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RESEARCH ARTICLE

A retrospective study of risk factors of Mucormycosis in COVID-19 patients at a dedicated COVID hospital

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ABSTRACT

Background: In the present scenario treating Mucormycosis is proving more challenging than COVID-19. **Aim and Objectives:** To describe the demographic profile, clinical presentations, and risk factors of COVID-19 associated Mucormycosis. **Materials and Methods:** A retrospective cross-sectional study was conducted in 30 patients. Diagnosed cases of Mucormycosis with a history of RTPCR or Rapid antigen positive for COVID infection were included in the study. Patients with a past history of Mucormycosis infection or patients not admitted in the hospital were excluded. The study began after obtaining the Institutional Ethical Committee Approval. The statistical analysis was done to study the Percentage distribution of the risk factors. **Results:** About 66.66% patients were male and 33.33% were females. The age of the patients was 52.8 ± 10.3 years. About 76.66% patients were farmers/farm workers. 90% of cases had Maxillary, 25 % Ethmoid and 5% had Sphenoid sinus involved. 23.33% were known diabetic. About 63.33% were having uncontrolled blood glucose level. About 23.33% were known hypertensive. About 66.66% had received steroids, 56.66% required oxygen therapy. 36.66% required Intensive care unit (ICU) and 6.66% required ventilator support during their management of acute COVID infection. None were fully vaccinated for COVID-19. **Conclusion:** The males are more susceptible to post-COVID 19 Mucormycosis infection as compared to females. Farmers/farm workers are at an increased risk too. Over use of steroids, uncontrolled blood sugar levels, oxygen therapy, long hospital stay, and ICU procedures and ventilators also contribute to the increased occurrence of post-COVID Mucormycosis. Most important factor that was observed was all the patients suffering from post-COVID Mucormycosis were not vaccinated.

KEY WORDS: COVID-19; Risk Factors; Mucormycosis; Retrospective Study

INTRODUCTION

As the medical facility in India is trying hard to cope up effectively with the COVID-19 pandemic crisis, India is witnessing a surge in Mucormycosis patients. In the present scenario treating Mucormycosis is proving more challenging than COVID-19. The mortality in Mucormycosis is ranging from 50% to 94% in India today.[1] India, before the COVID-19 era contributed to 40% of the total worldwide cases of Mucormycosis infection.[2] Mucorales are molds found extensively in the air and on decaying matter.[3] Our country is a tropical country and is predominately hot and humid. Hot and humid climate favors the growth of such molds. Moreover, many studies have found that hospitals in our country have very heavy mold spore count.[4] The severe acute respiratory syndrome coronavirus 2 (SARS-coV2) infection leads to immune dysregulation, dysfunction of cilia, microvascular coagulation, and cytokine storm devastating the whole immune, vascular and autonomic response of the patient.[5,6] Hence the long hospital stay of COVID patients, emergency invasive

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procedures conducted during the stay, and long term use of humidified oxygen therapy can also be a potent predisposing factors in such patients. Comorbidities such as Diabetes Mellitus was considered the major risk factor for Mucormycosis infection in Pre-COVID era.[7] ICMR had recommended the use of low-dose steroids for 5 days in treating moderate to severe cases.[8] However, the freehand prolonged use of high-dose steroids has become common practice in treating COVID patients. Hence, steroid-induced hyperglycemia may also be an important risk factor for COVID-associated Mucormycosis. Hence, the present retrospective cross-sectional study was planned to study and analyze the risk factors of COVID 19 associated Mucormycosis infection.

Need for Study

The study will help us to identify the major risk factors that predisposes the COVID-19 patients to the development of Mucormycosis infection. As prevention is always better than cure. The risk factors once identified can help us to cautiously identify the patients at risk of development of COVID-associated Mucormycosis infection. Regular scrutiny of such patients can help us in early diagnosis and preventing serious complications. This may even help us in decreasing the incidence of the infection.

Research Question

What may be major risk factors of COVID 19 associated Mucormycosis?

Hypothesis

Observational study

Not applicable.

Objectives

Primary

To describe the demographic profile, clinical presentations and risk factors of COVID-19 associated Mucormycosis.

Secondary

To study the outcome of study population after treatment.

MATERIALS AND METHODS

Study Design

A retrospective cross-sectional study.

Study Location

Dr. Vasantrao Pawar Medical College, Hospital and Research Centre, A Dedicated District COVID Hospital.

Period of Study

Study was conducted after Institutional Ethical Committee approval. The data of patients between May 2021 and June 2021 was taken.

Sample Size Calculation

The prevalence of Mucormycosis in India is 14 cases per one lakh population. Considering the relative precision 20% of prevalence and α as 0.05%, the minimum sample size calculated was 11. A total of 30 patients were decided to be included in the study.[2]

Sampling Technique

Hospital based.

Inclusion Criteria

Diagnosed cases of Mucormycosis (confirmed by KOH mount) with a past history of being RTPCR or Rapid antigen +ve for COVID infection or are presently RTPCR or Rapid antigen +ve irrespective of age and gender.

Exclusion Criteria

Patients have a history of Mucormycosis infection in the past.
Patients who do not have a history of COVID-19 infection
Patients who were not admitted in the hospital for the treatment of Mucormycosis as data will not be available.

Procedure

30 diagnosed patients of Mucormycosis infection with a past history of being RTPCR or Rapid antigen +ve for COVID infection or were presently RTPCR or Rapid antigen +ve were included in the study. The diagnosis of Mucormycosis was done by the KOH mount technique. The study began after obtaining the Institutional Ethical Committee Approval. The demographic details, past history, present history, clinical data, and investigation reports was obtained from the case files of these patients [Figure 1].

Statistical Analysis

The statistically analysis was done to study the Percentage distribution of the risk factors.

RESULTS

Table 1 shows the characteristic of medical records of 30 diagnosed cases of Mucormycosis admitted in the tertiary care hospital. Twenty out of 30 (66.66%) were male and 10 (33.33%) were female. All the patients had a past history of being RTPCR +ve for COVID infection. The duration

between RTPCR +ve report and symptoms of Mucormycosis was 14 ± 7 days but had now recovered, except for one patient who was RTPCR +ve while presenting with Mucormycosis infection. The age of the patients included in the study was 52.8 ± 10.3 years. Out of the 20 males, 18 were farmworkers/ farmers whereas out of the 10 females five were farm workers. Table 2: 22 out of 30 patients presented with involvement of unilateral paranasal sinuses (73.33%), one had bilateral paranasal sinuses invaded (3.33%) and 7 (23.33%) had eye invaded with unilateral paranasal sinuses involvement. About 90% cases had Maxillary sinus involved, 25 % had Ethmoid sinus involved and 5% had Sphenoid sinus involved. No case of intracranial involvement was observed. Table 1 - 7 out of 30 (23.33%) were known diabetic of which 3 had uncontrolled blood sugar level. Furthermore, 16 (53.33%) others had uncontrolled blood sugar level at the time of admission to the hospital for management of Mucormycosis.Seven out of 30 (23.33%) were known hypertensive since 3 ± 1.5 years. 20 out of 30 (66.66%) had received steroids either oral or parenteral during their management of acute COVID 19 infection. None of the patients had a history of asthma or any other systemic ailment. None of the patients were on immunosuppresant drugs or were suffering from any immunosuppressive disease (HIV, Cancer). 17 out of 30 patients (56.66%) had required oxygen therapy during their management of acute COVID infection. Mean ± Standard deviation. of the days for which these patients were given oxygen therapy is 7.77 ± 6.37 days. Of which 11 (36.66%) required Intensive care management and were shifted to the Intensive care unit (ICU) and 2 (6.66%) required ventilator support during their acute COVID-19 infection management. None were fully vaccinated for COVID-19. Out of the 30 patients, four died during treatment. Seventeen patients had to undergo extensive debridement as surgical management with liposomal Amphotercin B cover while nine patients did not require surgical intervention.

Table 1: Characteristics of 30 patients of post-COVID mucormycosis

Characteristics	Percentage
Demographic	
Male	66.66
Female	33.33
Age	52.8±10.3 years
Occupation	
Farmer/farm worker	76.67
Other	23.33
Vaccination status	
Non vaccinated	100
Fully vaccinated	0
Single dose vaccinated	0
Co-morbidity	
Known diabetic	23.33
Known hypertensive	23.33
Other, if any	--
Blood glucose level	
Uncontrolled	63.33
controlled	36.67
Uncontrolled with Keto-acidosis	0
Management during acute COVID 19 infection	
Oxygen therapy	56.66
Steroid therapy	66.66
ICU admission	36.66
Ventilator	6.66
Immunosuppressants	0

Table 2: Percentage distribution of site involved in mucormycosis in 30 patients

Site of involvement	Percentage
Maxillary sinus	90
Ethmoid sinus	25
Sphenoid sinus	5
Unilateral paranasal sinuses involved	73.33
Bilateral involvement of sinuses	3.33
Rhino-orbital involvement	23.33
Rhino-cerebral involvement	0

DISCUSSION

A cross-sectional retrospective study was conducted and the data of 30 patients was retracted from the medical records department of the District COVID hospital wherein a separate ward was established for patients of Mucormycosis.

SARS-CoV and Middle-east respiratory Syndrome, SARS-Cov-2 cause lower respiratory tract infection. It causes immunosuppression and hence may lead to increased susceptibility to secondary infections.[9] Mucormycosis is one such. Mucormycosis caused by mucormycetes is a serious angio-invasive infection. It is non-contagious but mainly infects immuno-compromised people.[10]

According to the letter published by WHO, the estimated prevalence of mucormycosis in India is 140/million population and the global incidence rate is 0.005 to 1.7/million population. The case fatality rate of which is 50%.[11] Hence awareness, scrutiny for risk factors to facilitate early diagnosis and treatment is the sole way to lead the patients to a better outcome.

In our study 20 out of 30 (66.66%) were males and 10 (33.33%) were females. The males were found to be more susceptible toward the development of COVID-associated Mucormycosis as compared to females. COVID-19 infection results into decrease in CD4+ count and decreased activity of CD8+ cells.[9] It causes alteration in chemotaxis, phagocytosis, and cytokine secretion increasing the vulnerability of the patients to secondary infections.[12]

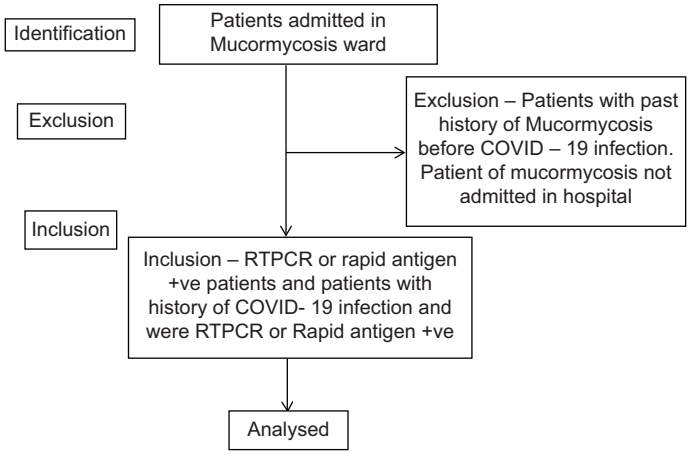

Figure 1: Flowchart of the study

SARS-Cov2 also causes dysregulation of ACE-2 expression in the β cells of the pancreas producing hyperglycemia. Dysregulation of ACE-2 in vascular endothelium leads to vascular thrombosis. Patients with phagocytic dysfunction, acidosis, and hyperglycemia are more susceptible to mucormycosis infection.[12,13]

Peckham *et al*. reported in his study that the risk of COVID-19 infections is same in both the sexes but the prevalence of severity, secondary infection, and requirement of ICU care is more in males as compared to females.[14]

The females have higher CD4+ T cells and CD8+ T cell activity and increased immunoglobulin production as compared to males. It was also noted that the antibody titer response to Influenza virus vaccination was much high in females as compared to males. It was proved through an experiment in mice that the testosterone level is inversely proportional to the antibody titer level to influenza vaccination. Hence both adaptive and innate immunity is better in females as compared to males. Moreover an antiviral cytokine, Type 1 interferon is also produced more in females as compared to males.[15]

Estradiol in females increases the neutrophil, macrophage/monocyte cytokine production. The entry of SARS-CoV2 virus is facilitated by ACE-2. Estradiol also influences the expression of ACE-2. Moreover, the genes related to it are on X chromosome where the genes avoid X-inactivation leading to unbound ACE-2 to form angiotensin and decrease the chances of complication.[16,17] Gupta *et al*. and Farhaan *et al*. also found that the males are more susceptible to COVID-19 infection and its complication as compared to females.[18,19] According to their study increase in age is also a risk factor for COVID-19 infection and the susceptibility to develop complications.[20] In our study too the age of the patients was observed as 52.8 ± 10.3 years.

Out of the 20 males 18 and out of the 10 females five were farm workers. This may be, as the major flow of the patients to this hospital was from the rural areas nearby where farming is the main occupation. Lusk *et al*. in their study concluded that evidence to prove that farmworkers are at a increased risk to COVID-19 infection is scanty but he also quoted that the countries where agriculture is the major occupation the rate of COVID-19 infection is the most.[21] Moreover, the spores of Mucormycosis causing mucor is present widely in soil, air, food, and decaying fruits and vegetables to which the farmers are more exposed.[21] The exposure of the farmers to pesticides due to its regular use also causes a scenario of depressed immunity in them, making them more susceptible to secondary infections such as mucormycosis. Poor economic status, lack of nutritious, balanced diet, and lack of easy availability of medical care may also have rendered them more susceptible to this disease.

The paranasal sinuses were the most common site of invasion of mucormycosis with either unilateral or bilateral involvement. In seven patients orbital involvement was also observed. The spores are extensively present in the environment hence it may enter the nasal cavity during inhalation and remain as a commensal in the nasal mucosa of healthy people. The spores germinate within the paranasal sinuses when the person becomes immunosuppressed as it is an opportunistic fulminant fungal infection. It invades the arteries causes thrombosis and leads to necrosis of the underlying tissue. Later, it spreads to the orbit or intracranially or to other nearby structures through blood vessels or by direct invasion. In our study 90% of cases had Maxillary sinus involved, 25 % had Ethmoid sinus involved and 5% had Sphenoid sinus involved. 22 out of 30 patients presented with involvement of unilateral paranasal sinuses (73.33%), one had bilateral paranasal sinuses invaded (3.33%) and 7 (23.33%) had eye invaded with unilateral paranasal sinuses involvement. No case of intracranial involvement was observed. Bhansali *et al*. in their study of mucormycosis in diabetes also found 100% involvement of paranasal sinuses with ethmoid (86%), maxillary (80%).[22] Gupta *et al*. in their retrospective study of risk factors of mucormycosis also found that paranasal sinuses were the most common site of involvement with maxillary sinuses 94%, ethmoids 79%, frontal 67%, sphenoid 62%. The most common in bilateral involvement was sphenoid followed by maxillary.[18] Whereas in our study only a single patient out of 30 was observed with bilateral involvement of maxillary sinuses.

A total of 19 patients had uncontrolled blood sugar levels when presented with Mucormycosis. Seven patients were known hypertensive and 20 had received steroids during their treatment of acute COVID 19 infection. Hartnett *et al*. in their review article before the COVID era had mentioned that un-controlled glucose levels, diabetes, ketoacidosis, and immunocompromised state are important risk factors for the development of Mucormycosis.[23]

In diabetic ketoacidosis the pH is low and blood glucose level is very high, which leads to dysfunctional phagocytes, impaired chemotaxis, and impaired inta-cellular lysis mechanism making such patients more vulnerable to Mucormycosis

infection. Moreover in ketoacidosis, due to low pH the iron gets released from the binding proteins, also proton-mediated dissociation of iron from transferrin results in an increase in serum iron levels. This iron is now available for the Mucorales for their growth.[18,24] Gupta *et al*. in their study had also observed that the patients with diabetic ketoacidosis are at an increased risk of contracting the mucormycosis infection.[18] But in our study, the patients had uncontrolled blood sugar levels but were not in acidosis. Greater availability of glucose to the pathogens, low pH-decreasing the inhibitory activity against the pathogen and increased expression of the host receptors which help in invasion and destruction of the host epithelial cells by Rhizopus are the mechanisms suggested for increased risk of high blood sugar level patients not in ketoacidosis to Mucormycosis.[24]

The guidelines specifically clearly mention that low-dose steroids for 5 days can be given to patients suffering from moderate to severe COVID-19 infection. Overzealous use of which can predispose them to secondary infections.[8] Moreover, the natural killer cell activity is also decreased. A recent review further suggests that the COVID-19 disease process, free hand use of steroids, and extensive use of broad-spectrum antibiotics is predisposing the patients further to the risk of secondary infection. Ravani *et al*. and Singh *et al*. in their study also have found an association between steroid use and COVID-19 associated Mucormycosis.[25,26]

Seventeen out of 30 patients (56.66%) had required oxygen therapy during their management of acute COVID infection. Of which 11 (36.66%) required Intensive care management and were shifted to ICU and 2 (6.66%) required ventilator support during their acute COVID-19 infection management. Long stay in hospitals, humidity, interventional procedures, and contaminated hospital tools may have increased their risk of developing Mucormycosis. ICU-related vascular procedures and ventilator support cause vascular endothelial injury and venous stasis. Elevated ferritin and iron hemolysis and associated acidosis provide a source of nutrition to Mucorales.[13]

None of the patients were fully vaccinated. During the first wave to the population was not vaccinated either but the cases of Mucormycosis seen was significantly more during the second wave. In an internal report of analysis of 300 patients of Mucormycosis associated with COVID-19 they observed that 86% patients were not vaccinated and 6% had received only single dose. They concluded that vaccination against COVID-19 is an important risk factor in the development of COVID-associated Mucormycosis.[27,28] The fatality was 4 (13.33%) out of 30 patients as compared to 50% as observed. This may be because none of the patients had received immunosuppressant drug-like Tocilizumab, early diagnosis, instant extensive surgical debridement, and last but not the least self-immunity also plays a vital role towards the positive outcome of the disease. Table 3 shows the various pre-disposing factors of post-COVID Mucormycosis with their percentage of prevalence.

Table 3: Probable pre-disposing factors of post-COVID mucormycosis

Pre-disposing factor	% of prevalence
Age	52.8±10.3 years
Not vaccinated	100
Farmer/Farm workers	76.67
Male	66.66
Steroid therapy	66.33
Uncontrolled Blood sugar level	63.33
Oxygen therapy	56.66
ICU admission	36.66
Known DM/HT	23.3
Ventilator support	6.66

CONCLUSION

In our study, we observed that the males are more susceptible to post-COVID 19 mucormycosis infection as compared to females. Farmers/farm workers are at an increased risk of suffering from COVID-associated Mucormycosis. Overuse of steroids, uncontrolled blood sugar levels, oxygen therapy, long hospital stay, and ICU procedures and ventilators also contribute to the increased occurrence of post-COVID Mucormycosis.Most important factor that was observed was all the patients suffering from post-COVID Mucormycosis were not vaccinated. Hence, the emphasis on vaccination of the population must top the priority list to fight effectively against this health crisis. Judicious use of steroids, maintaining blood sugar levels in normal ranges, giving oxygen therapy as and when required only and maintenance of contamination free instruments and rooms is very important. Awareness of the symptoms of this disease among the population is very important as only early and apt medical care at initial stage can lead to a better outcome of the disease. Moreover patients exposed to the above-mentioned risk factors should be scrutinized timely in the follow-up to diagnose the disease at an early stage. Fully vaccinated population and a highly suspicious eye on the patients of COVID-19 with suspected risk factors is the key to reduce the burden of the disease. Early diagnosis by imaging, expert and affordable health care team nearby can ensure a better outcome.

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