mucormycosis who were not willing to participate in study.

Methodology:

After getting ethical permission from ethics committee of MGM Medical College & Hospital, Aurangabad [MH], India, data was collected from Covid-19 with mucormycosispatients who satisfying inclusion and exclusion criterion of study. The purpose of the study was explained to the study participants. Only after their written consent patients were enrolled in the study. Confidentiality of the information was ensured.

For the purpose of data collection a detailed proforma was prepared. The proforma was included demographic profile (Name, age, sex and BMI), Personal history, comorbidity and detailed history of COVID-19, tratment during Covid-19.
Also diagnosis method of mucormycosis patients, patients according to involvement, antifungals receivedsurgical intervention and outcome of mucormycosis patients.
Statistical Analysis: The collected data was entered in Microsoft excel and analyzed using SPSS version 24th. Mean and SD was calculated for quantitative variables and proportions were calculated for categorical variables.
Observations & Results:

Table 1: Distribution of patients according to Demographic profile of patients

		No. of patients	Percentage
Age-Group In years	15-45	11	11.0
	45-60	40	40.0
	>60	49	49.0
	Total	100	100%
	Mean±SD	59.72±12.47 years	
Gender	Male	73	73.0
	Female	27	27.0

In present study out of 100 patients, maximum patients i.e. 49 (49.0%) were from age more than 60 years, 40(40.0%) were age-group of 45-60 years and only 11(11.0%) of patients were from age-group 15-45 years. The mean age of patients was 59.72±12.47 years. The male 73 (73.0%) predomiance than female 27(27.0%).

Table 2 : Distribution of patients according to Comorbidities

Comorbidities	No. of patients (n=100)	Percentage
Hypertension	31	31.0
Diabetic Mellitus	88	88.0
IHD/CHD	12	12.0
Hypothyroidism	01	01.0
Asthama	01	01.0

In present study, 88(88.0%) of patients were having Diabetic Mellitus, 31(31.0%) of patients were having hypertension and 12(12.0%) of patients were having CHD/IHD, one patient was having Hypothyroidism and Asthama.

Table 3 : Distribution of patients according to diagnosis method

diagnosis method	No. of patients (n=100)	Percentage
KOH	55	55.0
Hisopathology	36	36.0
Imaging	100	100.0

In present study, all 100(100%) of patients were diagnosed on Imaging and 55(55.0%) were positive on KOH and 36(36.0%) patients were positive on histopathology.

Table 4 : Distribution of patients according to involvement

involvement	No. of patients (n=100)	Percentage
Sinuses	100	100.0%
Occular	70	70.0%
Pulmonary	02	02.0%
Cerebral	03	03.0%

All 100 patients were reportedSinuses involvement, 70(70.0%) ptients were having occular, 02(2.0%) Pulmonary and 03(3.0%) patients were having cerebral involvement.

Table 5 : Distribution of patients according to tratment during Covid-19

		No. of patients (n=100)	Percentage
Antibiotic		**100**	**100.0%**
steroid		**100**	**100.0%**
ICU Admission		**15**	**15.0%**
Oxygen Requirement		**76**	**76.0%**
NIV/Ventilator		**03**	**3.0%**
HFOT		**08**	**8.0%**
No. of days steroid given in COVID-19	**0-5 Days**	00	00
	6-10 Days	67	67.0%
	11-15 Days	28	28.0%
	>15 Days	5	5.0%

All the patients were given Antibiotic &steroids during treatment of COVID-19 at hospitalisation. 15(15.0%) of patients were addmitted in ICU during treatment of COVID-19. 76(76.0%) patients were required Oxygen, 03(3.0%) were on NIV/Ventilator and 08 (8.0%) patients were on HFOT during treatment of COVID-19. 67 (67.0%) patients were used steroids for COVID-19 treatment for 6–10 days, 28(28.0%) study participants used steroids for 11-15 days. Where as 5(5.0%) patients were used steroids more than 15 days.

Table 6 : Distribution of patients according to antifungals received

antifungals received	No. of patients (n=100)	Percentage
Posaconazole	100	100.0
Amphotericin	100	100.0
Liposomal Amphotericin	17	17.0
Lipid Emulsion Amphotericin	67	67.0
Lyophilized Amphotericin	16	16.0

All the 100 patients were given Posaconazole& Amphotericin, 17(17%) & 16(16.0%) patients were given Liposomal Amphotericin and Lyophilized Amphotericin respectively. 67(67.0%) of patients were given Lipid Emulsion Amphotericin.

Table 7: Distribution of patients according to surgical intervention

surgical intervention	No. of patients (n=100)	Percentage
Functional endoscopic sinus surgery (FESS)	100	100.0%
Endoscopic Debridement	78	78.0%
Maxillectomy	16	16.0%

All the patients required Functional endoscopic sinus surgery (FESS), 78 (78.0%) of patients were doneEndoscopic Debridement where as 16(16.0%) patients done Maxillectomy.

Table 8: Distribution of patients according to Outcome

surgical intervention	No. of patients (n=100)	Percentage
Recovered	97	97.0%
Death	03	3.0%
Total	100	100.0%

Out off 100 patients 97(97.0%) of patients were recoved and 03(3.0%) were died during tratment of mucrmycosis.

Discussion:

In present study out of 100 patients, maximum patients i.e. 49 (49.0%) were from age more than 60 years, 40(40.0%) were age-group of 45-60 years and only 11(11.0%) of patients were from age-group 15-45 years. The mean age of patients was 59.72±12.47 years. Simillarfindindings was reported by BhagyashriJadhav et al [12]the mean age was 54.46±13.13, years ranging from 28 to 77 years. Also Ganesh Lokhande et al [13] observed mean age of the patient was 52.47 ±12.84 years with a minimum age of 26 and maximum age of 83 years. Study conducted by Sen et al.[14] observed that the mean age of the study participants was 51.9. A study conducted by Gupta[15] revealed that the mean age of the study participants was 50 years. Maximum study reported mean age of mucormycosis patients were above 50 years.

In present study the male 73 (73.0%) predomiance than female 27(27.0%). Simmillar male predomiance was observed by Patel et al [16] 69.5% of participants affected by mucormycosis were men. Sen et al.[14] observed 71% of the male. BhagyashriJadhav et al [12] Observed 75% of male patients. , LokhandeGS et al [13] also reported 61.34% were males.

In present study, 88.0% of mucormycosis patients were having Diabetic Mellitus. John et al.[17] observed that 94% of the patients with mucormycosis were diabetic. In 73.5% of cases with mucormycosis, diabetes was observed as a risk factor in India [18]. Sen et al.[14] observed that 78% of the patients with mucormycosis were having diabetes. 77% found by Priya et al. [19] In contrast to the findings in this study, LokhandeGS et al [13] reported (57%) were diabetic. COVID-19 cases with a history of diabetes are at increased risk of developing the severe disease and these patients are also at higher risk of fungal infections. Globally diabetes mellitus is identified as the leading underlying comorbidity in cases diagnosed with mucormycosis in post COVID-19 patients [20].

In present study 76.0% patients were required Oxygen, 3.0% were on NIV/Ventilator and 8.0% patients were on HFOT during treatment of COVID-19.Simillarly Sen et al.[14] observed that 79% of the patients with mucormycosis received O2 therapy for the treatment of COVID-19. Whereas Afroze SN et al [21] reported 80.22%. Whereas BhagyashriJadhav et al[12] reported 18.75% patients gave the history of receiving oxygen or mechanical ventilation during the treatment of COVID19.

In present study, all 100 patients were given steroids during treatment of COVID-19 at hospitalisation. Lokhande, et al [12] found that more than 90% of patients had a history of steroid use for the treatment of COVID-19. Also Sen et al.[14] revealed a history of use of steroids in 87% of patients admitted with mucormycosis. Use of corticosteroids was observed in 88% of the study participants with mucormycosis in the study conducted by John et al.[17]. In present study (67.0%) patients were used steroids for COVID-19 treatment for 6–10 days, (28.0%) study participants used steroids for 11-15 days. Where as (5.0%) patients were used steroids more than 15 days. Lokhande, et al [13] reported (77.11%) study participants used steroids for COVID-19 treatment for 7–14 days, whereas (20.48%) study participants used steroids for less than 7 days. The National Institute of Health recommends the use of dexamethasone (6 mg per day for a maximum of 10 days) in patients who are ventilated or require supplemental oxygen but not in milder cases. 17 The guidelines specifically mention the risk of developing a secondary infection.

In present study, all (100%) of patients were diagnosed on Imaging and (55.0%) were positive on KOH and (36.0%) patients were positive on histopathology. Lokhande, et al. [13] reported 57.14% of patients found positive on KOH.

In this study, All 100 patients were reported Sinuses involvement, (70.0%) ptients were having occular, (2.0%) Pulmonary and (3.0%) patients were having cerebral involvement. Singh et al. [21] found that 88.9% of Sinuses involvement, occular (1.0%), Pulmonary (7.9%) and Cerebral (22.2%).

In present study All the patients required Functional endoscopic sinus surgery (FESS), 78 (78.0%) of patients were done Endoscopic Debridement where as 16(16.0%) patients done Maxillectomy. Whereas contrast finding was reorted by BhagyashriJadhav et al [12] that in (25%) patients only medical line of treatment was sufficient whereas (62.5%) patients required surgical debridement during the treatment.

In our study, (97.0%) of patients were recoved and (3.0%) were died during tratment of mucrmycosis. BhagyashriJadhav et al [12] reported Overall survival was 90.62% .

Conclusion:

In Post COVID-19 patients, Mucormycosis is one of the complications observed in the later stage of the disease. Dabetes mellitus is identified as the leading underlying comorbidity in cases diagnosed with mucormycosis in post COVID-19 patients. Also use of steroid, duration of use of steroid, and oxygen therapy during the treatment of COVID-19 were risk factors observed in the patients with mucormycosis. A high clinical suspicion and early and accurate diagnosis of AIFR in COVID-19 patients are essential for better prognosis.

Limitations of Study:

It is a singlecentered study conducted at terchary care centre on limited sample size. Also the comparison group i. e Control group was not included.

References:

1. *Kubin CJ, McConville TH, Dietz D, et al. Characterization of Bacterial and Fungal Infections in Hospitalized Patients with COVID-19 and Factors Associated with Healthcare-associated Infections, Open Forum Infectious Diseases, 2021;, ofab201.*
2. *Song G, Liang G, Liu W. Fungal Co-infections Associated with Global COVID-19 Pandemic: A Clinical and Diagnostic Perspective from China. Mycopathologia. 2020 Aug;185(4):599-606.*
3. *Paltauf A. Mycosis mucorina. Virchows ArchPatholAnatPhysiolKlin Med 1885;102:543–64.*
4. *Baker RD. Mucormycosis-a new disease? J Am Med Assoc. 1957;163:805-808.*
5. *Eucker J, Sezer O, Graf B, Possinger K. Mucormycoses. Mycoses. 2001;44(7):253-260.*
6. *Sugar AM. In: Mandell GL, Bennett JE, Dolin R(eds) Mandell, Douglas, and Bennett's principles and practice of infectious diseases (5th edn), Churchill Livingstone, New York, USA, 2000.*
7. *Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: An Update. J Fungi. 2020;6(4):265.*
8. *Chander J, Kaur M, Singla N et al. Mucormycosis: battle with the deadly enemy over a five-year period in India. J. Fungi.2018:4(2);46-52.*
9. *Jeong W, Keighley C, Wolfe R, et al., The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports, Clin. Microbiol. Infect. 2019:25 (2019) 26–34.*
10. *Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003, 362, 1828–1838.*
11. *Hoang K, Abdo T, Reinersman JM, Lu R, Higuita NIA. A case ofinvasive pulmonary mucormycosis resulting from short courses of corticosteroids in a well-controlled diabetic patient. Med Mycol Case Rep. 2020;29(1):22-24.*
12. *Jadhav B, Patwardhan N. Invasive fungal rhinosinusitis associated with COVID-19: An observational study. IP Int J Med Microbiol Trop Dis 2021;7(4):237-241*
13. *Lokhande GS, Bavaskar YG, Malkar VR, Ramanand J, Surwade JB, Saji DA, et al. Mucormycosis in patients with COVID-19: Adescriptive study at a tertiary care hospital in North Maharashtra. MGM J Med Sci 2022;9:72-6.*
14. *Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, et al.; Members of the Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC) Study Group. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbitalcerebralmucormycosis in 2826 patients in India: Collaborative OPAIIJO study on mucormycosis in COVID-19 (COSMIC), report 1. Indian J Ophthalmol.2021;69:1670-92.*
15. *Gupta SK. Clinical profile of mucormycosis: A descriptive analysis. Int J Sci Stud.2017;5:160-3.*
16. *Patel A, Kaur H, Xess I, Michael JS, Savio J, Rudramurthy S, et al. Multicenter epidemiologic study of coronavirus disease-associated mucormycosis, India. ClinMicrobiol Infect 2020;26:944.e9-944.e15. 9.*
17. *John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: The perfect storm for mucormycosis. J Fungi (Basel) 2021;7:298.*
18. *Ludhar A, Nilakhe SS. Study of mucormycosis patients attending tertiary care hospital: A retrospective study. Int J Res Med Sci 2019;7:1622-5.*
19. *Priya P, Ganesan V, Rajendran T, Geni VG. Mucormycosis in a tertiary care center in south India: A 4-year experience. Indian J Crit Care Med 2020;24:168-71.*
20. *Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, et al. The epidemiology and clinical manifestations of mucormycosis: A systematic review and meta-analysis of case reports. ClinMicrobiol Infect 2019;25:26-34.*
21. *Afroze SN, Korlepara R, Rao GV, Madala J. Mucormycosis in a diabetic patient: A case report with an insight into its pathophysiology. ContempClin Dent 2017;8:662-6.*
22. *Singh AK, Singh R, Joshi SR, Misra A (2021) Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes MetabSyndrClin Res Rev. https://doi.org/10. 1016/j.dsx.2022.05.019 (Internet).*