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Original Article

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Demographic and Clinical Characteristics of COVID-19 Patients with Mucormycosis

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Abstract

***Background & Aims*:** Mucormycosis, commonly known as "Black Fungus," is an angio-invasive fungus and has become a significant concern during the Coronavirus disease 2019 (COVID-19) pandemic. This study aimed to determine the prevalence rate of mucormycosis and related risk factors among COVID-19 patients, making an essential contribution to further understanding this opportunistic disease.

Methods & Materials: This descriptive-analytical cross-sectional study was carried out among 276 patients. Patients were divided into two groups according to the presence of mucormycosis. The diagnosis of mucormycosis was established through a combination of clinical symptoms, imaging findings, and microbiological confirmation. The study examined demographic and clinical characteristics of the patients, including age, gender, duration of hospitalization, and laboratory results, such as C-reactive protein (CRP) and blood sugar levels. The statistical analysis was performed using the SPSS Statistics software package (version 26). Statistical significance was set at a P-value of 0.05.

Results: The mean age of patients participating in the study was 59±16 years. Among them, 158 patients (57.2%) were male, and 20 (7.2%) were diagnosed with mucormycosis. The analysis revealed a significant association between mucormycosis presence and various demographic and clinical variables, notably impacting hospitalization duration, blood sugar level, and serum CRP level.

Conclusion: Findings from our study indicate that elevated CRP and blood sugar levels, as well as prolonged hospitalization, are significant risk factors for mucormycosis in the patients.

***Keywords*:** Blood Sugar, C-Reactive Protein, Coronavirus Infection, Corticosteroids, Mucormycosis, Opportunistic Infection

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Introduction

Mucormycosis, also known as the black fungus, is an invasive, rare but rapidly progressing fungal infection that causes high mortality in case of delayed diagnosis and treatment (1, 2). Its pathogenesis involves the entry of the fungus into the body through the nasal cavity after inhalation, leading to various complications, particularly in individuals with underlying health conditions (3). Notably, the ongoing COVID-19 pandemic has drawn attention to the potential exacerbation of mucormycosis cases, particularly in patients with COVID-19. The relevance of COVID-19 to this study lies in its potential role in increasing the risk of mucormycosis. Here, the main risk factors included uncontrolled diabetes mellitus (DM), burns, organ transplantations, leukemia, acquired immunodeficiency syndrome (AIDS), neutropenia, anemia, malnutrition, as well as corticosteroid use, and chemotherapy (4, 5). Based on its clinical characteristics and the involvement of particular anatomical sites, mucormycosis can be further divided into the following clinical groups: rhino-cerebral, pulmonary, cutaneous, gastrointestinal, and disseminated (6, 7). The symptoms include dyspnea, cough, chest pain, hemoptysis, fever, and vascular invasion, which cause necrosis, cavitation, or hemoptysis (8, 9). Lobar consolidation, single mass, nodular disease, and cavity- or wedge-shaped infarction may be further seen on chest X-ray (9, 10). Given these considerations, understanding the link between COVID-19 and mucormycosis is crucial for clinicians and researchers alike.

Once the coronavirus disease (2019) (COVID-19) was detected in China and quickly spread to the neighboring cities and countries, the World Health Organization (WHO) declared it a global public health emergency (11). Considering the emergence of COVID-19 and the increased use of corticosteroid therapy as a main treatment, opportunistic fungal infections, including mucormycosis, have become a concern in hospital settings (12). The present study aimed to investigate the demographic characteristics and risk factors of mucormycosis among COVID-19 inpatients to determine the disease's prevalence rate, identify its risk factors, and make an essential contribution to the further understanding of this opportunistic disease.

Materials & Methods

Study design:

This descriptive-analytical cross-sectional study aimed to investigate the prevalence rate of mucormycosis among 276 COVID-19 patients and then compare the demographic and clinical characteristics of two groups with and without mucormycosis admitted to Firouzgar and Firouzabadi Hospitals in Tehran, Iran in the first half of 2021.

The choice of a cross-sectional study design was deemed appropriate for this investigation as it allowed for the simultaneous examination of variables within a specific time frame, aligning with the research objectives of assessing mucormycosis prevalence and associated demographic and clinical factors.

Ethical approval and permission for data collection were obtained from the Ethics Committee of Iran University of Medical Sciences and the hospital administrators (IR.IUMS.FMD.REC.1401.066). The study collected demographic and clinical data from patient files, including age, gender, laboratory test results upon admission (such as C-reactive protein (CRP) and fasting blood sugar (FBS)), and duration of hospitalization for the two groups. The study excluded individuals who were under the age of twelve, had a pre-existing diagnosis of mucormycosis upon admission, had a history of immunodeficiency disease, had incomplete medical records, or did not provide consent to participate in the research project.

Data collection took place over the specified period in the first half of 2021 to capture a representative sample of COVID-19 patients with mucormycosis during that time frame. The sample size of 276 patients was determined based on considerations of statistical power and feasibility to ensure adequate representation of the target population.

Statistical analysis:

After collecting the required information, the data were entered into the SPSS Statistics software package (version 26). The results for quantitative variables were

presented as mean and standard deviation (mean ± SD), while percentages were used to represent qualitative variables. SPSS was used to analyze data, and the Chi-Square test was used to evaluate the relationship or difference between two qualitative variables. If Chi-square assumptions were not met, Fisher's exact test was used instead. Moreover, the T-test in parametric conditions and Mann-Whitney U in non-parametric states were applied to compare a quantitative variable with a two-state qualitative variable. The level of significance was set at a P-value of 0.05.

Results

Sample Characteristics:

A total of 276 participants were included in the study. The mean age of the inpatients was 59±16 years. The mean duration of hospitalization until the release of the pathology reports in patients with mucormycosis was 7.5±6.4 days (Table 1).

Gender Distribution and Mucormycosis Diagnosis:

Among the recruited cases, 158 patients (57.2%) were male. Mucormycosis was diagnosed in 20 individuals (7.2%) (Table 1). There was no significant difference in the occurrence of mucormycosis between males and females.

Of the 276 cases recruited, 158 patients (57.2%) were men, and 20 individuals (7.2%) were diagnosed with mucormycosis. (Table 1)

Association with Demographic and Clinical Variables:

The study examined the relationship between the presence of mucormycosis and demographic and clinical variables. Analysis of the mean and frequency of these variables showed a significant association between mucormycosis and duration of hospitalization *(p=0.0001)*, blood sugar level (*p=0.009*), and serum CRP level *(p=0.004)*. These variables were identified as the main risk factors for the occurrence of mucormycosis (Table 1).

Table 1. The research quantitative and qualitative variables based on the presence Mucormycosis

Variables		Presence of Mucormycosis		*P-value*	Mean (± SD)
		No (n=256)	Yes (n=20)		
Age (year)		59.01±16.13	58.95 ± 14.77	0.976	59.00 (±16.01)
Duration of hospitalization (days)		9.14 ± 6.35	19.15 ± 13.05	0.0001	10.37(±8.13)
Blood sugar (mg/dL)		159.61 ± 97.88	260.50 ± 153.82	0.009	166.92(±105.85)
CRP (mg/L)		57.84 ± 37.93	96.68 ± 64.04	0.004	60.72(±41.54)
Gender	Female (n=118)	109 (42.6%)	9 (45%)	0.833	
	Male (n=158)	147 (57.4%)	11 (55%)		

The data are presented as Mean ± SD or n (%)

Interpretation of Findings:

The significant association between mucormycosis and the duration of hospitalization suggests that prolonged hospital stays may increase the risk of fungal infections. Similarly, elevated blood sugar levels and serum CRP levels were identified as important risk factors, indicating the potential role of hyperglycemia and inflammation in promoting fungal growth and dissemination.

Discussion

The present study aimed to investigate the prevalence of mucormycosis in COVID-19 inpatients and determine whether there were any differences in

demographic characteristics and laboratory results compared to other individuals. The mean age of the patients was approximately 59 years, the age range varied from 22 to 100 years, and most participants were in the 60-to-65-year-old age range. Additionally, there was no significant difference in the mean age between the group with mucormycosis and the group without mucormycosis (59 years and 58.9 years, respectively).

The study found that the COVID-19 inpatients were middle-aged, and both groups were matched for age *(p=0.976*) and gender (*p=0.833*), minimizing the confounding effect of these variables. The male-to-female ratio was approximately 1.33:1, with a higher proportion of males in both groups. Patients coinfected with COVID-19 and mucormycosis had a significantly more extended hospital stay (mean duration of about 10.3 days) than those with COVID-19 only (*p=0.001*). The group without mucormycosis had significantly better laboratory test results (e.g., blood sugar and CRP levels) upon admission than the group with mucormycosis. These findings may help predict a higher risk of mucormycosis in COVID-19 patients.

In this respect, Ramaswami et al. found that the prevalence rate of mucormycosis was 4.25% (n=70) among 1647 COVID-19 patients in India, while this value was 7.2% in the present study, which is relatively high. The mean age of the patients infected with mucormycosis in the study mentioned above and the present study was 44.5 and 58.9 years, respectively. One potential explanation for our study's elevated prevalence of mucormycosis is the weakened immune system associated with age and underlying medical diseases. The gender distribution of the patients in our study was similar to that of Ramaswami et al., with males comprising 55% and 60% of the cases, respectively (13).

Gupta et al. further conducted a survey on 115 confirmed mucormycosis patients, with a mean patient age of 54.2, while the present study had a mean age of 58.9. In the study mentioned above, male patients comprised 70.4% of the participants, compared to 55% in the present study. The mean hospitalization duration for mucormycosis patients in the above study was 10.3 days, while in the present study, it was 19.1 days. The mean CRP level of the mucormycosis group in the studies of Gupta et al. and the present study were 49.4 and 96.68 mg/l, respectively (14).

Further evidence of the variability in mucormycosis incidence comes from a study by Patel et al., which found a much lower prevalence rate of 0.27% among hospitalized COVID-19 patients, with a mean age of 55 years. This stark difference in prevalence rates, from as low as 0.27% to as high as 7.2% in our study, underscores the influence of geographic, demographic, and temporal factors on the incidence of mucormycosis among COVID-19 patients (15).

Our study's findings on COVID-19-associated mucormycosis (CAM) align with those reported by Hoengil et al., emphasizing the critical role of uncontrolled diabetes and systemic corticosteroid use as significant risk factors. While Hoengil et al. report a 49% mortality rate among CAM patients, highlighting severe outcomes such as vision loss, our study corroborates the high risk associated with these factors, noting a 7.2% incidence of mucormycosis among our cohort. Our data further identify prolonged hospitalization, elevated blood sugar levels, and increased serum CRP levels as key predictors of mucormycosis, underscoring the importance of vigilant monitoring and management of high-risk patients. Both studies underscore the grave implications of CAM in the context of the pandemic, stressing the need for early diagnosis and targeted interventions to mitigate its severe health impacts. This comparison enriches our discussion by confirming the global relevance of our findings and the urgent need to address CAM's risk factors in COVID-19 patients (16). A study by Sen et al. identified 92 confirmed cases (52% males and 48% females), one probable case, and 30 suspected cases of mucormycosis among 123 patients. The gender distribution in our study was also 57% for males and 42% for females, with a slight difference, similar to the above research. Therefore, the prevalence rate of mucormycosis was higher in males. Moreover, the subtle difference between the results of both studies could be due to the larger sample size in Sen et al. study. In this study, 42.4% of people had DM, suggesting this

underlying disease is the most common factor contributing to mucormycosis. This is consistent with the present study's findings, as the mean blood sugar level in patients with mucormycosis was 153.82±260.50, indicating hyperglycemia and the role of DM as a contributing factor in mucormycosis (17).

Chander et al. conducted a study on 22 patients with rhinocerebral mucormycosis at two centers to investigate the disease further. The majority of patients were female, with a mean age of 48. In contrast to the above study's findings, our study found a higher prevalence rate of mucormycosis in males. While the difference in prevalence rates could be due to various factors, such as the gender and age distribution of the two populations, both studies found that age and gender were not significant factors in the higher prevalence of mucormycosis. In addition, DM in this study was the patients' most common underlying disease (86.4%). Moreover, type 2 DM, and specifically diabetic ketoacidosis (DKA), could have adverse effects on the prognosis of these patients, in agreement with the findings of our study (18).

Jeong et al. conducted a survey on 22 patients with mucormycosis to investigate their background variables and clinical symptoms upon admission. The study included fifteen males and seven females with an age range of 1 to 80 years. Besides, DM was reported as the most common underlying disease, and more than 90% of the cases had rhinocerebral mucormycosis. DKA and uncontrolled DM were also introduced as the most common contributing factors. While the prevalence rates of the disease were similar in both studies, the frequency percentages were different due to the small number of patients and variations in age and gender distributions in the populations. Both studies reported hyperglycemia as a contributing and detrimental prognostic factor, consistent with previous findings highlighting the significant role of DM and its complications in the prevalence of mucormycosis (19). While statistical significance was observed, effect sizes such as odds ratios or relative risks were not calculated. Future studies could explore these effect sizes to provide a more comprehensive understanding of the practical significance of the associations observed.

Conclusion

According to the study's findings, the prevalence of mucormycosis among COVID-19 inpatients was 7.2%. The study also identified several risk factors, including elevated levels of CRP, high blood sugar levels, and prolonged hospitalization. These factors were found to be associated with an increased risk of developing mucormycosis in COVID-19 patients. However, its retrospective design and narrow setting may limit the generalizability and causal inference of the findings. Future research should focus on broader, multicentric studies to better understand the relationship between COVID-19 and mucormycosis and explore effective treatments and preventive measures.

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Ethical statement:

Ethical approval and permission for data collection were obtained from the Ethics Committee of Iran University of Medical Sciences and the hospital administrators (IR.IUMS.FMD.REC.1401.066).

Data availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions:

Not declared.

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Conflict of interest:

The authors declare no conflict of interest in relation to this study.

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