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Risk factors of mucormycosis in post-COVID-19 patients– A Retrospective study

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ABSTRACT

Background: Rhino-orbito-cerebral mucormycosis was seen in increasing severity in the recent second wave of COVID-19 in India. The incidence of mucormycosis is increased significantly in patients with diabetes. The most common cause attributed to the rise of mucormycosis in COVID-19 patients are uncontrolled diabetes. Lymphopenia and increased levels of certain cytokines, such as IL-6, have been closely associated with the disease severity. **Aims and Objectives:** The aims of this study were to analyze risk factors involved in Mucormycosis in 2nd wave of COVID-19. **Materials and Methods:** The study was done in the Mucormycosis ward, Department of ENT, Patna Medical College and Hospital, Patna, between May 2021 and July 2021. A total of 100 patients of both gender and all age groups were taken into the study. **Results:** Out of 100 patients included in the study, 57% (n = 57) of patients had history of steroid intake, while 43% (n = 43) had no history. About 41% (n = 41) of patients needed oxygen support during treatment,while 59% (n = 59) had no history of oxygen inhalation. About 88% (n = 88) of patients had prior history of diabetes or detected during treatment, while 12% (n = 12) had no prior history of diabetes or detected during treatment. About 91% (n = 91)of patients had uncontrolled hyperglycemia, while 9% (n = 9) had controlled blood sugar level. **Conclusion:** Uncontrolled hyperglycemia and delta strain are mainly associated major risk factors that lead to such high number of mucormycosis cases in India (post 2nd wave of COVID-19). Steroid role is not that much significant in our study and oxygen inhalation is not associated with mucormycosis.

Keywords: Mucormycosis; Diabetes mellitus; Steroid; Oxygen

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INTRODUCTION

The COVID-19 pandemic has brought new demands and difficulties in the domains of diagnostic and therapeutic management of the disease pattern, which ranges from mild to life-threatening pneumonia with associated comorbidities (e.g., diabetes mellitus, COPD) and immunocompromised conditions (e.g., corticosteroid therapy, ventilation, intensive care unit stay), these patients are susceptible to develop severe opportunistic infections. Rhino-orbito-cerebral mucormycosis was one such infection seen in increasing severity in the recent second wave of COVID-19 in India. The incidence of mucormycosis is increased significantly in patients with diabetes.

Mucormycosis, they were called as zygomycosis previously, refers to several different diseases caused by fungal infection in the order Mucorales. Fungi of the order Mucorales belong to seven families, all of which can cause mucormycosis. Among the Mucorales, *Rhizopus oryzae* and R. delmarva both in the family Mucoraceae are the most common causes of mucormycosis. Less frequently isolated species of the Mucoraceae that cause an identical spectrum of infections include *Rhizopusmicrosporus*, *Rhizomucorpusilus*, *Lichtheimiacorymbifera Apophysomyces* elegant, and *Mucor* species. Increasing incidence of mucormycosis due to infection with Cunninghamella species have also been reported, especially in immunocompromised patients.[1] Fungal spores are found ubiquitously in environment and soil and cause infection through inhalation. Depending on the clinical presentation, it is classified as sinonasal, rhino-orbital, rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal, or disseminated.

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The most common cause of mucormycosis in COVID-19 patients are uncontrolled diabetes. Lymphopenia and increased levels of certain cytokines, such as IL-6, have been closely associated with the disease severity. T-cells likely play a critical side in building the initial immune response. A marked decrease in T-cell counts is almost always observed in severe cases. Th1 cell response and cellular immunity arethe primary mechanism of control of infection. It would suggest that any immunosuppressive agent that suppresses T cell response, especially Th1 cells is detrimental in the fight against COVID-19.[2]

In diabetic patients, mucormycosis is aggressive and potentially fatal due to impaired host defense mechanism. In T2DM patients, there is diminished peripheral blood mononuclear cells function,that is, decreased chemotaxis as well as altered basal levels of intracellular calcium and superoxide. This impaired phagocytic activity in T2DM causes dysfunction of the immune response and immunocompromised state. Reduced binding of transferrin to iron in acidotic condition, increase GrP78 that it mediates invasion and damage of human endothelial cells by R. oryza, altered structure and function of platelets.[3]

Aims and objectives

The aims of this study were as follows:

1. To analyze risk factors involved in Mucormycosis in 2nd wave of COVID-19
2. To suggest treatment modifications of COVID-19
3. To suggest preventive measures of mucormycosis in future wave of COVID-19.

MATERIALS AND METHODS

A retrospective study was done in the Mucormycosis ward, Department of ENT, Patna Medical College and Hospital, Patna, between May 2021 and July 2021. A total of 100 patients of both gender and all age groups were taken into the study, each patient was explained about need and purpose of study; and ascent and consent for study was taken as per standard guidelines. The study was pre-approved by the Institutional Ethics Committee for the final permission. Diagnosis was done clinically, radiologically and/or laboratory test, namely, KOH mount and histopathological examination (Figures 1 and 2). All patients with mucormycosis in our hospital were evaluated by taking detailed history, previous laboratory and radiological reports. Various risk factors, disease extent, sites involved, and treatment previously taken were noted. The whole data were collected in a pro forma and data analyzed.

Inclusion criteria

The following criteria were included in the study:

1. Patients having COVID history
2. Patients of both genders
3. Patients of all age groups
4. Patients diagnosed as Mucormycosis– clinically, radiologically or on the basis of laboratory reports.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients having no COVID history
2. Patients who have not given informed consent.

RESULTS

Out of 100 patients included in the study 67 were males while 33 were females (Graph 1). The age distribution in 20 - 35 years age group was 14 patients; 36 - 50 years had 37 patients while 51 - 65 years age group had 39 patients and 65 years and above age group had 10 patients (Graph 2) Standard Deviation, s being 12.414, Mean value of 48.95 and Variance 154.10. Taking 99%, 2.576s$\bar{x}$ (confidence level)

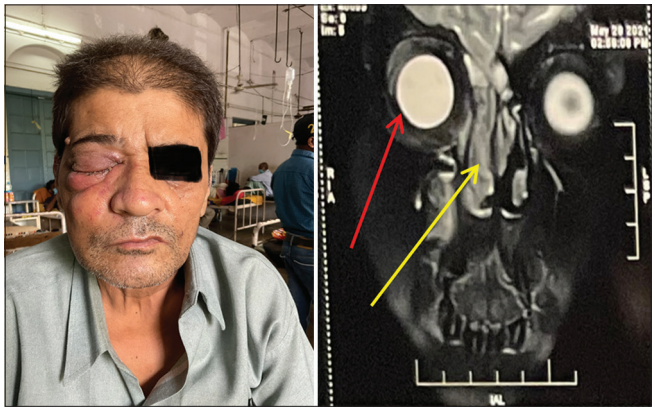


Figure 1: Proptosis, ptosis, and chemosis of the right eye. In T2W MRI, coronal section at the level of orbit shows proptosis of the right globe with surrounding inflammatory changes (red arrow). The right nasal cavity is filled with T2 isointense contents which are abutting superiorly the cribriform plate and laterally medial wall of orbit (yellow arrow)

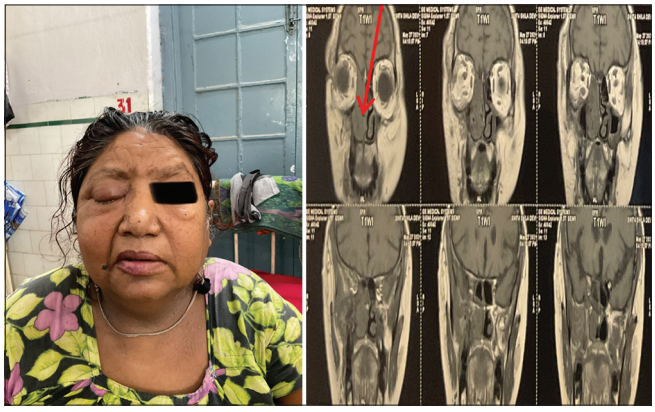


Figure 2: Proptosis and ptosis of the right eye. In T1W MRI, T1 hypointense lesion is noted involving right maxillary sinus, nasal cavity, posteriorly extending up to choana and anterosuperiorly, it is abutting the cribriform plate on the right side and antero-laterally it is abutting the lamina papyracea (red arrow)

margin of error calculated is 48.95 ±3.198 (±6.53%). 57% (n = 57) of patients had a history of steroid intake while 43% (n = 43) had no history (Table1). 41% (n = 41) of patients needed Oxygen support during treatment while 59% (n = 59) had no history of oxygen inhalation (Table 2). 88% (n = 88) of patients had prior history of diabetes or detected during treatment while 12% (n = 12) had no prior history of diabetes or detected during treatment (Figure 3). 91% (n = 91)of patients had uncontrolled hyperglycemia while 09% (n = 09) had controlled blood sugar level (Figure 4). 57% (n = 57) patients were treated at home while 43% (n = 43) patients were treated in hospital. Pearson Correlation Coefficient value of R is: 0.1713 for correlation of age of patients with CT severity index. Although technically a positive correlation, the relationship between our variables is weak (nb. the nearer the value is to zero, the weaker the relationship). The P-Value is 0.088365. The result is not significant as P > 0.05 (Graph 3).

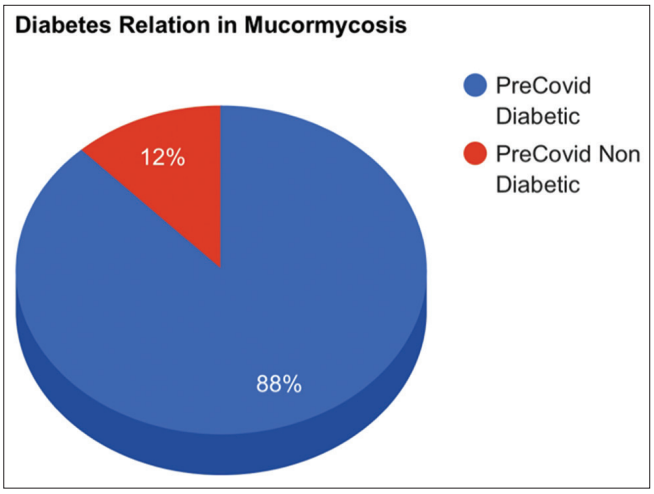


Figure 3: Pie chart showing diabetes relation in patients of mucormycosis

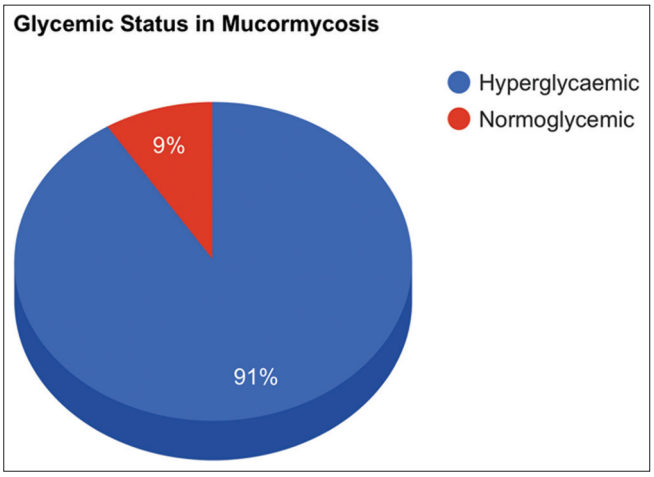


Figure 4: Glycemic status in mucormycosis patients

DISCUSSION

In our study, we found that mucormycosis is common in post-COVID male patients and is commonly seen in 36–65 years of age group. Steroid intake history during COVID treatment is not that much significant, oxygen support required during COVID-19 treatment that further affected with mucormycosis were lesser in numbers. About 88% of mucormycosis patients were diabetics.

In our study, we highlight several risk factors in causation of mucormycosis in post-COVID-19 patients. We have come to know from the pathogenesis of mucormycosis that phagocytic activity of mononuclear and polymorphonuclear cells of normal host kill mucorales by generation of oxidative metabolites and defensins. Hence, neutropenic and lymphopenic patients and those with dysfunctional phagocytes are susceptible to develop mucormycosis. In COVID-19, there is severe lymphopenia and in advance stages of viral replication accentuates inflammatory response and cellular influx in the blood stream. This leads to an imbalance between neutrophil and lymphocyte action making the patient more prone to systemic fungal infections.[4,5]

In diabetic patients, host defense mechanism is impaired that leads to mucormycosis aggressive and potentially fatal. In T2DM peripheral blood mononuclear cells, function is diminished that leads to decreased chemotaxis as well as altered basal levels of intracellular calcium and superoxide. Hence, phagocytic activity is impaired in T2DM and causes dysfunction of the immune response and immunocompromised state.[3]

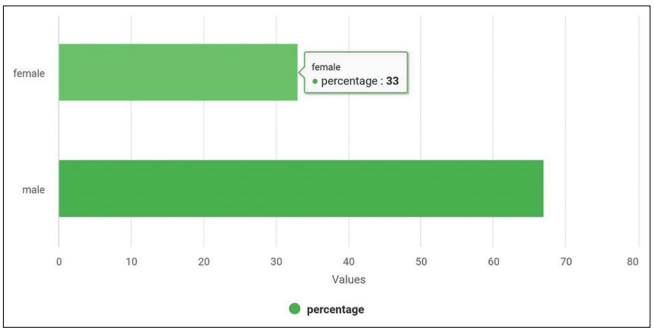
Mucorales are commonly found in surrounding environments (soils, plants, manure, rotting fruits, and so on). Exact epidemiological data of this infection are unknown, the prevalence of mucormycosis in India is 80 times higher than in developed countries.[6] Chakrabarti A et al,. estimated a prevalence of 14 cases per 100000 individuals in India previously by the computational model based method.[7] During and after first wave of COVID-19

Table 1: Steroid intake history in Mucormycosis patients during COVID treatment

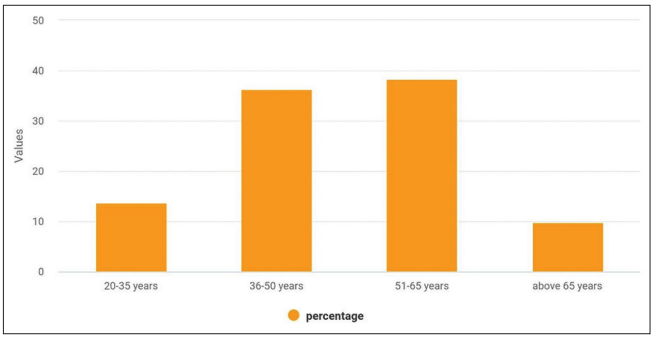
History of steroid intake	Yes	No	Total
Number	57	43	100

Table 2: Oxygen support history in mucormycosis patients during COVID treatment

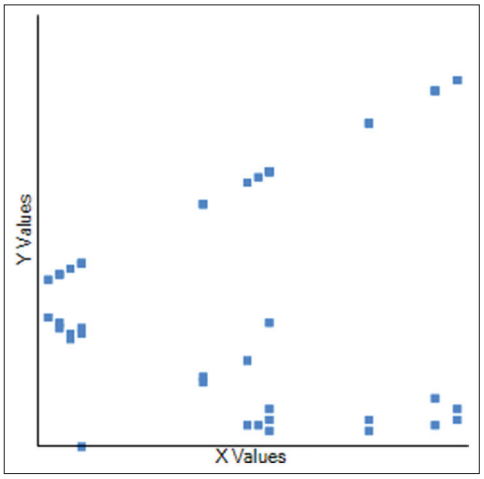
Oxygen support	Yes	No	Total
Number	41	59	100



Graph 1: Gender wise distribution of Mucormycosis in Post Covid patients



Graph 2: Age Distribution of Mucormycosis in Post Covid patients



Graph 3: Pearson correlation where x is CT severity score and y is age of patients

from September to December, 2020, 287 mucormycosis cases were found at different centers in India out of that 187 or over 65% were reported in COVID patients.[8] Since March to July 2021 (second wave of COVID-19),more than 2 crore cases of COVID-19 reported in India.[9] As of July 2021, India counted 45,432 confirmed cases and 4252 deaths due to mucormycosis. Among these, around 85% and 65% were comorbid with COVID-19 and diabetes,respectively.[8,10] There was many-fold rise in mucormycosis cases in India during the second wave of COVID-19 as compared to the first wave.[10]

Second wave of COVID-19 in India had been associated with the community transmission of the Indian variant of the SARS-CoV-2 virus (B.1.617.2) also known as Delta Variant. The WHO designated it as variant of concern. The variant has been called "double mutant" as it evolved through mutations in two separate sequences of the spike protein, namely, E484K and L452R, both of which are located essentially on the antibody recognizable site. It leads to severe infection of SARS-CoV2 causing mild to life-threatening pneumonia.

Limitations of the study

In our study, we couldn't consider various other proposed risk factors for causation of mucormycosis in post covid-19 patients viz. thrombus and serum ferritin levels.

CONCLUSION

In our study, we found that diabetic patients, uncontrolled hyperglycemia, and delta strain are mainly associated major risk factors that lead to such high number of mucormycosis cases in India (Post 2nd wave of COVID-19). Steroid role is not that much significant in our study and oxygen inhalation is not associated with mucormycosis. In COVID patients, strict blood sugar control should be done in appropriate manner, exercise and personal hygiene should be promoted in all.

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Authors Contribution:
SZ- Concept and design of the study, prepared first draft of manuscript, interpreted the results; **VS-** Reviewed the literature; **RK-** Reviewed the literature and manuscript preparation; **S-**Statistical analysis and interpretation.

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