ORIGINAL ARTICLE

J Mycol Infect 2023; 28(2): 35-41
pISSN:1226-4709, eISSN:2465-8278
https://dx.doi.org/10.17966/JMI.2023.28.2.35

JMI

Epidemiological and Demographic Study of Patients with Mucormycosis and COVID-19

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Background: Coronavirus disease 2019 (COVID-19) is associated with many bacterial and fungal diseases. *Aspergillus* and *Candida* have been reported as major pathogens resulting to comorbid infections in COVID-19 patients.

Objective: Recent studies have shown a considerable burden of cases affected by mucormycosis after coronavirus disease 2019 (COVID-19) infection worldwide, and some underlying factors may contribute to this condition. Hence, this study aimed to investigate the epidemiology and demographic characteristics of mucormycosis patients after COVID-19 infection in the Ahvaz province of Iran.

Methods: This descriptive-analytical epidemiological study was conducted on patients who developed mucormycosis following COVID-19 for a 6-month period in 2021. A checklist based on symptoms and possible risk factors was used to collect patient information.

Results: The results showed that conjunctivitis, ophthalmalgia, facial swelling, feeling of pain or pressure in the face, and sinusitis were the most common clinical manifestations of patients with mucormycosis following COVID-19. Additionally, there was a significant association between corticosteroid and prophylactic antibiotic use, pain or pressure in the face, and ophthalmalgia with the outcome variables including alive or dead (p-values = 0.002, 0.011, 0.034, and 0.004, respectively). No statistically significant difference was found between the ages of the two groups (p-value = 0.495).

Conclusion: The study findings revealed that the most common risk factors for mortality include diabetes, immune system defects, and use of prophylactic antibiotics or corticosteroids.

Key Words: COVID-19, Epidemiology, Mucormycosis

Received: March 1, 2023 Revised: March 9, 2023 Accepted: March 28

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INTRODUCTION

Evidence has shown that coronavirus disease 2019 (COVID-19) (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), with its different variants spread globally, is associated with many bacterial and fungal diseases[1,2]. *Aspergillus* and *Candida* have been reported as major pathogens resulting to comorbid infections in COVID-19 patients, and numerous cases of mucormycosis have recently been reported in COVID-19 patients worldwide[3,4].

Mucormycosis is an opportunistic infection that commonly occurs in immunocompromised individuals[5,6]. Clinical manifestations vary from rhinocerebral and pulmonary to cutaneous, gastrointestinal, and diffuse involvement[7,8]. Mucor is found in the environment, and most people encounter spores during the day[5,7]. This fungus is not life-threatening for immunocompetent individuals; however, it can cause infections in the nose, sinuses, and other body parts in immunocompromised people[9,10].

Rhinocerebral mucormycosis is an invasive fungal infection that affects immunosuppressed patients, particularly in patients with diabetes and immunodeficiency[11,12]. COVID-19 patients, particularly those who are comorbid with diabetes and immunodeficiency or are severely ill, are more susceptible to developing invasive fungal infections[13,14]. Rhinocerebral mucormycosis can develop during active SARS-CoV-2 infection but usually occurs 1 to 3 weeks after resolution of disease[15].

The fungus enters the body through nasal mucosa colonization, which allows it to enter the eye through the paranasal sinuses. Spores enter the nasal cavity, and following necrosis, symptoms then manifest[12,15].

Due to its high invasiveness to the vascular system, the mucor fungus eventually spreads to the maxillary and ethmoid sinuses, the cavernous sinus, and finally to the brain. The skin adjacent to the sinuses and the soft tissue of the infratemporal cavity are also involved[5]. The risk of mucormycosis infection in COVID-19 patients may be increased by various factors. Risk factors for rhinocerebral mucormycosis include diabetes mellitus, especially in uncontrolled cases, diabetic ketoacidosis, hematologic malignancies, and bone marrow transplants[5].

Therefore, to determine the underlying risk factors, this study aimed to investigate the epidemiology and demographic characteristics of rhinocerebral mucormycosis patients following COVID-19.

Table 1. Relationship between the patient's general characteristics and the outcome variable

General characteristics	Total number of patients (n=70)	Outcome		*p*-value¶
		Alive (n=50)	Dead (n=20)	
Sex				0.449
Female	33 (47.1)	25 (50.0)	8 (40.0)	
Male	37 (52.9)	25 (50.0)	12 (60.0)	
Education				0.760
No	30 (42.9)	22 (44.0)	8 (40.0)	
Yes	40 (57.1)	28 (56.0)	12 (60.0)	
Job				0.074
Housewife	32 (45.7)	24 (48.0)	8 (40.0)	
Self-employed	16 (22.9)	7 (14.0)	9 (45.0)	
Manual worker	9 (12.9)	9 (18.0)	0 (0.0)	
Retired	7 (10.0)	5 (10.0)	2 (10.0)	
Others	5 (7.1)	4 (8.0)	1 (5.0)	
Unemployed	1 (1.4)	1 (2.0)	0 (0.0)	

¶chi-square or Fisher's exact test

MATERIALS AND METHODS

1. Study design and participants

This descriptive-analytical epidemiological study was conducted on patients who developed mucormycosis following COVID-19 infection in a 6-month period in 2021. The study was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences, and written informed consent was obtained from all participants.

The inclusion criteria included patients over 18 years old who were admitted to the ENT department of Ahvaz University of Medical Sciences and diagnosed with mucormycosis following COVID-19. Infected patients with a history of COVID-19 of less than 2 months were selected. Patient information was collected using a checklist based on symptoms and possible risk factors from the patient's files. Exclusion criteria included lack of access to the patient, incomplete data from the

Table 2. Relationship between the patient's associated disease/conditions and the outcome variable

Associated disease/conditions	Total number of patients (n=70)	Outcome		*p*-value[¶]
		Alive (n=50)	Dead (n=20)	
Diabetes	57 (81.4)	39 (78.0)	18 (90.0)	0.322
COVID-19 stimulants	55 (78.6)	38 (76.0)	17 (85.0)	0.528
Hyperglycemia	49 (70.0)	38 (76.0)	11 (55.0)	0.083
Hospitalization for COVID-19	48 (68.6)	37 (74.0)	11 (55.0)	0.122
Immune system defects	45 (64.3)	35 (70.0)	10 (50.0)	0.115
Corticosteroids	44 (62.9)	37 (74.0)	7 (35.0)	0.002
Prophylactic antibiotics	41 (58.6)	34 (68.0)	7 (35.0)	0.011
High blood pressure	34 (48.6)	26 (52.0)	8 (40.0)	0.364
Kidney dysfunction	26 (37.1)	20 (40.0)	6 (30.0)	0.434
Dental abscess	25 (35.7)	18 (36.0)	7 (35.0)	0.948
Blood transfusions	23 (32.9)	16 (32.0)	7 (35.0)	0.809
Long-term ICU hospitalization	20 (28.6)	14 (28.0)	6 (30.0)	0.867
Voriconazole	19 (27.1)	11 (22.0)	8 (40.0)	0.126
Neutropenia	19 (27.1)	11 (22.0)	8 (40.0)	0.126
Malignancy	9 (12.9)	8 (16.0)	1 (5.0)	0.430
Contact with dust	8 (11.4)	6 (12.0)	2 (10.0)	0.999
AIDS	2 (2.9)	1 (2.0)	1 (5.0)	0.493
Cirrhosis	2 (2.9)	1 (2.0)	1 (5.0)	0.493
Pulmonary tuberculosis	2 (2.9)	2 (4.0)	0 (0.0)	0.999
Dialysis	2 (2.9)	2 (4.0)	0 (0.0)	0.999
Skin burns	2 (2.9)	2 (4.0)	0 (0.0)	0.999
Bone marrow transplant	1 (1.4)	1 (2.0)	0 (0.0)	0.999
Deferoxamine	1 (1.4)	1 (2.0)	0 (0.0)	0.999
Alcohol consumption	1 (1.4)	1 (2.0)	0 (0.0)	0.999

[¶]chi-square or Fisher's exact test

patient's file, and patient's dissatisfaction with participation in the study. Mucormycosis has intensified during the fifth peak of COVID-19 and the fifth peak terminated by the end of the first 6 months of 2021; thus, the time frame was selected from 21/03/2021 to 22/09/2021.

2. Mucormycosis diagnosis

Following a suspected mucormycosis after computed tomography scan, sampling was performed in the bronchoalveolar fluid using aspiration needles. Direct observation of hyphae after exposure to potassium hydroxide (KOH) 10~20% was performed using a light microscope. The finding of broad hyphae without a wide transverse wall (diameter 6~16 μm) with branches at a 90-degree angle was observed by an experienced expert.

Furthermore, the samples were cultured. For the successful isolation of Mucorales, the biopsy samples were not homogenized, and prior to inoculation in the culture medium, these were cut into small pieces using scissors. Undue homogenization damages the fragile cell wall of Mucorales, resulting in the fungus losing its ability to grow.

3. Statistical analysis

The qualitative variable was described using frequency and percentage, while the quantitative variables were described using the minimum and maximum, average, middle, and standard deviation indices. The normal distribution of data was examined using Shapiro-Wilk and Kolmogorov-Smirnov tests. The relationship between the studied variables and the patient's outcome was investigated using chi-square, Fisher's exact test, and Mann-Whitney *U* test. Statistical significance was set at a *p*-value <0.05. SPSS statistical software (version 22) was used for data analysis.

RESULTS

A total of 70 cases of mucormycosis following COVID-19

Table 3. Relationship between the clinical manifestations and the outcome variable

Clinical manifestations	Total number of patients (n=70)	Outcome		*p*-value[¶]
		Alive (n=50)	Dead (n=20)	
Eye				
Ophthalmalgia	53 (75.7)	43 (86.0)	10 (50.0)	0.004
Conjunctivitis	48 (68.6)	37 (74.0)	11 (55.0)	0.122
Painful eye movements	42 (60.0)	33 (66.0)	9 (45.0)	0.105
Drooping /heavy eyelids	34 (48.9)	25 (50.0)	9 (45.0)	0.705
Blurred vision/diplopia	30 (42.9)	22 (44.0)	8 (40.0)	0.760
Face				
Facial pain	51 (72.9)	40 (80.0)	11 (55.0)	0.034
Facial swelling	48 (68.6)	37 (74.0)	11 (55.0)	0.122
Facial numbness	37 (52.9)	28 (56.0)	9 (45.0)	0.405
Sinus pain	45 (64.3)	35 (70.0)	10 (50.0)	0.115
Inflammation in the nose	39 (55.7)	30 (60.0)	9 (45.0)	0.254
Palate				
Inflammation in the palate	31 (44.3)	21 (42.0)	10 (50.0)	0.543
Sore palate	25 (35.7)	21 (42.0)	4 (20.0)	0.083
Fever	35 (50.0)	25 (50.0)	10 (50.0)	0.999

[¶]chi-square or Fisher's exact test

were enrolled in this study. The mean age of participants was 55.3 ± 14.9, ranging from 26 to 91 years. Thirty-three (47.1%) of the studied population were female, and 37 (52.9%) were males. Moreover, 48 (68.6%) participants had a history of hospitalization due to COVID-19. Also, 78.6% of patients had stimulants for COVID-19 during the referral time. The patient's characteristics and risk factors are shown in Tables 1 and 2.

The participants had a history of corticosteroid use (62.9%), immunodeficiency (64.3%), and prophylactic antibiotics (58.6%). Most of the study participants had diabetes and coronary disease. Most of the participants did not have acquired immunodeficiency syndrome, cirrhosis, pulmonary tuberculosis, malignancy, neutropenia, and kidney disease, and most had no contact with dust, skin burns, history of dialysis, and bone marrow transplantation (Table 2).

Twenty participants (28.6%) had a long history of intensive care unit (ICU) hospitalization. The high iron intake with deferoxamine, voriconazole, and alcohol was uncommon (Table 2).

Most of the patients in this study had clinical manifestations of eye and face. Ophthalmalgia (75.7%) was the most common ophthalmic manifestations, followed by conjunctivitis (68.6%), painful eye movement (60.0%), blurred vison/diplopia (42.9%). Among facial manifestations, facial pain (72.9%) was the most common, followed by facial swelling (68.6%), facial numbness (52.9%). The sinus pain was 64.3%, and fever was 50% (Table 3).

A total of 20 participants (28.5%) expired during the study period. The relationship between the patient's characteristics and the outcome variable (alive and dead) is shown in Table 1-3. The results showed a significant association between corticosteroid, prophylactic antibiotic use, pain or pressure in the face, and ophthalmalgia with the outcome variable (p-values <0.05).

Moreover, the age comparison between alive and dead cases revealed that age is not risk factor for mortality in mucormycosis ($p = 0.495$).

DISCUSSION

One of the primary reasons why mucous spores begin to grow easily in COVID-19 patients is attributed to the hypoxic environment, high glucose (diabetes, new hyperglycemic cases, corticosteroid use), high levels of intracellular iron (high ferritin, which leads to the production of oxygen free radicals), and decreased white blood cell xenophobic function that is associated with long-term risk factors, such as hospitalization[1,15].

While various treatments for COVID-19 have been studied, systemic glucocorticoids have been shown to increase a patient's life expectancy. Unfortunately, the widespread use of glucocorticoids, especially long-acting, and high-dose drugs such as tocilizumab (an interleukin inhibitor) in patients with moderate to severe involvement can lead to secondary fungal or bacterial infections[16,17].

Hence, the epidemiology and demographic characteristics of mucormycosis patients with COVID-19 were evaluated, and the most common clinical disease presentation was as follows: conjunctivitis, ophthalmalgia, facial swelling, feeling of discomfort or pressure in the face, and sinusitis. Moreover, most of these patients had a history of hospitalization due to COVID-19, uncontrolled diabetes, immune system defects, and use of prophylactic antibiotics or corticosteroids. Nevertheless, corticosteroids, prophylactic antibiotic use, pain or pressure in the face, and ophthalmalgia were significantly associated with the patient's outcome.

Thus, the use of corticosteroids and antibiotics to treat COVID-19 can potentially predispose patients to mucormycosis through corticosteroid-induced hyperglycemia or other mechanisms such as immunosuppression[15]. Thus, elucidating the association between corticosteroids, antibiotic use, and diabetes mellitus associated with rhinocerebral mucormycosis is crucial[15].

In this regard, Singh et al., in a systematic review, investigated cases of co-infection with COVID-19 and mucormycosis[18]. This study was conducted on 101 patients, with 82 cases in India and 19 in other parts of the world. Among these patients, 59.4% had active COVID-19 disease, and 40.6% recovered from the disease. Approximately 80% of patients had a history of diabetes mellitus, but only 14.9% had concomitant diabetic ketoacidosis (DKA). According to our findings, most of their study population were males, and approximately 76.3% of patients received corticosteroids to manage COVID-19. Moreover, 88.9% of these patients had nasal and sinus mucormycosis, followed by ocular mucosa (56.7%), while 30.7% of the patients died[18].

Additionally, Muthu et al. also examined 275 cases of mucormycosis with COVID-19[19]. The most common underlying disease was diabetes, and 36.5% of these patients died. They reported that mucormycosis was associated with more diffuse or pulmonary mycosis or that ICU care was warranted[19]. Singh and Vishnu, in a study of patients with rhinocerebral mucormycosis in 2021, also found that 87% of patients with mucormycosis following COVID-19 used corticosteroids; 78% had diabetes, most of which was uncontrolled; and 15% presented with DKA[15].

According to previous investigations, the main risk factors predisposing to mucormycosis infection are the use of corticosteroids and diabetes. The primary treatment of COVID-19, especially in advanced cases and is also observed in diabetic individuals, is corticosteroids. With the increase in blood glucose, the risk of poor prognosis also increases[20]. Furthermore, in patients with DKA with mucormycosis, the causative fungus attacks the endothelium by binding of fungal CotH proteins to the GRP78 in the endothelium. Thus, there is an increase in surface expression in endothelial cells exposed to physiological concentrations of glucose and iron in patients. Therefore, controlling metabolic acidosis is beneficial for the prevention and management of this infection[21].

Furthermore, similar to our study, Mahalaxmi et al. elucidated that the higher incidence of diabetes and corticosteroid use to treat severe COVID-19 disease were the main risk factors of mucormycosis in COVID-19 patients[5]. Garg et al. also reported a 55-year-old man who developed severe pulmonary mucormycosis 19 days after hospitalization due to coronavirus[16]. The patient was administered amphotericin B and was discharged after 54 days of hospitalization[16].

This study has some limitations. This includes patient dissatisfaction in participating in the study, failure to complete the file, and incomplete case data, which was excluded from the survey. Nevertheless, the strengths of this study include the multicenter investigation of all COVID-19 mucormycosis cases, with data collection regarding the patients' clinical and demographical characteristics and evaluation of patient outcomes.

Finally, a history of corticosteroid and prophylactic antibiotic use is significantly related to the outcome of mucormycosis patients following COVID-19. However, the exact mechanism should be further elucidated due to the high prevalence. Hence, stringent planning and decision-making for an early and timely diagnosis should be conducted to prevent irreversible complications of mucormycosis and improve the patient's quality of life.

CONCLUSION

The results of this study demonstrated that conjunctivitis, ophthalmalgia, facial swelling, feeling of pain or pressure, and sinusitis were the most common clinical manifestations of patients with mucormycosis following COVID-19 infection. Most of these patients had a history of hospitalization due to COVID-19, suffered from diabetes or immune system defects, and used prophylactic antibiotics or corticosteroids. However, only corticosteroids and prophylactic antibiotic consumption, pain or pressure in the face, and ophthalmalgia were significantly associated with mortality.

CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

DATA SHARING STATEMENT

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

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ETHICAL APPROVAL STATEMENT

The study was approved by the Institutional Review Board of (IRB No. IR.AJUMS.REC.1400.530). This study was conducted in accordance with the principles of the Declaration of Helsinki.

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