









ORIGINAL RESEARCH

Mucormycosis in pre-COVID-19 and COVID-19 era: A study of prevalence, risk factors and clinical features

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Abstract

Objective: Mucormycosis is a rare yet devastating fungal disease with a frequently fatal outcome. The purpose of this study was to compare the prevalence of mucormycosis, evaluate its risk factors, and assess the patients' outcomes in pre-COVID-19 and COVID-19 era.

Methods: In this retrospective observational study, clinical data of 158 patients with confirmed histopathological diagnosis of mucormycosis were collected from the medical records departments of Imam Reza and Ghaem hospitals, Mashhad, Iran during 2018–2021. The collected data were risk factors associated with mucormycosis including age, gender, underlying diseases, details of corticosteroid administration, and complications such as blindness and mortality.

Results: Of 158 studied patients, 48 patients were diagnosed in the pre-pandemic period whereas 110 cases were admitted during the pandemic era. COVID-19 associated mucormycosis (CAM) was observed in 58.1% of the pandemic cases. In the pre-pandemic period, cancer (89.5% vs. 39%, $p < .001$) was significantly more prevalent while during the pandemic era, the prevalence of diabetes mellitus (16.7% vs. 51%, $p < .001$) was remarkably higher. Moreover, the mortality rate of mucormycosis was considerably reduced after the pandemic (64.6%–45.4%), especially in CAM patients (35.9%).

Conclusion: The COVID-19 pandemic has led to an increased prevalence of mucormycosis, due to the convergence of interlinked risk factors such as diabetes mellitus, corticosteroid therapy, and COVID-19. Therefore, clinicians must be aware of the probable occurrence of mucormycosis in the first or second week of COVID-19 infection in vulnerable patients and use the steroids cautiously.

Level of evidence: 4 Laryngoscope Investigative Otolaryngology, 2022.

KEYWORDS

black fungus, COVID-19, mucormycosis, risk factors, SARS-CoV-2

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1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral agent responsible for coronavirus disease 2019 (COVID-19), has spread rapidly across the globe, posing an unprecedented threat to mankind.¹ Despite being highly transmissible, COVID-19 has a mortality rate of only 5.7%.² In most cases, COVID-19 patients only experience mild to moderate respiratory illness and do not require hospitalization.³ However, certain risk factors such as old age, male gender, underlying diseases such as diabetes mellitus, chronic lung diseases, hypertension, obesity, heart, liver and kidney diseases, and pregnancy can increase the risk of the disease progressing into severe forms.⁴ In these patients, the infection may advance rapidly and even lead to acute respiratory distress syndrome (ARDS).⁵ Despite the global efforts to provide a comprehensive understanding of COVID-19, little is known about fungal infections in patients with COVID-19. Among fungal infections, COVID-19 associated mucormycosis (CAM) has a high mortality rate.⁶

Mucormycosis (MM) is a rare yet devastating infectious disease caused by a group of molds from the order Mucorales.⁷ By spreading spores from inside the nose, these fungi are able to reach the paranasal sinuses, throat, and intracranial cavity and cause life-threatening, progressive complications.⁸ Therefore, infection with MM must be treated immediately.⁹ The most prominent risk factors for this fungal infection include conditions such as diabetes mellitus, malignancies, cell or organ transplantation, immunodeficiencies, and extensive use of immunosuppressants.¹⁰ Immunosuppressive drugs, especially corticosteroids, have been proposed to mediate CAM infection as they are commonly prescribed when patients with COVID-19 are critically ill.¹¹ Whether triggered by the patient's underlying health condition, excessive use of corticosteroids or the immunomodulatory properties of the virus itself, CAM is infecting a growing number of patients worldwide.^{5,12,13} In India, the incidence of MM was reported to have increased 2.1 times during the COVID-19 outbreak.¹³ Likewise, several studies from Iran have found a high incidence of MM among COVID-19 patients.^{5,14}

The European Medical Mycology Confederation (ECMM) and the International Society of Human and Animal Mycology (ISHAM) are actively seeking to uncover the relationship between COVID-19 and MM.¹⁵ In hospital records, there is compelling evidence that the prevalence of MM has increased during the COVID-19 pandemic. Therefore, we conducted the current study to compare the prevalence of MM, evaluate its risk factors and assess the patients' outcomes in pre-COVID-19 and COVID-19 era.

2 | MATERIALS AND METHODS

2.1 | Study design

In this retrospective observational study, clinical data of patients with confirmed histopathological diagnosis of MM were collected from the medical records departments of Imam Reza and Ghaem hospitals,

Mashhad, Iran. To reliably compare the prevalence of MM before and after the COVID-19 pandemic, similar intervals of time were considered for screening the patients' documents. The pre-pandemic data was collected from March 2018 to September 2019 while the pandemic data was collected from March 2020 to September 2021. Also, to elaborate the effect of COVID-19, pandemic records were further analyzed in subgroups of cases with positive (rhino-orbital-cerebral COVID-19-associated mucormycosis or ROCCAM) and cases with negative (rhino-orbital-cerebral mucormycosis or ROCM) real-time reverse transcriptase polymerase chain reaction (RT-PCR) results. All patients received standard medical and surgical treatment for MM.¹⁶ The protocol of the present study was reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences under the code IR.MUMS.MEDICAL.REC.1400.795 and complied with the ethical considerations outlined in the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.2 | Data collection

Clinical data of all patients with the diagnosis of rhino-orbital-cerebral MM who referred to the ENT department of Imam Reza and Ghaem hospitals within the specified period of time were included in this study. To extract data from medical records, a pre-designed Microsoft Excel sheet was utilized. Risk factors associated with MM including age, gender, underlying diseases (such as diabetes mellitus, ischemic heart disease, hypertension, malignancies, etc.) and details of corticosteroid use of all patients were recorded into the datasheet. For those diagnosed with COVID-19, the severity of disease (classified according to the World Health Organization guideline for clinical management of COVID-19),¹⁷ history of drug treatment, the time interval between MM and COVID-19 and the need for oxygen therapy were additionally noted. MM-attributable complications such as no light perception (NLP) and 3-month mortality rate were recorded for both pre-pandemic and pandemic groups as well. After completion of data extraction, all variables were compared between the two groups.

2.3 | Statistical analysis

All data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp.). Descriptive statistics were defined as mean and standard deviation for quantitative variables and as frequencies (with percentages) for qualitative data. For comparison of qualitative and quantitative variables between the groups, chi-square and unpaired *t*-tests were used, respectively. After analyzing all the data, the value of $p < .05$ was considered statistically significant.

3 | RESULTS

After the exclusion of 15 patients with insufficient data, 158 cases were ultimately analyzed. Of these, 48 patients were admitted during

TABLE 1 Pre- to post-pandemic analysis of risk factors and clinical outcomes of mucormycosis

Variables	Pre-pandemic (n = 48)	Pandemic		Overall (n = 110)	p		
		ROCCAM (n = 64)	p			ROCM (n = 46)	p
Age (years), mean ± SD	35.4 ± 18	54 ± 14.4	<.001	41.7 ± 19.6	.283	48.8 ± 18.4	<.001
Sex, n (%)							
Male	28 (58.4)	39 (60.9)	.781	30 (65.2)	.492	69 (62.7)	.602
Female	20 (41.6)	25 (39.1)		16 (34.7)		41 (37.3)	
Underlying disease, n (%)							
Diabetes mellitus	8 (16.7)	45 (70.3)	<.001	12 (26.0)	.265	57 (51.0)	<.001
Ischemic heart disease	5 (10.4)	12 (18.8)	.224	8 (17.3)	.327	20 (18.2)	.219
Hypertension	3 (6.2)	25 (39.1)	<.001	9 (19.5)	.053	34 (31.0)	.001
Hematologic cancers	40 (83.3)	10 (15.6)	.302	29 (63.0)	.929	39 (35.4)	<.001
Non hematologic cancers	3 (6.2)	2 (3.1)		2 (4.3)		4 (3.6)	
Other ^a	3 (6.2)	9 (14.0)	.751	1 (2.1)	.328	10 (9.0)	.413
Corticosteroid therapy, n (%)							
Dexamethasone	24 (66.7)	51 (82.2)	.149 ^c	22 (75.8)	.716 ^c	73 (80.2)	.263 ^c
Prednisolone	3 (8.3)	4 (6.4)		1 (3.4)		5 (5.5)	
Hydrocortisone	3 (8.3)	0 (0.0)		3 (10.3)		3 (3.3)	
Combination	6 (16.7)	7 (11.2)		3 (10.3)		10 (11.0)	
Total	36 (75.0)	62 (96.8)	.001	29 (63.0)	.210	91 (82.7)	.261
Corticosteroid doses, ^b n (%)							
<5 mg/day	7 (21.2)	1 (1.5)	.002	2 (4.3)	.066	3 (3.4)	.004
5–10 mg/day	18 (54.5)	34 (53.1)		22 (47.8)		56 (63.6)	
10–15 mg/day	5 (15.2)	3 (4.6)		1 (2.1)		4 (4.5)	
15–20 mg/day	2 (6.1)	16 (25.0)		0 (0.0)		16 (18.2)	
20–25 mg/day	1 (3.0)	6 (9.3)		0 (0.0)		6 (6.8)	
≥25 mg/day	0 (0.0)	1 (1.5)		2 (4.3)		3 (3.4)	
NLP, n (%)	6 (12.5)	29 (45.3)	.001	7 (15.2)	.660	36 (32.7)	.011
Mortality, n (%)	31 (64.6)	23 (35.9)	.003	27 (58.6)	.557	50 (45.4)	.027

Abbreviations: NLP, no light perception; ROCM, rhino-orbital-cerebral mucormycosis; ROCCAM, rhino-orbital-cerebral COVID-19-associated mucormycosis.

^aOther diseases including chronic kidney disease, chronic obstructive pulmonary disease, and asthma.

^bDoses as dexamethasone equivalent.

^cp-Value was calculated considering corticosteroids of combinational therapy individually.

the pre-pandemic period whereas the rest were admitted during the pandemic era. The studied populations consisted of 28 (58.4%) and 69 (62.7%) males, with a significant difference in the mean age (35.4 ± 18 vs. 48.8 ± 18.4 years, $p < .001$). A large number of MM patients in both groups had a history of underlying diseases. In the pre-pandemic period, cancer (89.5% vs. 39%, $p < .001$) was significantly more prevalent while in the pandemic era, the prevalence of diabetes mellitus (16.7% vs. 51%, $p < .001$) and hypertension (6.2% vs. 31%, $p = .001$) were remarkably higher. Among MM patients with underlying cancer, nearly 90% had hematologic cancer (Table 1).

The mean daily administered doses of corticosteroids were almost similar before and after the pandemic (8.55 mg vs. 9.79 mg, $p = .496$). However, the average cumulative doses were higher in the pre-pandemic period (249.36 mg vs. 139.36 mg, $p = .001$). The total administered doses of corticosteroids were significantly higher in

ROCCAM patients when compared to the pre-pandemic cases ($p = .002$). Moreover, the frequency of NLP due to MM was remarkably higher in ROCCAM patients (45.3% vs. 12.5%, $p = .001$). The 3-month mortality rate for the pre-pandemic MM cases was 64.6% while it was 45.4% for the patients of the pandemic era, which is to a significant amount lower ($p = .003$) (Table 1).

With a prevalence of 58.2%, the majority of the pandemic cases had prior infection with COVID-19. The mean time interval between COVID-19 and MM was approximately 2 weeks. As shown in Table 2, the mean age of ROCM patients was significantly lower than ROCCAM cases ($p > .001$). In both ROCCAM and ROCM groups, men made up a larger percentage of patients (69.90% vs. 65.22%). In reviewing the underlying diseases, we found that the history of diabetes mellitus was significantly higher in ROCCAM cases ($p > .001$). Conversely, the history of hematologic cancers was higher among ROCM

Variables	ROCCAM (n = 64)	ROCM (n = 46)	p
Age (years), mean ± SD	54 ± 14.4	41.7 ± 19.6	<.001
Sex, n (%)			
Male	39 (60.9)	30 (65.2)	.647
Female	25 (39.1)	16 (34.7)	
Underlying disease, n (%)			
Diabetes mellitus	45 (70.3)	12 (26.0)	<.001
Ischemic heart disease	12 (18.8)	8 (17.3)	.855
Hypertension	25 (39.1)	9 (19.5)	.029
Hematologic cancers	10 (15.6)	29 (63.0)	<.001
Non-hematologic cancers	2 (3.1)	2 (4.3)	
Other ^a	9 (14.0)	1 (2.1)	.44
Corticosteroid therapy, n (%)			
Dexamethasone	51 (82.2)	22 (50.0)	.089 ^b
Prednisolone	4 (6.4)	1 (2.1)	
Hydrocortisone	0 (0.0)	3 (6.5)	
Combination	7 (11.2)	3 (6.5)	
Total	62 (96.8)	29 (63.0)	<.001
NLP, n (%)	29 (45.3)	7 (15.2)	.003
Mortality, n (%)	23 (35.9)	27 (58.6)	.018

TABLE 2 Comparison of the prevalence of risk factors and clinical outcomes of mucormycosis in patients positive and negative for COVID-19 during pandemic

Abbreviations: NLP, no light perception; ROCM, rhino-orbital-cerebral mucormycosis; ROCCAM, rhino-orbital-cerebral COVID-19-associated mucormycosis.

^aOther diseases including chronic kidney disease, chronic obstructive pulmonary disease, and asthma.

^bp-Value was calculated considering corticosteroids of combinational therapy individually.

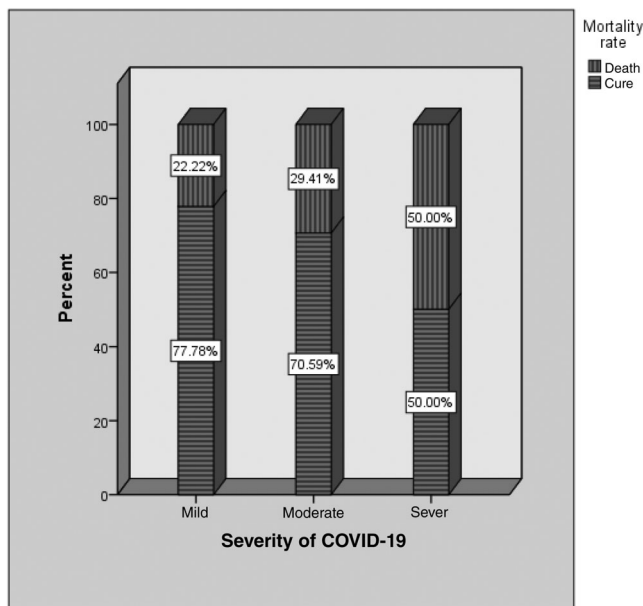


FIGURE 1 Mucormycosis 3-month mortality rate based on COVID-19 severity

group ($p > .001$). A novel finding of this study was that the incidence of NLP was significantly higher among ROCCAM cases ($p = .003$). Moreover, ROCCAM patients had a lower 3-month mortality rate in comparison to ROCM cases (35.9% vs. 58.6%, $p = .018$). The details

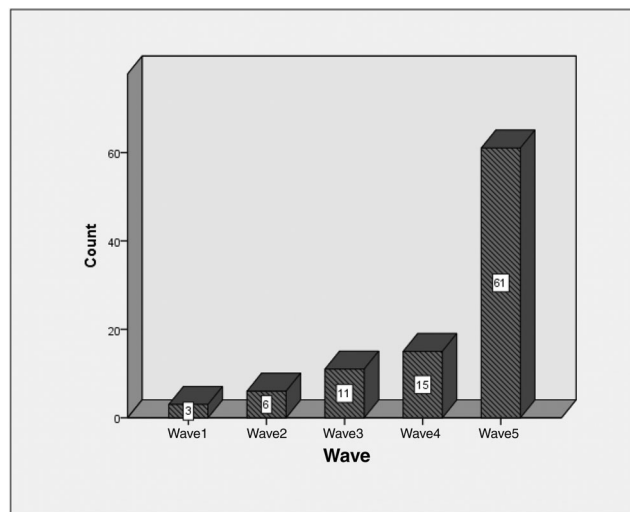


FIGURE 2 The number of mucormycosis cases in each wave of COVID-19 outbreak in Iran

of mortality rate in ROCCAM patients are presented in Figure 1. Accordingly, patients with severe COVID-19 had the highest and patients with mild COVID-19 had the lowest mortality rate due to MM (50% vs. 22.2%, respectively).

So far, five waves of COVID-19 outbreaks have occurred in Iran. As shown in Figure 2, the number of patients with MM has increased in each wave compared to the previous one. The highest number of

MM cases was reported in the fifth wave including 63.54% of the total MM patients.

4 | DISCUSSION

Mucormycosis, also known as black fungus, is a lethal opportunistic disease with a yearly incidence of 1.7 cases per one million population.¹⁸ The agents responsible for this fungal infection are widely present in the surrounding environment and all humans have daily exposure to their spores.¹⁹ However, the illness is only observed in people with a weakened immune system.²⁰ Almost all patients who develop MM have an underlying compromising condition.²¹ Diabetes mellitus, malignancies, cell or organ transplantation, immunodeficiencies, and extensive use of immunosuppressive drugs are among the main risk factors known for MM.¹⁰ Upon the emergence of a novel viral agent with a communicable, invasive nature, it seems an extension to the aforementioned list is needed for a newly diagnosed risk factor: COVID-19.

COVID-19 is an infectious disease of the respiratory system.²² Immunological dysregulation, the excessive use of corticosteroids and broad-spectrum antibiotics, and mechanical ventilation are all factors that can leave COVID-19 patients susceptible to opportunistic infections.²³ Moreover, COVID-19 can predispose patients to MM development by increasing the availability of free iron, an essential element in the life cycle of Mucorales.²⁴ Hyperferritinemic syndrome, a common manifestation in COVID-19 inflammatory responses, triggers a degenerative process that can eventually lead to the death of hepatic cells and release of the stored Fe^{2+} extracellularly.^{25,26} Also, the virus itself may target hemoglobin or induce hepcidin dysregulation which can elevate the amount of free iron available for fungal acquisition, thereby facilitating MM in COVID-19 patients.^{25,26}

Since the outbreak of COVID-19, Iran has experienced a large-scale spread of MM. According to our findings, MM incidence has surged by 2.3-folds during this time. Intriguingly, in over half of these cases, there was a prior infection with COVID-19, suggesting that this sudden rise might have been triggered by SARS-CoV-2 virus. While most of the current reports regarding the growing prevalence of CAM come from India, the United States and European countries have reported such cases as well.¹² This indicates that the rise in the prevalence of CAM is a universal trend. Along with these findings, the significant increase of CAM cases in the fifth wave of COVID-19 outbreak in Iran, which coincided with the outbreak of the SARS-CoV-2 delta variant, suggests that this particular viral variant may be associated with a high risk of MM infection in COVID-19 patients.²⁷ This is merely a hypothesis and to establish such a link accurate molecular genetic studies are needed.

Over the past decade, diabetes mellitus has been the predominant predisposing factor for MM in Iran.²⁸ However, in recent years, the trend appears to have shifted toward hematologic malignancies.²⁹ The incidence of MM in patients with hematologic cancers has been widely increased in different parts of the world such as the United States, France, and Greece.³⁰⁻³³ Likewise, in our study,

hematologic cancers were the major cause of MM infection before the COVID-19 pandemic. Nonetheless, with the outbreak of COVID-19, the prevalence of underlying hematologic cancers precipitously dropped from 83.3% to 35.4%. While the proportion has seemingly decreased to half, the absolute number has remained relatively unchanged. Looking at MM incidence trends, we observe that hematological cancers have retained a constant share of cases among the invasive fungal infections throughout the years.²⁹ Therefore, the lower percentage could be attributable to the emergence of COVID-19 as a novel risk factor for MM. In line with our findings, Patel et al. also reported a spike in MM prevalence during India's second wave of COVID-19 outbreak. Their study found that COVID-19 was associated with MM development in 65.2% of the cases.¹³ The decrease in the prevalence of hematologic cancers can also be attributable to COVID-19 induced new-onset diabetes mellitus.

Diabetes mellitus is the underlying medical condition responsible for 40% of MM infections worldwide.³⁴ According to estimates, people with diabetes mellitus are 7.5 times more likely to develop MM.³⁵ In the years since COVID-19 emerged, the global incidence of diabetes mellitus has steadily increased; a trend that can be linked to COVID-19 as experts have found SARS-CoV-2 can impair insulin secretion through damaging pancreatic beta cells.^{36,37} Defined by sudden hyperglycemia without any history of diabetes, normal HbA1c level and confirmed COVID-19, the prevalence of new-onset diabetes mellitus has been reported as 14.4% in hospitalized COVID-19 patients.³⁸ In our CAM cases, 14.06% had new-onset diabetes mellitus, suggesting that COVID-19 may not only facilitate MM infection itself, but also mediate it by promoting new-onset diabetes mellitus. In support of this argument, Kulkarni et al. investigated 49 cases of CAM in India and found that 81.7% had a history of diabetes mellitus. Interestingly, 18.4% of these patients had developed diabetes only after contracting COVID-19.³⁹ This association has also been demonstrated by a multicentric study of 122 cases that found new-onset diabetes mellitus responsible for the development of MM in 13.1% of COVID-19 patients.⁴⁰ As this topic is still relatively new, further research is needed to confirm these findings.

Almost all of our CAM patients underwent treatment with corticosteroids. Steroid therapy is a favorable treatment for COVID-19 as it has been proven to reduce all-cause mortality by controlling the systemic inflammatory reactions that generate lung damage and multi-organ dysfunction.^{41,42} However, since these drugs suppress the immune system through inhibiting a broad range of immune responses, they can also prepare the conditions for the growth of opportunistic infections.⁴³ The main factors that substantially change the benefit-risk equation for corticosteroids are dosage and duration of therapy.⁴⁴ Although the exact dosages and duration that leave patients susceptible to secondary infections likely varies by the individual and their underlying risk factors for infection, studies have repeatedly shown dose-dependent increases in risk for opportunistic infections.⁴⁵ The maximum dose of corticosteroid that is universally considered effective yet safe for the treatment of COVID-19 is as low as 6 mg/day for up to 10 days.⁴⁶ Accordingly, the majority of our COVID-19 patients who developed MM after recovery were treated

with low-dose corticosteroids. At this dose, as Ritter et al. with the hazard ratio of 1.45 (95% CI: 0.75–2.82; $p = .28$) demonstrated, the development of secondary infection is unlikely to occur as a result of corticosteroid use in critically ill COVID-19 patients.⁴⁷ Therefore, since steroids are administered moderately in COVID-19 patients, their use appears to have a minimal effect on facilitating CAM infection.

Delay in the initiation of treatment for MM is directly associated with a worse prognosis.⁴⁸ Previous studies have shown that patients who start their treatment within 6 days after the onset of symptoms have a survival rate of 76%–81%, while those who seek medical treatment with a delay of more than 12 days have a diminished survival rate of 36%–42%.⁴⁹ When MM infection is so far progressed that it affects the medial rectus muscle, optic nerve and orbital apex structures, permanent blindness is observed.⁵⁰ In our study, NLP occurred in 26.5% of MM cases. Interestingly, the incidence of NLP in CAM patients was three times higher than in non-CAM patients. As of yet, there is no scientific explanation for this incident, but we assume it might be related to the patients' late admission to the hospital. The early symptoms of MM are similar to those of COVID-19: headache, fever, and nasal congestion.⁵¹ Also, MM displays the ocular manifestations of COVID-19 such as conjunctivitis, eye redness and excessive tearing.^{52,53} Therefore, it is possible that patients misinterpreted MM symptoms as COVID-19 complications and delayed seeking medical attention. The mean time interval of 2 weeks between COVID-19 and MM infection supports our hypothesis.

MM is notorious for its fatal outcome.⁵⁴ The mortality rate of MM in our study was as high as nearly 50%, which is close to its universal mortality rate.⁵⁵ Notably, this rate was 35.9% among CAM patients, which is a considerably lower rate. This is significant because it suggests that despite being a prevalent risk factor for MM, COVID-19 is linked to a lower risk of death. In agreement with our findings, Hussain et al. pooled the data of 223 CAM patients and reported a mortality rate of 29.6%. The authors justified the reduced mortality rate by relating it to the site of involvement and by highlighting that they had only included patients with proven histopathological or microbiological diagnosis.⁴² However, we attribute this lower mortality rate to the fact that COVID-19 as an underlying disease can readily come under control. After only 2–4 weeks of infection, a vast majority of COVID-19 patients fully recover from the disease and since control of underlying disease, due to its known contribution in facilitating MM infection, is an important feature of MM therapy, a better prognosis is therefore expected.^{56,57} We also found a direct relationship between MM mortality and COVID-19 severity, which is not surprising since these patients receive high-dose corticosteroids for their treatment and have impaired immune function.⁵⁸

Despite its many strengths, our study had a few limitations. Since our study had a retrospective design, we could not record the clinical features of patients upon admission. Moreover, a small number of patients had insufficient data in their medical records which left us with no choice but to exclude them from the analysis. Regardless of its limitations, this study certainly adds to our understanding of the increasing prevalence of invasive fungal infections in the COVID-19 era.

5 | CONCLUSION

The COVID-19 pandemic has led to an increased prevalence of MM, due to the convergence of interlinked risk factors such as diabetes mellitus, corticosteroid therapy, and COVID-19. Apart from this, COVID-19 can potentially promote new-onset diabetes mellitus, and in turn, prepare the conditions for the development of mucormycosis. Therefore, clinicians must be aware of the probable occurrence of mucormycosis in the first or second week of COVID-19 infection in vulnerable patients and use the steroids cautiously.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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