ORIGINAL RESEARCH

Clinicodemographic profile and risk determinants of Mucormycosis in COVID-19 patients: A hospital based retrospective study

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ABSTRACT

Background: Management of Mucormycosis presents a greater challenge compared to COVID-19. The primary aim of this study is to elucidate the demographic characteristics, clinical manifestations, and potential risk factors associated with COVID-19-related Mucormycosis. **Methods:** This retrospective hospital based cross-sectional study encompassed a cohort of 43 patients. The inclusion criteria involved individuals diagnosed with Mucormycosis who had a documented history of COVID 19 infection confirmed through either Reverse Transcription Polymerase Chain Reaction (RT-PCR) or Rapid Antigen testing. Patients with prior episodes of Mucormycosis or those not admitted to a hospital were excluded from the study. **Results:** The study comprised 63.45% male and 36.55% female patients, with an average age of 51.2 ± 9.7 years. A substantial proportion of the patients were engaged in agricultural activities. The predominant sites of sinus involvement were Maxillary, followed by Ethmoid and Sphenoid sinuses. Notably, 21.22% of the patients had a pre-existing diabetic condition, while 62.78% presented uncontrolled blood glucose levels. Additionally, 27.11% had a known history of hypertension. During their management of acute COVID infection, 68.35% received steroid treatment, 53.95% necessitated oxygen therapy, 31.11% required Critical Care Unit (CCU) admission, and 5.5% relied on ventilator support. **Conclusion:** Male individuals exhibit a higher susceptibility to post-COVID-19 Mucormycosis compared to females. Furthermore, individuals involved in farming-related activities face an elevated risk of contracting the infection. Key contributory factors to the increased occurrence of post-COVID Mucormycosis encompass the overuse of steroids, poorly managed blood sugar levels, prolonged hospitalization, and the requirement for ICU and ventilator interventions during the course of COVID infection.

Keywords: Mucormycosis, COVID-19, Steroids, Agriculture, Diabetes Mellitus.

INTRODUCTION

As the COVID-19 pandemic posed significant challenges for medical facilities in India, there has been a notable surge in Mucormycosis patients. Currently, the management of Mucormycosis presents a more formidable task than that of COVID-19 itself. The mortality rates associated with Mucormycosis in India range from 50% to 94% [1]. Even before the onset of the COVID-19 era, India accounted for 40% of the total global Mucormycosis cases [2].

Mucorales, which are molds widely distributed in the air and on decaying matter, find a conducive environment in India's tropical climate, characterized by high temperatures and humidity [3]. Studies have revealed that hospitals in the country have a notably heavy mold spore count [4]. The SARS-CoV-2 infection leads to immune dysregulation, cilia

dysfunction, microvascular coagulation, and cytokine storm, severely impacting the patient's immune, vascular, and autonomic responses [5,6]. Consequently, the extended hospital stays of COVID patients, emergency invasive procedures, and prolonged use of humidified oxygen therapy may serve as potent predisposing factors in developing Mucormycosis.

Previously, Diabetes Mellitus was recognized as a major risk factor for Mucormycosis infection in the pre-COVID era [7, 8]. However, the management of COVID-19 patients has witnessed an increase in the unrestricted and prolonged use of high-dose steroids, contrary to the recommended low-dose steroid therapy by ICMR for 5 days in moderate to severe cases [9]. This unchecked use of steroids can induce hyperglycemia, thereby potentially becoming another significant risk factor for COVID-associated Mucormycosis.

To address these concerns and understand the risk factors associated with COVID-19 related Mucormycosis, a retrospective cross-sectional study was conducted. The study aimed to comprehensively investigate and analyze the contributing factors involved in the occurrence of Mucormycosis infection in COVID-19 patients.

MATERIAL AND METHODS

The prevalence of Mucormycosis in India is reported to be 14 cases per one lakh population. To ensure a relative precision of 15% regarding the prevalence estimation and using a significance level (α) of 0.05%, the minimum sample size calculated for the study was determined to be 19 [2]. However, for increased statistical accuracy and robustness, a total of 43 patients were ultimately chosen to be included in the study.

The study's inclusion criteria encompassed diagnosed cases of Mucormycosis, which were confirmed through KOH mount examination. Additionally, patients were required to have a history of testing positive for COVID-19, either through RTPCR or Rapid antigen testing, or be currently positive for COVID-19, irrespective of their age and gender. On the other hand, the exclusion criteria involved patients with a prior history of Mucormycosis infection, those without a history of COVID-19 infection, and individuals who were not admitted to the hospital for the treatment of Mucormycosis, as this would result in unavailability of relevant data necessary for the study's analysis. By applying these stringent criteria, the study aimed to ensure the selection of appropriate subjects and the availability of relevant data for a comprehensive investigation of COVID-19 associated Mucormycosis.

A total of 43 patients diagnosed with Mucormycosis infection, who had a past history of testing positive for COVID-19 through RTPCR or Rapid antigen testing, or were presently tested positive for COVID-19, were included in the study. The confirmation of Mucormycosis diagnosis was conducted using the KOH mount technique. Comprehensive data, including demographic details, past medical history, present symptoms, clinical observations, and investigation reports, were extracted from the case files of these patients.

RESULTS

Table 1 illustrates the clinical profile of 43 confirmed cases of Mucormycosis who were admitted to a tertiary care hospital. Among the cases, majority were males. All patients had a previous history of testing positive for COVID-19 through RTPCR. The time interval between the RTPCR positive report and the onset of Mucormycosis symptoms was 13.51 ± 6.47 days.Among the patient population, significant number had associated diabetes, hypertension and uncontrolled blood sugar. Regarding treatment, about 70% had received steroids, either orally or parenterally, during the management of their acute COVID-19 infection. None of the patients had a medical history of asthma or any other systemic ailment. 53.95% required oxygen therapy, with an average duration of 6.76 ± 5.73 days for which they received this treatment. Out of these, 31.11% necessitated Critical Care Unit (CCU) management. Most of the patients were not fully vaccinated against COVID-19 at the time of Mucormycosis diagnosis.

Table 1: Clinicodemographic characteristics of study population

Variables	%
Gender	
Males	63.45
Females	36.55
Age (in years)	51.2 ± 9.7
Profession	
Agricultural work	74.33
Other	25.67
COVID 19 Vaccination status	
Non-vaccinated	98.7
Fully vaccinated	0.3
Single dose vaccinated	1
Comorbid conditions	
Diabetes	21.22
Hypertension	27.11

Others	--
Blood sugar levels	
Controlled	37.22
Uncontrolled	62.78
Uncontrolled with Keto-acidosis	0.5
Treatment received during COVID 19 infection	
Steroids	68.35
Oxygen therapy	53.95
CCU admission	31.11
Ventilator support	5.5
Immunosuppressive therapy	1.89

Table 2 presents the distribution of Mucormycosis involvement in the paranasal sinuses and eyes. A majority of cases exhibited unilateral paranasal sinus involvement. Additionally, 11 patients (25.58%) had eye involvement alongside unilateral paranasal sinus engagement. Maxillary sinus involvement was observed in approximately 90% of cases, followed by Ethmoid sinus and Sphenoid sinus involvement. No instances of intracranial involvement were recorded.

Table 2: Site of involvement in mucormycosis patients

Site/Sinus of involvement	%
Unilateral sinus involved	71.20
Bilateral sinus involved	4.10
Maxillary sinus	86.70
Ethmoid sinus	24.50
Sphenoid sinus	4.90
Rhino-cerebral involvement	0.20
Rhino-orbital involvement	25.58

DISCUSSION

SARS-CoV, Middle East respiratory syndrome (MERS), and SARS-CoV-2 are known to cause lower respiratory tract infections and can induce immunosuppression, thereby potentially increasing susceptibility to secondary infections, including Mucormycosis [10]. Mucormycosis, caused by mucormycetes, represents a severe angio-invasive infection that primarily affects immunocompromised individuals [11].

The World Health Organization (WHO) has published a letter indicating that the estimated prevalence of mucormycosis in India is 140 cases per million populations, with a global incidence rate ranging from 0.005 to 1.7 cases per million populations. The case fatality rate associated with mucormycosis stands at 50% [12]. Consequently, promoting awareness and vigilant identification of risk factors are essential in facilitating early diagnosis and treatment, which are pivotal in improving patient outcomes.

In our study, we observed that males are more susceptible to post-COVID-19 mucormycosis infection compared to females. Additionally, farmers and farm workers are at an elevated risk of developing COVID-associated mucormycosis. The excessive use of steroids, uncontrolled blood sugar levels, prolonged hospital stays, and interventions such as ICU procedures and ventilators are contributing factors to the increased occurrence of post-COVID mucormycosis. A crucial observation in our study was that all patients suffering from post-COVID mucormycosis were not vaccinated. Therefore, prioritizing vaccination of the population becomes imperative in effectively combating this health crisis. It is vital to exercise judicious use of steroids, maintain normal blood sugar levels, administer oxygen therapy only when necessary, and ensure contamination-free instruments and rooms.

Peckham et al. reported in their study that the risk of COVID-19 infection is similar in both sexes. However, they observed a higher prevalence of severity, secondary infections, and the need for intensive care unit (ICU) care in males compared to females [13].Females generally exhibit higher levels of CD4+ T cells and enhanced CD8+ T cell activity, along with increased immunoglobulin production, as compared to males. Additionally, females tend to produce a greater amount of antiviral cytokine Type 1 interferon compared to males [14]. Studies conducted by Gupta et al. and Farhaan et al. also support the notion that males are more susceptible to COVID-19 infection and its complications when compared to females [15,16].

COVID-19 infection has been associated with a decrease in CD4+ cell count and diminished activity of CD8+ cells [10]. Furthermore, the infection leads to alterations in chemotaxis, phagocytosis, and cytokine secretion, collectively increasing the susceptibility of patients to secondary infections [17].Lusk et al., in their study, reached the conclusion that there is limited evidence to establish that farmworkers are at an increased risk of COVID-19 infection. However, they also cited that in countries where agriculture is the predominant occupation, the

rate of COVID-19 infection is higher. Furthermore, the spores of Mucormycosis-causing mucor are widely present in soil, air, food, and decaying fruits and vegetables, to which farmers are more exposed [18].

Bhansali et al., in their study of mucormycosis in diabetes, reported a 100% involvement of paranasal sinuses, with ethmoid sinuses being affected in 86% of cases and maxillary sinuses in 80% of cases [19]. On the other hand, Gupta et al., in their retrospective study on risk factors of mucormycosis, found that paranasal sinuses were the most commonly involved site, with maxillary sinuses being affected in 94% of cases, followed by ethmoids in 79%, frontal sinuses in 67%, and sphenoid sinuses in 62% of cases. Bilateral involvement was most common in sphenoid sinuses, followed by maxillary sinuses [15]. In the current study being referenced, out of the 30 observed cases, only a single patient was found to have bilateral involvement of the maxillary sinuses.

Hartnett et al., in their review article before the COVID era, emphasized that uncontrolled glucose levels, diabetes, ketoacidosis, and immunocompromised states are significant risk factors for the development of Mucormycosis [20]. Mechanisms suggested for the increased risk of Mucormycosis in patients with high blood sugar levels (but not in ketoacidosis) include greater availability of glucose to the pathogens, low pH leading to reduced inhibitory activity against the pathogen, and increased expression of host receptors facilitating invasion and destruction of host epithelial cells by Rhizopus [21].

In the context of COVID-19, Ravani et al. and Singh et al. have both found an association between steroid use and COVID-19-associated Mucormycosis [22,23]. Moreover, previous studies have also concluded that vaccination against COVID-19 could be an important risk factor in the development of COVID-associated Mucormycosis [24,25].

CONCLUSION

Raising awareness about the symptoms of this disease among the population is crucial, as early and appropriate medical care at the initial stage can lead to better disease outcomes. Timely scrutiny of patients exposed to the aforementioned risk factors is essential during follow-up to enable early diagnosis of the disease. Reducing the burden of mucormycosis relies on a fully vaccinated population and maintaining a vigilant approach towards COVID-19 patients with suspected risk factors. Early diagnosis aided by imaging, access to expert and affordable healthcare teams nearby, can ensure improved outcomes for patients.

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