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RISING INCIDENCE OF MUCORMYCOSIS IS A NEW PANIC CHALLENGE IN SOUTHWEST OF IRAN DURING COVID-19 PANDEMIC: ASSOCIATED RISK FACTORS AND PREVENTIVE MEASURES

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Abstract

Background: *The increase in mucormycosis after COVID-19 pandemic has become a serious medical concern, leading to widespread complications and deaths worldwide. It is essential to identify the factors affecting mortality and associated complications. Therefore, the aim of this study is to investigate the rise in mucormycosis incidence as an important challenge in southwest Iran during the COVID-19 pandemic.*

Material and methods*: In this study, demographic and clinical information of COVID-19 patients, including age, gender, underlying medical conditions, etc., were extracted from patients' files. The analyzes 48 mucormycosis patients and 52 controls, utilizing measures of central tendency, dispersion, frequency, and odds ratios.*

Results*: Our study revealed that the distribution of age, gender, and history of organ transplantation in the case and control groups was similar. Most mucormycosis patients were in the age group of 41 to 60 years (45.3%). Most study participants were males (28 individuals, 58.3%). The most prevalent underlying comorbidities among patients with mucormycosis were diabetes (93.8%) and hypertension (41.7%). Twenty-four individuals (50%) had a history of steroid use. In the control group, the most common underlying conditions were hypertension (32%), hyperlipidemia (21%), and diabetes (19%). Only 3 individuals (5.7%) in the control group had a history of steroid use, and an equal number (5.7%) had a history of other immunosuppressive drug use. Risk factors associated with an increased chance of mucormycosis included diabetes compared to non-diabetic individuals, with an odds ratio of 63, 95% confidence interval of 16.28-244; corticosteroid treatment with an odds ratio of 16.3, 95% confidence interval of 4.47-59.67; and treatment with other immunosuppressive drugs with an odds ratio of 6.06, 95% confidence interval of 1.60-22.89.*

Conclusion: *Diabetes, corticosteroids, and immunosuppression increase the risk of COVID-19-associated mucormycosis risk. Avoiding corticosteroids in mild cases and closely monitoring blood sugar level can help to reduce of COVID-19-associated mucormycosis.*

Keywords: *mucormycosis, COVID-19, incidence*

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Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has presented with a wide range of clinical symptoms, from mild to severe. While some patients have recovered from the initial infection, many continue to experience persistent post-COVID complications. Alarmingly, there has been a surge in secondary fungal infections, including COVID-associated pulmonary aspergillosis and candidemia, among these individuals, underscoring the importance of proactive monitoring and treatment [*Nucci M et al., 2021*].

The increase in mucormycosis after the COVID-19 pandemic has become a serious medical concern. Mucormycosis is a rare and serious fungal infection caused by Mucorales fungi. This infection mostly occurs in individuals with weakened immune systems, such as those with diabetes, lymphoma, organ transplant recipients, HIV-infected individuals, and those using immunosuppressive medications or having a high iron load [*Sharma S et al., 2021*]. Clinical symptoms of mucormycosis may vary depending on the site and severity of the infection. Rhino-orbital-cerebral mucormycosis is one of the most common types, affecting various body parts, including the nasal and sinus regions, brain, and other respiratory and gastrointestinal areas [*Ramadorai A et al., 2019*]. Mucormycosis is transmitted by inhaling fungal spores into the respiratory system and nose. Additionally, direct contact with injured wounds or damaged skin can also allow the fungus to enter the body [*Richardson M, 2009*]. Moreover, this infection has the potential to directly disseminate into the paranasal sinuses, and from there, it can further spread into the surrounding orbital and intracranial spaces through two possible routes: direct extension or hematogenous dissemination, where the infection enters the bloodstream and is transported to other areas [*Wiersinga W et al., 2020*]. Prevention of mucormycosis includes strict diabetes control and moderating the use of steroids to reduce the risk of infection [*Huang C et al., 2020*]. The diagnosis of mucormycosis involves the use of features such as hyphal diameter, septation, pigmentation, and branching angles, which distinguish this disease from other fungal infections. Various diagnostic methods, including direct microscopy, fungal culture, histopathology, sensitivity testing, antigen testing, antibody testing, and molecular tests (DNA and RNA) from suspected patient samples, are used to diagnose fungal infections [*Kozel T, Wickes R, 2014*]. The treatment of mucormycosis involves surgical removal of infected tissue, antifungal medications such as Amphotericin B and Posaconazole, and management of underlying conditions such as diabetes [*Yoon Y et al., 2010; Kyvernitakis A et al., 2016*]. Due to the severity of this infection and its rising occurrence following the COVID-19 pandemic, it is crucial to promptly diagnose and treat this infection and to implement suitable prevention and management programs [*Cornely O et al., 2019*]. Furthermore, educational programs to increase public and medical staff awareness about the signs and risk factors for this infection are essential. the increase in mucormycosis cases post-COVID-19 pandemic is a serious medical concern that requires immediate attention. By understanding the risk factors, clinical manifestations, diagnostic approaches, and treatment strategies, we can combat this fungal infection effectively. Additionally, public awareness and education campaigns can play a vital role in preventing the spread of mucormycosis and improving patient outcomes. Therefore, this study aimed to assess the associattion between risk factors and preventive measures of mucormycosis is a new panic challenge in southwest of Iran during COVID-19 pandemic.

Material and Methods

In this case-control study, an examination was carried out on the medical records of patients archived at Imam Khomeini Hospital in southwest Iran (Ahvaz) (January 2021 to October 2021). Demographic and clinical information of COVID-19 patients (including age, gender, underlying medical conditions, etc.) was extracted from the patient's files. After extracting the demographic and clinical information, the relationship between the identified factors (age, gender, corticosteroid use, immunosuppressive drug use, organ transplant history, underlying diseases: diabetes, hypertension, coronary artery disease, chronic kidney and liver diseases) and the incidence of mucormycosis was investigated. The data were divided into two groups, case and control, in a 1:1 ratio: those with confirmed mucor-

mycosis and individuals without mucormycosis. Patients diagnosed with mucormycosis based on histopathology and/or culture, definitively indicating Mucormycosis, and having a history of COVID-19 infection or active COVID-19 disease were included. It should also be noted that the criterion for COVID-19 was a positive polymerase chain reaction test with the COVID-19 pattern on the patient's chest CT scan. The data were subjected to binary logistic regression analysis to evaluate potential risk factors for Mucormycosis.

The study population included hospitalized patients with confirmed rhino-orbital-cerebral mucormycosis who had a history of COVID-19 or were active COVID-19 patients. The inclusion criteria were as follows: COVID-19 diagnosis based on at least one of the following criteria by an infectious disease specialist: a) Diagnosis of new coronavirus nucleic acid in respiratory or blood samples using Real-time polymerase chain reaction, b) Typical lung patterns of COVID-19 on chest CT scan. The diagnosis of mucormycosis required assessment by the relevant specialist. The exit criteria for the study were as follows: 1) Lack of information in the medical records, 2) No history of or current COVID-19 infection. Statistical analysis of the data was performed using SPSS 21 software. To compare between groups, the Chi-square test, Mann-Whitney U test, and Regression analysis were used. The logistic regression model was also used to express the impact of variables. The significance level was set at $p<0.05$ in this study. The mean, median, standard deviation, minimum and maximum values, and range were calculated, and data were presented as mean ± SD (standard deviation). Written informed consent was obtained from the patients. In recording patient data, their personal information were not included, and during the research, codes was used for data categorization instead of mentioning the patients' names. Furthermore, all religious, ethical, and legal standards have been followed for all stages of plan implementation.

RESULTS

The current study was conducted to investigate the increase in the occurrence of mucormycosis as a significant challenge in southwestern Iran during the COVID-19 pandemic. The analysis included 48 patients (28 men, 20 women) with mucormycosis and 52 individuals as controls. In the mucormycosis group, the mean age of the study participants was 52.9 ± 9.53 years (ranging from 27 to 88 years) (Figure, 1A). Most of the patients in the study fell within the age group of 41 to 60 years (45.3%). The majority of the study participants with mucormycosis were male (28 individuals, 58.3%). Among the patients with mucormycosis, the most prevalent underlying conditions were diabetes (93.8%) and hypertension (41.7%) (Table 1). In the control group, the mean age of the study subjects was 59.48±1.71 years (ranging from 27 to 85 years). Only 24 individuals (50%) had a history of steroid use. 13 individuals (27.1%) had a history of using other immunosuppressive drugs, excluding corticosteroids. Finally, only 3 individuals (6.3%) had a history of organ transplantation.

In the control group, the mean age of the study subjects was 59.48±1.71 years (ranging from 27 to 85 years). Most of the patients in the control group (27 men, 25 women) were in the age range of 41 to 60 years (50%) (Figure, 1B). The majority of the study participants in the control group were male (27 individuals, 51%). Among the control group participants, the most prevalent underlying conditions were hypertension (32%), dyslipidemia (21%), and diabetes (19%) (Table 2). Three individuals (8.5%) had a history of steroid use. Only also 3 individuals (7.5%) had a history of using immu-

TABLE 1

Prevalence of different underlying diseases in the control group and in the mucormycosis group

Past medical history	%	Frequency
Control Group		
Diabetes mellitus	**19.2**	10
Hypertension	**32.7**	17
Hyperlipidemia	**21.2**	11
Ischemic heart disease	**9.6**	5
Kidney disease	**1.9**	1
Liver disease	**3.8**	2
Patients with Mucormycosis		
Diabetes mellitus	**93.8**	45
Hypertension	**41.7**	20
Hyperlipidemia	**12.5**	6
Ischemic heart disease	**10.4**	5
Kidney disease	**4.2**	2
Liver disease	**2.1**	1

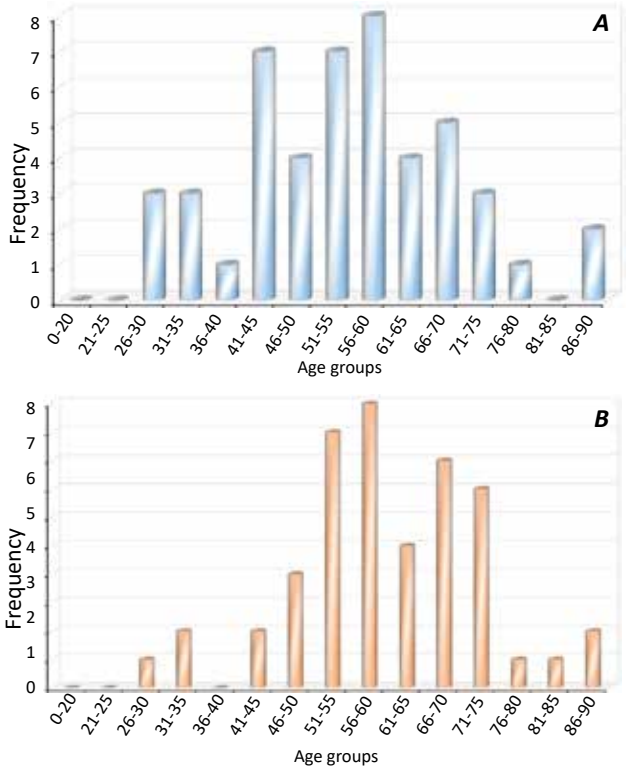

Figure 1. *Prevalence of different age groups in the control group (A) and in patients with mucormycosis (B)*

nosuppressive drugs, excluding corticosteroids. The risk factors associated with an increased likelihood of mucormycosis were diabetes compared to non-diabetic individuals, with an adjusted odds ratio of 63 (95% confidence interval: 16.28-244) (Table 2). Additionally, corticosteroid treatment was a significant risk factor, with an odds ratio of 16.3 (95% confidence interval: 4.47-59.67) (Table 2). Finally, only 2 individuals (8.3%) had a history of organ transplantation. Use as well as treatment with immunosuppressive drugs , excluding corticosteroids, was a significant risk factor (odds ratio=6.06, 95% confidence interval: 1.60-22.89) (Table 2).

Therefore, diabetes, corticosteroid use, and immunosuppressive drug use were the predominant risk factors for mucormycosis.

Discussion

The present study was conducted to investigate the increased occurrence of mucormycosis as a significant challenge in the southwest of Iran during the COVID-19 pandemic. Diabetes, corticosteroid use, and immunosuppressive drugs were predominant risk factors for mucormycosis. Generally, the global incidence of mucormycosis ranges from 0.003 to 0.005 cases per 1.7 million individuals in different populations. However, in the years 2019 to 2020, the prevalence in India was more than 80 times higher than any other country [*Chander J et al., 2018; Prakash H, Chakrabarti A, 2019; Skiada A et al., 2020*], turning India into the country with the highest number of mucormycosis cases in the world. The COVID-19 is now associated with a considerable number of opportunistic fungal and bacterial infections [*Kubin C et al., 2021*]. The primary reason for the proliferation of these opportunistic fungal infections is the ability of fungal spores to germinate in the ideal environment created by the respiratory system of COVID-19 patients

Table 2

Odds Ratio of Mucormycosis Incidence in Diabetic Patients Compared to Non-Diabetic, in Patients Using Corticosteroids and in Patients Using Other Immunosuppressive Drugs Compared to Individuals Not Using Other Immunomodulatory Medications

Step 1[a]	B	S.E.	Sig.	EXP (B)=Odds ratio	5% Confidence interval for EXP (B)	
					Lower	Upper
Diabetic Patients Compared to Non-Diabetic						
Diabetes mellitus	4.270	0.700	0.000	71.556	18.147	282.150
Constant	-2.639	0.598	0.000	0.071		
Patients Using Corticosteroids.						
corticosteroid	2.793	0.661	0.000	16.333	4.470	59.679
Constant	-0.714	0.249	0.004	0.490		
Using Other Immunosuppressive. Drugs Compared to Individuals Not Using Other Immunomodulatory Medications						
Other immunosupressive drug	1.803	0.678	0.008	6.067	1.607	22.897
Constant	-0.336	0.221	0.128	0.714		

[*Mahalaxmi I et al., 2021*]. COVID-19 patients typically exhibit low oxygen, high glucose levels, acidic environment (metabolic acidosis), diabetic ketoacidosis, elevated iron concentration (increased ferritin), and reduced phagocytic activity [*Palermo N et al., 2020*]. Early diagnosis of mucormycosis is the primary cornerstone for facilitating and initiating antifungal treatment [*Zubair S et al., 2017*]. This was also indicated in the study by Pal et al. in 2021 in India, where 72% of individuals with COVID-19-associated mucormycosis were hospitalized. Among them, 78% were male, and 85% had diabetes. Furthermore, 85% of the patients were non-ketoacidotic, and 85% of the patients had a history of corticosteroid use [*Pal R et al., 2021*]. In our study, a total of 48 patients with mucormycosis and 52 individuals as controls were included for analysis. The mean age of the study group with mucormycosis was 52.9 ± 9.53 years (27 to 88 years). Most of the patients in the age group of 41 to 60 years (45.3%) were included. The majority of the patients in the study were male (28 individuals, 58.3%). In a study conducted by Sundaram N et al. in India in 2021, various risk factors such as diabetes, sinusitis, renal failure, organ transplantation, trauma, malnutrition, neutropenia, acquired immunodeficiency disease, corticosteroid use, broad-spectrum antibiotics, and drug abuse were found to be significant contributors to mucormycosis [*Al Awaidy S, Khamis F, 2019*]. In our study, it has been identified that diabetes, treatment with corticosteroids, and the use of immunosuppressive agents are associated risk factors for mucormycosis in COVID-19 patients."

Currently, corticosteroids are the mainstay of treatment in severe COVID-19 patients [*Nehara H et al., 2021*]. It has been demonstrated that corticosteroids effectively increase survival and reduce mortality in COVID-19 patients [*Sterne J et al., 2020*]. However, corticosteroid use diminishes the phagocytic capability of white blood cells and renders patients susceptible to fungal infections. Moreover, corticosteroid-induced diabetes, either as a new onset or exacerbation of previous Diabetes mellitus, may enhance mucormycosis growth [*Lionakis M, Kontoyiannis D, 2003*]. The use of immunosuppressive drugs, particularly corticosteroids, should be minimized or discontinued whenever feasible [*Maini A et al., 2021*]. In our study, in the mucormycosis group (50%) had a history of steroid use and (27.1%) had a history of using immunosuppressive drugs excluding corticosteroids , which significantly correlated with an increased occurrence of mucormycosis. The expression of two angiotensin-converting enzyme receptors in pancreatic islets in COVID-19, coupled with increased insulin resistance due to a cytokine storm, might explain the diabetogenic nature of COVID-19 [*Owolabi J, Bekele A. 2021*]. Excessive glucose occupies the binding sites of ferritin and transferrin in hyperglycemia. Consequently, free iron levels increase, leading to heightened sensitivity to mucormycosis. Additionally, diabetic ketoacidosis can lead to an acidic state, providing more available free iron for fungal growth, thus increasing the risk of mucormycosis [*Ibrahim A et al., 2012*]. In our study, diabetes and hyperglycemia were also among the risk factors for increased mucormycosis. Therefore, meticulous blood glucose control is crucial in the prevention and treatment of these patients. Some studies have reported cases involving lymphoma, leukemia, and solid organ transplantation patients [*Arana C et al., 2021; Zurl C et al., 2021*]. While these observations do not align with our study, based on available evidence, malignancies, organ transplants, and hemopathies are recognized risk factors for mucormycosis [*Sugar A, 1992; Cornely O et al., 2019*]. Furthermore, in an observational study by Patel et al. (2020), malignancy and organ transplant were identified as the most significant risk factors after. This is in contrast to our study, where a low percentage had a history of organ transplantation. Such discrepancies may stem from the small sample size and variations in sampling.

CONCLUSION

In this study, potential pre-existing risk factors (such as diabetes, corticosteroid use, immunosuppressive drugs, etc.) were investigated in southwestern Iran and revealed that this conditions increase the risk of COVID-19-associated mucormycosis risk. Avoiding corticosteroids in mild cases and closely monitoring blood sugar level can help to reduce of COVID-19-associated mucormycosis. Limitations of this study include not examining the type and dosage of immunosuppressive drugs, the patients' ferritin levels, and the consequences and prognosis of mucormycosis cases.

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