



REVIEW ARTICLE

# COVID-19-associated mucormycosis of head-and-neck region: A systematic review

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## ABSTRACT

**Background and Aim:** With the second wave of COVID-19, there has been a substantial rise in opportunistic infections like mucormycosis. Mucormycosis is a fatal fungal infection and understanding the associated risk factors and their management plays a key role to reduce mortality and morbidity caused due to such infections. This systematic review was conducted to assess the risk factors, clinical characteristics and to understand the pathogenesis of COVID-19-associated mucormycosis (CAM) affecting the head-and-neck region.

**Methods:** The PubMed database was searched with the keywords; ((Mucormycosis) OR (invasive fungal sinusitis)) AND (COVID-19) and the PRISMA chart was prepared for the selection of the reports based on the inclusion and exclusion criteria.

**Results:** A total of 261 cases of CAM affecting the head-and-neck region were analyzed in this systematic review. Most of the patients presented with rhino-orbital/rhino-orbito-cerebral form of mucormycosis (rhino-orbital mucormycosis/rhino-orbital-cerebral mucormycosis). Pulmonary mucormycosis along with rhino-orbital form, involvement of hard palate, and maxillary sinus was seen in one case each. A total of 224 (85.8%) patients were diabetic, 68 (30.3%) of them had poor glycemic control. Steroids were administered in 210 (80.4%) patients. Except for two, antifungal treatment was given to all patients. Follow-up data revealed 67 (25.6%) deaths and 193 (73.9%) were alive with one patient lost during follow-up.

**Conclusion:** The findings of this systematic review suggested that the occurrence of mucormycosis in COVID-19 patients is related to the inherent effects of COVID-19 infection on the immune system, comorbidities especially diabetes, and treatment aspects. Hence, a detailed understanding of these factors may aid in the personalized management of CAM and improve the disease outcome.

**Relevance for Patients:** The risk factors in patients affected by CAM should be recognized and closely monitored in post-COVID-19 patients. A multidisciplinary team must be in place to reduce the mortality and morbidity in such patients.

## 1. Introduction

Mucormycosis is a rare, life-threatening fungal infection characterized by widespread angioinvasion, rapid host tissue destruction, and dissemination [1-3]. It is caused by *Mucorales* species found in forest or agricultural soils or decaying organic material [2,3]. Rhinocerebral mucormycosis is the most common form accounting for one-third to one-half of all the cases [4]. Multifactorial predisposing conditions such as uncontrolled diabetes, immunosuppression, iron overload, organ, and hematopoietic transplantation have been suggested. The mortality rate remains high ranging from 33.3% to 80% [5].

Since the emergence of COVID-19 infection which was declared as a global pandemic on March 11, 2020, by the WHO [6], the challenges faced by the health-care sector have considerably increased. These include issues related to health infrastructure, standard treatment protocol, and complications related to superimposed infections, which have a huge impact on morbidity and mortality. COVID-19-associated mucormycosis (CAM) is one such challenge that has gained a matter of concern in recent times. The incidence of CAM is increasing drastically affecting the quality of life and often leading to death. Hence, this systematic review was undertaken to report and analyze CAM regarding risk factors, clinical characteristics and to understand the associated pathogenesis. Furthermore, we aimed to propose the guidelines for the management and prevention of CAM.

## 2. Material and Method

### 2.1. Search strategy

In the present systematic review, an electronic search of the PubMed database was conducted using search terms; ([Mucormycosis] OR [invasive fungal sinusitis] AND COVID-19). The search strategy was restricted to articles in the English language and human studies published between January 2020 and July 1, 2021. Additional records of relevance were also included in the study.

### 2.1. Selection and data extraction

The articles were selected based on the following inclusion and exclusion criteria. Inclusion criteria were; full-text articles describing rhino-orbital mucormycosis or rhino-orbital-cerebral mucormycosis, papers with sufficient patient information, articles describing CAM with a confirmatory diagnosis of COVID-19, and mucormycosis. Exclusion criteria were; reports on postmortem diagnosis of CAM, duplicate articles, irrelevant articles such as narrative reviews and opinions, reports on mucormycosis affecting other sites, articles with lack of data on mucormycosis cases, and articles on cases of COVID-19 associated with other fungal infections.

Bibliographies of relevant articles were also reviewed. The eligible articles were thoroughly assessed by two authors independently focusing on the aim of the review and detailed data of each included CAM case was extracted. The difference of opinion was settled by consensus after discussion with the remaining authors.

A total of 95 articles were obtained following the PubMed search strategy. One eligible paper from Google Scholar search which was not found in the database was also included in the study. Hence, a total of 96 papers were initially selected. Duplicated and non-relevant items were excluded after the initial analysis. Finally, 33 full-text papers were included in the review based on the inclusion and exclusion criteria. The step-wise search strategy is summarized in Figure 1.

## 3. Results

A total of 261 patients were affected by CAM, between the 3<sup>rd</sup> and 7<sup>th</sup> decades of life of which 193 (73.9%) were male and 68

(26.05%) were female. In all the cases, the diagnosis of COVID-19 was based on reverse transcriptase-polymerase chain reaction test on nasopharyngeal/oropharyngeal swabs, and mucormycosis was confirmed by histopathology and/or culture. In 220 (84.2%) patients, CAM was observed either during treatment or post-COVID-19 recovery, and 41 (15.7%) presented with concurrent COVID-19 infection. All the cases presented with rhino-orbital or rhino-orbito-cerebral type except for one case each showing rhino-orbito-cerebral form with pulmonary involvement, hard palate involvement, and maxillary sinus involvement respectively. An intracranial extension was noted in 64 (24.5%) cases. A total of 224 (85.8%) patients suffered from diabetes of which 68 (30.3%) had poor glycemic control. Among the patients with diabetes, diabetic ketoacidosis (DKA) was observed in 22 (9.8%) cases (of whom five patients developed DKA during the treatment for COVID-19 infection). Other comorbidities such as hypertension (31.03%), ischemic heart disease (3.4%), chronic renal disease (4.9%), coronary artery disease (5.3%), HIV (0.7%), hematologic malignancy (1.1%), and immunomodulating drugs (2.2%) were noted with or without diabetes. More than one comorbidity was seen in 153 (58.6%) cases. Few patients did not report any comorbidities (n = 5, 1.9%). The detailed data of cases are depicted in Tables 1 and 2.

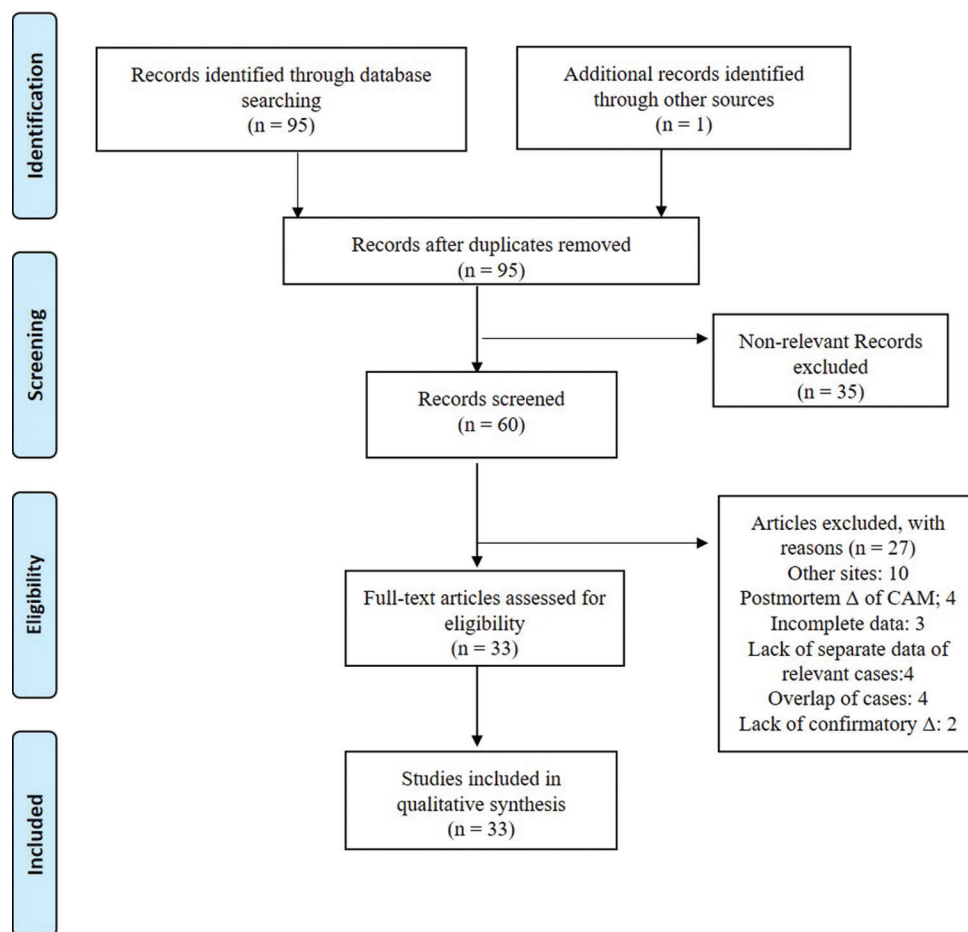
As a part of the treatment for COVID-19 infection, 210 (80.4%) patients received steroids and 54 (20.6%) patients received antibiotics. Based on the data available, 131 (50.1%) patients received oxygen supplements of whom 40 (30.5%) were given mechanical ventilation.

Except for two, all the patients received antifungal treatment. Surgical debridement was done in 145 (55.5%) patients of whom 29 (11.1%) underwent orbital exenteration. At the time of follow-up, 193 (73.9%) patients were alive and 67 (25.6%) patients succumbed to death. One patient was lost to follow-up.

## 4. Discussion

Globally, the incidence of mucormycosis varies from 0.005 to 1.7/million population, whereas in India, it is much higher, that is, 0.14/1000 individuals [11]. In addition, the presence of risk factors increases the prevalence [4]. Extensive angioinvasion, leading to vascular thrombosis and tissue necrosis, is the hallmark of mucormycosis. This aggressive behavior of *Mucorales* is attributed to innate thermotolerance, rapid growth, an affinity for endothelial cell surfaces, ability to obtain iron from the host, and impairment of host defense mechanism (involved in pathogen recognition, tissue repair, etc.) [2]. Hence, the risk factors that predispose to mucormycosis include compromised immune response (as seen in uncontrolled diabetes, DKA, and neutropenia), elevated free iron levels, defect in zinc metabolism, and immunosuppressant therapy for an organ transplant [2-4,38].

Similarly, the extent and outcome of newly emerged COVID-19 infection has been linked to associated comorbidities such as diabetes, chronic obstructive pulmonary disease, and immunosuppression (corticosteroid therapy, ventilation, and intensive care unit [ICU] admission). Hence, opportunistic



**Figure 1.** Summary of the search strategy

infections like CAM are on an alarming rise. However, a lack of clarity on the exact mechanism for such incidence prompted us to analyze the reports on CAM.

According to our review, most CAM-affected patients were male (73.9%). Similar findings were reported by Patel *et al.* [39]. Even in the pre-COVID-19 era, male predominance was observed [40]. Although mucormycosis is not gender dependent, COVID-19 infection has been reported more in males [16]. The most common form of mucormycosis observed in the present set of patients was rhino-orbital or rhino-orbito-cerebral ( $n = 258$ ). While one patient showed pulmonary involvement along with rhino-orbital form, one case with only maxillary sinus and one case with only hard palate involvement was noted. According to the literature, the most common form of mucormycosis is rhino-orbito-cerebral (44–49%), followed by cutaneous, pulmonary, disseminated, and gastrointestinal types [16]. Literature reports have suggested that rhino-orbito-cerebral form is commonly associated with diabetes and DKA [4].

When the geographic location of CAM was analyzed, the current data show that there is a rise in mucormycosis cases in India ( $n = 218$ , 83.5%). Population density, the sheer number of patients affected by COVID-19, diabetic burden (second highest country), indiscriminate use of steroids, etc., can be speculated

as probable reasons. In addition, seasonal climatic changes have been known to affect the prevalence of fungal spores. Hot and dry summer conditions in tropical countries like India are conducive for the small sporangiospores of *Mucorales* to aerosolize and scatter in the environment [41].

Most of the patients presented with CAM either during treatment/recovery (84.2%) and concurrent infection was noted in 15.7% of patients. There is a possibility that initial asymptomatic presentation of COVID-19 with incident diagnosis in such patients derailing the innate immunity might have encouraged the growth of *Mucorales* species, leading to CAM. CAM during treatment/recovery can be related to adverse effects of treatment protocols including steroid therapy, oxygen supplement with ventilator support, and prolonged stay in ICU [1,18]. According to the National Institute of Health, conferring to the Randomized Evaluation of COVID-19 Therapy (“RECOVERY”) collaborative group, the use of steroids must be reserved only for patients on supplemental oxygen or ventilator and not in milder cases. In addition, the risk of secondary infection is also specified [5]. However, the injudicious use of steroids suppresses the immunity and the prolonged ICU stay with supplemental oxygen makes them prone to secondary infections like mucormycosis [42,43].

Moreover, the COVID-19 infection that results in reduced fungal

Table 1. Details of patients included in the present systematic review

Author	Region	No. of cases	Age/sex	Type of CAM extension	CAM Δ	Diabetes	DKA	Other illness	Treatment			Outcome	
									Steroid	Antibiotics	Antifungal		Oxygen supplement
1 Mehta et al. [7]	India	1	60/M	No	Post Rx	Type II	No	No	Yes	Yes	Yes Non-invasive	Antivirals	Death
2 Meonnen et al. [8]	USA	1	60/M	No	Post Rx	Type II (poor control)	No	-HTN -Others-2	Yes	Yes	Yes	-Remdesivir -Convalescent plasma - Debridement	Death
3 Sen et al. [11]	India	6	60.5 years M=6	Yes N=5	Post Rx (n=5) Concurrent =1	Type II poor control (n=4) -onset with COVID (n=2)	n=3	No	Yes	Yes	No	Sinus debridement =6 Orbital exenteration-1	Alive
4 Sarkar et al. [9]	India	10	45.5 (Mean) M=8 F=2	No	Concurrent	Type II (poor control)	-n=4 -n=5 (with Rx)	No	Yes	No	Yes (n=9)	-Remdesivir =4 -debridement =7	Death-4 Alive-6
5 Passero et al. [10]	Italy	1	66/M	No	Post Rx	No	No	-HTN -Multiple organ failure	Yes	No	Yes	Yes Mech. vent	Death
6 Maini et al. [11]	India	1	38/M	No	Post Rx	No	No	No	Yes	Yes	No	-HCQ -Antivirals -RRT (renal replacement therapy)	Alive
7 Karimi et al. [12]	Iran	1	61/F	No	Post Rx	Type II	No	No	Yes	No data	Yes	-Remdesivir -Debridement	Alive
8 Sharma et al. [5]	India	23	Age – NA M-15 F-8	Yes n=2	-Post Rx- 19 Concurrent- 4	-Type II -21 -Poor control (12)	No	HTN-14 Renal Failure-1	Yes	No data	No	-Remdesivir -Interferon -alpha -Debridement with exenteration	Alive
9 Veisi et al. [13]	Iran	2	40/F	Yes	During Rx	No	No	No	Yes	Yes	Yes	Remdesivir Debridement	Death
10 Waizel-Haiat et al. [14]	Mexico	1	24/F	No	Concurrent	Type II controlled Diagnosed on admission- poor control	Yes	Obesity	Yes	Yes	Yes	Remdesivir Debridement	Alive

(Contd...)

Table 1. (Continued)

Author	Region	No. of cases	Age/sex	Type of CAM extension	CAM Δ	Diabetes	DKA	Other illness	Treatment			Outcome
									Steroid	Antibiotics	Antifungal	
11 Revannavar et al. [15]	India	1	32/F	ROM	No	Type II poor control	No	No	Yes	No	Symptomatic Rx for COVID	Alive
12 Moorthy et al. [16]	India	17	35-68 years M-15 F-2	ROCM	n=8	15- Poor control	No	No	Yes	No	Debridement with or without maxillectomy	Alive -10 LTF-1 Death-6
13 Alekseyev et al. [17]	USA	1	41/M	ROM	Yes	concurrent	Yes	No	Yes	No	Debridement Heparin therapy HCQ	Alive
14 Pauli et al. [18]	Brazil	1	50/F	Hard palate	No	Type II poor control	No	No	Yes	No	Debridement	Alive
15 Arora et al. [19]	India	60	57 years (mean) M-45 F-15	ROCM	6	Type II n=59	3	HTN-14 CAD-6 CKD-2 Others-9	Yes n=60	Yes-30 No-30	Debridement -12 Exenteration -2	Alive n=60
16 Roushdy T et al. [20]	India	2	75/M 59/M	ROM ROM+ <i>Klebsiella</i>	No Yes	Type II Type II-uncontrolled	No No	HTN, IHD HTN	Yes Yes	No No	Debridement Debridement	Alive Alive
17 Thonthoni et al. [21]	India	1	59/M	ROM	No	Type II	No	No	Yes	Yes	Remdesivir	Alive
18 Bonates et al. [22]	Brasil	1	56/M	ROCM	No	Type II	Yes	No	yes	Yes	No	death
19 Arjun et al. [23]	India	10	53 years mean M=8 F=2	ROM	1	Type II uncontrolled n=10	No	HTN-2 CAD-3 CKD-1 Others-2	Yes n=10	Yes n=8	Debridement -10	Alive-9 Death-1
20 Baskar et al. [24]	India	1	28/M	ROM	No	Concurrent	No	No	Yes	No	-Debridement with exenteration	Alive
21 Joshi et al. [25]	India	25	55.2 years Meanh M=16 F=9	ROCM	10	Type II n=22 Uncontrolled -13	No	HIV-2 Immuno modulating drugs-6	Yes n=25	Yes Mechanical ventilation -12	Debridement with exenteration	Alive-11 Death-14

(Contd...)

Table 1. (Continued)

Author	Region	No. of cases	Age/sex	Type of CAM extension	CAM	Diabetes	DKA	Other illness	Treatment			Outcome		
									Steroid	Antibiotics	Antifungal		Oxygen supplement	Others/surgical debridement
22 Selarka et al. [26]	India	47	55 years mean M=35 F=12	ROCM (16 pts. conf. with other fungal and bacterial infection)	Yes n=11	Post Rx	No	HTN-27 IHD-6 Others-11	Yes n=45	Yes n=16	Yes n=47	Yes n=38	Debridement -38 Remdisivir -27 Antiviral-1	Alive-36 Death=11
23 Fouad et al. [27]	Egypt	6	53.6 years M=4 F=2	ROCM	Yes n=3	Concurrent-5 Post Rx-1	1	CKD-2 IHD-1	Yes n=2	No	Yes n=6	Debridement -3	Debridement -3 Death-3	Alive-3 Death-3
24 Buil et al. [28]	Netherlands	1	70/M	ROCM	Yes	Post Rx	No	No	yes	No	Yes	No	debridement	Death
25 Pakdel et al. [29]	Iran	15	52 years M=10 F=5	ROM/ROCM/SM/	Yes n=7	Post Rx	1	HTN-7 hematological malignancy -2 CVD-2 Others-5	Yes n=7	No	Yes n=15	Yes n=10 Mech .v-1	Debridement -12 Exenteration -5 ITF- 2 Remdesivir =1 HCQ-1	Alive-8 Death-7
26 Meshram et al. [30]	India	1	47/M	ROM	Yes	Post Rx	No	HTN Kidney trans plantation	Yes	No	No	No	Debridement with exenteration	death
27 Bayram et al. [31]	Turkey	11	73.1 years M=9 F=2	ROM	Yes n=3	Concurrent	No	HTN-7 CRF-3 CAD-2 MDS-1 Others-2	Yes	No	Yes	Yes n=5	Surgical debridement -11	Alive-4 Death-7
28 Arama et al. [32]	Spain	1	62/M	ROM	No	Post Rx	No	HTN Renal failure Transplant IHD Disseminated cry ptococcosis	Yes	Yes	Yes	Mech. vent	Debridement	alive
29 Sai Krishna et al. [33]	India	1	50/M	ROM	No	Type II uncontrolled	No	No	No	Yes	Yes	No	Debridement	alive
30 Rao et al. [34]	India	1	66/M	ROM	No	Type II uncontrolled	No	No	Yes	No	Yes	No	Debridement with exenteration	Alive

(Contd...)



Table 1. (Continued)

Author	Region	No. of cases	Age/sex	Type of CAM extension	CAM Δ	Diabetes	DKA	Other illness	Steroid			Treatment			Outcome
									Steroid	Antibiotics	Antifungal	Oxygen supplement	Others/surgical debridement		
31 Sebastian et al. [35]	India	3	59/M	ROM	No	Type II	No	HTN CAD	Yes	Yes	Yes	Mech. vent	Debridement	Death	
			60/M	ROM	No	Type II	No	CKD	Yes	Yes	Yes	Mech. vent	-	Death	
			64/M	ROM	No	Type II	No	CKD	Yes	No	No	Mech. vent	Renal replacement	Death	
32 Nehara et al. [36]	India	5	62.2 years	ROCM	Yes	Type II	Yes	HTN-2	Yes	Yes	Yes	1	Debridement	Alive-3	
			M-1		3	5	1		3	5	5	Mech. vent	-1	Death-2	
			F-4										Remdesivir		
33 Dallalzadeh et al. [37]	USA	1	48/M	ROCM	No	Type II	Yes	No	Yes	No	Yes	No	Remdesivir	Alive	
Our case	India	1	65/M	Maxillary sinus	No	Type II	No	HTN IHD H/O angioplasty	Yes	Yes	Yes	No	Remdesivir	Death	
Total		261	M=193 (73.94%) F=68 (26.05%)		n=64 (24.52%)	n=224 (85.82%) Poor - 68 (30.35%)	22 (9.82%)		210 (80.45%)	54 (20.68%)	259 (99.23%)	n=131 (50.19%) Mech. vent=40 (30.53%)	Debridement 145 With exenteration-29 Remdesivir -41 Conv.plasma-2 HCO-3 ITF-alpha-3	Alive=193 (73.94%) Death=67 (25.67%) LTF=1	

M: Male, F: Female, PNS: Paranasal sinus, Δ: Diagnosis, Rx: Treatment, DKA: Diabetic ketoacidosis, HTN: Hypertension, CAD: Coronary artery disease, CKD: Chronic renal disease, HIV: Human immunodeficiency virus, CVD: Cardiovascular disease, IHD: Ischemic heart disease, MDS: Myelodysplastic syndrome, CRF: Chronic renal failure, HCQ: Hydroxychloroquine, H/O: History of, Mech. vent: Mechanical ventilation, LTF: Lost to follow-up

**Table 2.** Summary of CAM cases w.r.t various parameters

Risk factor	Parameter	n (%)	
Gender	Males	193 (73.9)	
	Females	68 (26.05)	
Intracranial extension	Yes	64 (24.5)	
	No	197 (75.4)	
CAM diagnosis	Post Rx	220 (84.2)	
	Concurrent	41 (15.7)	
Diabetes mellitus (DM)	Total	224 (85.8)	
	Poor control	68 (30.3)	
	Diabetes ketoacidosis	22 (9.8)	
	No DM	37 (14.1)	
Other comorbidities	Hypertension	81 (31.03)	
	Renal diseases	13 (4.9)	
	CVD/CAD	14 (5.3)	
	IHD	9 (3.4)	
	HIV	2 (0.7)	
	Hematologic malignancy	3 (1.1)	
	Immunomodulating drugs	6 (2.2)	
	Others	30 (11.4)	
	No comorbidities	5 (1.9)	
	Treatment	Steroids	210 (80.4)
		Antibiotics	54 (20.6)
Antifungals		259 (99.2)	
Supplemental O <sub>2</sub>		131 (50.1)	
Surgical debridement		145 (55.5)	
Orbital exenteration		29 (11.1)	
Remdesivir		41 (15.7)	
Convalescent plasma		2 (0.7)	
Interferon-alpha		3 (1.1)	
HCQ		2 (0.7)	
Outcome		Alive	193 (73.9)
	Death	67 (25.6)	
	Lost to follow-up	1 (0.3)	

immunity by the reduction in CD4<sup>+</sup> and CD8<sup>+</sup> and T-cell levels provides a conducive environment for the growth of opportunistic pathogens like *Mucorales* [44,45]. The cytokine storm that occurs during COVID-19 infection can induce ferritin expression which can prompt the release of pro- and anti-inflammatory cytokines as well. Literature suggests that the H subunit of ferritin is an immunomodulator that can lead to both pro-inflammatory and immunosuppressive functions [46]. Hence, the elevated ferritin levels intensify the immunosuppression caused by a cytokine storm.

In the present study, the most common comorbidity found in patients with CAM was diabetes (85.8%) which is similar to the study by Ravani *et al.* (96.7%) [47]. Poor glycemic control was seen in 30.3% of diabetic patients. Even in non-CAM patients, diabetes was reported to be the most common risk factor (88.2%) [39,40]. On the contrary, according to the data from a global fungal infection registry, hematological malignancy (63%) has been reported to be

the most frequent associated risk factor [40]. This might be due to the geographic variations. According to the International Diabetes Federation, 451 million adults live with diabetes worldwide in 2017 with a projected increase to 693 million by 2025 [48,49]. In the general population, the prevalence increases with age and also in COVID-19 patients [6]. India ranks second with a prevalence of 11.8% as of 2019 data [12]. Inherent effects of diabetes on the immune system include impaired neutrophil function with poor chemotaxis and phagocytosis [2,17]. In addition, SARS-Co-V-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors that are expressed in  $\beta$ -cells of the pancreas, leading to  $\beta$ -cell dysfunction and insulin resistance and leading to abnormal glycemic control [6,49]. Moreover, SARS-Co-V-2 also induces cytokine storm that facilitates insulin resistance and altered beta-cell function [48,49].

DKA was observed in 9.9% of patients in the current review, of which some of them developed it with treatment, thus indicating the effect of SARS-CoV-2 on the pancreas. Patel *et al.* found DKA to be less frequent in CAM patients compared to non-CAM patients [39]. Studies have shown that SARS-CoV-2 attaches to the ACE 2 receptors which are abundantly found in high levels in the endocrine pancreas. This leads to beta-cell dysfunction and insulin resistance, leading to hyperglycemia [48]. DKA exaggerates the phagocytic dysfunction caused by hyperglycemia, resulting in defective motility and the killing of pathogens. The attachment of *Mucorales* to endothelial cells occurs through spore coat homolog (CoH) proteins that bind to host endothelial receptor GRP78. In addition, acidosis stimulates the expression of GRP78 and CoH, thus favoring the endothelial attachment of *Mucorales* [2]. Literature suggests that the acidic condition seen in DKA also causes dissociation of iron-protein complexes, resulting in increased levels of free iron [4,17]. Recent updates on fungal pathogenesis suggest that elevated availability of free iron in tissues facilitates *Mucorales* growth by affecting phagocytosis [2,3]. Thus, DKA favors the growth of *Mucorales* by facilitating iron uptake for its metabolism [14,17].

Apart from diabetes, other comorbidities such as hypertension (31.03%), ischemic heart disease (3.4%), renal disease (4.9%), coronary artery disease (5.3%), HIV (0.7%) hematologic malignancy (1.1%), and immunomodulating drugs (2.2%) were also seen in few of the patients included in this review. About 153 (58.6%) patients had more than one comorbidity. Similar studies have also observed these comorbidities in their patients [39,40,47]. In general, comorbidities affect immune dysfunction. Although the exact mechanism of the effect of these illnesses on the prevalence of SARS-Co-V-2 is unclear, the following possibilities are reported. SARS-CoV-2 targets ACE2 receptors which have physiological anti-inflammatory responses expressed in the lungs, heart, kidney, brain, and liver. In addition, it is suggested that some of the treatments of diseases like hypertension increase the expression of ACE receptors thus promoting the progression of the infection [6]. Renal replacement therapy causes iron overload [2] and the role of iron in fungal growth is already mentioned above. The harmful effects of obesity include; (a) detrimental restrictive ventilatory effect of abdominal fat, (b) provide prothrombotic



condition with disseminated coagulation, (c) immune dysfunction and chronic inflammation leading to organ failure, and (d) high expression of ACE receptors in epicardial adipose tissue in obese patients promotes internalization of the virus into adipocytes and elevate tumor necrosis factor-alpha and interleukin-6 release [6]. In addition, it has been observed that obese people are physically inactive, more insulin resistant, and show gut dysbiosis, which elevates the inflammatory response to SARS-CoV-2 infection [6]. Moreover, these are known risk factors for mucormycosis as well.

In our review, a large cohort of patients received steroids (80.4%). The adverse effect of steroid treatment include; long-term disruption of glycometabolic control and compromised response of pulmonary macrophages to prevent germination of fungal spores. Few of the patients included in the present work also received drugs such as remdesivir, tocilizumab, interferon-alpha, hydroxychloroquine, and plasma therapy (Table 1). However, their benefits in the treatment of COVID-19 infection are not fully proven.

It is noteworthy that one patient who did not receive steroids or oxygen supplements and without any comorbidities still developed mucormycosis. On the contrary, few patients without any comorbidities who had received steroids/oxygen supplements also developed CAM. In addition, CAM was seen in patients with comorbidities but without steroids and oxygen supplementation. These observations indicate that each of the factors such as

SARS-CoV-2, comorbidities, steroids, and oxygen supplements may act independently or collectively to provide a conducive environment for mucormycosis. Hence, the pathogenesis of CAM may be unique in each patient, depending on the risk factor/factors involved. However, despite the stringent inclusion criteria, some of the reports lacked individual case details. Hence, the exact role of each of the risk factors was not possible to analyze in the present review.

Literature indicated the inadvertent use of iron and zinc supplements during COVID-19, especially in the Indian population [50,51]. It is a well-known fact that increased intake of zinc, more than the daily requirement may affect zinc metabolism. Zinc deprivation causes cellular stress in fungi and inhibits fungal development by restricting the activity of zinc-binding proteins [38,52]. Hence, increased availability has been linked with a favorable environment for the growth of fungus. Furthermore, failure to use sterile water in oxygen cylinders may be an additional burden that favors fungal growth. The summary of probable risk factors for CAM is depicted in Figure 2.

Hence considering the above-mentioned facts, it can be speculated that there is a “MULTIDIRECTIONAL HIT” on the immune system which is related to the inherent effect of SARS-CoV-2 (target on ACE receptors, cytokine storm, and iron overload), comorbidities (diabetes in particular), side effects of treatment (injudicious use of steroids, oxygen supplement

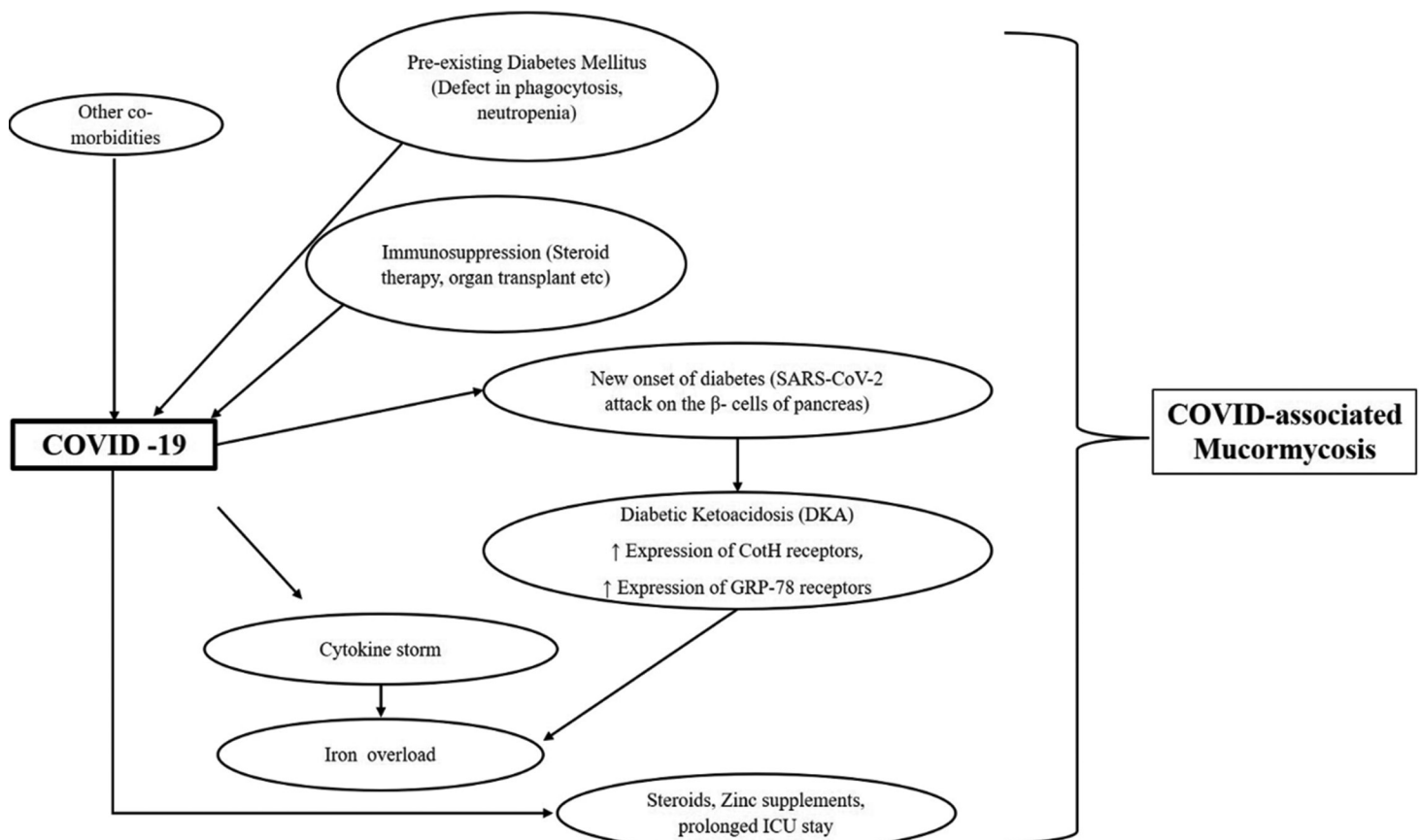


Figure 2. Summary of probable risk factors for CAM

**Table 3.** Recommendations to minimize the occurrence and complications of CAM\* [57,58]

Related to COVID-19	Related to mucormycosis
Follow National Institute of Health guidelines for the use of steroids	Early diagnosis and immediate treatment of mucormycosis
Avoid unnecessary use of broad-spectrum antibiotics, antivirals	Multidisciplinary approach for appropriate management
Closely monitor comorbidities, especially obesity and diabetes, during and after treatment	Educate patients with COVID-19, regarding the symptoms of mucormycosis by infographics
Avoid overuse of prophylactic supplements	Avoid wearing unwashed masks for a prolonged period
Plan for individualized treatment by a thorough examination	Encourage proper hygiene practices; frequent hand wash, respiratory hygiene, eye protection, maintain social distance, etc.,

\*Level 5 evidence according to Oxford standards

with ventilator support, antibiotics, and antivirals), and post-treatment prophylactic supplements (like zinc supplements) that are conducive for the occurrence of mucormycosis. The pathogenesis of both COVID-19 and mucormycosis has been postulated to resemble thrombotic microangiopathies resulting in angioinvasion and endothelial damage thus exaggerating the disease process [16].

The treatment of mucormycosis needs a multidisciplinary approach that addresses early diagnosis, thorough surgical debridement, and topical or systemic antifungal agents along with a close check on comorbidities/risk factors. Delay in the diagnosis with delayed initiation of treatment even by 6 days may increase the mortality from 35% to 66% [1]. Early surgical debridement should be initiated to prevent spread to adjacent structures. In the present review, antifungal treatment was rendered in almost all the patients, and 55.5% of them underwent surgical debridement for mucormycosis. This is similar to the findings of other studies and a study by Patel *et al.* [40,47] in the pre-COVID-19 period who reported surgical management in 62.2%. However, some of the patients were treated conservatively with antifungal agents whereas, in a few of the cases, surgical management was not possible because of underlying medical conditions. Orbital exenteration was done in 11.1% of cases. Sen *et al.* [53] reported orbital exenteration in 17% of their study subjects. In the pre-COVID-19 period, Harris *et al.* [54] reported orbital exenteration in 27.2% of their cases. Literature reports on the role of orbital exenteration on mortality rate are varied [1,53,55]. It is suggested that orbital exenteration can be considered in selected cases depending on the extent and to prevent progression [56]. The most common antifungal agent used for mucormycosis is amphotericin B deoxycholate or liposomal amphotericin B (has reduced nephrotoxicity). In some cases, other agents like posaconazole are used due to the nephrotoxic effect of amphotericin B. Similarly, in some of the patients [5,8] in our review, posaconazole was preferred due to a history of renal failure or subsequent development of renal injury with amphotericin B. Recently, adjunctive therapies

such as hyperbaric oxygen, echinocandins, and triazoles have shown promising results.

At the time of follow-up, 73.9% of patients were alive and 25.6% of patients succumbed to death. One patient was lost to follow-up. Overall, the mortality rate has been reported to range from 33.3% to 80% [5]. It has been observed that the mortality rate is low in CAM than in non-CAM cases [40]. The mortality depends on the time of diagnosis and initiation of treatment, surgical debridement, and control of comorbidities.

Overall, our study featured the risk factors and their association with the increased prevalence of CAM among a large cohort of patients. We also highlighted the various measures to curtail this disease (Table 3). The study was limited by the inability to assess the strength of association between various risk factors and mortality.

## 5. Conclusion

This systematic review highlighted the various risk factors and clinical challenges in the management of CAM. CAM needs to be monitored closely since the adverse effects of treatment, presence of comorbidities, and extension of infection to the adjacent vital structures increase the morbidity and mortality rates. Hence, an integrated team approach will be beneficial; judicious use of steroids, close monitoring of glycemic status during and after COVID-19 infection (Table 3). It is crucial to educate society regarding the fact that overmedication of zinc and vitamin supplements may be the possible risk factor for CAM. Further studies on a large and varied population will help to expand our knowledge on CAM. This will help to overcome the current challenge of CAM as well as brace ourselves for future challenges. Maintaining a CAM registry can also be recommended for future prospective.

## Conflicts of Interest

The authors declare no conflicts of interest.

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