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Is mucormycosis an addition to the pandemic spectrum: an observational study

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ABSTRACT

Background and Objective: A concerning increase in occurrences of COVID-19-associated mucormycosis (CAM), has been reported worldwide in people who are coping with COVID-19 disease. Despite this apparent correlation, the exact association is yet unknown. To ascertain the degree to which mucormycosis and coronavirus illnesses are associated, this study was conducted to analyze the relationship between COVID-19 and mucormycosis infection.

Methods: This observational study examined 35 individuals who had been diagnosed with mucormycosis at Lahore General Hospital, Lahore, Pakistan. The relationship between mucormycosis and coronavirus disease was determined by analyzing the patient's demographics, gender, COVID-19 status, and co-morbidities.

Results: The mean age of the enrolled patients was 49.40 ± 13.511 years with the majority (54.3%) being male. A total of 25.7% had confirmed COVID-19-positive disease. Notably, diabetes mellitus (DM) was the predominant co-morbidity in a significant proportion of patients (74.3%), followed by comorbidity of DM with chronic kidney disease (11.4%), chronic liver disease (8.6%), and hypertension (5.7%). The presence of co-morbidities and COVID-19 were significantly correlated ($p < 0.05$) in mucormycosis patients, whereas age and gender had no significant association ($p > 0.05$).

Conclusion: In conclusion, mucormycosis could be an additional aspect of the pandemic's spectrum. The data from our study supports this claim since a significant percentage of the patients with mucormycosis had a positive COVID-19 disease concomitantly.

Keywords: COVID-19, mucormycosis, COVID-19-associated mucormycosis (CAM), diabetes mellitus, pandemic, comorbidities.

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Introduction

Corona virus was first detected in December 2019 in Wuhan, China, and had spread worldwide in a few days to weeks.¹⁻³ It was named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) by the World Health Organization (WHO) on 11th Feb 2020 leading to pneumonia as coronavirus disease 2019 COVID-19.⁴⁻⁶ The SARS-CoV-2 infectivity is morphologically different from earlier identified coronavirus that caused pneumonia. On 11 March 2020, COVID-19 was declared by WHO as a pandemic and in April 2021, COVID-19 infectivity was confirmed among 135 million individuals with 2.92 million fatalities across the globe,⁷ with a case fatality rate (CFR) of about 5.4 % and an infection fatality rate of 0.9 %. Among low and middle-income states, Pakistan was the first country affected by the epidemic and the reported

coronavirus cases were 398,024 with 8025 mortalities (CFR 2.51%) by the year 2020.⁸

COVID-19 has been linked with several opportunistic fungal and bacterial contaminations.⁹ Both *Candida* and *Aspergillus* have been stated as major fungal bacteria for co-infection among COVID-19 individuals.¹⁰ COVID-19-associated mucormycosis (CAM) is a novel entity¹¹ and currently, mucormycosis cases among COVID-19-positive people have increasingly been reported in the United States, Austria, Brazil, Mexico, Italy, France, Iran, and India.¹² The major cause that seems to be assisting Mucorales spores to develop among COVID-19 patients is the best environment of low oxygen, high glucose, high levels of iron, acidic medium, and reduced phagocytic activity of the white blood cells because of immunosuppression (steroid-mediated, SARS-CoV-2 mediated or background comorbidities) along with

other several common risk factors such as extended hospital stay with/without mechanical ventilators.¹³

Mucormycosis is one of the terms used for diseases caused by fungus which have filaments with non-septate hyphae.¹⁴ It is one of the opportunistic fungal infections that belongs to the zygomycete family and is ever-present within the environment. The main route of infectivity is via spores inhalations, which then spread to paranasal sinuses and lungs.¹⁵ Usually mucormycosis causes nose reddening or discoloration, double or blurred vision, and difficulty breathing blood with sputum by coughing.¹⁶ The infection is increasingly reported in patients with diabetes mellitus (DM)¹⁷ Also, DM has been linked with severity in COVID-19.¹⁸ It has been observed that patients with DM are at an elevated risk of dying than those with no diabetes and an elevated death rate with CAM remains a major concern.¹⁹ An important rise among this disease cases is very strongly associated with systemic steroid use, especially corticosteroids in diabetic patients with COVID-19 disease.²⁰

A casual association between mucormycosis and COVID-19 remains uncovered in the literature.²¹ Pakistan is also affected by the COVID-19 pandemic and various mucormycosis cases are recognized as [Black Fungus]²²⁻²⁴. Therefore, the current study aims to find out the association between mucormycosis and coronavirus disease, 2019 in the local population.

Methods

This was an observational study conducted at the Otorhinolaryngology Department of Lahore General Hospital, Lahore, Pakistan. Thirty-five patients diagnosed with COVID-19 were included and patient demographic data, including age, gender, and so on, the status of mucormycosis infection and co-morbidities such as DM, hypertension (HTN), and so on, were screened for developing associations. The COVID-19-positive disease was diagnosed by culture of a sample taken by nasal swabs and undergone Polymerase Chain Reaction (PCR) to detect the SARS-CoV-2 virus. Most patients presented to the Otorhinolaryngology department with symptoms of acute rhinosinusitis and its complications, i.e., headache, fever, altered consciousness, nasal crusting, and decreased visual acuity along with double vision while being under treatment for COVID-19 disease in the medical department. Mucormycosis was diagnosed by taking an endoscopic biopsy from the nose and sending a specimen for both histopathology and fungal culture in a hospital laboratory. All patients gave written informed consent and the study was approved by the Institutional Ethical Board.

Statistical analysis

The data were analyzed using Statistical package of Social Sciences (SPSS) version 24.0. Qualitative data was

represented by frequencies and percentages and quantitative data by mean with frequencies and percentages \pm SD. The association between different variables was calculated by applying the chi-square test. A *p*-value of < 0.05 was considered statistically significant.

Results

Of the 35 COVID-19 patients, 25.7% (*n* = 9) were under 40 years old, while the majority 74.3% (*n* = 26) were over 40 years of age, with a mean age of 49.40 ± 13.511 years. Gender distribution showed 54.3% males and 45.7% females. Major symptoms were headache in 57% (*n* = 20), fever in 23% (*n* = 8), and orbital symptoms in 20% (*n* = 7). A total of 25.7% of patients with mucormycosis tested positive for COVID-19 while the rest (74.3%) tested negative (Fig 1). The most common co-morbidities reported were DM accounting for 74.3% of patients, followed by co-morbidity of diabetes and Chronic Kidney Disease (DM/CKD) at 11.4%, Chronic Liver Disease (DM/CLD) at 8.6%, and HTN at 5.7%. (Table.1)

The analysis of COVID-19 and risk variables among mucormycosis patients (Table 2) found significant findings (*p* < 0.05) for co-morbidities, whereas age and gender showed insignificant relationships (*p* > 0.05). These data highlight

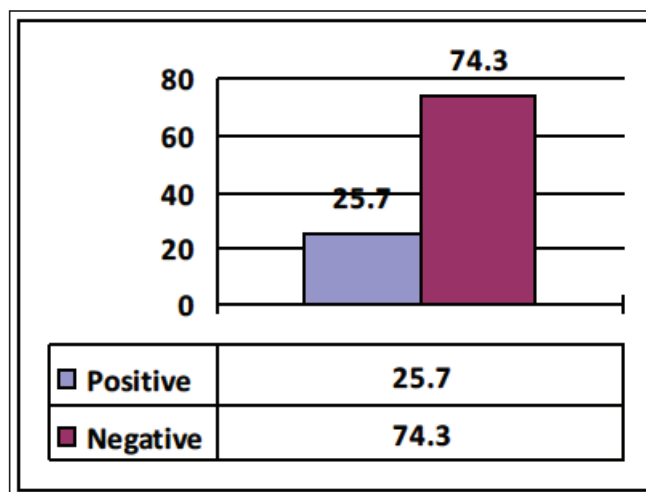


Figure 1. Frequency (%) of concomitant positivity of mucormycosis and COVID-19.

Table 1. Frequency distribution of mucormycosis patients according to co-morbidities.

	Frequency	Percentage (%)
DM	26	74.3
DM / CKD	4	11.4
DM / CLD	3	8.6
DM / HTN	2	5.7
Total	35	100.0

Table 2. Association between COVID-19 and risk factors among mucormycosis patients.

Risk factors	COVID-19		Total	p-value*
	Positive	Negative		
Age				
≤40 years	1 (2.8%)	8 (22.9%)	9 (25.7%)	0.228
>40 years	8 (22.9%)	18 (51.4%)	26 (74.3%)	
Total	9 (25.7%)	26 (74.3%)	35 (100.0%)	
Sex				
Male	5 (14.3%)	14 (40.0%)	19 (54.3%)	0.929
Female	4 (11.4%)	12 (34.3%)	16 (45.7%)	
Total	9 (25.7%)	26 (74.3%)	35 (100.0%)	
Co-morbidities				
DM	4 (11.4%)	22 (62.9%)	26 (74.3%)	0.020
DM/CKD	1 (2.8%)	3 (8.6%)	4 (11.4%)	
DM/CLD	2 (5.7%)	1 (2.9%)	3 (8.6%)	
DM/HTN	2 (5.7%)	0 (0.0%)	2 (5.7%)	
Total	9 (25.7%)	26 (74.3%)	35 (100.0%)	

*chi-square test.

the potential relevance of co-morbidities in mucormycosis patients.

Discussion

Mucormycosis is a fungal disease that causes angio-invasion and bears a high rate of morbidity and mortality worldwide. The incidence of the disease has increased significantly owing to COVID-19 pandemic interplay. Several mucormycosis cases have been reported in COVID-19 patients. A group of 35 mucormycosis patients was included in the study and it was found that the majority of patients (74.3%) were 40 years old or above and 25.7% of patients were up to 40 years while the mean age of the patients was 49.40 ± 13.511 years. The results from a recently published study conducted in Karachi, Pakistan, showed a much higher [63 years (range 33-86 years)] median age of the patients²⁴ while Ravani and colleagues²⁵ reported that the majority of the individuals (90.3%) were more than 40 years old and only 9.7% patients were up to 40 years old and average age of 56.3 years was reported.

The present study discloses that mucormycosis was more prevalent among the male gender (54.3%) than the female (45.7%). The results of this study are consistent with the local studies; Irfan and colleagues also reported that mucormycosis was more prevalent among males (60%).²² Zameer et al reported the 145th case of CAM in the world from Pakistan in a male patient²³ while Nasir and colleagues²⁴ reported a male-to-female ratio of 3:2 in CAM patients. Similarly, Singh and coworkers exhibited a similar scenario that male patients (78.9%) were more affected by disease than female patients

(21.1%).²⁶ Pal and colleagues also confirmed that the majority of mucormycosis patients were males (78.0%).²⁷

The CAM is a new entity and currently mucormycosis has been increasingly reported among COVID-19 patients in numerous parts of the world. The findings of the present study revealed that among mucormycosis patients, 25.7% were found positive for COVID-19. Similar findings were reported in local studies from Pakistan where Irfan and colleagues²² reported a much higher frequency (51%) of COVID-19 positive history among mucormycosis patients while only 10 patients out of enrolled 2839 individuals by Nasir and colleagues²⁴ were identified as CAM. Unlike this finding, Ravani and colleagues²⁵ confirmed at least 2.5 times higher rate (61.2%) of con-infection with COVID-19.²⁵ A study published by Sharma et al²⁸ showed the worst scenario where 100% of patients had mucormycosis due to COVID-19. However, Mishra and fellows²⁹ indicated that among 953 patients only 32 (3.36%) had mucormycosis due to COVID-19.

When the co-morbidities among mucormycosis patients were evaluated, we found that DM was predominantly prevalent among all patients. The majority of the patients (74.3%) had only DM, followed by DM/CKD (11.4%), DM/CLD (8.6%), and DM/HTN (5.7%). Irfan and Nasir et al.^{22,24} from Pakistan also reported DM as the commonest (88.4% and 70% respectively) comorbidity. A study done by Sharma et al²⁸ also elucidated that the majority of their patients (91.3%) had DM. Similar results were also reported by Ravani and colleagues²⁵ who stated that diabetes was more prevalent (96.7%) among mucormycosis patients followed by HTN (54.8%), CKD (6.5%), and ischemic heart

disease (3.2%). Pakdel and comrades³⁰ also confirmed in their study that most of the mucormycosis patients (86.0%) had DM, followed by, HTN (46.0%), cardiovascular disease (13.0%), and hepatic cirrhosis (6.0%). The present study also assessed the association between COVID-19 and risk factors among mucormycosis patients where a significant ($p \leq 0.05$) association was found with co-morbidities while age and sex showed insignificant results ($p > 0.05$).

Conclusion

The findings of the present study conclude that mucormycosis could be an addition to the pandemic spectrum because only 25.7% mucormycosis patients had concomitant COVID-19 positivity. Additional studies are required to be conducted on a larger sample size to determine the real-time data for CAM.

Limitations of the Study

The small size of the sample and study conducted in one center may limit the generalized analysis of the findings to a wider population. The lack of a control group complicates the establishment of causal linkages and limits the capacity to compare mucormycosis rates in COVID-19 patients to those without the virus. The study's reliance on data from a single time period may miss potential changes in mucormycosis patterns throughout time, limiting the temporal significance of our findings.

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List of Abbreviations

CAM	COVID-19 associated mucormycosis
CFR	Case fatality rate
CKD	Chronic kidney disease
CLD	Chronic liver disease
DM	Diabetes mellitus
HTN	Hypertension
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2)
WHO	World Health Organization

Conflict of interest

None to declare.

Grant support and financial disclosure

None to disclose.

Ethical approval

This study was approved by the Institutional Review Board of Ameer ud Din Medical College/Postgraduate Medical Institute, Lahore, Pakistan, vide Letter No. 450/23 dated 18 Mar 2023.

Authors' Contributions

MI: Conception and design of study

GDK: Analysis of data

GR: Acquisition of data

HK, AN: Acquisition of data, drafting of manuscript

WJ: Critical intellectual input

ALL AUTHORS: Approval of the final version of the manuscript to be published

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