Section A-Research paper

Evaluation of elevated levels of Hba1c, Serum ferritin, Serum Zn, and Absolute Neutrophil Count as risk factors for Covid-19 associated Mucormycosis

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ABSTRACT
Background: Rhino orbital cerebral Mucormycosis is a disease most commonly seen in immunosuppressed individuals. It is a rare fungal infection caused by Mucorales. During the Covid-19 pandemic, there is a sudden rise in these cases in the Indian subcontinent. There are

several risk factors like diabetes, corticosteroids use, and organ transplant which were studied previously. The study aims to evaluate the level of Hba1c, serum ferritin, serum zinc, and absolute neutrophil count as risk factors for mucormycosis in patients with covid-19 infection. It is a retrospective observational study. Two groups each consisting of 100 patients are selected. Group-A will have only covid-19 patients and Group-B will have mucormycosis patients. Hba1c levels, serum ferritin levels, serum Zinc levels, and absolute neutrophil counts are compared in both groups. Results are analyzed. It is found that mucormycosis is more common in males within the age group of 35-55 years. Elevated Hba1c levels and serum ferritin levels are found to be risk factors for mucormycosis in Covid-19 patients and those who recovered from the covid-19. No major difference is found between the two groups when serum zinc levels and absolute neutrophil counts are compared.

Introduction: The covid-19 pandemic in India has led to a rise in opportunistic fungal infections. During the second wave of covid in India there is a sudden surge in mucormycosis cases associated with covid-19 infection in the months of May and June 2021.

Most of the mucormycosis patients presented with either active covid infection or post covid status. It is presented in different forms like rhinoorbitocerebral, pulmonary, and cutaneous mucormycosis. Fungi of the order Mucorales is the causative agent. several factors play a key role in the causation of this fungal infection. Mucormycosis is mostly seen in immunocompromised patients with a history of uncontrolled diabetes, corticosteroid abuse, and hematological malignancies. studies done during the pre-pandemic era showed diabetes, iron overload, corticosteroid therapies, malignancies, and the immunocompromised state as risk factors for mucormycosis. As the mortality with mucormycosis is high, identifying at-risk patients helps in decreasing the fatal outcomes and morbidity associated with it. we aim to study the risk factors for mucormycosis associated with covid-19 infection. In this study, Hba1c levels, serum ferritin levels, serum zinc, and absolute neutrophil count are studied as risk factors for mucormycosis.

Methods

It is a retrospective observational study conducted at a tertiary care center in the state of Telangana, India. Medical records from a total of 200 patients are included in the study. Out of 200 patients, 100 patients are with active covid-19 infection and another 100 patients are with active mucormycosis infection. The group consisting of covid-19 patients is named Group-A and the group with mucormycosis patients is named Group B. Data from two groups are collected. Data regarding the covid-19 status, mucormycosis infection, age group, sex ratio, HBa1c levels, serum ferritin levels, serum zn levels, and absolute neutrophil count is collected from each group and analyzed.

Results

Data from medical records showed the age groups, sex ratio, laboratory values of Hba1c, serum ferritin, serum zinc, and absolute neutrophil count.

In group-A, the age group of patients ranges from 22yrs to 92yrs and the Mean age is 48.3 years[fig1]. In group-B age group ranges from 13yrs to 74yrs and the Mean age is 47.6 years. most of the patients are from 35 yrs to 55 yrs in group B [fig.2].

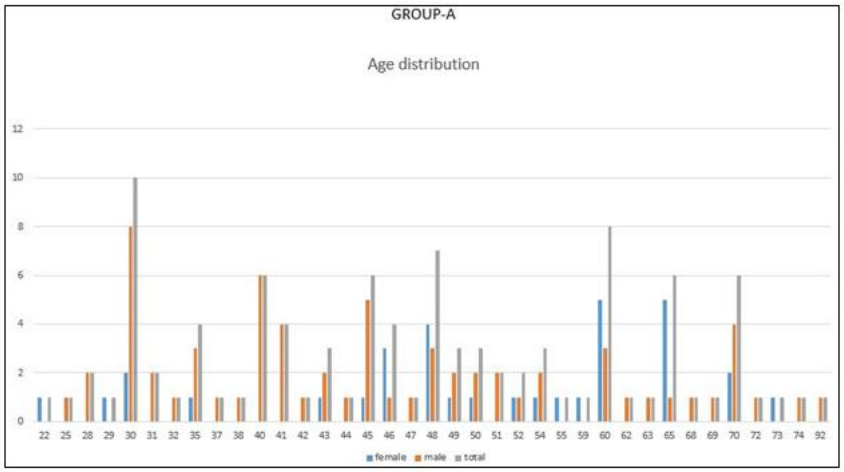

Figure 1: Age distribution of covid-19 patients from group-A

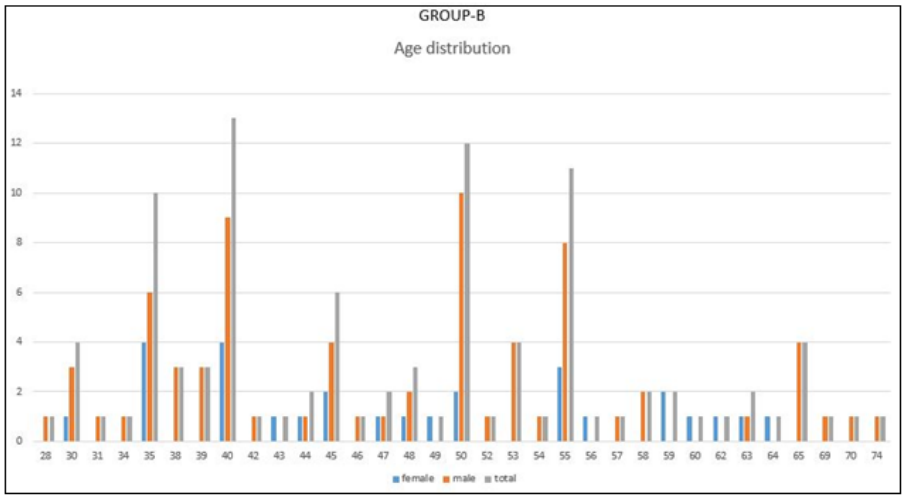

Figure 2: Age distribution of mucormycosis patients from group B.

In both the groups males are more in number. Out of 100 patients in group-A, 67 patients are males and 33 patients are females. In group B,72 patients are males and 28 patients are females[fig.3].

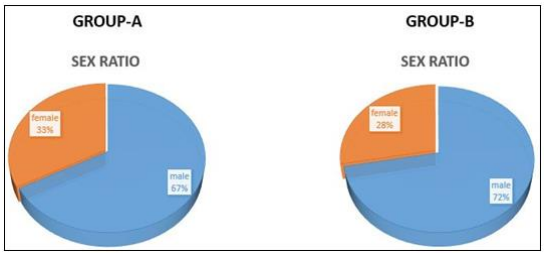

Figure 3: Sex ratio showing higher incidence among males in both covid-19 patients and mucormycosis patients.

Hba1c levels are categorized into normal range, prediabetic range, and diabetic range. Hba1c level, less than 5.7% is considered normal with good blood sugar control. Hba1c level between 5.7% to 6.4% is the prediabetic range and Hba1c 6.5% or higher is considered as a diabetic range with poor blood sugar control. our study showed in 59% of patients in group-A are diabetic and 98% of patients in Group B are diabetic[table-1].

Table 1: Comparison of Hba1c levels in group-A and group-B

Hba1c level	Group-A	Group-B
<5.7%	19	0
5.7-6.4%	22	2
6.5% or higher	59	98

Elevated serum ferritin levels are observed in both group-A and group B [table-2].89 patients from group-A and 95 patients from group B showed elevated serum ferritin levels. Serum ferritin levels in both groups showed iron overload which is more in group B [84 out of 100 patients].

Table 2: Serum ferritin levels in group-A and group-B

Serum ferritin	Group-A	Group-B
Normal range [50-200ng/ml]	11	5
Elevated > 200ng/ml	89	95
Iron overload	63 out of 100	84 out of 100

[Ref:Loscalzo, J., Fauci, A. S., Kasper, D. L., Hauser, S. L., Longo, D. L., & Jameson, J. L.(2022). *Harrison's Principles of Internal Medicine*.]

A comparison of Serum zinc levels in both groups showed no major difference. elevated zinc levels are seen in 37% of patients from group-A and 28% of patients from group B [table-3].

Table 3: serum zinc levels in group-A and group-B

Serum zinc	Group-A	Group-B
Zinc deficiency [< 70 mcg/dl]	13	24
Normal range [70-120 mcg/dl]	50	48
Elevated > 120mcg/dl	37	28

[Ref:Loscalzo, J., Fauci, A. S., Kasper, D. L., Hauser, S. L., Longo, D. L., & Jameson, J. L. (2022). *Harrison's Principles of Internal Medicine*.]

Absolute neutrophil count showed normal values in 31% of patients in group-A and 54% of patients in group B. Elevated neutrophil count is seen in 69% of group-A patients and 46% of group-B patients [table-4]

Table 4: absolute neutrophil count in group-a and group-b

Absolute neutrophil count	Group-A	Group-B
Normal range [1426-6340 /mm3]	31	54
Elevated [> 6340 /mm3]	69	46

[Ref:Loscalzo, J., Fauci, A. S., Kasper, D. L., Hauser, S. L., Longo, D. L., & Jameson, J. L. (2022). *Harrison's Principles of Internal Medicine*.]

Discussion

SARS COVID-19 pandemic, which is caused by viral infection also paved the path for many opportunistic infections. covid-19 causes acute respiratory distress in severe cases and in some cases, acute cardiac injury, kidney injury, liver injury, coagulopathy, and shock are

seen(Guo et al., 2020)(Hoenigl et al., 2021). It also causes cytokine release syndrome leading to high fever, thrombocytopenia, elevated serum ferritin, and elevation of other inflammatory markers(Mehta et al., 2020).

Both Covid-19 and mucormycosis affect immuno-compromised patients with diabetes, hypertension, obesity, organ transplant, and patients on corticosteroid therapy.

Corticosteroid therapy leads to uncontrolled blood sugars which is a key factor for opportunistic infections among covid-19 patients(Lionakis & Kontoyiannis, 2003)

Mucormycosis is caused by the filamentous fungi of the Mucorales order of the class of Zygomycetes(Skiada et al., 2020). Based on anatomic location, mucormycosis can be classified into (1) rhinoorbitocerebral, (2) pulmonary, (3) cutaneous,(4) gastrointestinal, (5) disseminated, and (6) uncommon presentations(Petrikkos et al., 2012). Mucorales species are angioinvasive, causing tissue infarctions(Gonzalez et al., 2002)(Petrikkos et al., 2012). several risk factors play key role in the disease causation. Immunosuppression being the center of these factors, diabetes melliitus, corticosteroid abuse, iron overload, organ transplant, and several malignancies are the significant risk factors that are considered(Petrikkos et al., 2012). In India, the disease spike occurred during the second wave of covid-19 pandemic between May and June 2021(Mashal, 2021). It is seen in patients associated with covid-19 infection either in active covid-19 infection or in those recovered from covid-19.

Fungal spores enter the human body through inhalation, ingestion, or direct inoculation. The most common species is Rhizopus arrhizus (formerly Rhizopus oryzae). Other fungi belong to the genera Mucor, Rhizomucor, Saksenaea, Apophysomyces, Cokeromyces, Actinomucor, and Syncephalastrum(Walther et al., 2019).

The human body responds to the invasion of fungal spores by different mechanisms. Macrophages and neutrophils play a key role in the defense against fungal invasion. There are two types of defense against Aspergillus and Rhizopus. Macrophages act against Aspergillus conidia and Rhizopus spores. The neutrophil acts against hyphal form of Aspergillus and Rhizopus.(Waldorf, 1989).

Diagnosis of mucormycosis is made by direct microscopic examination of the biopsy specimen. Clinical history like retro-orbital pain, headache, nasal discharge, facial edema, blackish discoloration of the hard palate, cheeks, and diplopia are characteristic of invasive mucormycosis. CT scan shows the involvement of disease in deeper structures. Early diagnosis

is most important for patient survival. Due to angioinvasion in rhino-orbitocerebral form of mucormycosis, several infarcts in the brain and other infected tissues lead to increased mortality. Mucormycosis is treated by a combination of systemic antifungal therapy with surgical resection of necrotic tissue.

Covid infection is seen in immunocompromised patients most commonly diabetics. Patients

with diabetes are more prone to complications of covid like severe acute respiratory distress syndrome, microvascular thrombosis, ventilator associate pneumonia, and diabetic ketoacidosis.

Treatment with corticosteroids has led to uncontrolled blood sugar levels in these patients and increased susceptibility to opportunistic infections.

The binding of viral proteins to ACE receptors in the pancreas downregulates their expression and might damage the pancreatic islets causing acute diabetes (Yang et al., 2010).

Monitoring blood sugars is very important in covid-19 patients as uncontrolled blood sugars will further complicate the condition of the patient.

Elevated Hba1c levels are studied as a risk factor for mucormycosis in our study.

A report published in 2009 by an International Expert Committee on the role of HbA1c in the diagnosis of diabetes recommended that HbA1c can be used to diagnose diabetes and that the

diagnosis can be made if the HbA1c level is ≥6.5% (*Glycated Haemoglobin (HbA1c) for the Diagnosis of Diabetes*, 2011). Levels of HbA1c just below 6.5% may indicate the presence of intermediate hyperglycemia. The precise lower cut-off point for this has yet to be defined, although the ADA has suggested 5.7 – 6.4% as the high-risk range(*Glycated Haemoglobin (HbA1c) for the Diagnosis of Diabetes*, 2011)("International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes," 2009).patients with A1C levels between 6.6 to 7% are prone to microvascular complications"(Sabanayagam et al., 2009).

In our study, Hba1c levels are compared between the covid-19 group and the mucor group which shows 59% of patients in group-A[covid group] have 6.5% or higher Hba1c levels while 98% of patients in group-B[mucor group] are with 6.5% or higher Hba1c levels. There is a significantly higher level of Hba1c among the mucor group. It indicates uncontrolled blood sugars play a key role in the incidence of mucormycosis among these patients. Thus Proper diabetic management is the most important management measure in covid-19 and diabetes patients.

Ferritin is a storage protein and helps in the storage of intracellular iron(Orino & Watanabe, 2008). It is elevated in acute and chronic inflammation. Ferritin also suppresses immunity by inhibiting lymphocyte function(Matzner et al., 1979). Elevated ferritin also causes free radical injury(Orino & Watanabe, 2008b). Cytokine Strome in covid-19 is supposed to increase the serum ferritin levels causing further progress in the proinflammatory mechanism(Ruddell et al., 2009). Circulating ferritin levels may not only reflect an acute phase response but may play a critical role in inflammation(Rosário et al., 2013). The acidic environment in DKA patients inhibits ferritin to bind with iron thus increasing free iron levels. This free iron is utilized by Mucorales for their growth(Artis et al., 1982). Increased disease severity is seen in patients with iron overload [>500ng/ml].

In our study serum ferritin levels are elevated in both the groups. In group-A, 89% of patients presented with elevated serum ferritin levels while in group B, 95% of patients presented with elevated serum ferritin. when iron overload is compared 63% of patients in group-A and 84% of patients in group B are found to be having serum ferritin levels of more than 500ng/ml. These findings suggest that serum ferritin levels help in identifying at-risk patients for mucormycosis among covid patients. Monitoring serum ferritin levels helps in the early identification of mucormycosis. Iron overload among these patients helps us to find mucor-prone patients.

Zinc is an essential mineral in the human body and is involved in the synthesis of many enzymes. During covid-19 pandemic, zinc supplementation was tried as an immunity booster for patients with covid-19 infection. The mucociliary clearance of respiratory mucosa is improved with zinc supplementation thus helping in viral clearance and preventing secondary bacterial infections (Woodworth et al., 2010)(Darma et al., 2020). Zinc also directly inhibits virus pathogenesis and suppresses host cell-virus growth(Ishida, 2019). Zinc levels either in excess or deficient will cause a disturbance in immunity which leads to increased susceptibility to infections and the development of inflammatory diseases(Maywald et al., 2017). During covid-19 pandemic zinc supplementation in large doses is given as supportive treatment.

Isolates of R arrhizus showed a visible increase in growth in zinc-enriched media. It helps in the growth of pathological fungi including Mucorales (Wilson, 2015). But these studies do not conclusively support the hypothesis that zinc supplementation contributed to the pathogenesis of mucormycosis(Muthu et al., 2021)(Nath & Baidya, 2021)(Kumar et al., 2022b).

In our study serum zinc levels in both the groups are compared. In group-A,13% of patients have zinc deficiency, 50% of patients have a normal range of serum zinc level and only 37% of patients have elevated serum zinc levels. In group B, 24% of patients have zinc deficiency,

48% have normal serum zinc levels and 28% of patients have elevated serum zinc levels. This data shows no major difference in covid-19 patients and mucormycosis patients which suggests there is no significant contribution from zinc supplementation in the causation of mucormycosis. Further studies are recommended to prove this association.

Lab investigations in patients with severe disease in COVID-19 showed increased neutrophil-to-lymphocyte ratio and high expression of neutrophil-related cytokines IL-8 and IL-6 in serum, and neutrophilia has been described as a predictor of poor outcomes in these patients(Liu et al., 2020b)(Zeng et al., 2021b). Patients with COVID-19 with severe disease had significantly higher absolute neutrophil counts(Itelman et al., 2020). Covid-19 is also known to cause transient neutropenia(López-Pereira et al.). The neutrophils act against hyphal form of Aspergillus and Rhizopus(Waldorf, 1989).

In our study, Absolute neutrophil count showed normal values in 31% of patients in group-A and 54% of patients in group B. Elevated neutrophil count is seen in 69% of group-A patients and 46% of group-B patients. A higher proportion of Covid-19 patients showed elevated Neutrophil count. The neutrophil count can not be used as a risk factor for mucormycosis as it is normal in 54% of mucormycosis patients. Neutropenia is not observed in either Group.

Conclusion

Several risk factors were studied for the causation of covid-19 associated mucormycosis. In our study, most of the patients were males within the age group of 35-55 years. The study suggests identifying uncontrolled diabetes and elevated serum ferritin helps in the early detection of mucormycosis infection in at-risk patients. serum zinc levels and absolute neutrophil count have no significant role in the early detection of mucormycosis in covid infected patients. HBa1c levels and serum ferritin levels can be helpful in monitoring disease progression among covid-19 patients and early detection of mucormycosis-prone patients.

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