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ORIGINAL ARTICLE

Clinical profile and outcome of COVID-19 associated mucormycosis in Shiraz, South Iran: a longitudinal study

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ABSTRACT

Background and Objectives: Numerous cases of mucormycosis appeared among COVID-19 patients, predominantly in Asian countries. This study aimed to investigate the clinical profile, in-hospital outcome, and one-year prognosis of COVID-19-associated mucormycosis (CAM).

Materials and Methods: All patients who developed CAM in Shiraz, South Iran, between July and October 2021 were included in this study. We collected data on presentations, comorbidities, risk factors, and outcomes.

Results: Sixty-two patients with CAM were analyzed; the mean age was 59.3 years, and 58.1% were male. Diabetes mellitus was present in 80.6% (11.2% uncontrolled), hypertension in 54.8%, and chronic kidney disease in 11.3%. All patients had sinonasal involvement; ophthalmic, cutaneous, cerebral, gastrointestinal, pulmonary, and renal involvement occurred in 41.9%, 8.1%, 6.4%, 6.4%, 1.6%, and 1.6%, respectively. In-hospital and one-year mortality were 40.3% and 48.3%. Concurrent CAM and COVID-19, hypertension, older age, and radiologically severe COVID-19 lung involvement were associated with higher mortality. In multivariable analysis, age ≥60 years predicted in-hospital (OR: 5.47; 95% CI: 1.53-19.56) and one-year mortality (OR: 7.65; 95% CI: 1.90-30.84). Long-term mortality was also associated with ≥3 risk factors (OR: 4.12; 95% CI: 1.09-15.52) and lung severity index >30 (OR: 9.35; 95% CI: 1.01-86.63).

Conclusion: These findings emphasize the critical role of age in immune responses to opportunistic infections and highlight the impact of multiple comorbidities and severe lung damage on long-term prognosis in CAM.

Keywords: COVID-19; Mucormycosis; Risk factors; Comorbidity; Treatment outcome; Prognosis

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INTRODUCTION

Mucormycosis is a severe, life-threatening, airborne, opportunistic fungal infection caused by species from the Mucorales order, including *Rhizopus*, *Mucor*, *Lichtheimia*, and *Cunninghamella*. It primarily involves the upper respiratory tract (including paranasal sinuses), which can spread to the orbit and brain (rhino-orbito-cerebral manifestations). This infection can also extend to the pulmonary, gastrointestinal, and cutaneous systems. Conventional risk factors include diabetes mellitus (DM), hematologic malignancies, hematopoietic stem cell or solid organ transplants, or other immunocompromised states (1).

The COVID-19 pandemic, which began in late 2019, profoundly affected healthcare systems worldwide. As the COVID-19 pandemic grew, many cases of COVID-19-associated mucormycosis (CAM) emerged, particularly in association with DM and glucocorticoid use (2, 3). The incidence of CAM was notably higher in the Middle East and South Asia, especially in low- and middle-income countries, such as Iran and India, which faced a high prevalence of uncontrolled DM, low public hygiene, substantial challenges in controlling viral transmission, and where glucocorticoids were widely used in hospitalized patients (4, 5).

In COVID-19 patients, the development of mucormycosis is likely attributed to the combination of immune dysfunction from the virus itself, an exaggerated inflammatory response, prolonged hospital and intensive care unit admissions, and extensive corticosteroid use. Steroids exacerbate hyperglycemia and compromise neutrophil and overall immune function. Concurrently, COVID-19–related cytokine storm, hypoxia, and acidosis further diminish host defenses, creating an ideal environment for mucor invasion and growth (6). Clinically, CAM typically presents with non-specific symptoms like facial swelling, headache, and fever. Ophthalmic symptoms, particularly impaired vision, are common, and many patients also develop rhinosinusitis, nasal ulcerations, and facial pain.

Additionally, CAM is associated with poor outcomes, with case-fatality rates approaching 50%, particularly among patients with pulmonary, disseminated, or cerebral involvement. Even among survivors, long-term, life-altering sequelae are frequent, and nearly half may suffer permanent loss of vision (7). Early screening, heightened diagnostic strategies, and a deeper understanding of the risk factors, clinical progression, and outcomes are crucial for managing this rare but fatal infection. This imperative is especially urgent in regions like Iran, where CAM has reached critical levels and controversial reports have emerged (8, 9).

In this study, we sought to explore the manifestations, symptoms, system involvements, and outcomes of CAM patients. This investigation focused on the fifth national COVID-19 wave in Iran, driven predominantly by the Delta variant, during which the country experienced its highest rates of COVID-19–related hospitalizations and mortality.

MATERIALS AND METHODS

Patients, study design, and data collection. We consecutively included all patients with mucormycosis (post-COVID-19 or concurrent) admitted to Namazi and Faghihi hospitals in Shiraz, Iran, between July 23 and October 22, 2021. COVID-19 was confirmed by positive RT-PCR and/or lung HRCT findings consistent with COVID-19 (10). Inclusion criteria comprised all adult patients (≥18 years) with confirmed COVID-19 and proven or probable mucormycosis. We excluded patients without documented COVID-19, those with an alternative diagnosis explaining the lesions, and those with incomplete clinical or microbiological records. Mucormycosis is diagnosed based on clinical manifestations plus either histopathological/microbiological confirmation or characteristic radiological findings on CT scan (11). To confirm the diagnosis, specimens were obtained from the involved site whenever feasible. For rhino-orbito-cerebral disease, we collected nasal or sinus tissue, necrotic turbinates or palatal eschar, and, when applicable, orbital tissue during debridement. The diagnosis of cutaneous mucormycosis was established by deep skin and subcutaneous tissue biopsies. Direct microscopic examination was performed on fresh samples using 10-20% potassium hydroxide (KOH) preparations to identify broad, ribbon-like, pauciseptate hyphae with right-angle branching. Histopathologic examination was performed on formalin-fixed paraffin-embedded tissue using hematoxylin and eosin (H&E) and periodic acid–Schiff and/or Gomori methenamine silver (GMS) stains to demonstrate tissue-invasive hyphae and angioinva-

sion. Specimens were not examined for culture or genus detection because of the unavailability of these methods. Radiologic evidence and manifestations were used to diagnose central nervous system (CNS), gastrointestinal, pulmonary, and renal involvement, and also to confirm nasal, sinus, and orbital involvement when present. On CT of the orbit and sinuses, characteristic findings included unilateral or asymmetric sinus opacification, bone erosion of the sinus walls or hard palate, orbital fat stranding, extraocular muscle enlargement, or cavernous sinus involvement. Intracranial extension on brain CT (parenchymal lesions, abscess, or meningeal enhancement adjacent to involved sinuses) was considered highly suggestive of CAM. Pulmonary involvement was suspected based on the presence of focal or multifocal consolidation, cavitating lesions, nodules or masses with surrounding ground-glass opacity (reverse halo sign), wedge-shaped infarct-like opacities, or pleural effusion. Gastrointestinal mucormycosis was suspected based on findings such as segmental bowel wall thickening, hypoenhancing or non-enhancing bowel segments, pneumatosis intestinalis, mesenteric fat stranding, or free air/fluid indicating perforation. Renal involvement was suspected based on CT findings such as an enlarged kidney with poorly enhancing or non-enhancing wedge-shaped cortical or medullary areas, cortical necrosis, or perinephric fat stranding without another clear cause. Cutaneous and subcutaneous involvement was suspected in the presence of compatible skin lesions supported by CT findings such as skin thickening, subcutaneous fat stranding, fluid collections or abscesses, and, occasionally, soft-tissue gas.

All patient data were documented, including age, sex, clinical manifestations, initial symptoms, the time interval between the onset of mucormycosis and COVID-19, underlying conditions, history of diabetes, use and type of antibiotics, steroid usage, tocilizumab or antifungal use, supplemental oxygen use, hospitalization due to COVID-19, absolute neutrophil count (ANC), fasting and postprandial blood glucose levels, radiologic severity index of COVID-19, and long-term outcomes over one year. Patients with fasting glucose lower than 130 mg/dl and postprandial blood glucose lower than 180 mg/dl were considered to have controlled DM based on the American Diabetes Association (ADA) guidelines (12). Antifungal therapy (mainly fluconazole or itraconazole) was initiated empirically for suspected oral or oropharyngeal candidiasis based on clinical manifestations, especially during the acute course of COVID-19. Treatment with liposomal amphotericin B was started before microbiological or histopathological confirmation of mucormycosis. The radiologic severity index of COVID-19 provides a score of 0 to 40; a score of 0 means without lung involvement, and a score of 40 represents the most radiologically severe lung involvement (13). A score of ≥30 was used to define radiologically severe COVID-19 lung involvement.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board/Ethics Committee of Shiraz University of Medical Sciences (ethical approval code: IR.SUMS.MED.REC.1400.409). Written informed consent was obtained from all patients. Patient confidentiality was maintained, and all data were anonymized.

Statistical analysis. The relative frequency was determined to evaluate the prevalence of the specified diseases and the use of antibiotics or other medications. Patient demographic information is presented as frequencies (percentages) for qualitative data and as means (standard deviations) and medians (interquartile ranges) for quantitative data. We analyzed associations using the chi-squared test and the independent t-test.

To better understand factors associated with mortality and to control for potential confounding, we evaluated both in-hospital and one-year mortality using multivariable logistic regression with forward selection. Age was entered into the model first, followed by the sequential addition of each candidate risk factor or comorbidity (DM, CKD, hypertension, steroid use prior to diagnosis, cancer, and history of transplantation) and the radiologic COVID-19 severity index (≥30). Variables were retained if they improved model fit and were statistically significant ($p < 0.05$). The final adjusted model included three covariates: age ≥60 years (elderly), presence of multiple (≥3) risk factors for mucormycosis, and radiologically severe COVID-19 lung involvement (radiologic COVID-19 severity index ≥30). For both in-hospital and one-year mortality models, we report adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and P values. All analyses were conducted using Stata version 18 (StataCorp LLC, College Station, Texas), with statistical significance defined as a P-value <0.05.

RESULTS

This study analyzed 62 patients with COVID-19-associated mucormycosis (CAM) admitted to hospitals affiliated with Shiraz University of Medical Sciences in Shiraz, southern Iran. The majority were male (58.1%). The mean age was 59.29 ± 10.95 years (range 35-84).

Among the patients, 50 (80.6%) had diabetes mellitus (DM). Of these, 7 (11.2% of the total cohort) had uncontrolled DM; six of these seven presented with diabetic ketoacidosis (DKA) at the time of hospitalization for mucormycosis. DM was newly diagnosed in seven individuals.

Hypertension was present in 54.8% of patients, and chronic kidney disease (CKD) in 11.3%. Solid organ transplantation and hematologic malignancies were less common, observed in 6.5% and 1.6% of patients, respectively. The majority of patients received antibiotics (90.3%), with levofloxacin being the most commonly prescribed. Other treatments administered included remdesivir (56.4%), steroids (82.3%), tocilizumab (9.7%), and empirical antifungals for candidiasis (fluconazole or itraconazole) (9.7%). Additionally, zinc supplements were used by 8.1% of the patients.

The majority of mucormycosis diagnoses were made after a COVID-19 infection (91.9%), with a smaller percentage diagnosed simultaneously with COVID-19 (8.1%). The mean interval between COVID-19 and the first presentation of mucormycosis was 39.47 (± 31.73) days, with a range of 3-130 days. Nearly half of the patients (46.8%) required supportive oxygen therapy upon admission. Only one patient, who had a hematologic malignancy, presented with neutropenia (Absolute Neutrophil Count = 350). Based on lung CT scans, radiologically severe COVID-19 lung involvement was present in 38.7% of patients, while 61.3% had less severe features (severity index < 30). Long-term outcomes were poor, with a one-year mortality rate of 48.3% (Table 1).

The most common initial presentation was facial swelling, affecting 60% of the patients. This was followed by headache and impaired visual acuity, each observed in approximately 33.3% of cases. Less common symptoms included eye pain, nasal ulceration, and facial pain, each reported in about 20% of patients. Unspecific presentations such as body pain, fever, dyspnea, odynophagia, epistaxis, toothache, and vertigo were also reported, albeit less frequently (Fig. 1). Mucormycosis affected the nose or paranasal sinuses in all cases. Subsequently, a significant proportion of patients demonstrated ophthalmic involvement. Less common manifestations of mucormycosis, such as cutaneous, cerebral, gastrointestinal, lung, and renal involvements, were observed in 8.1%, 6.4%, 6.4%, 1.6%, and 1.6% of patients, respectively (Fig. 2).

The in-hospital and one-year mortality rates were 40.32% and 48.27%, respectively. We analyzed the association between mortality and various factors, including age, gender, presence of CKD, hypertension, DM status (newly diagnosed, controlled, and uncontrolled), history of glucocorticoid use, remdesivir use, tocilizumab use, in-hospital antibiotic use, zinc supplementation, supportive oxygen therapy, and the timing of mucormycosis infection (either simultaneous with or after COVID-19 infection). Age ≥60 years, concurrent diagnosis of mucormycosis and COVID-19, and radiologically severe COVID-19 lung involvement were associated with both in-hospital and one-year mortality (Table 2). Additionally, hypertension was associated with higher one-year mortality. After adjusting for advanced age, both having multiple risk factors for mucormycosis and having radiologically severe COVID-19 lung involvement were associated with long-term mortality but not with in-hospital mortality (Table 3). These findings identify age ≥60 years as the primary determinant of both in-hospital and one-year mortality. Furthermore, among hospital survivors, advanced age, the presence of multiple risk factors, and radiologically severe COVID-19 lung involvement were independent predictors of one-year mortality.

DISCUSSION

While healthcare systems were overwhelmed by COVID-19 and its complications, physicians also faced the additional challenge of mucormycosis. The emergence of mucormycosis cases in various regions, especially in low- and middle-income countries located in the Middle East and South Asia, has been linked to COVID-19 or its treatment. Whereas mucormycosis had been reported rarely beforehand, 101 reports were published worldwide within a few months of the COVID-19 pandemic (2). This study aimed to characterize the clinical profile and outcomes of post-COVID-19 mucormycosis in Iran, a setting marked by pandemic management challenges and conflicting reports about the disease. We demon-

Table 1. Patients' characteristics

Characteristic		Frequency (percentage)
Age	≥60	18 (29.1%)
	<60	44 (70.9%)
Gender	Male	36 (58.1%)
	Female	26 (41.9%)
Comorbidities	Diabetes mellitus	50 (80.6%)
	Hypertension	43 (54.8%)
	Chronic kidney disease	7 (11.3%)
	Solid organ transplant	4 (6.45%)
	Hematologic malignancy	1 (1.6%)
Medications before admission	Antibiotics (mostly levofloxacin)	56 (90.3%)
	Remdesivir	35 (56.4%)
	Steroids	51 (82.3%)
	Tocilizumab	6 (9.7%)
	Antifungals (fluconazole, itraconazole)	6 (9.7%)
	Zinc	5 (8.1%)
Admission with diagnosis of mucormycosis	After COVID-19	56 (90.3%)
	Simultaneous with COVID-19	6 (9.7%)
Absolute Neutrophil Count	<6000	25 (40.3%)
	≥6000	37 (59.7%)
Supportive oxygen therapy	Yes	29 (46.8%)
	No	33 (53.2%)
Radiologically COVID-19 lung involvement	Severe (severity index ≥ 30)	10 (16.1%)
(radiologic COVID-19 severity index)	Not severe (severity index < 30)	52 (83.9%)
In-hospital outcome	Death	25 (40.3%)
	Discharge	37 (59.7%)
Long-term outcome	Death	28 (45.2%)
	Alive for at least one year	30 (54.8%)

* Frequency (%) of baseline characteristics, in-hospital, and one-year mortality among study population.

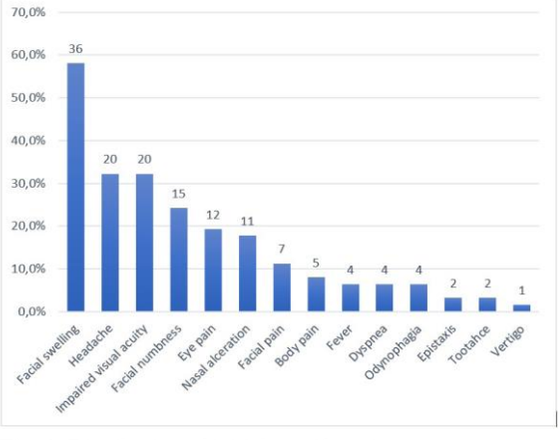

Fig. 1. Distribution of initial manifestations
* Frequency (%) of patients reporting each initial presenting symptom.

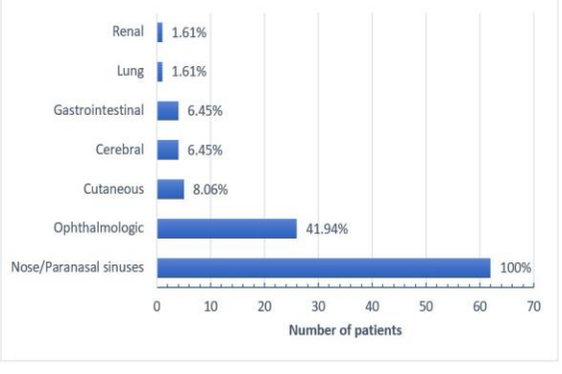

Fig. 2. Mucormycosis sites of involvement
* Percentage of patients with COVID-19–associated mucormycosis according to organ/system involvement.

Table 2. In-hospital and one-year outcomes of COVID-19-associated mucormycosis patients and the related risk factors

Variable		In-hospital outcome (N=62)		P-value	One-year outcome (N=58)		P-value
		Death	Survival (Discharge)		Death	Survival	
Age	<60	5 (17.2%)	24 (82.8%)	0.001	5 (20.0%)	20 (80.0%)	0.000
	≥60	20 (60.6%)	13 (39.4%)		23 (69.7%)	10 (30.3%)	
Sex	Female	9 (34.6%)	17 (65.4%)	0.436	11 (44.0%)	14 (56.0%)	0.571
	Male	16 (44.4%)	20 (55.6%)		17 (51.52%)	16 (48.48%)	
Chronic KidneyDisease	No	20 (36.4%)	35 (63.6%)	0.075	23 (45.1%)	28 (54.9%)	0.191
	Yes	5 (71.4%)	2 (28.6%)		5 (71.4%)	2 (28.6%)	
Hypertension	No	8 (28.6%)	20 (71.4%)	0.087	8 (29.6%)	19 (70.4%)	0.008
	Yes	17 (50.0%)	17 (50.0%)		20 (64.5%)	11 (35.5%)	
Diabetes Mellitus	New case	1 (11.1%)	8 (88.9%)	0.053	1 (14.3%)	6 (85.7%)	0.055
	Controlled DM	18 (52.9%)	16 (47.1%)	0.026	20 (58.8%)	14 (41.2%)	0.056
	Uncontrolled DM	2 (28.6%)	5 (71.4%)	0.501	3 (42.9%)	4 (57.1%)	0.760
	NO	4 (33.3%)	8 (66.7%)	0.583	4 (40.0%	6 (60.0%)	0.565
History of	No	5 (41.7%)	7 (58.3%)	0.916	5 (45.6%)	6 (54.5%)	0.835
Glucocorticoids use	Yes	20 (40.0%)	30 (60.0%)		23 (48.9%)	24 (51.1%)	
History of	No	9 (33.3%)	18 (66.7%)	0.324	10 (40.0%)	15 (60.0%)	0.272
Remdesivir use	Yes	16 (45.7%)	19 (54.3%)		18 (54.5%)	15 (45.5%)	
History of	No	23 (41.1%)	33 (58.9%)	0.713	26 (50.0%)	26 (50.0%)	0.439
Tocilizumab use	Yes	2 (33.3%)	4 (66.7%)		2 (33.3%)	4 (66.7%)	
In hospital antibiotic	No	1 (16.7%)	5 (83.3%)	0.214	1 (20.0%)	4 (80.0%)	0.186
use	Yes	24 (42.9%)	32 (57.1%)		27 (50.9%)	26 (49.1%)	
Zinc use	No	24 (42.1%)	33 (57.9%)	0.334	27 (50.9%)	26 (49.1%)	0.186
	Yes	1 (20.0%)	4 (80.0%)		1 (20.0%)	4 (80.0%)	
Supportive O2 therapy	No	11 (33.3%)	22 (66.7%)	0.231	12 (40.0%)	18 (60.0%)	0.192
	Yes	14 (48.3%)	15 (51.7%)		16 (57.1%)	12 (42.9%)	
Association	Simultaneous	6 (100.0%)	0 (0.0%)	0.002	6 (100.0%)	0 (0.0%)	0.007
with Covid	After	19 (33.9%)	37 (66.1%)		22 (42.3%)	30 (57.7%)	
Lung severity index	≥30	8 (80.0%)	2 (20.0%)	0.005	9 (90.0%)	1 (10.0%)	0.004
	<30	17 (32.7%)	35 (67.3%)		19 (42.5%)	29 (57.5%)	
Absolute Neutrophil	<6000	9 (36.0%)	16 (64.0%)	0.568	11 (50.0%)	11 (50.0%)	0.837
Count	≥6000	16 (43.3%)	21 (56.8%)		17 (47.2%)	19 (52.8%)	
Antifungal	No	23 (41.1%)	33 (58.9%)	0.713	25 (48.1%)	27 (51.9%)	0.929
(fluconazole,	Yes	2 (33.3%)	4 (66.7%)		3 (50.0%)	3 (50.0%)	
itraconazole) use							

* Frequency (%) of COVID-19–associated mucormycosis cases stratified by in-hospital and 1-year mortality, with p values for the corresponding association tests.

Table 3. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from multivariable logistic regression models assessing the association of age ≥60 years, ≥3 risk factors for mucormycosis, and radiologically severe lung involvement (severity index >30) with in-hospital and 1-year mortality in patients with COVID-19–associated mucormycosis.

Variable	In hospital mortality		One-year mortality	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age ≥ 60 years	5.47 (1.53-19.56)	0.009	7.65 (1.90-30.84)	0.004
Multiple risk factors (≥3 risk factors)	2.42 (0.72-8.11)	0.153	4.12 (1.09-15.52)	0.036
Radiologically severe COVID-19 lung involvement (radiologic severity index >30)	5.41 (0.96-30.54)	0.056	9.35 (1.01-86.63)	0.045

*OR, odds ratio; CI, confidence interval.

strated that while age ≥60 years is the primary determinant of mortality, the presence of multiple comorbidities (especially hypertension) and radiologically severe COVID-19 lung involvement are also associated with higher one-year mortality.

Our study included 62 patients with mucormycosis, most of whom (93.5%) were followed for at least 12 months. In line with prior reports, we noted a male predominance (58.1%), though the proportion of female subjects was higher than in some previous studies (2). The mean age was 59.29 ± 10.95 years (range 35-84). This distribution is consistent with those reported in other studies, demonstrating that CAM affects a wide adult age range (14-16). The most common comorbidities were diabetes mellitus (80.6%) and hypertension (54.8%). Other conditions included chronic kidney disease (11.3%), solid organ transplantation (6.5%), and hematologic malignancy (1.6%). Despite uncontrolled DM being a risk factor for mucormycosis (16-19), only 11.6% of our patients had an uncontrolled glycemic state, compared with over 50% in other studies (20, 21). Previous studies on non-COVID-19 patients have shown that mucormycosis is rare among patients with controlled DM, contrasting with our findings (22). Hence, we should suspect mucormycosis even in post-COVID-19 patients with well-controlled DM. A systematic review by Shivaraj Nagalli and Nidhi Shankar Kikkeri showed that only 29.5% of 115 patients with COVID-19-associated mucormycosis had hypertension, a prevalence nearly half of that observed in our cohort (54.8%) (23). Our finding is comparable with a similar study from Iran, which showed that 61.4% of patients with COVID-19-associated mucormycosis (CAM) had hypertension (3). While our findings regarding CKD were similar to those in other reports (23), our work indicates that hypertension may be a risk factor for developing post-COVID-19 mucormycosis. In contrast to previous reports, we found that 6.45% of our patients were solid organ transplant recipients, and one had received a hematopoietic stem cell transplant. Given that such immunocompromised patients are at high risk for mucormycosis, a high index of suspicion is warranted, particularly in the post-COVID-19 setting.

As expected, 82.25% of patients had received steroids for COVID-19 treatment, a finding similar to most other studies (23, 24). However, one study from India revealed no cases of mucormycosis among hospitalized COVID-19 (ICU or ward) patients from the beginning of the COVID-19 pandemic until May 2021, despite a high rate of diabetic patients and steroid usage (25). Although high cumulative doses of corticosteroids (e.g., >600-700 mg prednisone equivalent) are a known risk factor for mucormycosis, the incidence reported in general at-risk populations is far lower than the surge of cases observed following COVID-19 (26). This disparity suggests that SARS-CoV-2 infection itself may be the predominant risk factor in the current pandemic context. Chronic antibiotic use, particularly broad-spectrum antibiotics, increases the risk of opportunistic infections like mucormycosis (18, 20, 27). Therefore, we specifically assessed antibiotic usage before mucormycosis development, finding that 56 patients (90.3%) had used antibiotics, especially levofloxacin. Although this high prevalence suggests a potential role for antibiotics in increasing risk, further studies are needed to confirm this association. Zinc supplementation was common and has been discussed as a potential factor in fungal infections in India, a country that reported a high burden of post-COVID-19 mucormycosis cases (28). The rate of zinc usage was not significantly high in our study. Muthu et al. measured zinc levels among COVID-19 patients, finding low levels in both the mucormycosis and non-mucormycosis groups (29). Evidence is insufficient to confirm the role of zinc supplements in post-COVID-19 mucormycosis. Furthermore, 9.7% of participants had received fluconazole or itraconazole prior to symptom onset. A previous study suggested prophylactic voriconazole as a risk factor for mucormycosis among hematologic stem cell transplant recipients (30). This highlights that unnecessary antifungal use must be avoided. Remdesivir was used in approximately 50% of our patients, a rate compatible with other studies (14). Due to the high rate of remdesivir use during the pandemic, it is hard to suggest remdesivir as a risk factor for mucormycosis. Furthermore, 9.7% of our patients had received a single dose of tocilizumab. Importantly, tocilizumab was typically administered to patients with severe, life-threatening COVID-19, a population at high baseline mortality, not all of whom developed mucormycosis. There are no reports of serious infections following the administration of tocilizumab in COVID-19 patients, except for a case of disseminated mucormycosis following severe COVID-19 found on autopsy (31, 32). While studies on tocilizumab among rheumatoid arthritis patients revealed no significant infections, judicious

use seems necessary.

Regarding clinical features, our findings are consistent with prior works, as the majority of cases were rhino-orbital mucormycosis (33, 34). However, we also noted a significant proportion of cutaneous (8.1%) and gastrointestinal (6.5%) involvement. Therefore, clinicians must maintain a high index of suspicion to diagnose unusual manifestations of post-COVID-19 mucormycosis. This is particularly relevant given our finding that supplemental oxygen had been administered to at least 75.8% of patients prior to mucormycosis presentation. Oxygen may play two opposite roles. Hypoxia is a risk factor for mucormycosis, and the high rate of oxygen requirement may be an index of hypoxia. It is also relevant that, in our setting, oxygen cylinders and resources were sometimes shared between two or three patients. This raises two questions for future research: Have oxygen resources been contaminated? Is it possible to be infected by direct inoculation of the fungus into the upper respiratory tract? As demonstrated in previous reports, oxygen delivery systems and oxygen humidifiers can serve as routes of transmission for various pathogens and, less commonly, for fungal infections (35). In addition, a few studies have identified contaminated hospital linens as a source of Mucorales transmission (36). The COVID-19 pandemic created highly crowded and overwhelming conditions, characterized by limited resources, overcapacity, suboptimal sterilization, and exhausted staff. Within this environment, it is plausible that contamination of oxygen delivery and ventilation systems contributed to the risk of infection. At present, this remains a hypothesis, and our study cannot establish any causal link. Future environmental and microbiological investigations are needed to assess the microbiological quality of oxygen delivery systems, determine whether Mucorales can colonize such equipment, and clarify whether this could represent a plausible route of transmission for CAM in resource-limited settings.

In our study, mucormycosis occurred after COVID-19 in 56 patients (90.3%) and simultaneously with COVID-19 in 9.7% of patients. The mean interval between COVID-19 and the first presentation of mucormycosis was 39.47 ± 31.73 days, with a wide range of 3-130 days. While mucormycosis presented more than one month post-COVID-19 in most of our patients, studies by Singh et al. and Dave et al. reported a concurrent presentation in approximately half of their cases (2, 37). All patients admitted with mucormycosis concurrent with COVID-19 died during their hospital stay, highlighting the need for careful management and intensive care for these patients. Additionally, in our cohort, DM was the dominant comorbidity (>80%) and is the most plausible driver of CAM development, given that hyperglycemia and ketoacidosis impair neutrophil function, increase free iron, and facilitate Mucorales invasion, an effect amplified by steroid-induced dysglycemia in COVID-19. Hypertension and CKD, although not direct causal factors for mucormycosis, indicate a higher cardiometabolic and frailty burden and are linked to worse COVID-19 severity and poorer host resilience, which may lower the threshold for CAM. In contrast, solid organ transplantation and hematologic malignancy, though less frequent, represent classic risk factors through chronic immunosuppression. Consistent with this, having multiple risk factors (≥3) was independently associated with one-year mortality, highlighting the cumulative effect of comorbidities and treatment-related immunosuppression on the course of CAM.

We followed our patients for at least one year to identify risk factors associated with poor prognosis and mortality. Our analysis showed that concurrent mucormycosis with COVID-19, hypertension, advanced age, and radiologically severe COVID-19 lung involvement were each associated with higher mortality. However, after adjusting for age and conventional risk factors, age emerged as the sole significant determinant of in-hospital mortality. Long-term (one-year) mortality was significantly influenced by age ≥60 years, the presence of ≥3 risk factors, and a radiologic COVID-19 severity index >30. These findings demonstrate the importance of age in immune system responses to opportunistic infections and highlight the significance of comorbidities and the severity of lung damage in long-term prognosis. One possible explanation is that extensive lung involvement reflects a more severe systemic inflammatory response, prolonged hypoxia, and greater overall organ dysfunction, which may lead to persistent immune dysregulation, frailty, and reduced physiologic reserve after hospital discharge. These factors could, in turn, impair recovery from mucormycosis and increase vulnerability to subsequent complications and late deaths. Future studies should validate this association in larger, multicenter cohorts and further elucidate the underlying pathophysiologic pathways linking severe COVID-19 lung disease

with adverse long-term outcomes in CAM. Hypertension was the most significant comorbidity. While its effect on in-hospital mortality was not statistically significant, it was significantly associated with long-term mortality—a finding that may reflect the high background prevalence of hypertension in our population. A larger sample size is needed to evaluate the effect of hypertension on mortality more accurately.

Strengths and limitations. The strengths of this study include the large number of patients compared to similar studies, long-term follow-up, the assessment of numerous potential factors, and the evaluation of a radiologic severity index effect on the prognosis of CAM. However, there are several limitations. We could not compare non-COVID-19-related mucormycosis cases with our cohort. These patients were not available in sufficient numbers. We did not perform species-level diagnostic tests for Mucorales in our patients; therefore, we were unable to determine the exact etiologic species, assess potential species-specific differences in pathology, or analyze outcomes separately by species. Finally, we were unable to measure HbA1c levels and had to categorize diabetic patients based on fasting and postprandial blood glucose levels.

CONCLUSION

CAM in our cohort most commonly presented with symptoms such as facial swelling, headache, and impaired vision. Although the rhino-orbital form was predominant, clinicians should remain alert to other presentations, including cutaneous, CNS, gastrointestinal, pulmonary, renal, and disseminated forms, particularly in older adults with DM or other comorbidities. To reduce the risk of CAM, management of at-risk COVID-19 patients should prioritize strict glycemic control and judicious use of corticosteroids, antibiotics, oxygen therapy, and antifungals, adhering to guideline-based indications, the lowest effective dose, and the shortest necessary duration. Advanced age, multiple risk factors, and a high radiologic lung severity index were associated with higher mortality and warrant closer clinical and radiologic monitoring in the weeks following COVID-19, with early ENT/ophthalmologic evaluation of sinonasal or orbital symptoms and rapid initiation of diagnostic work-up when CAM is suspected. Oxygen delivery systems and humidification circuits may play a role in mucormycosis transmission in hospitals, particularly during outbreaks, and further studies are required to evaluate this hypothesis.

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