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ORIGINAL ARTICLE

Original Article

Mucormycosis in patients with COVID-19: A cross-sectional descriptive multicentre study from Iran

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Abstract

Purpose: The aim of the study was to report clinical features, contributing factors and outcome of patients with coronavirus disease 2019 (COVID-19)-associated mucormycosis (CAM).

Methods: A cross-sectional descriptive multicentre study was conducted on patients with biopsy-proven mucormycosis with RT-PCR-confirmed COVID-19 from April to September 2020. Demographics, the time interval between COVID-19 and mucormycosis, underlying systemic diseases, clinical features, course of disease and outcomes were collected and analysed.

Results: Fifteen patients with COVID-19 and rhino-orbital mucormycosis were observed. The median age of patients was 52 years (range 14–71), and 66% were male. The median interval time between COVID-19 disease and diagnosis of mucormycosis was seven (range: 1–37) days. Among all, 13 patients (86%) had diabetes mellitus, while 7 (46.6%) previously received intravenous corticosteroid therapy. Five patients (33%) underwent orbital exenteration, while seven (47%) patients died from mucormycosis. Six patients (40%) received combined antifungal therapy and none that received combined antifungal therapy died.

Conclusion: Clinicians should be aware that mucormycosis may be complication of COVID-19 in high-risk patients. Poor control of diabetes mellitus is an important predisposing factor for CAM. Systematic surveillance for control of diabetes mellitus and educating physician about the early diagnosis of CAM are suggested.

KEYWORDS
COVID-19, diabetes, mucormycosis, Orbital mucormycosis, rhino-orbital infection, SARS-CoV-2 co-infection

1 | BACKGROUND

Coronavirus disease 2019 (COVID-19) is devastatingly sweeping throughout the world and became the pandemic threat.[1] Although the majority of the COVID-19 cases will experience mild to moderate form of respiratory illness and improved without taking special medications, aged individuals and those with underlying medical conditions are more probably to develop the severe form of COVID-19.[2–5] The infection in these patients progresses rapidly evolving respiratory deterioration and may lead to acute respiratory distress syndrome (ARDS).[4–6] The bacterial and fungal co-infections have been documented in patients suffering from severe acute respiratory syndrome (SARS), Middle East respiratory syndrome and influenza, but the knowledge on co-infections particularly fungal infections among critically ill COVID-19 patients is limited.[7] Accordingly, paying attention to opportunistic fungal infections in COVID-19 patients,[6,8,9] with a list of predisposing factors, is important for healthcare providers who are confronting the COVID-19 pandemic.[1,3,10] COVID-19 patients suffering from ARDS, those who require a long stay in an intensive care unit (ICU) and mechanical ventilation, taking high doses of corticosteroids, immunomodulators, interleukin antagonists and broad-spectrum antibiotics, are at manifold risk to develop fungal infections such as mucosal candidiasis, aspergillosis, mucormycosis, *pneumocystis jiroveci* pneumonia and candidemia.[1,3,6,10–14] There is a paucity of data regarding the rate of COVID-19-associated mucormycosis (CAM).[15] To the best of our knowledge, the rate, clinical features and course of CAM in patients who simultaneously infected with COVID-19 has never reported before. We aimed to investigate the clinical features, temporal relationship to COVID-19 and course of patients with CAM.

2 | METHODOLOGY

2.1 | Study design

A cross-sectional descriptive study on biopsy-proven mucormycosis patients with laboratory-confirmed COVID-19 was conducted with collaboration of five COVID-19 hospitalised canters in Tehran, Iran (Imam Khomeini hospital complex, Farabi hospital, Imam Hossein hospital, Shariati hospital and Firoozgar hospital) from April to September 2020. The protocol of this study was in accordance with the principles established by the Declaration of Helsinki and approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.VCR.REC.1399.152).

2.2 | Case definition, data collection and histopathological examination

Patients with following criteria included the following: 1. Angioinvasive mucormycosis should be confirmed on histopathologic examination using haematoxylin and eosin (H&E) staining 2. A verified case of COVID-19 defined as documentation of a positive result of real-time reverse transcriptase polymerase chain reaction (RT-PCR) for nasopharyngeal or oropharyngeal swab, tracheal aspirate and/or bronchoalveolar lavage (BAL) samples 3. The interval between two infections should not be more than 3 months. Clinical and paraclinical data including demographics, underlying diseases, clinical features and outcome were collected. The COVID-19 infection was categorised according to World Health Organization (WHO) guideline: mild, moderate and severe.[16] For attributing the clinical form of mucormycosis, the location and extension of the disease, computerised tomography (CT) scan of the orbit, paranasal sinuses and lung were used for all patients as the initial imaging study. Gadolinium-enhanced magnetic resonance imaging (MRI) of the orbits, brain and paranasal sinuses was also performed for patients who needed based on their symptoms. Clinical characteristics of each patient who met inclusion criteria were recorded. Patients were informed, and written consent was obtained after explaining that their clinical and biological data may be used for research purposes. Clinical radiological investigations, operative and outpatient follow-up data were recorded and analysed for possible predisposing factors, demographic profile, clinical features of COVID-19 and mucormycosis, complications and outcome. Neutropenia was defined as absolute neutrophil count ≤1000 cells/mm^3 at the time of diagnosis of mucormycosis.

2.3 | Statistical analysis

All data were analysed using SPSS Statistics (Version 19.0, IBM Corp.). Descriptive analysis was used for demographic and clinical characteristics. Bivariate analysis was performed on all variables of this study using the chi-square test.

3 | RESULTS

Fifty-eight patients were evaluated with suspicion of mucormycosis in these canters during the period time; finally, fifteen patients with laboratory-confirmed COVID-19 and mucormycosis were included in this study. Median age of patients was 52 years (14–71),

TABLE 1 Characteristics of fifteen COVID-19 patients co-infected with rhino-orbital mucormycosis

Case no.	Gender/ Age	Underlying diseases	Severity of COVID-19 based on Thoracic CT scan	O2 therapy	IV dexamethasone therapy	ICU (day)	Mucormycosis-associated risk factor
1	F/56	Diabetes, Hypertension	Severe	Nasal Cannula	Yes	No	Uncontrolled Diabetes, Steroids
2	M/50	Diabetes, Hypertension	Severe	Nasal Cannula	Yes	Yes (7)	Uncontrolled Diabetes, Steroids, Neutropenia
3	M/66	Diabetes, Hypertension	Moderate	Nasal Cannula	No	No	Diabetes, Hypertension
4	F/52	Diabetes, Asthma, Cardiovascular Disease, Hypothyroidism	Severe	Simple Mask	No	No	Uncontrolled Diabetes
5	F/50	Diabetes	Moderate	Simple Mask	No	No	Uncontrolled Diabetes
6	M/52	Diabetes	Severe	MV	Yes	Yes (11)	Uncontrolled Diabetes, Steroids
7	M/49	Diabetes	Moderate	Nasal Cannula	No	No	Uncontrolled Diabetes

Clinical manifestations of mucormycosis	Clinical form of mucormycosis	Day of Mucormycosis detection after COVID-19 Dg	Orbital exenteration	Palate exenteration	sinus debridement	Antifungal treatment	Outcome
Unilateral facial swelling, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, ptosis, proptosis, cranial nerve palsies, acute vision loss	OM	7	Yes	No	No	AMB	Alive
Headache, unilateral facial swelling, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, ptosis, proptosis, cranial nerve palsies, acute vision loss	OM	1	Yes	No	No	AMB, PSZ	Alive
Palate necrosis, orbital inflammation, eyelid oedema, ptosis	ROM	21	No	No	Yes	AMB, PSZ	Alive
Unilateral periorbital facial pain, orbital inflammation, eyelid oedema, ptosis, cranial nerve palsies, acute vision loss	ROM	21	Yes	No	Yes	AMB	Alive
Fever, palate necrosis, unilateral facial swelling, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, cranial nerve palsies, acute vision loss	ROM	21	No	No	No	AMB	Death
Fever, necrotic nasal, unilateral facial swelling, unilateral periorbital facial pain, Orbital inflammation, eyelid oedema, ptosis, proptosis, cranial nerve palsies, acute vision loss	ROM	21	No	No	Yes	AMB, PSZ, CSP	Alive
Headache necrotic nasal, unilateral facial swelling, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, ptosis, proptosis, cranial nerve palsies, acute vision loss, otologic symptoms	ROM	1	No	No	Yes	AMB, CSP	Alive

(Continues)

TABLE 1 (Continued)

Case no.	Gender/ Age	Underlying diseases	Severity of COVID-19 based on Thoracic CT scan	O2 therapy	IV dexamethasone therapy	ICU (day)	Mucormycosis-associated risk factor
8	F/49	Diabetes, Hypertension	Moderate	Nasal Cannula	Yes	Yes (4)	Uncontrolled Diabetes, Steroids
9	M/32	Haematological Malignancy	Mild	Nasal Cannula	No	No	AML, Chemotherapy, Neutropenia
10	M/71	Diabetes, Hypertension, Cardiovascular Disease	Severe	Simple Mask	Yes		Uncontrolled Diabetes, Steroids
11	M/55	Diabetes, Hypertension, Cirrhotic Liver	Severe	NIV	No	Yes (2)	DKA
12	M/44	Diabetes	Severe	Simple Mask	No	Yes (6)	Uncontrolled Diabetes
13	F/70	Diabetes	Mild	Nasal Cannula	Yes	No	Uncontrolled Diabetes, Steroids
14	M/14	Haematological Malignancy	Moderate	Nasal Cannula	No	No	AML, Chemotherapy, Neutropenia
15	M/66	Diabetes, Hypertension, Asthma, Tuberculosis	Severe	Simple Mask	Yes	No	Uncontrolled Diabetes, Steroids

Abbreviations: AMB, amphotericin B; AML, acute myeloid leukaemia; CSP, caspofungin; CT, computed tomography; Dg, diagnosis; DKA, diabetes ketoacidosis; F, female; HE, histopathological examination; IV, intravenous; M, male; MV, mechanical ventilation; NA, not applicable; NIV, non-invasive ventilation; OM, orbital mucormycosis; PSZ, posaconazole; ROM, rhino-orbito mucormycosis; SM, sinonasal mucormycosis; SOM, sino-orbital mucormycosis.

Clinical manifestations of mucormycosis	Clinical form of mucormycosis	Day of Mucormycosis detection after COVID-19 Dg	Orbital exenteration	Palate exenteration	sinus debridement	Antifungal treatment	Outcome
Necrotic nasal, palate necrosis, unilateral facial swelling, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, ptosis, proptosis, cranial nerve palsies, acute vision loss	ROM	5	No	Yes	Yes	AMB	Death
Fever, headache, necrotic nasal, nasal blockage, unilateral periorbital facial pain, Orbital inflammation, eyelid oedema, proptosis, cranial nerve palsies,	SOM	7	No	No	Yes	AMB	Death
Ptosis, proptosis, acute vision loss	SOM	14	No	No	Yes	AMB, PSZ	Alive
Necrotic nasal, palate necrosis, unilateral facial swelling, cranial nerve palsies	SOM	1	No	Yes	Yes	AMB	Death
Necrotic nasal, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, ptosis, proptosis, acute vision loss	SOM	2	Yes	No	Yes	AMB	Death
Headache, necrotic nasal, palate necrosis, unilateral facial swelling, unilateral periorbital facial pain, orbital inflammation, eyelid oedema, ptosis, proptosis, acute vision loss,	ROM	6	Yes	No	Yes	AMB	Death
Fever, headache, necrotic nasal, nasal blockage, unilateral, facial swelling	SM	37	No	No	Yes	AMB, CSP	Alive
Necrotic nasal, unilateral periorbital facial pain, Orbital inflammation, eyelid oedema, ptosis, proptosis, acute vision loss	SOM	18	No	No	Yes	AMB	Death

TABLE 2 Contributing factors, interventions and outcome in patients with COVID-19-associated mucormycosis

Demographic	Gender, Male (*n*, %)	10 (66%)
	Age (Median Years, range)	(14-71)
	Length of hospitalisation (Median days, range)	30 (3-90)
Comorbidities (n, %)	DM	13 (86)
	Hypertension	7 (46)
	Haematologic malignancies	2 (13)
	Asthma	2 (13)
	Cardiovascular disease	2 (13)
	Hepatic cirrhosis	1 (6)
	Hypothyroidism	1 (6)
	Tuberculosis	1 (6)
Risk factors (*n*, %)	Immunosuppressive therapy	7 (46)
	Chemotherapy	2 (13)
	Neutropenia	3 (20)
	Ketoacidosis	1 (6)
Site of mucormycosis infection (*n*, %)	ROM	7 (47)
	SOM	5 (33)
	OM	2 (13)
	SM	1(7)
Clinical manifestations (*n*, %)	Nasal congestion or blockage	2 (13)
	Fever	4 (26)
	Headache	5 (33)
	Palate necrosis	5 (33)
	Unilateral facial swelling	9 (60)
	Unilateral periorbital facial pain	11 (73)
	Ptosis	11 (73)
	Proptosis	11 (73)
	Acute vision loss	11 (73)
	Cranial nerve palsies	9 (60)
	Otological symptoms	1 (7)
Laboratory results (Mean ± SD)	WBC	9391 ± 5886
	Lymph count	1689.3 ± 1879.2
	ESR	81.6 ± 22.9
	CRP	81.73 ± 61.2
	HbA1c	9.86 ± 2.3
Medication (*n*, %)	Amphotericin B	15 (100)
	Posaconazole	4 (27)
	Caspofungin	3 (20)
	Combined therapy	6 (40)
Improvement of clinical presentation (*n*, %)	Improved	1 (7)
	Exenterated	5 (33)
	Non-exenterated blind frozen eye	8 (53)
	Non-exenterated seeing eye	1 (7)
Mortality (*n*, %)	Died	7 (47)
	Survived	8 (53)

Abbreviations: CRP, C-reactive protein; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; lymph count, lymphocyte counts; OM, orbital mucormycosis; ROM, rhino-orbito mucormycosis; SM, sinonasal mucormycosis; SOM, sino-orbital mucormycosis; WBC, white blood cells.

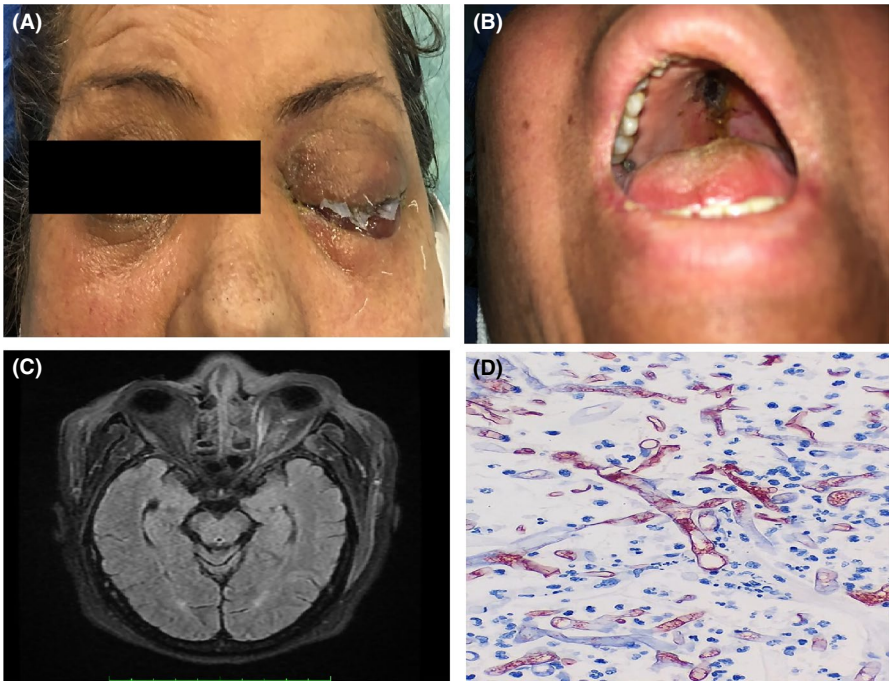

FIGURE 1 Clinical, radiological and histological features in one of our patients with COVID-19-associated mucormycosis. (a) Complete eyelid ptosis, restricted eye movements and no-light perception in left eye. (b) Palate eschar. (c) Brain MRI, T1-weighted image after gadolinium injection revealed left ethmoid sinus opacity with mucosal thickening. Enlargement of medial rectus muscle and orbital fat infiltrative pattern. (d) Haematoxylin and eosin (H&E) staining showing broad aseptate right angled hyphae of mucormycosis (1000×magnification)

and 66% were male. Demographics and clinical characteristic of our patients are summarised in Table 1. The most common symptoms of COVID-19 were anosmia (60%), fever (33%), cough (27%), dyspnoea (27%) and myalgia (27%). Eight out of 15 patients (53%) had diffuse lung involvement, so were categorised as severe form. The median interval time between the onset of COVID-19 and first symptoms of mucormycosis was seven days (1–37). All patients had underlying diseases including diabetes mellitus (DM) and hypertension that were the most common comorbidities documented in 13 (87%) and 7 (46%) patients, respectively (Table 2). Seven patients (46%) had received intravenous corticosteroids (either dexamethasone or methylprednisolone) for the management of COVID-19. One patient had undergone mechanical ventilation support. Two patients (13%) had received interferon, one patient remdesivir and one patient favipiravir along with hydroxychloroquine as anti-viral treatment. Nine patients (60%) had received nasal O2 support during their COVID-19 course. Three patients (20%) were neutropenic at the time of admission for mucormycosis, of whom two were suffering from acute myeloid leukaemia (AML) and were taking chemotherapeutic agents (Table 1). In addition, all of the patients showed raised erythrocyte sedimentation rate (ESR) (mean = 81.67, SD = 22.9) and C-reactive protein (CRP) levels (mean = 81.73, SD = 61.2) during COVID-19 course. Clinical manifestations of mucormycosis included the following: unilateral periorbital pain and oedema (73%), eyelid ptosis (73%), acute vision loss (73%), proptosis (67%), unilateral facial oedema (60%), cranial nerve palsy (60%), headache (33%), fever (27%), nasal blockage (13%) and ear pain (7%). Based on imaging, intra-operative endoscopic observation and histopathology evaluation, rhino-orbital mucormycosis (ROM) was the most frequent form of mucormycosis as evidenced in seven (47%) of COVID-19 patients, sino-orbital mucormycosis (SOM) involved 33% of the patients, 13% had isolated orbital involvement, and one patient (7%) was affected by sinonasal mucormycosis (SM). No patient had pulmonary mucormycosis. The most common form of paranasal sinus

TABLE 3 Comparison of demographic and clinical characteristics between survivors and non-survivors

Characteristic	Survivors 8 (%)	Non-survivors 7 (%)	*p*-value
Age (>60 years)	2 (25)	2 (28.5)	.876
Sex (male)	6 (75)	4 (57.1)	.464
Diabetes Mellitus	7 (87.5)	6 (85.7)	.919
Corticosteroid therapy	4 (50)	3 (42.8)	.782
Chest CT scan severity (severe)	5 (62.5)	3 (42.8)	.398
Antifungal combination therapy	6 (75)	0 (0)	.003
Day of Mucormycosis Detection after COVID-19 (>7)	5 (62.5)	2 (28.5)	.189
ICU admission	3 (37.5)	3 (42.8)	.464
O2 therapy (MV/NIV)	1 (12.5)	1 (14.2)	.632

TABLE 4 Clinical characteristics, risk factors, treatment and outcome of reported COVID-19-associated mucormycosis

Author/year/References	Country	Age/gender	Outcome	Surgical intervention	Antifungal treatment	Clinical form of mucormycosis
Mehta S/2020[26]	India	M/60	Died	Yes	AMB	ROCM
Sen et al./2021[27]	India	M/46	Survived	Yes	AMB, VRZ, PSZ	ROCM
		M/61	Survived	Yes	AMB, PSZ	ROM
		M/74*	Survived	Yes	AMB, PSZ	ROCM
		M/73	Survived	Yes	AMB, PSZ	ROCM
		M/62	Survived	Yes	AMB, PSZ	ROCM
		M/62	Survived	Yes	AMB	ROCM
Sarkar et al./2021[28]	India	10 cases**/M (*n* = 8), F (*n* = 2)/45.5	Survived (*n* = 6), Died (*n* = 4)	Yes (*n* = 7)	AMB (*n* = 10)	ROM (*n* = 9), ROCM (*n* = 1)
Moorthy et al./2021[29]	India	17 cases/M (*n* = 15), F (*n* = 2)/55	Survived (*n* = 11)	Yes	AMB	SM (*n* = 3), ROM (*n* = 6), ROCM (*n* = 5), RCM (*n* = 3)
Karimi Galougahi et al./2021[30]	Iran	F/61	Survived	Yes	Systemic antifungals	ROM
Veisi et al./2021[31]	Iran	F/40	Died	Yes	AMB	ROCM
		M/54	Survived	Yes	AMB, PSZ	ROM
Werthman/2020[32]	USA	F/33	Died	Yes	AMB	ROCM
Mekonnen/2020[33]	USA	M/60	Died	Yes	AMB, CSP, PSZ	ROM
Dallalzadeh et al./2021[34]	USA	M/48	Died	No	AMB/ISZ	ROM
Hanley/2020[35]	UK	M/22	Died	No	No	Disseminated (involving the hilar lymph nodes, heart, brain, and kidney)/
Waizel-Haiat et al./2021[36]	Mexico	F/24	Died	No	AMB	ROM

Abbreviations: AMB, amphotericin B; CAD, coronary artery disease; CSP, caspofungin; DKA, diabetes ketoacidosis; F, female; HTN, hypertension; ISZ, isavuconazole; ISZ, isavuconazole; IV, intravenous; M, male; NA, not applicable (not mentioned in the article); NIV, non-invasive ventilation; PSZ, posaconazole; RCM, rhino-cerebral mucormycosis; ROCM, rhino-orbito-cerebral mucormycosis; ROM, rhino-orbital mucormycosis; SM, sinonasal mucormycosis; VRZ, voriconazole.

*As per the EORTC-MSG criteria, the case was categorised as possible mucormycosis.; **As per the EORTC-MSG criteria, three patients were defined to have possible mucormycosis.

involvement was pansinusitis. In ten (67%) cases, mucormycosis was extended to skull base spaces. Among patients, 53.3% had pterygopalatine fossa involvement. Cavernous sinus involvement developed in seven cases (46%). Clinical, radiological and histological features in a patient with COVID-19-associated mucormycosis are shown in Figure 1. All of the patients were treated with intravenous amphotericin B liposomal (Ambisome Gilead Co.) (IV 5 mg/kg daily for 4–6 weeks), and four (27%) cases took oral posaconazole (Noxafil MSD Co.) (5 ml every 6 h/orally/for 2 weeks) (Combination antifungal agents as a salvage treatment). Three (20%) patients took additional IV Caspofungin (Letocan Nano Alvand Co.) (IV 70 mg stat and 50 mg daily) for 2 weeks (Table 2). The clinical and demographic characteristics of survivors and non-survivors cases are compared in Table 3. Antifungal combination therapy was significantly associated with better outcome (p = .003). Seven patients (47%) succumbed as the result of mucormycosis. All patients with ROM, SOM and SM underwent sinus debridement, except one patient (case number 5) who had severe lung involvement caused by COVID-19. Five patients (33%) underwent orbital exenteration, and 2 patients (13%) underwent extensive palatal debridement. At 3 months of follow-up

Interval between diagnosis of COVID-19 and mucormycosis occurrence (days)	Mucormycosis-associated risk factor	Local/systemic corticosteroid therapy	O2 supplementation	Underlying Conditions
12	Uncontrolled diabetes, Steroid for COVID-19	Yes- IV methylprednisolone and dexamethasone	NIV, MV	Diabetes
0	Uncontrolled diabetes, Steroid for COVID-19	No	NA	Diabetes
17	Uncontrolled diabetes, Steroid for COVID-19	Yes- IV methylprednisolone, oral prednisolone	NA	Diabetes, HTN
30	Diabetes, Steroid for COVID-19	Yes- IV dexamethasone, oral prednisolone	NA	Diabetes, HTN, CAD
14	Uncontrolled diabetes, Steroid for COVID-19	Yes- oral prednisolone	NA	Diabetes
42	Uncontrolled diabetes, Steroid for COVID-19	Yes- IV dexamethasone	NA	Diabetes, HTN
3	Uncontrolled diabetes, Steroid for COVID-19	Yes- IV dexamethasone	NA	Diabetes, CAD
NA	Diabetes (*n* = 1), DKA (*n* = 9), steroid for COVID-19 (*n* = 10)	Yes- IV dexamethasone (*n* = 10)	MV (*n* = 9)	Diabetes (*n* = 10)
NA	Uncontrolled diabetes (*n* = 15)	Yes (*n* = 15)	NA	Diabetes (*n* = 15) Died (*n* = 6)
21	Glucocorticoid-induced diabetes, Steroid for COVID-19	Yes	NA	No
15	Steroid for COVID-19	Yes- IV dexamethasone	NA	No
7	Diabetes, Steroid for COVID-19	Yes- IV dexamethasone	NIV	Diabetes
2	DKA	No	NA	Diabetes, Asthma, HTN
7	Uncontrolled diabetes, Steroid for COVID-19	Yes- IV dexamethasone	MV	Diabetes, Asthma, HTN, Hyperlipidaemia
6	Diabetes, Steroid for COVID-19	Yes-IV dexamethasone	MV	Diabetes
NA	Steroid for COVID-19	Yes	MV	Pancreatitis
1	DKA	NA	MV	Obesity, Diabetes

time, eight patients (53%) had blind frozen eye without exenteration, one patient had frozen seeing eye, and one patient showed improvement of eye symptoms. The all-cause 30 days of mortality was 47%. No patient died secondary to known COVID-19 problems.

4 | DISCUSSION

Recent reports indicate the association between COVID-19 and mucormycosis. However, the frequency of COVID-19-associated aspergillosis and candidiasis as the most frequent fungal complications in hospitalised COVID-19 patients has been highlighted in previous studies.[2,3] In our previous investigation, 5% of COVID-19 patients with a history of corticosteroid treatment (47%) and broad-spectrum antibiotics (92%) developed oropharyngeal candidiasis during hospital admission.[3] White et al. rated invasive fungal infections (IFIs) in 135 COVID-19 patients. They found a 26.7% incidence of IFIs (commonly aspergillosis (14.1%), or yeast infection, majorly candidiasis (12.6%) among their patients; nonetheless, no case of mucormycosis in their subjects was detected. Corticosteroid

therapy and a history of chronic pulmonary disease were the most frequent IFI-associated risk factors.[17] In this study, we tried to report a series of histology-proven mucormycosis cases with recent history of COVID-19. Our study highlights that SARS-CoV-2 infection and its related medication may be risk factors for mucormycosis and emphasized the need to monitor high-risk COVID-19 patients.[6] The mean interval time between COVID-19 and mucormycosis was seven days (range: 1–37 days). Consistent with our observation, the mean interval time between diagnosis of COVID-19 and clinical presentations of oropharyngeal candidiasis and pulmonary aspergillosis was 8 and 11 days, respectively.[3,18] Similarly, the result of our literature review of 42 COVID-19-associated ROM and ROCM cases demonstrated that mucormycosis was clinically diagnosed at a mean of 12.6 days (range = 0–42 days) after COVID-19 diagnosis[19] (Table 4). Therefore, based on the available information, it seems that clinicians should be aware of the possible occurrence of mucormycosis during the first to the second week of COVID-19 in high-risk patients.[6,18] Although the immune responses alleviated and COVID-19-associated cytokine storm will be controlled ensuing corticosteroid usage, neutrophil immigration to mucosal surfaces including sinus surfaces will be impaired and vulnerability for developing secondary infections like mucormycosis will be simultaneously increased particularly in patients with DM.[6,20] Overall, 47% of our CAM cases were receiving IV corticosteroid for COVID-19 treatment. Similarly, 40%-66% of COVID-19-associated aspergillosis and 47% of COVID-19-associated oropharyngeal candidiasis had a history of steroid therapy.[2,3] Of 42 COVID-19-associated ROM and rhino-orbito-cerebral mucormycosis (ROCM) previously reported cases, 36 cases (85.7%) had a history of systemic corticosteroid treatment prior to mucormycosis diagnosis (Table 4). Comparatively, Hoenigl et al.[19] found that 75% of 80 COVID-19 patients with mucormycosis had been treated with systemic corticosteroids which in 80% of them, systemic corticosteroids had been started prior to the diagnosis of mucormycosis that supports our finding. It seems reasonable to apply systemic corticosteroids cautiously in patients with COVID-19.[6] As evidenced previously, uncontrolled DM documented as the prevailing risk factor implicated in mucormycosis development.[21,22] In our study, 87% of CAM cases had poorly controlled DM and one patient had DKA when mucormycosis diagnosed. The data were found to be consistent with the findings of our literature review regarding COVID-19-associated ROM and ROCM (38/42, 90%) (Table 4) and Hoenigl et al's review (66/80, 82.5%).[19] Geographically, diabetes was even more frequently observed as risk factor in cases from India (32/34, 94%) and USA (3/3, 100%) vs 3/5 (60%) among COVID-19-associated ROM and ROCM cases reported from other countries (Table 4). Not only the combination of corticosteroid therapy and diabetes mellitus can result in poorly controlled status of diabetes and synergistically paralyse the function of innate immunity but also corticosteroid-induced diabetes may occurr in healthy individuals who are receiving long term steroid therapy, thereby augmenting the risk of mucormycosis in a susceptible individual.[6] Meanwhile, it is supposed that ketosis or ketoacidosis and induced diabetic ketoacidosis may be caused by COVID-19 in those with diabetes.[23,24] In addition, the possible role of blood acidosis in a severe form of COVID-19 and elevated levels of serum ferritin cannot be ignored for mucormycosis susceptibility.[4,6,20] The presence of DM along with other COVID-19-associated medications and complications could be important risk factors for mucormycosis. Two of our subjects (13.3%) were undergoing chemotherapy due to acute myeloid leukaemia (AML) and had profound neutropenia (<100 cells/mm^3). Regardless of COVID-19 status and receiving corticosteroids, as affirmed by our data, patients with profound neutropenia and those suffering from acute haematological malignancies (HMs) are at high risk to develop mucormycosis.[20] Besides, Hoenigl et al. equally noted that 5/80 patients (6.2%) were suffering from HMs. However, none of 42 COVID-19-associated ROM and ROCM previously reported cases were suffering from either neutropenia or HM (Table 4). Although ROCM is the commonest manifestation of mucormycosis in patients with poorly controlled diabetes, the lung is the more frequent site of involvement in patients with HMs.[21,25] The early manifestation of mucormycosis in 73% of our patients was orbital apex syndrome. This shows a rapid progression of the disease to orbit at presentation. Nonetheless, no case of ROCM was observed in our investigation that was not in agreement with the observation of Hoenigl et al.[19] reporting rhino-orbital-cerebral infection as the most commonly presented form of mucormycosis in COVID-19 patients (59/80, 74%). In the present study, despite antifungal treatment and surgical measures, the mortality rate was as high as 47%. Given the acuteness and aggressiveness of the infection, a timely diagnosis for prompt antifungal therapy is highly recommended in order to decrease the rate of mortality.[24] Interestingly, 100% of our patients who received combined antifungal treatment survived (Appendix 1). More so, 75% of 8 COVID-19-associated ROM and ROCM previously reported cases who received combined antifungal treatment survived (Table 4). Combined antifungal treatment may be associated with improved response and a higher rate of survival (p-value: .003). Limitations of this study include limited sample size preventing a subgroup analysis, absence of a control group for comparing clinical, imaging features, therapeutic interventions, comparison of all COVID-19 clinical and laboratory factors between those affected and not affected by mucormycosis. The role of combined antifungal treatment and the effect of disease stage on prognosis is the subject of future studies.

In conclusion, the findings of this study showed that clinicians should be more alert about mucormycosis especially during the first to second week after COVID-19 in diabetic and immunocompromised patients. Poor control of DM seems to be important predisposing factor.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Farzad Pakdel : Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (lead); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Kazem Ahmadikia:** Data curation (equal); Methodology (equal); Resources (equal); Software (equal); Writing-original draft (equal); Writing-review & editing (equal). **Mohammadreza Salehi:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Azin Tabari:** Investigation (equal); Methodology (equal); Resources (equal); Visualization (equal). **Rozita Jafari:** Investigation (equal); Resources (equal); Visualization (equal); Writing-review & editing (equal). **Golfam Mehrparvar:** Investigation (equal); Software (equal); Visualization (equal); Writing-review & editing (equal). **Yasaman Rezaie:** Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal); Software (equal); Writing-original draft (equal). **Shahin Rajaeih:** Investigation (equal); Methodology (equal); Resources (equal). **Neda Alijani:** Investigation (equal); Methodology (equal); Resources (equal). **Aleksandra Barac:** Validation (equal); Writing-review & editing (equal). **Alireza Abdollahi:** Investigation (equal); Methodology (equal); Resources (equal). **sadegh Khodavaisy:** Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal).

ETHICAL APPROVAL

This study approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.VCR.REC.1399.152). To ensure anonymity, details that might disclose the identity of the subject under the study were not included. Written informed consent was obtained from the patient prior to being included in the study.

CODE AVAILABILITY

All data were analysed using SPSS Statistics (Version 19.0, IBM Corp.).

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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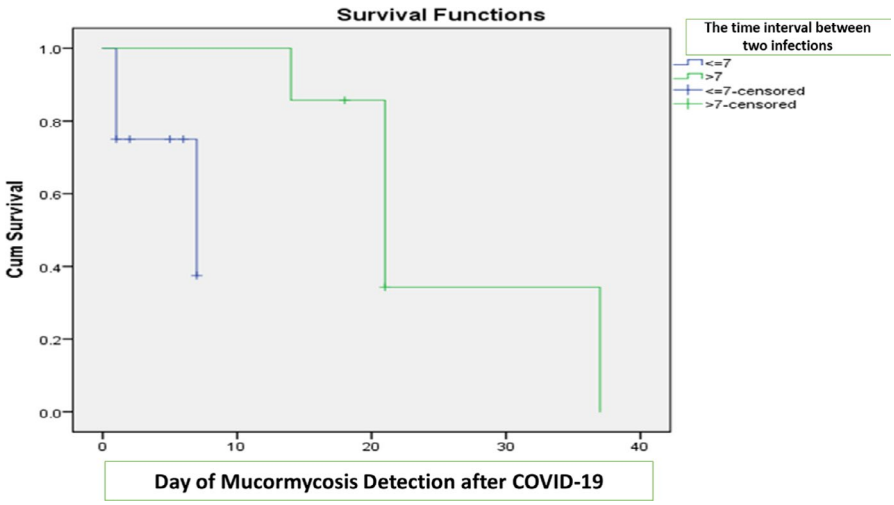
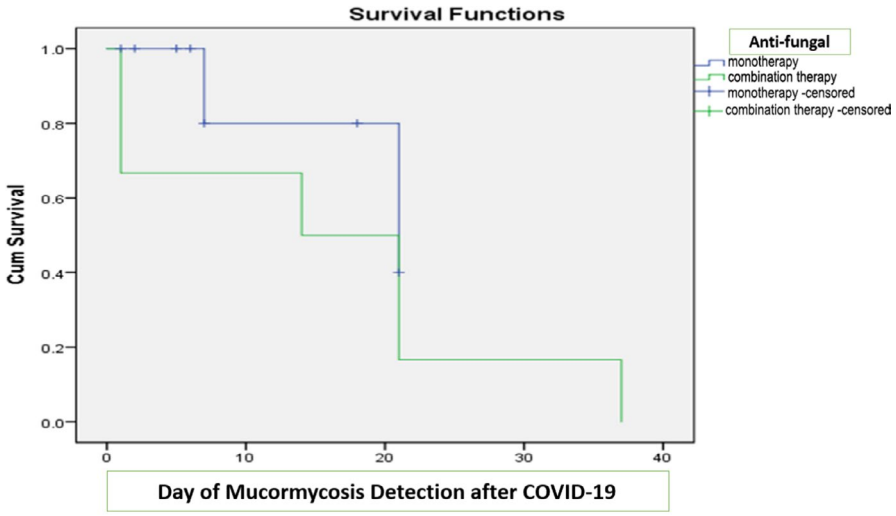
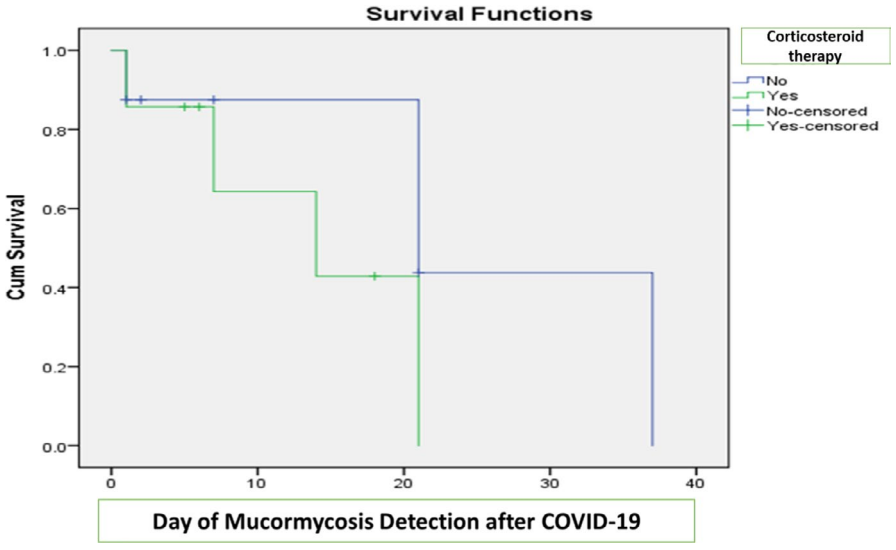
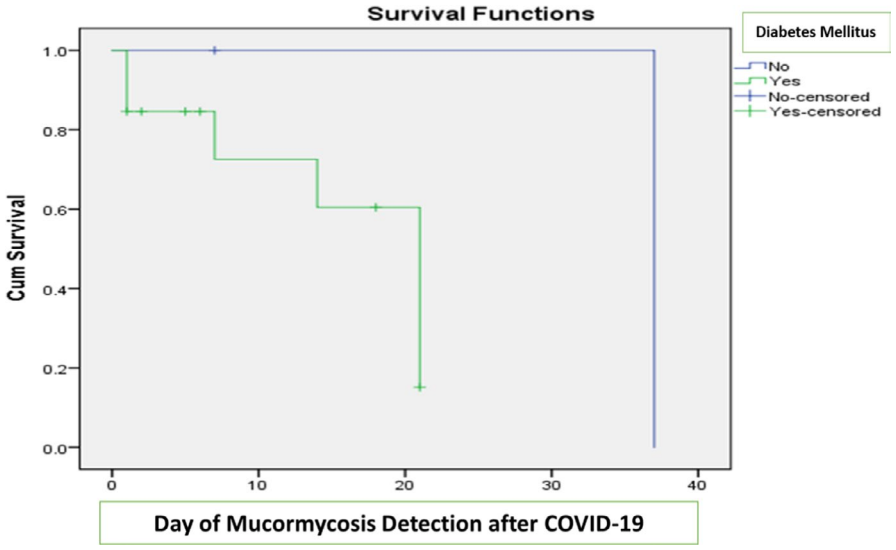
APPENDIX 1

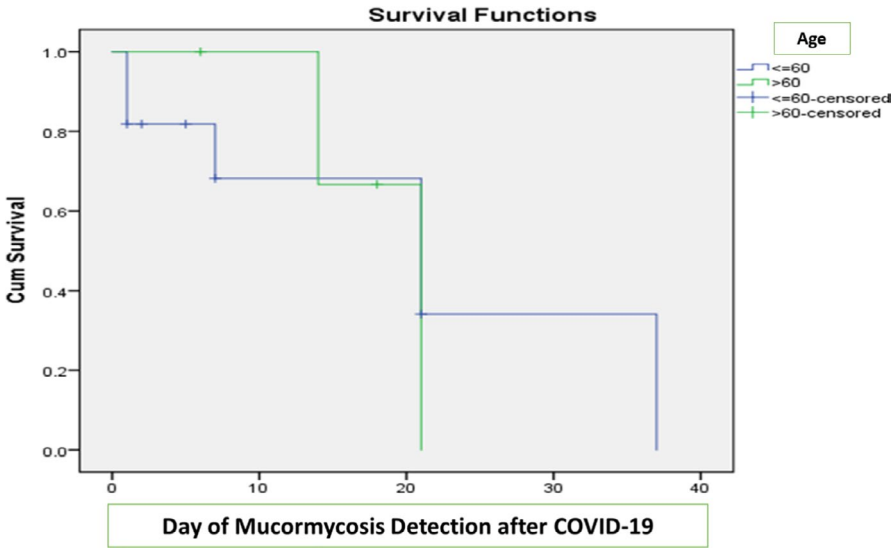
Kaplan-Meier curves for survivors




Survival Functions
Anti-fungal
monotherapy
combination therapy
monotherapy -censored
combination therapy -censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Day of Mucormycosis Detection after COVID-19


Survival Functions
Corticosteroid therapy
No
Yes
No-censored
Yes-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Day of Mucormycosis Detection after COVID-19


Survival Functions
Diabetes Mellitus
No
Yes
No-censored
Yes-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Day of Mucormycosis Detection after COVID-19


Survival Functions
Age
<=60
>60
<=60-censored
>60-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Day of Mucormycosis Detection after COVID-19