

Mucormycosis during COVID Pandemic: A Cross-Sectional Study in a Tertiary Care Hospital

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Abstract

Background and Objectives: The COVID-19 pandemic had affected multiple aspects of health. Injudicious use of antibiotics had led to the development of drug resistance. Moreover, some patients during or after COVID infection developed mucormycosis. Hence, we mapped this study to evaluate the incidences of mucormycosis among COVID patients.

Methods: In this cross-sectional study, we included adult patients of either gender, who tested positive for SARS-CoV-2 by RT-PCR and were admitted to the ICU either due to COVID-19 or mucormycosis. Relevant clinical and microbiological data were retrieved from the case sheets of the participants. All clinical specimens were processed according to standard microbiological procedures. Isolates were identified using VITEK-2 automated identification systems. The risk factors for mucormycosis were evaluated. We adopted convenience sampling for this study. R software (version 4.4.1) was leveraged for the data analysis.

Results: We applied our study criteria to 4027 patients in total. 846 subjects (21.0%) satisfied the requirements for eligibility. There were 414 (48.9%) females among them. The study population was 53.5 (45.0-63.0) years old on average [female: 52.0 (45.0-63.0) years, male: 53.0 (45.0-64.0) years, $p = 0.42$]. The risk of mucormycosis was greater in the steroid-using patients (OR: 1.146, $p = 0.006$). The likelihood of developing mucormycosis was increased in patients with active COVID-19 disease (OR: 1.200, $p = 0.003$). The mortality rate was higher among patients with mucormycosis than among those without (OR: 11.125, $p < 0.001$).

Conclusion: Most of the patients were middle-aged. The risk of mucormycosis was higher among those with active COVID-19 disease and those treated with corticosteroids. The risk of mortality was higher among those with mucormycosis.

Keywords: COVID-19 Infection; Mucormycosis; Steroids; ICU; Comparative Analysis

Abbreviations

AST: Antimicrobial Susceptibility Testing; BHI: Brain Heart Infusion; COVID: Corona Virus Disease; CI: Confidence Interval; DKA: Diabetic Ketoacidosis; DM: Diabetes Mellitus; ICU: Intensive Care Unit; IQR: Interquartile Range; LPCB: Lactophenol Cotton Blue; KOH: Potassium Hydroxide; OR: Odds Ratio; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; SDA: Sabouraud Dextrose Agar; WHO: World Health Organization

Introduction

The COVID-19 pandemic has many detrimental impacts on various aspects of health. There was deterioration of global health and financial landscape. There was turmoil of the healthcare systems because of the unprecedented morbidity and mortality rates [1]. As of 3rd May 2021, WHO confirmed 152,387,917 COVID-19 cases and 3,195,624 deaths round the globe. In India, there were 19,925,604 cases and 218,959 deaths due to COVID-19. During the second wave (1st March to 3rd May), there were 8,813,363 cases and 61,802 deaths in India [2].

Mucormycosis is an emerging infection caused by fungi belonging to the order Mucorales family, with *Rhizopus*, *Mucor*, and *Lichtheimia*, accounting for > 90% of all cases [3]. It was previously termed zygomycosis, is a rare fungal infection, instigated by the mucormycete mould, that occurs extensively in soil, leaves, decayed wood and putrified manure. The major risk factors for mucormycosis include uncontrolled diabetes mellitus (DM) and ketoacidosis, other forms of metabolic acidosis, treatment with corticosteroids, organ or bone marrow transplantation, neutropenia, trauma and burns, malignant hematologic disorders, and deferoxamine therapy in patients receiving hemodialysis [4-6].

The COVID-19 pandemic in India has resulted in a tremendous increase in mucormycosis cases, especially in patients with uncontrolled DM and corticosteroid use. Mucormycosis has pleiotropic clinical presentations, with rhino-orbital/rhino-cerebral, sinopulmonary and necrotizing cutaneous forms being the predominant manifestations [3,5].

Therapy of mucormycosis is multidisciplinary and requires a high index of suspicion for initiation of early Mucorales-active antifungals. Reversal of underlying immunosuppression, if feasible, rapid diabetic ketoacidosis (DKA) correction and in selected patients, surgical debulking are crucial for improved outcomes [6,7].

Although antibiotics are ineffective against COVID-19, they were often used in suspected cases due to the difficulty in excluding secondary bacterial infections-a serious and common complication in hospitalized patients, occurring in 10-15% of cases [8,9]. The mortality rate in COVID-19 patients with secondary bacterial infections is approximately 50% [9]. This cross-sectional study was carried out to determine the incidence and associated factors of mucormycosis among COVID-19 patients.

Materials and Methods

This cross-sectional study was carried out from November 2020 to October 2021 at Kalinga Institute of Medical Sciences, India. Before beginning the study, we got the ethics approval from the concerned authority (KIIT/KIMS/IEC/761/2021 dated 28/10/2021). All participants or their close relatives provided consents before the enrolment.

Our study included adult patients of either gender, who tested positive for SARS-CoV-2 by RT-PCR and were admitted to the ICU irrespective of their COVID-19 status. We analyzed all of their samples used for culture and sensitivity testing. We excluded people with viral infections, contaminated samples, normal flora, or missing records.

Specimens were collected and transported in sterile, humidified, leak proof container having brain heart infusion (BHI) media for survival of the organism. The specimens' culture in SDA tubes within few hours of the collection and reaching to the microbiology department. Necrotic materials from the specimen were usually processed. The Sabouraud dextrose agar (SDA) tubes were kept at 22°C for three weeks. The tubes were observed for fungal growth every alternate day.

Mucorales were identified through direct microscopy. The specimen put in 10% KOH and broad irregular hyphae were seen under high power. There was fast growing white, floccose and devoid of pigmentation on the reverse side within 10 to 14 days of incubation.

From the growth, lactophenol cotton blue (LPCB) mount was done. On LPCB mount, there was broad, hyaline, aseptate, branching hyphae producing sporangiophores. If there was no growth within 21 days then the tubes are reported as negative. Also, other fungal growths also identified based on their KOH, culture characteristics. The demographic data such as age, gender, socioeconomic status, COVID-19 RT-PCR positive report, treatment history like usage of corticosteroids, and remdesivir, mortality, and presence of mucormycosis were collected.

For this cross-sectional study, we adopted convenience sampling as we did not know the prevalence of COVID and related mucormycosis in our institution. We used the Shapiro-Wilk test to ensure that the collected data were normally distributed. For categorical variables, frequency and proportion were used as summary statistics. The continuous data was presented using the median and interquartile range (IQR). Descriptive statistics were used to summarize patient characteristics, types of bacterial isolates, and resistance patterns. We used Pearson’s chi-square test to compare sociodemographic characteristics. The Wilcoxon test was calibrated to analyze the continuous data. The odds ratio (OR) was presented with 95% confidence interval (CI). For data analysis, we used R software (version 4.4.3) [10]. The statistical tests were two-tailed. The p-values less than 0.05 were interpreted as statistically significant.

Results

We scrutinized a total of 4027 patients with our study criteria. 1852 patients had incomplete data. 1086 patients had contaminated flora in their culture reports. 243 patients did not have RT-PCR positive reports for COVID-19 infection. Hence, we excluded those 3181 people. The remaining 846 (21.0%) subjects met the eligibility criteria. Of them, 414 (48.9%) were females. The sociodemographic traits have been illustrated in [table 1](#). The distribution of the study population is portrayed in [figure 1](#). The median age of the study population was 53.5 (45.0-63.0) years [female: 52.0 (45.0-63.0) years, male: 53.0 (45.0-64.0) years, p = 0.42]. The age distribution of the study participants is shown in [figure 2](#).

Parameter	Value
Age (years)	53.5 (45.0-63.0)
Age > 60 years	249 (29.4%)
Females	414 (48.9%)
Socioeconomic class	
Lower	247 (29.2%)
Lower-middle	449 (53.1%)
Upper-middle	150 (17.7%)
COVID-19 disease	
Active	529 (62.5%)
Recovered	317 (37.5%)
Ongoing medications	
Steroids	649 (76.7%)
Remdesivir	197 (23.3%)
Mucormycosis	
Present	6 (0.7%)
Absent	840 (99.3%)

Table 1: The sociodemographic and clinical parameters of the study population.

The continuous and categorical variables are presented as median (IQR) and frequency (proportion), respectively.

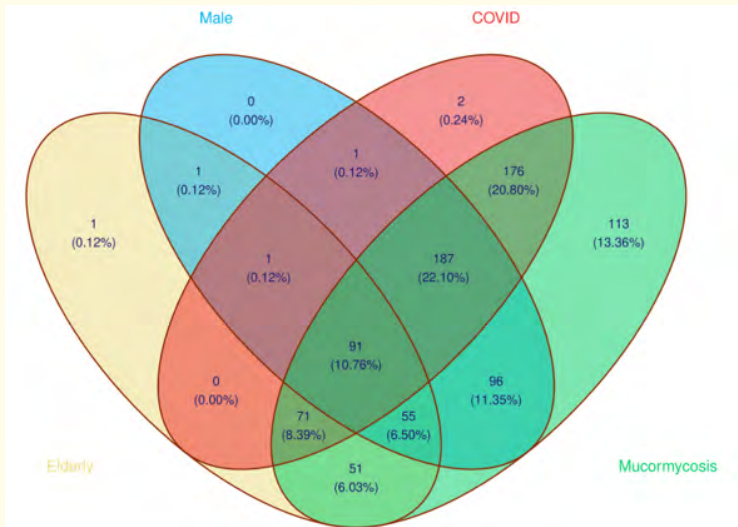


Figure 1: Distribution of the study population.

The Venn diagram portrays the distribution of the study population. The divisions are based on the gender (male or female), age group (elderly or young), COVID-19 status (active or recovered), and mucormycosis (absent or present). The frequency and proportions denote the study participants with the corresponding parameters. The COVID (shown in red colour) and mucormycosis (shown in green colour) groups denote patients with active COVID infection and without mucormycosis, respectively.



Figure 2: Age distribution of the participants.

The box-violin-jitter plots demonstrate the age distribution of the female and male patients. The width of the violin plot corresponds to the number of participants with their corresponding age shown on the y-axis. The box-whisker and jitter plots illustrate the age distribution. The Mann-Whitney test was used to calculate the p-value.

Table 2 demonstrates the associated factors of mucormycosis. The patients on steroids had a higher chance of mucormycosis (OR: 1.146, p = 0.006). The patients with active COVID-19 disease had a higher risk of getting mucormycosis (OR: 1.200, p = 0.003). The patients with mucormycosis had higher mortality rate as compared to those without mucormycosis (OR: 11.125, p < 0.001).

Parameters	Mucormycosis (n = 6)	No mucormycosis (n = 840)	Odds ratio (95% CI)	p-value
Drugs consumed				
Steroids only	4	534	1.146 (1.020 - 1.268)	0.006
Remdesivir	2	306		
Outcome				
Death	4	128	11.125 (8.337 - 16.844)	< 0.001
Discharge	2	712		
Active COVID-19				
Yes	4	525	1.200 (1.014 - 1.408)	0.003
No	2	315		

Table 2: Associated factors of mucormycosis.

Discussion

This cross-sectional study was carried out in a tertiary care hospital to evaluate the incidence and risk factors of mucormycosis among patients with COVID-19 infection. We evaluated a total of 4027 patients using our study criteria. 846 participants (21.0%) met the eligibility criteria. Among them were 414 (48.9%) females. The average age of the study participants was 53.5 (45.0-63.0) years [male: 53.0 (45.0-64.0) years, female: 52.0 (45.0-63.0) years, p = 0.42]. Our study findings concorded with some recently conducted studies [11,12]. Incidences of mucormycosis were higher among the individuals with active COVID-19 infection [13]. We also found similar data through our study. The higher incidences of mucormycosis among active COVID-19 patients could be attributed to the lowered immunity of those individuals.

In our study, we noted that patients who used steroids had a higher risk of developing mucormycosis (OR: 1.146, p = 0.006). This observation could be attributed to the lowered immunity because of the chronic administration of the steroids. This finding is supported by the study conducted by Pakdel., *et al.* [14]. Patients with active COVID-19 disease had a higher chance of acquiring mucormycosis (OR: 1.200, p = 0.003). The active COVID-19 disease might have lowered the immunity. The ongoing corticosteroids treatment aggrandizes the situation and favours the development of mucormycosis. Our observations were backed up by the study carried out by Singh., *et al.* [15].

Patients with mucormycosis had a greater mortality rate than those without (OR: 11.125, p < 0.001). Two recently conducted studies advocated that the overall mortality rate of COVID-19 patients increases if the individual had active mucormycosis infection [16,17].

Conclusion

The majority of patients were middle-aged. People who were receiving corticosteroid treatment and those who had active COVID-19 disease were more likely to develop mucormycosis. Those who had mucormycosis had a greater risk of morbidity and mortality. We warrant more numbers of prospective studies with larger sample sizes and longer durations to generalize the study findings.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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