ORIGINAL ARTICLE

Risk factors affecting outcome of rhino-orbital-cerebral mucormycosis in COVID-19 patients

Mina Fayez Saleeb*[ORCID], Sabry Magdy Sabry, Mohammad Salah Mahmoud and Mena Maher Nassif

Abstract

Background Mucormycosis is a serious life-threatening fungal infection that recently made severe sudden and devastating surge during the second wave of the COVID-19 epidemic with a mortality rate of up to 50%.

Although the causality link between COVID-19 and rhino-orbito-cerebral mucormycosis (ROCM) remains unclear, many factors including poor diabetes control, high doses of steroids, viral-induced lymphopenia, and cytokine storm have been attributed to ROCM in patients with COVID-19.

Orienting to risk factors and early recognition of this potentially fatal opportunistic infection is the key to optimal management and improved outcomes. In these contexts, we conducted a prospective study for 33 patients admitted to our tertiary hospital to determine the risk factors for ROCM in patients with COVID-19 and the cumulative mortality rates.

Results This study found a statistically significant relation between the fate of death in COVID-MUCOR patients who had presented fever, ophthalmoplegia, facial skin necrosis, and visual loss with those who received dose of steroid to control their respiratory symptoms $P < 0.001$.

Death from COVID-MUCOR was statistically significant related to the prolonged interval from the onset of the symptoms to start of treatment and intervention. Also, it was found that there was a significant decrease in duration between COVID-19 infection and the start of mucormycosis (days) with incidence of DKA on admission. Nineteen (57.6%) of the patients had uncontrolled diabetes mellitus (hemoglobin A1C (HbA1c) of > 7.0%).

Conclusion Mucormycosis epidemic was precipitated by a unique confluence of risk factors: diabetes mellitus, widespread use of steroids, and perhaps SARS-CoV-2 infection itself. Restricting steroid use in patients with severe COVID-19 requiring oxygen therapy, and screening for and optimally controlling hyperglycemia, can prevent COVID-MUCOR in a large majority.

Keywords Rhino-orbito-cerebral mucormycosis, COVID-19, Uncontrolled diabetes mellitus, Invasive fungal infection, Steroids

Background

The 2019 coronavirus disease pandemic (COVID-19) has a catastrophic impact throughout the world and has overwhelmed healthcare facilities and caused dramatic increases in excess mortality. Secondary bacterial and fungal infections in patients hospitalized with COVID-19 pneumonia contribute to increased morbidity and mortality. Opportunistic infections, such as mucormycosis, in

*Correspondence:
Mina Fayez Saleeb
minafayezw@gmail.com
Department of Otolaryngology, Faculty of Medicine, Ain Shams
University, Cairo, Egypt

Saleeb *et al. The Egyptian Journal of Otolaryngology*   (2023) 39:95

Page 2 of 12

patients with coronavirus disease 2019 (COVID-19) have become a new health challenge [1].

The surge in COVID-19 cases recorded in Egypt has been associated with an unexpected increase in mucormycosis cases reported in the context of the COVID-19 disease. It has been estimated to be 2.1 times greater in cases in India compared to the pre-pandemic period [2].

The clinical course of mucormycosis is unpredictable, and treatment is challenging and often requires surgery and prolonged antifungal therapy. Mucormycosis is often associated with high mortality even with standard care (approximately 50% and > 90% with disseminated disease) due to the angioinvasive nature of infection that can cause tissue necrosis due to thrombosis and infection dissemination [3].

Since opportunistic infections can exacerbate the status of COVID-19 patients, it is important to identify risk factors to prevent, diagnose, and treat them as soon as possible. Viral, fungal, environmental, and host factors may be responsible for this situation. Long hospital stays, impaired host immune system function due to viral infection, and excessive glucocorticoids consumption in the management of patients with COVID-19 are the main risk factors for the increased risk of mucormycosis in patients with COVID-19 [4].

Other risk factors include comorbidities such as diabetes mellitus, organ transplantation, malignancies (especially hematological), immunosuppressive therapy including corticosteroids, prolonged neutropenia, iron overload, chronic antibiotic use, severe burns, intravenous drug abuse, and malnutrition, leading to immunocompromise [5].

Aim of work

The purpose of this study is to identify risk factors for the incidence of mucormycosis in COVID-19 patients and correlate the extent of the disease, the condition of the patients, and the intervention plan with the final outcome of the cases.

Methods

A prospective study involved all patients with mucormycosis presented to the ENT department, Ain Shams University Hospital (Demerdash and Obour Hospitals), in the duration from January 2021 to January 2022.

This study was approved by Ain Shams University Faculty of Medicine Research Ethics Committee (REC) FWA 00017585. Informed written consent to participate in the study was provided by all.

- Detailed history taking of the disease, possible risk factors, and cognitive status

- Full examination including nasal, oral, orbital, and neurological examination
- CT paranasal to assess extension of the disease
- COVID-19 PCR by nasopharyngeal swab to confirm the diagnosis of COVID-19
- Full laboratory investigations
- Management of each case individually as follows: either use of antifungal or surgical debridement with or without exenteration or combination of both
- Statistical analysis was performed for all recorded data. Categorical variables are presented as numbers and percentages, and differences between groups are compared using the Pearson chi-square test or Fisher's exact test.
- Time-to-event analysis is done using the Kaplan-Meier method.

Results

The study enrolled 33 patients with COVID and mucormycosis (CO-MUCOR). Although the median age of the entire series was 54 years, the ages of the cases ranged widely from 32 to 82 years in the entire analyzed group, with a slight male predominance (51.5% were men, and 48.5% were women), and all the women were housewives. Thirty (90.9%) of the patients were diabetic, either previously known (28 patients) or newly diagnosed (2 patients) (Figs. 1 & 2).

The demographic characteristics of the patients are shown in Table 1. Fasting blood sugar was markedly elevated, and about 26.7% of the patients had coexisting diabetic ketoacidosis on admission. Details are presented in the documentation (Table 1).

Nineteen (57.6%) of the patients had uncontrolled diabetes mellitus (hemoglobin A1C (HbA1c) of > 7.0%).

Regarding symptoms, most of patients (69.7%) with COVID-MUCOR had headache, facial pain, and orbital swelling. About half of the patients firstly presented with eye swelling (55.5%) or had ophthalmoplegia (54.5%) and visual loss (48.5%) (Table 2).

On examination, most patients (87.9%) with COVID-MUCOR had intranasal necrosis, and more than half (57.6%) had palatal necrosis (Table 2).

A total of 66.7% of CO-MUCOR patients had previously known COVID, and the median CT CO-RAD score in patients with COVID-MUCOR in this study was 3, and the median duration between COVID-19 infection and the start of mucormycosis was 30 days (Table 3).

Steroid use was common, even in mild disease, and was strongly associated with COVID-MUCOR ($P <$ 0.001). In the majority (88%, 29 patients) of the study, patients had received high-dose steroids (> 40 mg of prednisolone or equivalent) for the management of
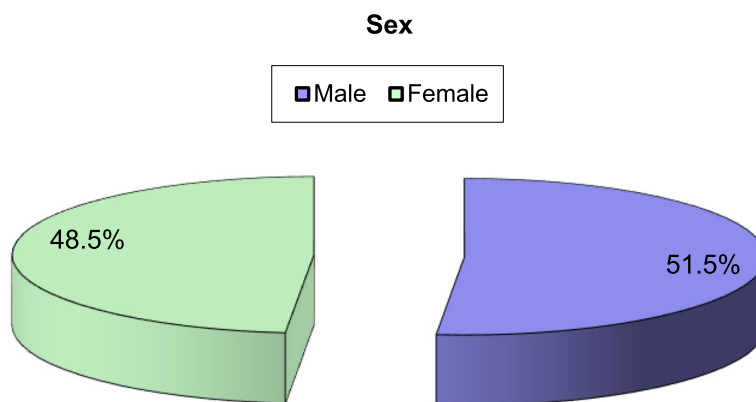
Sex

Fig. 1 Percentage of female and male patients included in the study
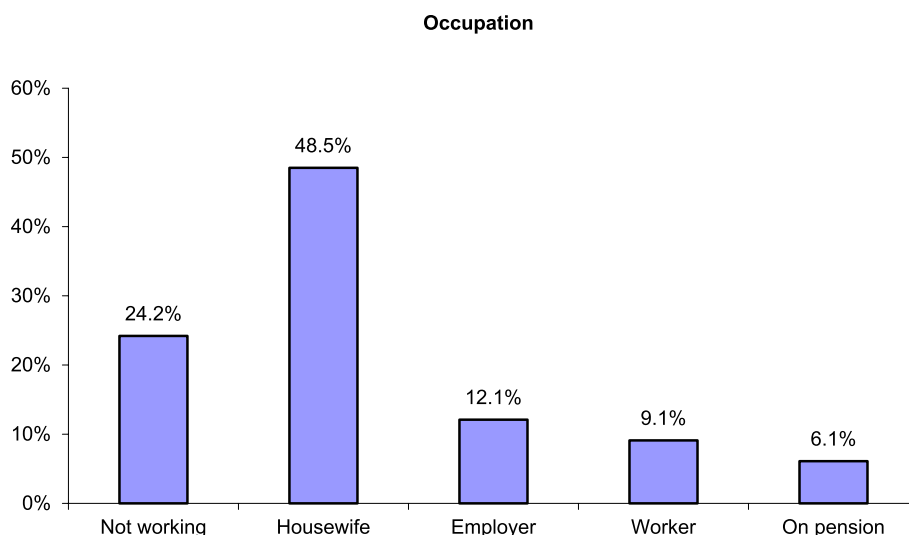
Occupation

Fig. 2 Distribution of occupations of patients included in the study

COVID-19. Only 18.2% had received anti-IL-6 actemra (tocilizumab) or antiviral (remdesivir) (Table 4).

Regarding sinus affection in CT scan, pansinusitis was the most common involvement followed by the left ethmoid sinus (27 patients, 81.8%), followed by the left maxillary sinus (26 patients, 78.8), and followed by the Lt sphenoid sinus (24 patients, 72.7%). A total of 57.6% of patients with CO-MUCOR had unilateral sinus affection (Table 3).

In our study, all patients received systemic antifungal therapy (amphoterecin B). About two-thirds of the patients (24 patients, 72.7%) underwent endoscopic sinus surgery for mucormycosis, 7 patients (21.2%) underwent combined (endoscopic & external) management, and only 2 patients (6.1%) were managed by external approach to the paranasal sinuses.

Repeated surgical intervention was needed in some cases, 8 patients (25.0%) underwent two surgeries, and 1 (3.6%) patient underwent 3 surgical interventions. During sinus surgery (ESS), most of included patients needed inferior turbinectomy (97.0%), middle turbinectomy (93.9%), middle meatal antrostomy (97.0%), and ethmoidectomy (93.9%). Nine of the patients had died during the study period (Table 5).

In the current study, we found that there was a significant decrease in duration between COVID-19 infection and the start of mucormycosis (days) with incidence of DKA on admission with median (IQR) = (14 (14–23) vs. 40 (25–75)) and P-value = 0.018.

In addition, a significant decrease in duration between −19 infection and the start of mucormycosis was observed in patients with facial swelling (P-value 0.043)

Saleeb *et al. The Egyptian Journal of Otolaryngology*   (2023) 39:95

Page 4 of 12

Table 1 The demographic characteristics of the patients

		Total no. = 33
Age		
	Mean ± SD	54.27 ± 12.73
	Range	32–82
Sex		
	Male	17 (51.5%)
	Female	16 (48.5%)
Occupation		
	Not working	8 (24.2%)
	Housewife	16 (48.5%)
	Employer	4 (12.1%)
	Worker	3 (9.1%)
	On pension	2 (6.1%)
Smoking		8 (24.2%)
Diabetes		30 (90.9%)
Controlled		11 (36.7%)
Uncontrolled		19 (57.6%)
Newly diagnosed		2 (6.7%)
DKA on admission		8 (26.7%)
Immunosuppressive drugs		0 (0.0%)
Chronic liver disease		1 (3.0%)
Chronic kidney disease		1 (3.0%)
Hematologic malignancy		0 (0.0%)
Prolonged antibiotic or antiviral therapy		9 (27.3%)
Autoimmune disease		1 (3.0%)
Prolonged steroid use		29 (88%)
Chemotherapy		0 (0.0%)
Thrombocytopenia		2 (6.1%)

Table 2 Symptomatology at presentation

		Total no. = 33
Fever		14 (42.4%)
Facial numbness		20 (60.6%)
Facial swelling		19 (57.6%)
Headache		23 (69.7%)
Facial pain		23 (69.7%)
Rhinorrhea, blood stained		11 (33.3%)
Orbital swelling		23 (69.7%)
Ophthalmoplegia		18 (54.5%)
Visual loss		16 (48.5%)
Disturbed conscious		8 (24.2%)
Motor or sensory weakness (stroke)		6 (18.2%)
First presentation		
	Eye swelling	5 (55.6%)
	Disturbed conscious	3 (33.3%)
	Facial swelling	1 (11.1%)
Intranasal necrosis		29 (87.9%)
Palatal necrosis		19 (57.6%)
Ophthalmoplegia		18 (54.5%)
Proptosis		13 (39.4%)
Visual loss		16 (48.5%)
Cavernous sinus thrombosis		18 (54.5%)
Facial skin necrosis		2 (6.1%)
Cranial nerves involvement		
	Negative	27 (81.8%)
	Facial	6 (18.2%)

and proptosis (*P*-value 0.046) (Tables 5 & 6) and in those who received prolonged antibiotic or antiviral therapy (*P*-value 0.011) (Tables 6, 7, & 8).

All patients who died were diabetics, and nearly two-thirds had coexisting ketoacidosis on admission. Therefore, we found a highly statistically significant relation between the presence of diabetic ketoacidosis (DKA) and then aggressiveness of mucormycosis that ends in death in patients with COVID with *P*-value = 0.001 (Table 9, Fig. 3).

Also, we found a statistically significant increase in the probability of death in those who had received prolonged high steroid use during COVID management (Table 9).

In the present study, all patients who had facial skin necrosis died. And most of patients (8 out of 9) who died had orbital swelling ophthalmoplegia and intranasal necrosis (88.9% for each). Most of the dead (7 of 9) had fever, headache, facial pain, visual loss, and cavernous sinus thrombosis (77.8% for each).

After statistical analysis, we found a statistically significant relation between the fate of death in

Table 3 Radiological score

		Total no. = 33
CT PNS		
	Rt max. S	16 (48.5%)
	Lt max. S	26 (78.8%)
	Rt ethmoid	20 (60.6%)
	Lt ethmoids	27 (81.8%)
	Rt sphenoid	19 (57.6%)
	Lt sphenoid	24 (72.7%)
	Rt frontal	13 (39.4%)
	Lt frontal	15 (45.5%)
	Bony erosions	17 (51.5%)
	Bilateral involvement	14 (42.4%)
COVID status		
	Previous COVID	22 (66.7%)
	PCR at presentation	6 (18.2%)
CT CO-RAD score		
	Median (IQR)	3 (1–4)
	Range	1–5

Table 4 Previous medication during COVID treatment period

Duration between COVID-19 infection and start of mucormycosis	
Median (IQR)	30 (21–60)
Range	7–90
Steroids dose	29 (88%)
Anti-IL-6 actemra (tocilizumab)	6 (18.2%)
Antiviral (remdesivir)	6 (18.2%)

Table 5 Extent of intervention done and fate

	Total no. = 33
Interval from symptom onset to treatment	
Median (IQR)	7 (4–10)
Range	1–63
Endoscopic treatment	24 (72.7%)
Combined (endoscopic and external)	7 (21.2%)
External	2 (6.1%)
Total no. of surgical procedures	
0	2 (7.1%)
1	18 (64.3%)
2	7 (25.0%)
3	1 (3.6%)
Inf. turb.	32 (97.0%)
Middle turb.	31 (93.9%)
MMA	32 (97.0%)
Septectomy	17 (51.5%)
Palatal debrid.	3 (9.1%)
Ethmoidectomy	31 (93.9%)
Sphenoidotomy	25 (75.8%)
Death	9 (27.3%)
Onset of death or discharge (days)	
Median (IQR)	30 (14–30)
Range	5–90

COVID-MUCOR patients who had presented fever, ophthalmoplegia, facial skin necrosis, and visual loss (with *P*-value of 0.012, 0.015, 0.017, and 0.039, respectively) (Table 10) and with those who received dose of steroid control their respiratory symptoms $P < 0.001$ (Table 11, Fig. 4).

Death from COVID-MUCOR was statistically significant related to the prolonged interval from the onset of the symptoms to the start of treatment and intervention (Tables 12 & 13).

DiscussionMucormycosis is a sporadic disease that occurs almost exclusively in immunosuppressed patients. The sudden spike in the incidence of mucormycosis in the COVID-19 pandemic raises the possibility that COVID-19 infection may itself predispose

Table 6 Duration between COVID-19 infection and start of mucormycosis

	Duration between COVID-19 infection and start of mucormycosis (days)		Test value	*p*-value	Sig.
	Median (IQR)	**Range**			
Sex					
Male	30 (21–60)	14–90	−0.298[a]	0.765	NS
Female	30 (20–45)	7–90			
Occupation					
Not working	30 (25–40)	21–0	1.124[b]	0.891	NS
Housewife	30 (20–45)	7–90			
Employer	21 (14–90)	14–90			
Worker	37 (14–60)	14–60			
On pension	60 (60–60)	60–60			
Smoking					
No	30 (20–60)	7–90	−0.213[a]	0.832	NS
Yes	25 (21–60)	14–80			
Diabetes					
No	25.5 (21–30)	21–30	−0.517[a]	0.605	NS
Yes	30 (20.5–60)	7–90			
Controlled					
No	40 (14–60)	7–80	−0.305[a]	0.760	NS
Yes	30 (21–60)	14–90			
Newly diagnosed					
No	30 (21–60)	7–90	−0.958[a]	0.338	NS
Yes	20 (20–20)	20–20			
DKA on admission					
No	40 (25–75)	14–90	−2.367[a]	**0.018**	S
Yes	14 (14–20)	7–45			
Prolonged antibiotic or antiviral therapy					
No	42.5 (30–60)	14–90	−2.540[a]	**0.011**	S
Yes	20.5 (14–23)	7–80			
Prolonged steroid use					
No	30 (21–60)	7–90	−0.714[a]	0.476	NS
Yes	21 (21–21)	21–21			
Fever					
No	30 (21–67.5)	7–90	−1.001[a]	0.317	NS
Yes	25 (14–45)	14–60			
Facial numbness					
No	27.5 (21–30)	14–90	−0.398[a]	0.691	NS
Yes	42.5 (17–60)	7–90			
Facial swelling					
No	37.5 (27.5–67.5)	21–90	−2.023[a]	**0.043**	S
Yes	20.5 (14–40)	7–90			
Headache					
No	30 (25–80)	21–90	−0.993[a]	0.321	NS
Yes	30 (14–60)	7–90			
Facial pain					
No	30 (25–80)	21–90	−0.853[a]	0.394	NS
Yes	30 (17–52.5)	7–90			

Saleeb *et al. The Egyptian Journal of Otolaryngology*   (2023) 39:95

Page 6 of 12

Table 6 (continued)

	Duration between COVID-19 infection and start of mucormycosis (days)		Test value	*p*-value	Sig.
	Median (IQR)	Range			
Rhinorrhea, blood stained					
No	21 (14–75)	7–90	−1.418[a]	0.156	NS
Yes	45 (30–60)	25–60			
Orbital swelling					
No	50 (25.5–85)	14–90	−1.648[a]	0.099	NS
Yes	27.5 (20–45)	7–75			
Ophthalmoplegia					
No	30 (21–60)	7–90	−0.429[a]	0.668	NS
Yes	30 (20–60)	14–80			

P-value > 0.05, nonsignificant; *P*-value < 0.05, significant; *P*-value < 0.01, highly significant

The previous table shows that there was significant decrease in duration (days) with incidence of DKA on admission with median (IQR) = (14 (14–23) vs 40 (25–75)) and *P*-value = 0.018

[a] Mann-Whitney test

[b] Kruskal-Wallis test

to mucormycosis. This may occur directly through its impact on the immune system or indirectly due to interventions related to COVID-19 prevention and management [6].

It should be mentioned that our current understanding of the link between COVID-19 and mucormycosis is incomplete, based on observational analyses, and invalidated by basic experimentation. A link between both infections could be through the biochemical alterations caused by the viral infection, and DM and corticosteroid therapy just contribute to such alteration [7].

We report on the experience from Egypt where we studied a total of 33 patients with COVID and mucormycosis (CO-MUCOR) in Ain Shams University Hospitals during the third pandemic wave in the country that spanned the summer of 2021.

Most of the CO-MUCOR cases globally reported so far is from the Indian population. However, the burden of mucormycosis in the Indian population was high before the beginning of the COVID-19 pandemic. The country has also further experienced a surge in COVID-19 cases during the second wave, probably relating to prevalent strain variants [8].

The largest national-wide survey of CO-MUCOR to date is the collaborative OPAI-IJO study on mucormycosis in COVID-19 (COSMIC), by Sen et al. in 2021, which analyzed the data of 2826 patients who presented from the start of the pandemic January 2020 until May 2021. DM was present in 78% of the patients, and 87% had received corticosteroids for COVID-19,

Table 7 Duration between covidCOVID-19 infection and start of mucormycosis

	Duration between COVID-19 infection and start of mucormycosis		Test value	*p*-value	Sig.
	Median (IQR)	Range			
Visual loss					
No	30 (21–45)	7–90	−0.134[a]	0.893	NS
Yes	30 (21–60)	14–80			
Disturbed conscious					
No	30 (25–60)	7–90	−1.892[a]	0.059	NS
Yes	20 (14–21)	14–45			
Motor or sensory weakness (stroke)					
No	30 (25–60)	7–90	−1.222[a]	0.222	NS
Yes	21 (20–21)	14–80			
First presentation					
Eye swelling	27.5 (23–30)	21–30	4.909[b]	0.086	NS
Disturbed conscious	17 (14–20)	14–20			
Facial swelling	40 (40–40)	40–40			
Intranasal necrosis					
No	20 (20–20)	20–20	−1.031[a]	0.303	NS
Yes	30 (21–60)	7–90			
Palatal necrosis					
No	37.5 (25–82.5)	14–90	−1.133[a]	0.257	NS
Yes	27.5 (21–45)	7–80			
Ophthalmoplegia					
No	30 (20–60)	7–90	−0.165[a]	0.869	NS
Yes	30 (21–60)	14–80			
Proptosis					
No	42.5 (30–75)	7–90	−1.991[a]	**0.046**	S
Yes	21 (17–27.5)	14–60			
Visual loss					
No	30 (21–45)	7–90	−0.134[a]	0.893	NS
Yes	30 (21–60)	14–80			
Cavernous sinus thrombosis					
No	30 (25–60)	14–90	−1.123[a]	0.261	NS
Yes	21 (14–60)	7–80			
Facial skin necrosis					
No	30 (21–60)	7–90	−1.348[a]	0.178	NS
Yes	14 (14–14)	14–14			
Cranial nerves involvement					
Negative	30 (21–45)	14–90	−0.128[a]	0.898	NS
Facial	40.5 (14–67.5)	7–75			

P-value > 0.05, nonsignificant; *P*-value < 0.05, significant; *P*-value < 0.01, highly significant

[a] Mann-Whitney test

[b] Kruskal-Wallis test

Saleeb *et al. The Egyptian Journal of Otolaryngology*   (2023) 39:95

Page 7 of 12

Table 8 Duration between covidCOVID-19 infection and start of mucormycosis

	Duration between COVID-19 infection and start of mucormycosis		Test value	*p*-value	Sig.
	Median (IQR)	Range			
Total no. of surgical procedures					
1	27.5 (17–57.5)	14–90	0.078[b]	0.962	NS
2	25.5 (21–60)	7–90			
3	30 (30–30)	30–30			
Septectomy					
No	23 (14–60)	7–90	−0.995[a]	0.320	NS
Yes	30 (25.5–60)	14–90			
Palatal debrid					
No	30 (20.5–52.5)	7–90	−0.632[a]	0.527	NS
Yes	55.5 (21–90)	21–90			
Sphenoidotomy					
No	14 (10.5–22)	7–30	−2.355[a]	**0.019**	S
Yes	35 (21–60)	14–90			
Death					
No	30 (21–60)	7–90	−0.355[a]	0.723	NS
Yes	30 (14–45)	14–80			

P-value > 0.05, nonsignificant; *P*-value < 0.05, significant; *P*-value < 0.01, highly significant

[a] Mann-Whitney test

[b] Kruskal-Wallis test

suggesting that both factors are the most important predisposing factors for CO-MUCOR. This is in line with the findings of our study, in which 90.9% of the patients had DM and 88% had a history of corticosteroid treatment [9].

The prevalence of diabetes in CO-MUCOR in our study was higher than historical cohorts of mucormycosis (Binder et al., 2014) not associated with COVID (90.9% vs. 76%). Newly detected diabetes is reportedly less prevalent in CO-MUCOR compared to mucormycosis not associated with COVID-19 (6% versus 10%). This disagreed with Arora et al. in 2022 who performed a case-control study of 352 patients (152 cases and 200 controls) diagnosed with COVID-19, and they found that newly detected diabetes was much higher in CO-MUCOR patients (20%) [6, 10].

Diabetic ketoacidosis is detected in 26.7% of patients with mucormycosis at presentation, which is a rare occurrence in the natural history of type 2 diabetes; otherwise [11], this agrees with Arora et al. (2022) who observed the appearance of DKA in 22% of CO-MUCOR at presentation [6]. However, DKA was previously identified to be uncommon among CO-MUCOR compared to mucormycosis not associated with COVID-19 (8.6%) in the study of Patel et al. in 2021 [2].

Reports of CO-MUCOR outside the Indian population are scarce, most of which are case reports (Hussain et al., 2021) [12]. In Iran, two cross-sectional studies in 2021 from Tehran by Pakdel et al. and West Iran by Avatef Fazeli et al. have reported on 15 and 12 cases of CO-MUCOR of which 86% and 87.3% had DM, with a mortality rate of 47% and 66.6%, respectively. These two studies agree with our study in percent of diabetics, but they reported a markedly higher mortality rate that may be due to smaller sample size than our current study [13, 14].

Our study also agrees with a series of 10 cases with CO-MUCOR reported in Pakistan by Nasir et al. in 2021 of which 70% were diabetic and 80% had received corticosteroids [15].

In contrast to our study, Rabagliati et al. in 2021 had reported 16 cases from Chile, 15 of which had received corticosteroids, but only 4 (25%) were diabetic, and none was immunocompromised, suggesting different predisposing factors within different settings [16].

In Egypt, Fouad et al., in December 2021, performed a multicentric retrospective analysis of 26 patients with CO-MUCOR, 96.2% had poorly controlled diabetes mellitus, and 76.9% had received corticosteroid treatment for COVID-19. They also reported that 61.6% of CO-MUCOR patients had visual loss. These findings come in accordance of our study (90.9% DM, 88% STEROID, 48.5% presented with visual loss). But on the other hand, Fouad et al. reported a shorter median duration from COVID-19 until the onset of CO-MUCOR was 20.5 days versus 30 days in our study, and a higher mortality rate was 46.2% despite surgical debridement in half of the cases that died (27.3% in our study) [17].

In older studies in Egypt, Fouad et al., in August 2021, reported 12 cases with rhino-orbital-cerebral mucormycosis presenting to a university hospital in Cairo during the first viral pandemic wave including 6 patients with prior or concurrent COVID-19. El-Kholy et al. in 2021 had also conducted a prospective longitudinal study on invasive fungal sinusitis that spanned the duration of the second Egyptian pandemic wave at a university hospital in another governorate, Mansoura, and detected 28 cases with CO-MUCOR. Alfishawy et al., in 2021, reported 21 patients with CO-MUCOR from 11 different hospitals in Metropolitan Cairo during the third pandemic wave, of which 19 (90.5%) had DM and all had received corticosteroid treatment [18, 19].

The previous findings of our study and previous studies lead us to the conclusion that Egypt comes second to India in the number of published reports of CO-MUCOR cases. The high prevalence of DM in the country, which ranges in recent cluster analyses in different regions from 16.7% (Asaad et al., 2018)

Table 9 Comparison of demographics between patients who had an adverse outcome (death) vs. those who were alive

	Alive No. = 24	Death No. = 9	Test value	*p*-value	Sig.
Age					
Mean ± SD	54.75 ± 11.05	53.00 ± 17.18	0.347[b]	0.731	NS
Range	32–78	34–82			
Sex					
Male	13 (54.2%)	4 (44.4%)	0.248[a]	0.619	NS
Female	11 (45.8%)	5 (55.6%)			
Occupation					
Not working	7 (29.2%)	1 (11.1%)	2.855[a]	0.582	NS
Housewife	11 (45.8%)	5 (55.6%)			
Employer	2 (8.3%)	2 (22.2%)			
Worker	2 (8.3%)	1 (11.1%)			
On pension	2 (8.3%)	0 (0.0%)			
Smoking	6 (25.0%)	2 (22.2%)	0.028[a]	0.868	NS
Diabetes	21 (87.5%)	9 (100.0%)	1.238[a]	0.266	NS
Controlled	9 (42.9%)	2 (22.2%)	1.155[a]	0.282	NS
Newly diagnosed	1 (4.8%)	1 (11.1%)	0.408[a]	0.523	NS
DKA on admission	2 (9.5%)	6 (66.7%)	10.519[a]	**0.001**	HS
Immunosuppressive drugs	0 (0.0%)	0 (0.0%)			
Chronic liver disease	1 (4.2%)	0 (0.0%)	0.387[a]	0.534	NS
Chronic kidney disease	1 (4.2%)	0 (0.0%)	0.387[a]	0.534	NS
Hematologic malignancy	0 (0.0%)	0 (0.0%)	–	–	–
Prolonged antibiotic or antiviral therapy	5 (20.8%)	4 (44.4%)	1.840[a]	0.175	NS
Autoimmune disease	1 (4.2%)	0 (0.0%)	0.387[a]	0.534	NS
Prolonged steroid use	29 (88%)	0 (0.0%)	1.238[a]	0.266	NS
Chemotherapy	0 (0.0%)	0 (0.0%)	–	–	–
Thrombocytopenia	2 (8.3%)	0 (0.0%)	0.798[a]	0.372	NS

P-value > 0.05, nonsignificant; *P*-value < 0.05, significant; *P*-value < 0.01, highly significant

[a] Chi-square test

[b] Independent *t*-test
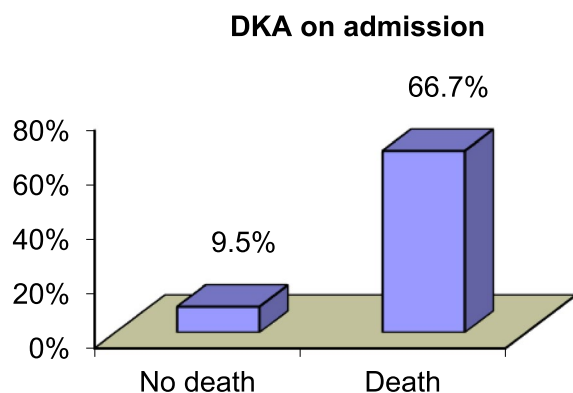
Fig. 3 Correlation between DKA and fate of the disease

to 20.9% (AlSawahli et al., 2019), could explain the burden of CO-MUCOR. Other factors noticed in our sample that can contribute to the disease load include delay in presentation (median 30 days), inadvertent use of corticosteroids in mild-moderate cases (88% of patients), and self-medication for viral infection at home instead of seeking hospital care for moderate-severe cases [20, 21].

The high surge of CO-MUCOR in diabetics and those receiving steroids can be contributed to the modulation of immune system. Neutrophils and macrophages kill sporangiospores and hyphal forms of *Mucorales* and constitute the main barrier to invasion [22].

An adaptive immune response is stimulated and characterized by strong Th-17 activation that initiates a stronger neutrophil response. Simultaneously, the immune response to COVID-19 is complex. Neutrophils in the nasopharyngeal epithelium demonstrate markers

Table 10 Comparison of clinical characteristics between patients who died vs. those who were alive

	Alive	Death	Test value	*p*-value	Sig.
	No. = 24	No. = 9			
Fever	7 (29.2%)	7 (77.8%)	6.332*	**0.012**	S
Facial numbness	15 (62.5%)	5 (55.6%)	0.132*	0.716	NS
Facial swelling	13 (54.2%)	6 (66.7%)	0.419*	0.518	NS
Headache	16 (66.7%)	7 (77.8%)	0.383*	0.536	NS
Facial pain	16 (66.7%)	7 (77.8%)	0.383*	0.536	NS
Rhinorrhea, blood stained	7 (29.2%)	4 (44.4%)	0.688*	0.407	NS
Orbital swelling	15 (62.5%)	8 (88.9%)	2.158*	0.142	NS
Ophthalmoplegia	10 (41.7%)	8 (88.9%)	5.887*	**0.015**	S
Visual loss	9 (37.5%)	7 (77.8%)	4.251*	**0.039**	S
Disturbed conscious	4 (16.7%)	4 (44.4%)	2.750*	0.097	NS
Motor or sensory weakness (stroke)	4 (16.7%)	2 (22.2%)	0.136*	0.712	NS
First presentation					
Eye swelling	5 (62.5%)	0 (0.0%)	2.250*	0.325	NS
Disturbed conscious	2 (25.0%)	1 (100.0%)			
Facial swelling	1 (12.5%)	0 (0.0%)			
Intranasal necrosis	21 (87.5%)	8 (88.9%)	0.012*	0.913	NS
Palatal necrosis	13 (54.2%)	6 (66.7%)	0.419*	0.518	NS
Proptosis	8 (33.3%)	5 (55.6%)	1.354*	0.245	NS
Cavernous sinus thrombosis	11 (45.8%)	7 (77.8%)	2.694*	0.101	NS
Facial skin necrosis	0 (0.0%)	2 (22.2%)	5.677*	**0.017**	S
Cranial nerves involvement					
Negative	18 (75.0%)	9 (100.0%)	2.750*	0.097	NS
Facial	6 (25.0%)	0 (0.0%)			

of premature activation, while adaptive immunity cells (T cells, NK cells, and B cells) are reduced in numbers [23].

These abnormalities tend to peak in the 2nd week, which may explain the clustering of CO-MUCOR cases in the 3rd week after the appearance of the COVID-19 symptoms. Furthermore, endothelial dysfunction and vasculopathy due to COVID-19 can support angioinvasion and the spread of mucorales [24, 25].

Diabetes or impaired glucose tolerance is reported in the majority of patients with mucormycosis with or without COVID-19. Hyperglycemia inhibits neutrophil chemotaxis, macrophage phagocystosis, and degranulation of NK cells [25]. Promote the expression of surface glucose-regulated protein (GRP78) on the endothelium, which is essential for mucorales invasion. Additionally, supraphysiological stress during COVID-19 illness and viral-mediated islet cell damage can contribute to hyperglycemia. Prolonged corticosteroid intake is a risk factor for the development of mucormycosis. This may be mediated by inhibition of macrophages and neutrophils and the tendency to cause hyperglycemia [26].

We noticed the predominance of headache and facial pain in most patients (69.7%) with CO-MUCOR which is consistent with Desai et al. (2021) who studied 100 patients with a documented history of SARS-CoV-2 infection; the most common complaints were headache and facial pain (55%). Also, Garg et al. (2021) reported a series of 10 cases of CO-MUCOR, and all of them (100%) complained of headache. The difference in percentage may be attributed to smaller sample size in their study [27, 28].

On examination, ophthalmoplegia was a common sign and was present in more than half of patients (54.5%), which is in line with Abdelsamie et al. in 2022 that reported the same percent (54.5%), and also was consistent with El-Kholy et al., in 2021, Desai et al. in 2021, and Mitra et al. in 2021 who found restricted eye movements were present in 63.9%, 58%, and 41% of patients, respectively [27, 29, 30].

In our study, 57.6% of CO-MUCOR patients had unilateral sinus affection. This finding disagrees with Abdelsamie et al. in 2022 who studied 22 patients with CO-MUCOR, and all of them had unilateral sinus affection [29].

In our study, we found that the left ethmoid sinus (81.8%) was the most commonly infected with CO-MUCOR. These finding is consistent with Sharma et al. (2021) study that reported 100% involvement of the

Table 11 IIncidence of death compared to various factors

	No death No. = 24	Death No. = 9	Test value	*p*-value	Sig.
CT PNS					
Rt max. S	12 (50.0%)	4 (44.4%)	0.081*	0.776	NS
Lt max. S	18 (75.0%)	8 (88.9%)	0.755*	0.385	NS
Rt ethmoid	15 (62.5%)	5 (55.6%)	0.132*	0.716	NS
Lt ethmoids	19 (79.2%)	8 (88.9%)	0.416*	0.519	NS
Rt sphenoid	14 (58.3%)	5 (55.6%)	0.021*	0.886	NS
Lt sphenoid	18 (75.0%)	6 (66.7%)	0.229*	0.632	NS
Rt frontal	9 (37.5%)	4 (44.4%)	0.132*	0.716	NS
Lt frontal	12 (50.0%)	3 (33.3%)	0.733*	0.392	NS
Bony erosions	13 (54.2%)	4 (44.4%)	0.248*	0.619	NS
Bilateral involvement	10 (41.7%)	4 (44.4%)	0.021*	0.886	NS
COVID status					
Previous COVID	17 (70.8%)	5 (55.6%)	0.688*	0.407	NS
PCR at presentation	3 (12.5%)	3 (33.3%)	1.910*	0.167	NS
CT CO-RAD score					
Median (IQR)	2 (1–3)	3.5 (2.5–4.5)	−1.951≠	0.051	NS
Range	1–5	1–5			
Duration between COVID-19 infection and start of mucormycosis					
Median (IQR)	30 (21–60)	30 (14–45)	−0.355≠	0.723	NS
Range	7–90	14–80			
Steroids use	20 (83%)	9 (100%)	0.001*	0.001	HS
Anti-IL-6 actemra (tocilizumab)	4 (16.7%)	2 (22.2%)	0.136*	0.712	NS
Antiviral (remdesivir)	4 (16.7%)	2 (22.2%)	0.136*	0.712	NS
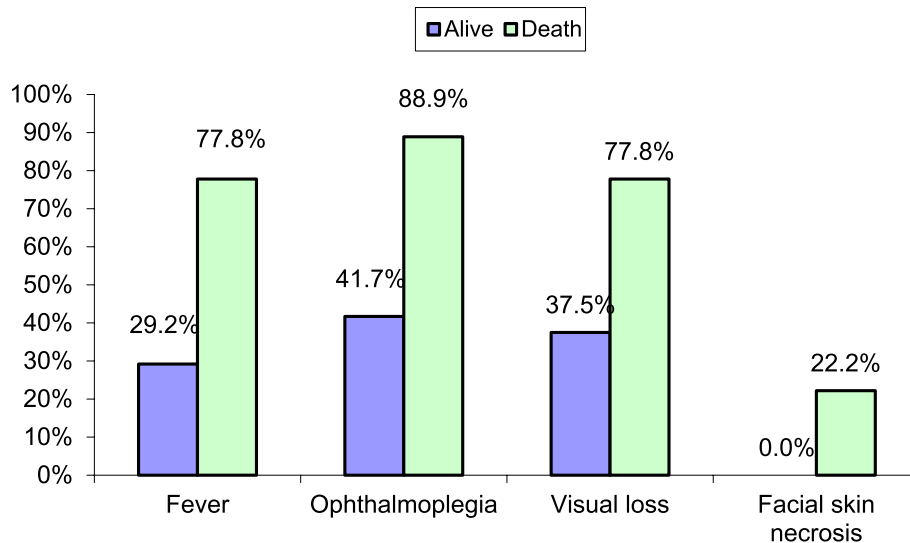
Fig. 4 Correlation of symptoms and signs and the fate of the disease

ethmoid sinus in all 23 patients included. On the other hand, Nagalli and Kikkeri in their systematic review of the literature in 2021 found that the maxillary sinus was most commonly infected (47.4%) [31].

In our study, all patients received systemic antifungal. About two-thirds of the patients (24 patients, 72.7%) underwent endoscopic sinus surgery for mucormycosis. This agrees closely with Abdelsamie et al. in 2022

Table 12 Incidence of death compared to various factors

	No death No. = 24	Death No. = 9	Test value	*p*-value	Sig.
Interval from symptom onset to treatment					
Median (IQR)	8 (5–12)	5 (3–7)	−1.524[b]	0.127	NS
Range	2–63	1–14			
Endoscopic treatment	19 (79.2%)	5 (55.6%)	1.840[a]	0.175	NS
Combined (endoscopic and external)	4 (16.7%)	3 (33.3%)	1.088[a]	0.297	NS
External	2 (8.3%)	0 (0.0%)	0.798[a]	0.372	NS
Total no. of surgical procedures					
0	1 (4.8%)	1 (14.3%)	4.000[a]	0.261	NS
1	12 (57.1%)	6 (85.7%)			
2	7 (33.3%)	0 (0.0%)			
3	1 (4.8%)	0 (0.0%)			
Inf. turb.	23 (95.8%)	9 (100.0%)	0.387[a]	0.534	NS
Middle turb.	22 (91.7%)	9 (100.0%)	0.798[a]	0.372	NS
MMA	23 (95.8%)	9 (100.0%)	0.387[a]	0.534	NS
Septectomy	11 (45.8%)	6 (66.7%)	1.137[a]	0.286	NS
Palatal debrid.	2 (8.3%)	1 (11.1%)	0.061[a]	0.805	NS
Ethmoidectomy	22 (91.7%)	9 (100.0%)	0.798[a]	0.372	NS
Sphenoidotomy	20 (83.3%)	5 (55.6%)	2.750[a]	0.097	NS

P-value > 0.05, nonsignificant; *P*-value < 0.05, significant; *P*-value < 0.01, highly significant

[a] Chi-square test

[b] Mann-Whitney test

•Independent *t*-test

Table 13 Relation between interval from symptom onset to treatment and onset of death or discharge

	Interval from symptom onset to treatment	
	r	*p*-value
Onset of death or discharge (days)	0.153	0.396

P-value > 0.05, nonsignificant; *P*-value < 0.05, significant; *P*-value < 0.01, highly significant. Spearman correlation coefficient

who reported that 90.9% of the patients received liposomal amphotericin B, and 81.8% of the patients underwent surgical debridement, and the mortality rate was 27.3% [29].

The overall mortality rate in our study was 27.3% (9 out of 33); this is equal to the overall mortality rate reported by Abdelsamie et al. in 2022, 27.3% (6 out of 22 patients). This close agreement may be due to the fact that both studies were performed in Egypt with similar predisposing factors and similar resources of treatment and more or less similar sample size [29].

On the other hand, the overall mortality in the COS-MIC report was 14% (Sen et al., in 2022) which is markedly lower than in our patient group (27.3%). This could probably be attributed to the delay in presentation which is reflected by the median onset of CO-MUCOR following COVID-19 symptoms (13 days in the COS-MIC report versus 30 days in our group) [9].

ConclusionThe current mucormycosis epidemic was precipitated by a unique confluence of risk factors: diabetes mellitus, widespread use of steroids, and perhaps SARS-CoV-2 infection itself. Restricting steroid use in patients with severe COVID-19 requiring oxygen therapy and screening for and optimally controlling hyperglycemia can prevent COVID–Mucor in a large majority.

Our findings call for the avoidance of steroids in mild COVID-19 in view of the risk of CAM. In general, it appears that neutrophil dysfunction (due to COVID-19, hyperglycemia, and steroids) and endothelial dysfunction (due to diabetes and COVID-19) may be the main pathogenetic mediators of CAM.

Declarations

References

1. Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP (2020) Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clin Microbiol Infect 26:1395–1399
2. Patel A, Agarwal R, Rudramurthy S et al (2021) Multicenter epidemiologic study of coronavirus disease–associated mucormycosis, India. Emerg Infect Dis 27:2349–2359
3. Narayanan S, Chua JV, Baddley JW (2021) Coronavirus disease 2019–associated mucormycosis: risk factors and mechanisms of disease. Clinical Infectious Diseases J 74(7):1279-1283. https://doi.org/10.1093/cid/ciab726.
4. Mahmoud MS, Taha MS, Mansour OI et al (2022) Prevalence and outcomes of olfactory and gustatory dysfunctions in hospitalized SARS-CoV-2-infected patients. Egypt J Otolaryngol 38:19. https://doi.org/10.1186/s43163-022-00207-z
5. Rezk M, Saleeb M (2022) Comparative study for use of steroids in treatment of sudden sensorineural hearing loss in COVID19 patients. Egypt J Hosp Med 89(1):4848–4853. https://doi.org/10.21608/ejhm.2022.260751
6. Arora A, Megha Priyadarshi A, Varidh Katiyar B, Manish Soneja A, Prerna Garg A, Ishan Gupta A, Vishwesh Bharadiya A, Parul Berry A, Tamoghna Ghosh A, Lajjaben Patel A, Radhika Sarda A, Shreya Garg C, Shubham Agarwal A, Veronica Arora D, Aishwarya Ramprasad A, Amit Kumar A, Rohit Kumar Garg A, Parul Kodan A, Neeraj Nischal A, Gagandeep Singh E, Pankaj Jorwal A, Arvind Kumar A, Upendra Baitha A, Ved Prakash Meena A, Animesh Ray A, Prayas Sethi A, Immaculata Xess E, Naval Vikram A, Sanjeev Sinha A, Ashutosh Biswas A, Alok Thakar C, Sushma Bhatnagar F, Anjan Trikha G (2022) Risk factors for coronavirus disease-associated mucormycosisUmang. Naveet Wig J Infect 84:383–390
7. Pandiar D, Kumar NS, Anand R, Kamboj M, Narwal A, Shameena PM (2021) Does COVID 19 generate a milieu for propagation of mucormycosis? Med Hypotheses. 152:110613. https://doi.org/10.1016/j.mehy.2021.110613
8. Singh AK, Singh R, Joshi SR, Misra A (2021) Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr Clin Res Rev. 15(4):102146. https://doi.org/10.1016/j.dsx.2021.05.019
9. Sen M, Honavar SG, Bansal R et al (2021) Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India – collaborative OPAI-IJO study on mucormycosis in COVID-19 (COSMIC), report 1. Indian J Ophthalmol. 69(7):1670–1692
10. Binder U, Maurer E, Lass-Flörl C (2014) Mucormycosis–from the pathogens to the dis- ease. Clin Microbiol Infect OffPubl Eur Soc Clin Microbiol. Infect Dis 6:60–66 20 Suppl
11. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE (2020) Diabetic ketoacidosis. Nat Rev Dis Primer 6(1):40
12. Hussain S, Baxi H, Riad A et al (2021) COVID-19-associated mucormycosis (CAM): an updated evidence mapping. Int J Environ Res Public Health. 18(19):10340. https://doi.org/10.3390/ijerph181910340
13. Pakdel F, Ahmadikia K, Salehi M et al (2021) Mucormycosis in patients with COVID-19: a cross-sectional descriptive multicentre study from Iran. Mycoses. 64:1238–1252
14. Avatef Fazeli M, Rezaei L, Javadirad E et al (2021) Increased incidence of rhino-orbital mucormycosis in an educational therapeutic hospital during the COVID-19 pandemic in western Iran: an observational study. Mycoses. 64(11):1366–1377. https://doi.org/10.1111/myc.13351
15. Nasir N, Farooqi J, Mahmood SF, Jabeen K (2021) COVID-19 associated mucormycosis: a life-threatening complication in patients admitted with severe to critical COVID-19 from Pakistan. Clin Microbiol Infect. 27(11):1704–1707. https://doi.org/10.1016/j.cmi.2021.07.038
16. Rabagliati R, Rodríguez N, Núñez C, Huete A, Bravo S, Garcia P (2021) COVID-19-associated mold infection in critically ill patients, Chile. Emerg Infect Dis 27(5):1454–1456. https://doi.org/10.3201/eid2705.204412
17. Fouad YA, Bakre HM, Nassar MA, Shaat GMA, AK. (2021) Characteristics and outcomes of a series of COVID-associated mucormycosis patients in two different settings in Egypt through the third pandemic wave. Clin Ophthalmol. 15:4795–4800. https://doi.org/10.2147/OPTH.S344937
18. El-Kholy NA, El-Fattah AMA, Khafagy YW (2021) Invasive fungal sinusitis in post COVID-19 patients: a new clinical entity. Laryngoscope. 131(12):2652–2658. https://doi.org/10.1002/lary.29632
19. Alfishawy M, Elbendary A, Younes A et al (2021) Diabetes mellitus and coronavirus disease (Covid-19) associated mucormycosis (CAM): a wake-up call from Egypt. Diabetes Metab Syndr. 15(5):102195. https://doi.org/10.1016/j.dsx.2021.102195
20. Assaad Khalil SH, Megallaa MH, Rohoma KH et al (2018) Prevalence of type 2 diabetes mellitus in a sample of the adult population of Alexandria, Egypt. Diabetes Res Clin Pract 144:63–73. https://doi.org/10.1016/j.diabres.2018.07.025
21. AlSawahli H, Mpyet CD, Ezzelarab G et al (2021) Population-based cross-sectional prevalence survey of diabetes and diabetic retinopathy in Sohag—Egypt, 2019. BMJ Open. 11(6):e047757. https://doi.org/10.1136/bmjopen-2020-04775
22. Ghuman H, Voelz K (2017) Innate and adaptive immunity to mucorales. J Fungi Basel Switz 3(3):E48
23. Lucas C, Wong P, Klein J, TBR C, Silva J, Sundaram M et al (2020) Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature 584(7821):463–469
24. Mahmoud MS, Diab AG, Ngombu S, Prevedello DM, Carrau RL (2021) Endoscopic transorbital ligation of the maxillary artery through the inferior orbital fissure. Head Neck. 43(6):1830–1837. https://doi.org/10.1002/hed.26655 Epub 2021 Mar 10. PMID: 33751697
25. Afiat B, Nofri R, Adi IT, Rovina R (2020) Type 2 diabetes and its impact on the immune system. Curr Diabetes Rev 16(5):442–449 May 31 . 16
26. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP (2012) Pathogenesis of mucormy- cosis. Clin Infect Dis 54(suppl_1):S16–S22
27. Desai EJ, Pandya A, Upadhya I et al (2021) Epidemiology, clinical features and management of rhino orbital mucormycosis in post COVID 19 patients. Indian. J Otolaryngol Head Neck Surg.:1–5. https://doi.org/10.1007/s12070-021-02807-2 [Epub ahead of print], indexed in Pubmed: 34414101
28. Garg R, Bharangar S, Gupta S et al (2021) Post Covid-19 infection presenting as rhino-orbital mycosis. Indian. J Otolaryngol Head Neck Surg.:1–8. https://doi.org/10.1007/s12070-021-02722-6 indexed in Pubmed: 34307112.[Epub ahead of print]
29. Abdelsamie AM, Abdelazim HM, Elnems MG, Abdelhakam RB, Abdelalim AA Covid-19-related acute invasive fungal sinusitis: clinical features and outcomes. Int Arch Otorhinolaryngol 26 1/2022
30. Mitra S, Janweja M, Sengupta A (2021) Post-COVID-19 rhino-orbito-cerebral mucormycosis: a new addition to challenges in pandemic control. Eur Arch Otorhinolaryngol. https://doi.org/10.1007/s00405-021-07010-1 [Epub ahead of print], indexed in Pubmed: 34309754
31. Nagalli S, Kikkerl NS (2021) Mucormycosis in COVID-19: a systematic review of literature. Infez Med. 29(4):504–512. https://doi.org/10.53854/liim-2904-2

Publisher's Note