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Clinical spectrum and outcome of mucormycosis patients with diabetes and Covid 19 in a tertiary care hospital

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Abstract

COVID -19 has infected humans in all age groups, of all ethnicities, both males and females by spreading at an alarming rate. With the limited experience we have about the nature of this virus, there is still more to be learned. It is believed that COVID-19 associated mucormycosis with underlying comorbidities like diabetes had an increasingly rapid and severe progression, often leading to severe complications in the post recovery phase. Diabetes mellitus predisposes patients to many fungal and bacterial infections. There is increasing evidence of mucormycosis with COVID 19 infection and their outcomes associated with poor glycaemic control estimated by their HbA1C values. The main aim of this study was to understand the clinical spectrum of COVID 19 associated mucormycosis with their diabetic state estimated through HbA1c.

Materials & methods: This observational study was conducted at a COVID care Centre in southern Tamil Nadu from July 2021 to September 2021. 50 patients with Diabetes, Tissue biopsy-confirmed Mucormycosis with history of COVID 19 were enrolled for the study.

Results: Among the 50 patients, 43 (86%) patients had good response to the treatment given and were discharged with stable vitals. The mean HBA1C in this patient group was 12.6 and the mean blood glucose level was 316.5 mg/dl, with an average hospital stay duration to be around 22 days. 3 patients (6.9%) among these 43 patients had complaints of sickness in the post follow up period. 2 patients (4%) had died in hospital with the

cause of death to be COVID 19 associated pneumonia with mucormycosis with a mean HBA1C value of 14.7 and a very poor glycaemic control with an average blood glucose level of 375 mg/dl. Their average duration of stay was at around 18 days.5 patients (10%) who were sick and recovering with mean HBA1C of 12.55 and an average glucose level of 311.4 mg/dl. Their duration of stay was the highest at 40 days on average.

Conclusion: The incidence and outcome of mucormycosis has increased widely being associated with COVID 19 infection and poor glycaemic control of diabetes estimated through HbA1c.

Keywords: mucormycosis, pneumonia, phagocytic

Introduction

The pandemic COVID-19 continues to be a big problem worldwide. While numerous therapy strategies have been studied, none but systemic glucocorticoids were found to increase survival in COVID-19. Conversely, the extensive use of glucocorticoids could result in secondary bacterial or fungal infections. Invasive respiratory aspergillosis affecting the course of COVID-19 is widely recognized [1], nevertheless, mucormycosis is infrequently suspected or diagnosed. Recently, multiple cases of mucormycosis in patients with COVID-19 have been increasingly recognized worldwide, in especially from India. The main reason that would seem to be enabling Mucorales spores to germinate in people with COVID-19 is an ideal place of low oxygen (hypoxia), rising glucose (diabetes, new-onset hyperglycemia, steroid-induced hyperglycemia), acidic medium (metabolic acidosis, diabetic ketoacidosis [DKA]), altered iron metabolism(like increased ferritins) and decreased phagocytic activity of white blood cells (WBC) due to immunosuppression (SARS-CoV-2 mediated, steroid-mediated or background comorbidities) combined with other shared risk factors such as prolonged hospitalization with or without mechanical ventilators.

Mucormycosis is a lethal opportunist Angio invasive infection that thrives in immunocompromised hosts. Globally, mucormycosis prevalence ranges between 0.005 and 1.7 per million people, although it is approximately 80 times more prevalent (0.14 per 1000) in India than in industrialized countries, according to a new projection for the years 2019–2020 [2].

Mucormycosis can manifest itself in a variety of ways, including rhino – orbital-cerebral, pulmonary, disseminated, cutaneous, gastrointestinal, and disseminated forms. Diabetes, neutron penia, iron overload status, malignancy, and organ transplantation are all key risk factors for the condition [3].

Diabetes is the most prevalent metabolic condition and is a risk factor for severe COVID-19 and Mucormycosis on its own. Superinfection with Mucormycosis in individuals with diabetes who are infected with COVID-19 will result in a worse clinical outcome and length of hospital stay. In the other words, India has the greatest prevalence of mucormycosis worldwide. Despite this, India already has the world's second biggest population with diabetes mellitus (DM) and was, until recently, the diabetes capital of the world [4].

Notably, diabetes mellitus has been identified as the most common risk factor for mucormycosis in India [5]. Nonetheless, diabetes mellitus remains the primary risk factor for mucormycosis worldwide, with a 46 percent overall fatality rate.

The purpose of this study is to determine the clinical spectrum of Mucormycosis in individuals with COVID-19 and diabetes, mainly based on HbA1C.

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Materials & methods

Study settings

This observational study was conducted at a COVID care Centre in southern Tamil Nadu from July 2021 to September 2021.All laboratory confirmed COVID 19 cases by RTPCR (Real Time Reverse Transcription Polymerase Chain Reaction) nasopharyngeal or throat swab admitted in the Centre and with clinical presentation for mucormycosis and post COVID cases reported to the OPD with symptoms confirmatory for mucormyocosis were enrolled for the study.COVID 19 infection was defined by SP02<92% or respiratory rate >30 min at admission or during the hospital stay. Post COVID cases were defined who had either clinical recovery from respiratory symptoms.

After getting, the approval from the ethics committee of our institute, observational study was conducted from July 2021 to September 2021.This study was performed in the Department of General Medicine, Mahatma Gandhi Memorial Hospital, Trichy.

Questionnaire were designed based on the parameters to be analysed after obtaining a written consent from the patient. Patient upon admission to the hospital detailed history on the presenting /past illness, presenting complaints, duration, treatmentgiven were collected from the patient and attenders and the questionnaire were filled.

Study population

Patient admitted in a single centered study done in a tertiary care hospital in southern India (Tamilnadu-Trichy) on 50 patients with Diabetes,Tissue biopsy-confirmed Mucormycosiswith history of COVID 19 were enrolled for the study. Patient presenting in the emergency unit with symptoms suggestive for mucormycosis, post COVID recovery were admitted and blood samples, tissue biopsy were sent for the investigations.

Inclusion criteria

1. More than 18-year-old patients.
2. Mucormycosis proven by tissue biopsy.
3. HbA1C more than 6.5%
4. Patients who are able to give written informed consent.
5. Active COVID cases and Post COVID cases were added to the study.
6. Newly detected diabetic and diabetic patients on treatment with HBA1C more than 6.5.

Exclusion criteria

1. Patients who had been on long-term immunosuppressive therapy.
2. Patients with a history of Haematological malignancies on follow-up.
3. Patients who had prior organ-transplantation.

They were also excluded as they were treated with chronic immunosuppressant drugs, which increases the risk of acquiring mucormycosis.

Methods

All patients with mucormycosis diagnosed by tissue biopsy were chosen, followed up in the inpatient department and later observed for three months during their OP visit and through phone calls. During their hospital stay,they underwent FESS (functional endoscopic sinus surgery) or maxillectomy or orbital exenteration based on the stage and extension of Mucormycosis. All were treated with an injection liposomal amphotericin B (5 mg/kg) intravenously for two weeks followed by oral Posaconazole 100 mg TDS for 8 weeks or more as per recovery. Past history of diabetes mellitus, COVID19 illness and other comorbidities were noted and the treatment were given

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accordingly. Diabetic specific investigations like Fasting blood glucose, 2 hours postprandial blood glucose, and HbA1C (HbA1C was estimated by HPLC method High performance liquid chromatography) were taken at the time of admission. Routine blood investigations like complete blood count, renal function test done and the parameters were analysed.

Case definitions

Diabetes – HbA1C more than 6.5%.

Newly diagnosed diabetes- HbA1C>6.5% with no prior history of diabetes mellitus.

COVID-19 illness- based on RTPCR positivity

COVID19 associated Mucormycosis (CAM) those who acquired mucormycosis during the COVID19 illness or following recovery from COVID19.

Post COVID19- those who had COVID19 prior and were recovered and discharged.

Recovered- those who were discharged without symptoms.

Sick- those who had persistent symptoms during the period of follow up.

Death- those who died of mucormycosis related complications during the period of follow up.

Statistical analysis

MS Excel was used to compile the data, and SPSS ver 20.0 was used to analyse it. For quantitative variables, descriptive statistics were reported as mean and standard deviation; for qualitative data, they were presented as frequencies with percentages

Results

Demography

During this study period, 50 patients' data with mucormycosis infection who were eligible with the study inclusion criteria were hospitalized and analysed, out of them, 22(44%) patients were treated for COVID 19 infection, 28(56%) were admitted for post Covid mucormycosis The mean age of the study population was 53yearswhere the mean male age was (53.03 years) and the female mean age (53.47 years). Among the 50 patients diagnosed with mucormycosis, around66% of the patients were male and 34% of them were female.The patients were admitted in a dedicated covid ward and treated for mucormycosis treatment protocol.

Risk factors:

In patients with mucor and a history of covid illness, diabetes was the most common comorbidity. The mean blood glucose value was 318 $\pm$ 70.43 g/dl at the time of admission.The mean HBA1C value for this study population was 12.73. There were no patients with a history of diabetic ketoacidosis in our study. The majority of the patients enrolled in the study around 70% had steroid exposure in the form of either injection methyl prednisolone or dexamethasone. None of the patients enrolled in this study received anti –IL6 therapy or monoclonal antibodies. There were no cases of malignancy, organ transplant or HIV/AIDS with mucormycosis in our study.

Covid19 Status

In patients with CAM, headache, nasal symptoms in the form of rhinorrhoea, nasal stuffiness, and eye symptoms in the form of redness or pain in the eyes were common.On admission, 22/50 (44%) patients had a history or presented with COVID 19 pneumonia. At the time of diagnosis of CAM, 28/50 had hypoxemia (56%) and required supplemental oxygen (42%). The mean duration of onset of Mucormycosis was 17.28 (±11.36) days after the onset of COVID-19. None of the patients selected for this study had taken covid 19 vaccine. From theCT scan taken for the entire study population at the time of admission, 44/50 (88%) had CT chest findings

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suggestive of COVID 19. For an average of 7-14 days,35/50 (70%) of patients were exposed to steroids in the form of either injection methylprednisolone or dexamethasone.

Comorbidities

All were diabetic, among which 33(66%) were known cases of diabetes on OHA medications and 17(34%) were newly diagnosed.4 had systemic hypertension (8%) on medications, 3 had chronic kidney disease (6%) and 1 had anaemia (2%).

Treatment and Outcome

Patients treated in our Centre were started on were treated with an injection liposomal amphotericin B (5 mg/kg) intravenously for two weeks followed by oral Posaconazole 100 mg TDS for 8 weeks or more as per recovery with glycaemic control and other medications as according to the existing comorbities. All the patients had rhino-orbital involvement for which FESS (functional endoscopic sinus surgery) or maxillectomy or orbital exenteration based on the stage and extension of Mucormycosis was done. Based on the FESS findings 3 had a cerebral extension.

Table 1:Mean and significance values of variables.

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	50	32	71	53.18	9.129
CT Chest (%)	50	0.00	50.00	18.7450	13.49173
Steroid therapy (days)	50	0	20	5.60	5.099
Oxygen therapy (days)	50	0	30	3.28	6.021
Urea	50	16	91	29.84	12.296
Creatinine	50	.6000	4.2000	.962000	.5134477
WBC	50	2000	28400	13176.20	5780.269
PMNL	50	48	91	75.32	10.852
LYMP	50	3	43	17.12	9.942
NLR	50	1.1000	30.3000	6.931400	5.7307303
PLAT	50	1.4000	8.5000	3.800400	1.3921969
HB	50	6.7000	14.9000	11.314000	1.9000548
RBC	50	3.0000	5.5000	4.240400	.6259489
FBS	50	78	453	207.42	91.797
PPBS	50	116	498	322.28	92.790
Duration of stay	50	14	60	24.04	9.941
Ferritin	50	15.2000	1650.0000	518.832000	362.9634200
CRP	44	24	233	89.30	60.667
HbA1C	50	7.8000	17.8000	12.732000	2.4900160
Avg glucose	50	177.2000	467.0000	318.364000	70.4321059

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Following treatment around 43(86%) patients had good response to the treatment given and were discharged with stable vitals.The mean HBA1C in this patient group was 12.6 and the mean blood glucose level was 316.5mg/dl, with an average hospital stay duration to be around 22 days.3 patients (6.9%) among these 43 patients had complaints of sickness in the post follow up period.2 patients (4%) had died in hospital with the cause of death to be COVID 19 associated pneumonia with mucormycosis with a mean HBA1C value of 14.7 and a very poor glycaemic control with an average blood glucose level of 375 mg/dl. Their average duration of stay was at around 18 days. The 5 patients (10%) who were sick and recovering. This group had a mean HBA1C of 12.55 and an average glucose level of 311.4 mg/dl. Their duration of stay was the highest at 40 days on average.

Table 2: Descriptive statistics of variables.

Variable	Mean				P value
	Death(n= 2)	Discharged(n= 43)	Recovering(n= 5)	Total(n=50)	
CT chest (%)	45.0000	17.1221	22.2000	18.7450	.011
Oxygen therapy	3.5000	2.6744	8.4000	3.2800	.131
Steroid therapy	3.5000	5.7209	5.4000	5.6000	.836
Urea	28.5000	29.9535	29.4000	29.8400	.984
Creatinine	.8500	.9721	.9200	.9620	.933
WBC	17250.0000	12786.0465	14902.0000	13176.2000	.450
PMNL	84.0000	74.2093	81.4000	75.3200	.194
LYMP	10.0000	18.2093	10.6000	17.1200	.159
NLR	11.6000	5.9079	13.8660	6.9314	.005
PLAT	2.6000	3.9051	3.3800	3.8004	.342
HB	12.1000	11.2000	11.9800	11.3140	.583
RBC	4.8000	4.2186	4.2040	4.2404	.443
FBS	192.0000	207.4651	213.2000	207.4200	.964
PPBS	336.5000	324.5814	296.8000	322.2800	.805
Duration of stay	17.5000	22.4884	40.0000	24.0400	.000
Ferritin	1008.0000	439.2465	1007.6000	518.8320	.000
CRP	172.5000	64.2558	164.2000	78.5800	.000
HbA1C	14.7000	12.6628	12.5400	12.7320	.528
Average glucose	374.7000	316.5535	311.4000	318.3640	.517

Laboratory evaluation and findings

Upon admission, the biochemistry investigations were performed on all the patients enrolled for the study. The mean HBA1C of the study population was 12.7320 $\pm$2.49, with an average blood sugar value of 318 $\pm$ 70.43, indicating a very poor glycaemic control on the study

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population. Additionally, the mean fasting blood sugar value was 207.42 ± 91.79 mg/dl and mean PPBS was 322.28 ± 92.79 mg/dl.Diabetic medications were recommended as per the guidelines for both the newly detected and the pre-existing diabetic patients in the study and advised to repeat the investigations after 3-4 months during the follow-up.

On admission,the mean of the renal parameters was as follows: urea (29.84) and creatinine (0.962), where 3 patients were known cases of chronic kidney disease.Medications were altered based on the GFR for these patients. Complete blood count investigation at admission had a mean Hb of (11.314), mean WBC counts 13176.2 and the mean platelet count was 3.8004. Polymorphonuclear leukocyte and Neutrophil-Lymphocyte Ratio (NLR) mean were 75.32 and 6.93 respectively.

Discussion

Mucormycosis etiologic agent is widespread in nature and hence easily acquired; different researchers have researched its worldwide distribution; and it may constitute a concern during an ongoing pandemic, as was shown in India [6]. Due to the dramatic increase in mucormycosis (black fungus infection) cases during the second COVID-19 pandemic wave, as well as its relationship with severe sequelae and a higher fatality rate in post-COVID-19 patients, this rare disease has been designated as a notifiable condition in India. Using non-sterile medical supplies has been linked to spore contamination and increased patient exposure to mucormycosis [7].

Diabetes and Mucormycosis

In our study all, the patients were diabetic with poor glycaemic control (Mean HbA1c was12.7320 ± 2.49). Diabetes mellitus is a significant risk factor for mucormycosis, according to a meta-analysis of 600 (70%) of 851 individuals with rhino-orbital–cerebral mucormycosis [8]. Diabetes mellitus was predicted to be present in 17% of patients with COVID-19 in one study [9] and 9% in another study [10]. The median incubation period of Mucormycosis is unknown and is considered 7–10 days after percutaneous exposure [9]. Hence, exposure of Mucormycosis during hospitalization or Healthcare Associated Mucormycosis requires consideration [10].

However, diabetes mellitus prevalence may be higher in other populations, exceeding 50%. Diabetes mellitus was associated 2.40 (95 percent confidence interval [CI] 1.98–2.91) for severe disease in one meta-analysis [11], an OR of 1.64 (95 percent CI 2.30–1.08) in another meta-analysis [12], and an OR of 2.04 (95 percent CI 1.67–2.50) in a third meta-analysis [12]

Diabetes is the most common comorbidity associated with Mucormycosis, accounting for around 73.5 percent of cases in India [13]. However, diabetes is related with 17% of instances of Mucormycosis in western countries [14].

India is the country with the greatest global prevalence of Mucormycosis. Mucormycosis has a prevalence of 140 cases per million people in India, according to a computer model [Prakash et al., 2019]. [14]. A recent paper revealed 187 occurrences of CAM (COVID-associated Mucormycosis) in India, with an incidence of 0.27 percent among hospitalized cases between September and December 2020. Mucormycosis cases have increased by 2.1-fold in the preceding year [Patel et al., 2021]. As of May 28, 2021, 14,872 instances of CAM had been reported in India. [14].

Immunosuppressive Agents and its correlation with the Rising incidence of mucormycosis in patients with

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COVID-19 was another another challenge for India amidst the second wave [15].

Mucormycosis is an Angio invasive fungal infection with high mortality. The disease has surged in COVID 19 pandemic due to uncontrolled diabetes and improper corticosteroid use. The majority of the patients had poor glycemic control with a mean HbA1c of 9.06%. Out of the total study population, 93% had prior exposure to high dose corticosteroids where 12.5% patients of CAM did not survive. [16].

Zygomycosis is an important emerging fungal infection Total mortality in the entire cohort was 47%. On multivariate analysis, factors associated with survival were trauma as an underlying condition (p 0.019), treatment with amphotericin B (p 0.006) and surgery (p <0.001); factors associated with death were higher age (p 0.005) and the administration of caspofungin prior to diagnosis (p 0.011) it remains a highly lethal disease. Administration of amphotericin B and surgery, where feasible, significantly improve survival. [17].

Mucormycosis has an incidence of approximately 1.6 cases per 1000 diabetic people [18]. Diabetes was associated in our study with all the cases of CAM, with poor glycaemic control, in form mean blood glucose of 242.63 (±84.81) g/dl & mean glycated haemoglobin (HbA1c) of 12.7320 $\pm$ 2.49 at admission as shown by Yogendra Mishra et al (9.06%).[13]

All the cases had rhino orbital involvement, while 3 exhibited cerebral mucormycosis. The pattern of participation is consistent with earlier reports, with diabetes serving as the primary risk factor. [19]. Rhino cerebral Mucormycosis has been shown to have a mortality rate of 40–50% in people with diabetes [19]. Early surgical debridement improves the prognosis in patients with Sino nasal illness, and mortality has been found to be less than 10%. [20]. The mortality appears to be less in our case, possibly due to early diagnosis with early treatment with antifungals and surgical debridement.

Diabetes was the most often occurring comorbidity in our study. Diabetes mellitus and COVID-19 are both associated with unfavorable outcomes in a bidirectional manner. Diabetes is an inflammatory condition that impairs the control of SARS-CoV-2 replication and results in severe COVID 19 infections [21]. Due to the virus's direct pathogenic action on pancreatic islet cells, SARS-CoV-2 infection results in reduced insulin production, which may be the reason for the newly diagnosed diabetes (22 in our study). Additionally, it results in insulin resistance as a result of the temporary hyperinflammatory state [22]. Following that, hyperglycemia is created, promoting invasive mucormycosis growth.

Role of Steroids

In our study, 35 patients in the post-COVID group were exposed to steroids in the form of injection methylprednisolone or dexamethasone for average 7-14 days. Corticosteroids are deemed necessary therapy for COVID 19 patients receiving supplemental oxygen. Though the use of prednisolone or an equivalent dose of 1 mg/kg for three weeks or longer has been traditionally associated with a risk of Mucormycosis [23], certain case reports have documented the occurrence of Mucormycosis following a brief course of steroids [Hoang et al., 2020]. Corticosteroids have a variety of effects in CAM. To begin with, they can result in immunosuppression by impairing macrophage migration, phagocytosis, and phagolysosome formation. Second, they result in drug-induced hyperglycemia and deterioration of glycemic control in diabetic patients.

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Additionally, in places such as India, where steroids are available over the counter, incorrect and extended steroid use may increase vulnerability to Mucormycosis.

Patients on chronic corticosteroid therapy have a higher risk for pulmonary mucormycosis, but there are much fewer reports of mucormycosis occurring in patients after only short courses of steroid therapy [24].

Triad of covid19, diabetes and mucormycosis

SARS-CoV-2 infects immunological cells (CD3, CD4, and CD8 T cells), causing lymphocytes to undergo apoptosis. As a result of the resulting lymphocytopenia, innate immunity is impaired, resulting in immunological dysregulation and a cytokine storm [Varga et al., 2020]. Diabetes mellitus compromises the adaptive immune system by impairing neutrophil chemotaxis, phagocytosis, and intracellular pathogen killing [25].

Thus, infection with SARS-CoV-2 in a diabetic patient result in immunological dysregulation.

To add insult to injury, the use of steroids results in immunosuppression.

COVID-19, diabetes, and corticosteroid use all increase the risk of invasive fungal infections.

SARS-CoV-2 infection results in endothelial dysfunction as a result of direct viral invasion and the inflammatory response of the host, which results in endothelial cell death and pyroptosis [26].

In general, hyperglycemia in diabetic patients and COVID-19 treatment increase the incidence of Mucormycosis by the following mechanism:

a) Induction of a defect in the neutron phil-macrophage phagocytic system;

b) Upregulation and increased expression of the GRP78 receptor in humans and the Mucorales-specific protein CotH;

c) Hyper glycation of iron-sequestering proteins, resulting in iron sequestration disruption and increased iron delivery to Mucorales. [27]

Diabetes is an inflammatory chronic condition associated with endothelial dysfunction. Mucorales invasion requires endothelial adherence and angioinvasion.

Thus, persons with diabetes who are infected with COVID-19 are at an increased risk of developing invasive Mucormycosis. From Deepak Pandiar et al [28]

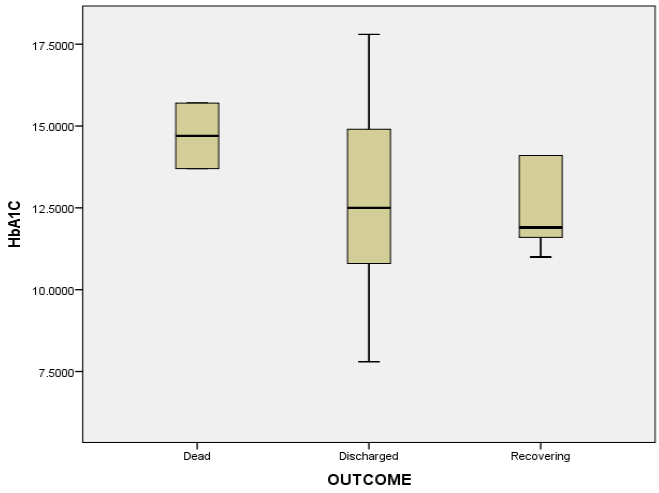

Fig 1: Box and whisker plot showing the relationship of HbA1c with the outcome in patients with COVID associated mucormycosis.

COVID19 and Mucormycosis

The mean duration of onset of Mucormycosis was 17.28 (±11.36) days after the onset of COVID-19. The majority of patients, 28/50(56%) patients of CAM, were in post COVID syndrome (PCS), after clinical recovery from COVID-19.

The current surge in Mucormycosis cases is possibly due to the high burden of COVID-19 in the country.

In our study,2/50 (4%) patients did not survive in the study period of twelve weeks, recording lesser mortality compared to other studies [29]

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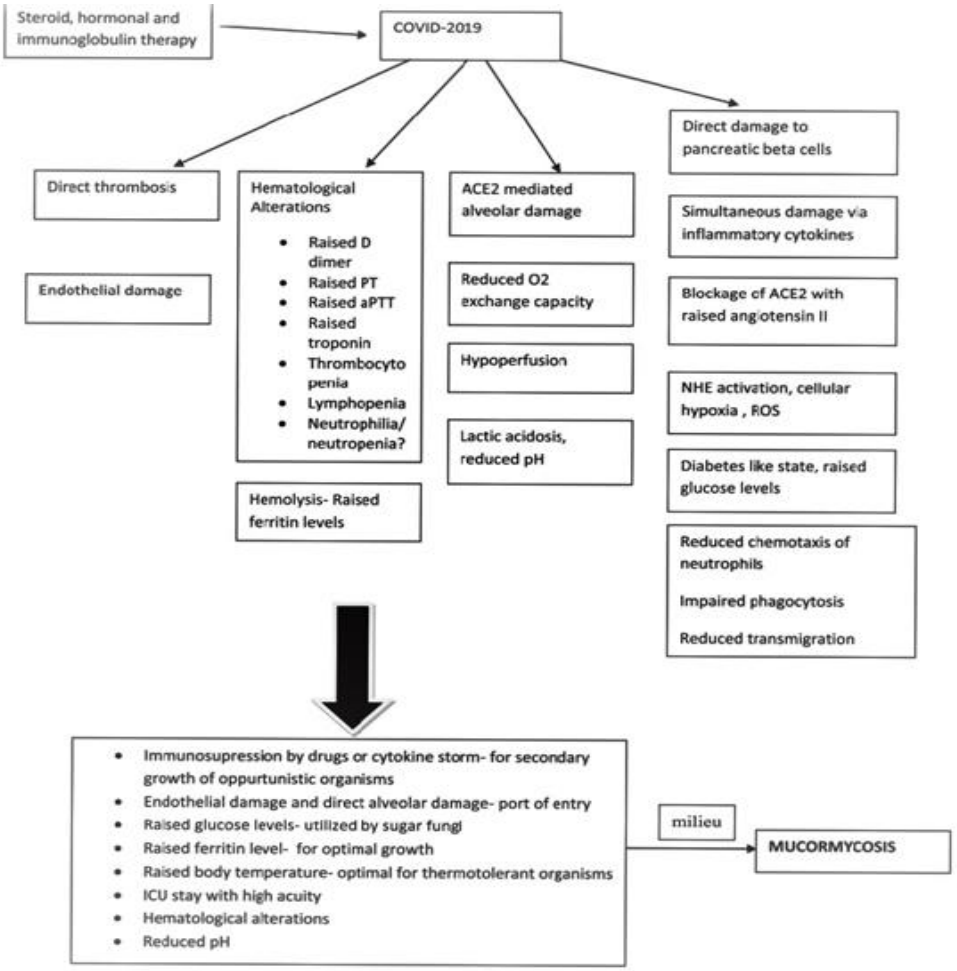

India has the highest prevalence of Mucormycosis among COVID-19 patients in the world. The incidence of mucormycosis has increased dramatically during the second wave of COVID-19, with over 14,872 cases reported to date. COVID 19's second wave has been traced to the SARS-CoV-2 B.1.617 mutation, also known as the 'double mutant' or 'delta' variant [26]. SARS-CoV-2 variant B.1.617 is thought to cause more infections and has higher virulence. The effect of the B1.617 variation on an elevated risk of Mucormycosis warrants more study and investigation.

Limitations

Our study has some significant limitations. It is a single centered study with a small number of Mucormycosis cases and hence may not accurately reflect the current status of the world. Additionally, we examined the attributability of diabetes and COVID19 to Mucormycosis risk because we lacked data on other risk variables such as cancer, neutropenia, HIV, or organ transplantation (actually we excluded them). We did not have a control group of patients with Mucormycosis who did not have COVID-19(6 had no prior covid). Additionally, we lack data on CAM outcomes after 12 weeks or on the attributability of death. However, this study sheds light on the demographic and clinical characteristics of CAM and its association with diabetes.

Conclusion

Mucormycosis is an Angio invasive fungal infection that is associated with a high rate of morbidity and mortality. The condition has increased rapidly in recent years because of the COVID 19 epidemic, uncontrolled diabetes, and inappropriate corticosteroid use, all of

which contribute to pathogenic invasion and bad effects. The incidence and outcome of mucormycosis has increased widely being associated with COVID 19 infection and poor glycaemic control of diabetes estimated through HbA1c.Early identification, surgical debridement, and antifungal medications all contribute to a patient's survival. Judicious use of steroids and proper glycaemic control among the Diabetic and COVID19 patients can prevent Mucormycosis and its complications.

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