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An Update on COVID-19 Associated Mucormycosis Characteristics, Risk Factors, and Outcomes: a Systematic Review and Meta-Analysis

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Abstract

Purpose of Review This meta-analysis aimed to identify the CAM manifestations, clinical presentations, relevant risk factors, mortality risk factors, treatments, outcomes, and survival.

Recent Findings COVID-19-associated mucormycosis (CAM) increased dramatically, with mucormycosis development estimated to be 50 times higher than before the COVID-19 pandemic. CAM is a high-mortality disease with significant morbidities in survivors. A significant association between uncontrolled diabetes and CAM has been indicated. In addition, high-dose corticosteroid therapy and ICU admission were present in many rhino-orbito-cerebral mucormycosis (ROCM) patients and non-ROCM, respectively. In the present study, we systematically searched PubMed, Scopus, WoS, and PMC, preprint databases, and the reference lists of the included relevant studies until Oct 2021. Studies that report mucormycosis cases (proven/probable) with individual patient details with confirmed COVID-19 infection were included according to the PRISMA statement. Pooling data of 210 CAM patients (proven, 87.6%; probable, 12.4%) was retrieved from 60 case reports/series studies from 17 countries.

Summary Primary or corticosteroid-induced diabetes was the leading independent risk factor for rhino-maxillo-orbito-cerebral mucormycosis (RMOCM) development (OR:18.29). In contrast, ICU admission was the main independent risk factor for non-RMOCM development (OR:11.64). In the absence of the mentioned risk factors, the risk of CAM is low (3.33%). CAM mortality was high (43.5%), with significantly higher fatality in non-RMOCM (77.3%). Severe/critically ill COVID-19 (OR: 3.66), ICU admission (OR: 6.78), and mechanical ventilation (OR: 6.27) were associated with a higher risk of CAM mortality. Cerebral and orbital involvement increased mortality (OR: 3.253 and OR: 3.205) in RMOCM patients; conversely, the surgical intervention improved outcomes (OR: 18.922). Control of hyperglycemia and COVID-19 infection and evidence-based corticosteroid therapy is essential to prevent CAM development. Identifying and controlling the pre-existing/predisposing and mortality risk factors of CAM combined with the implementation of aggressive evidence-based management with a multidisciplinary approach can reduce CAM-related morbidity and mortality. An update to the traditional mucormycosis classification was also introduced to refer to maxillary involvement.

Keywords SARS-CoV-2 · COVID-19-associated mucormycosis · Mucormycosis · COVID-19 · Meta-analysis

Introduction

The COVID-19 disease presents a wide clinical range, from asymptomatic to severe, and makes patients vulnerable to a variety of opportunistic infections. It is estimated that 26.7% of secondary infections are fungal [1]. During the COVID-19 pandemic, there was a significant increase in the number of mucormycosis cases among patients infected with SARS-CoV-2. Hence, it is described as COVID-19-associated mucormycosis (CAM), estimated to be 50 times higher than before the COVID-19 pandemic [2].This increase may indicate the predisposing role of COVID-19 in the current outbreak [3, 4••]. Mucormycosis (MCR) is a rare but highly

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invasive and fatal infection that primarily affects individuals with risk factors such as uncontrolled diabetes, hematologic malignancies, organ transplantation, prolonged corticosteroid therapy, and immunosuppressant therapy [5–7]. Although the causal relationship between COVID-19 and mucormycosis has not been identified, SARS-CoV-2 infection may induce multiple inflammatory pathways that lead to the development of inflammatory conditions susceptible to CAM [8].

Diabetes mellitus (DM) is a significant risk factor for both COVID-19 and mucormycosis [5–7, 9]. During the COVID-19 outbreak, the role of diabetes became more prominent, emerging as the single most crucial risk factor for CAM [3, 4••]. COVID-19 infection and corticosteroid therapy used in its treatment can lead to dysregulation of blood glucose levels (hyperglycemia) [10, 11] and immunosuppression [12]. The role of corticosteroids in predisposing individuals to diabetes and increasing the risk of mucormycosis has been highlighted during the COVID-19 epidemic. Inappropriate corticosteroid therapy can lead to corticosteroid-induced diabetes in healthy individuals or, when combined with DM, lead to uncontrolled diabetes and suppress the immune system [13, 14].

Objectives

Given that CAM is a recently identified disease and many of its characteristics have not been well analyzed, our aim was to conduct a comprehensive analysis of a larger scale of CAM patients. This analysis aims to provide in-depth insight into the disease manifestations, clinical presentations, relevant comorbidities/predisposing factors, relevant parameters, mortality risk factors, treatments, disease outcomes, and survival in the recent mucormycosis outbreak.

Materials and Methods

This comprehensive systematic review with meta-analysis was conducted according to the preferred reporting items for systematic review and meta-analyses (PRISMA) [15] and registered in the International Prospective Register of Systematic Reviews (PROSPERO) database with the registration number CRD42021286926.

Eligibility Criteria

Eligibility criteria were set as follows:

1. Patients with proven/probable mucormycosis;
2. The mucormycosis case, which was diagnosed during the active phase or within a few months (< 6 months) after COVID-19 confirmation;
3. Case reports/series with individual patient details.

Exclusion criteria were set as follows:

1. Non-COVID-19-associated mucormycosis;
2. Non-Mucor fungal infection;
3. Unspecified fungal infection;
4. Possible mucormycosis diagnosis;
5. Mucormycosis with unspecified infection site;
6. Patients with unconfirmed COVID-19 or without previous serological evidence.

Mucormycosis was defined based on recent criteria by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) [16]. The proven disease criteria remained unchanged. However, the probable mucormycosis was defined as a combination of SARS-COV-2 infection as the host factor and the clinical-radiological MCR features with mycological evidence from a non-sterile specimen [17]. Also, the cases were defined as "possible" without mycological criteria.

Information Sources and Search Strategy

Using search strategies (Supplementary material Table S1 and S2), a systematic search was performed in four major databases, including Medline (via PubMed), Scopus, WoS, and PMC. Additional manual searches were also performed in Google Scholar, pre-print archives, relevant review references, and cited and citing papers of the relevant studies to supplement the database searches. The search included all articles published until Oct 2021 during the recent mucormycosis outbreak.

Study Selection, Data Collection, and Data Items

All eligible studies were included in the data extraction process based on the predetermined inclusion and exclusion criteria. Using preconstructed data extraction forms, the data were collected independently from the selected articles by two reviewers (M.H.A and H.A). The collected data were then cross-checked and verified by the third author (K.K). In the event of a disagreement, it was resolved through discussion, and if needed, experts were consulted to make a final decision.

Extracted data included study-related information (authors, year, country), patient demographics, mucormycosis classification, COVID-19-related information (disease severity, active or recovery phase, ICU-related information, time between COVID-19 and mucormycosis infection), treatments received for COVID-19 (corticosteroids, other medicines), mucormycosis-related information (clinical findings, anatomic site, mycological evidence), preexisting comorbidities

(diabetes-related information, other co-morbidities/predisposing factors), treatments (antifungal therapy, surgical intervention), disease outcome (mortality, morbidity), and survival. The rhino-orbito-cerebral mucormycosis (ROCM) refers to the entire range of invasion from the rhino/sinus to cerebral involvement. Since sinus and nasal involvement usually co-occur, we considered them together (rhino/sinus) to reduce diagnostic heterogeneity. To include the involvement of the alveolar/palatal region, maxillary mucormycosis (M) was incorporated into the conventional ROCM.

Mucormycosis was defined in the active COVID-19 phase (A) if diagnosed:

1. Concomitant with COVID-19 positive RT-PCR result or treatment/hospitalization;
2. Within 14 days after COVID-19 diagnosis.

Mucormycosis was defined in the recovery COVID-19 phase (R) if diagnosed:

1. Two weeks after COVID-19 diagnosis.
2. Negative RT-PCR result [3].

In the case of concomitant COVID-19 and MCR diagnosis, the time interval between the two diseases was considered zero. Treatments received during the COVID-19 course were considered risk factors for CAM. Regarding corticosteroid therapy, it was defined as "appropriate" if used only for patients in need of supplemental oxygen and with a maximum of 6 mg/day dexamethasone for up to 10 days; otherwise, it was defined as "inappropriate" [18].

Risk of Bias, Applicability Assessment

The risk of bias was assessed independently based on Joanna Briggs Institute's Critical Appraisal Checklist for case reports/series studies [19] by two reviewers (M.H.A and H.A), then reviewed by the third author (K.K). Finally, scoring decisions were discussed before critical appraisals.

Summary Measures and Data Analysis

Statistical analyses were performed using SPSS 25 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to check the normality of the extracted data. Normally distributed data were expressed as mean ± standard deviation (SD), while nonparametric data were expressed in median (interquartile range, IQR). Categorical data were expressed as proportions (%). The comparison of demographic and other parameters between groups (alive vs. deceased) was made using independent samples *t*-test (for continuous variables) or Pearson chi-square test/Fisher's exact test (for categorical variables). Survival probability was estimated using the Kaplan–Meier method. For all tests, *P*-values ≤ 0·05 defined statistical significance.

Results

Pooling data of 210 CAM patients with individual details (proven, 184 cases (87.6%); probable, 26 cases (12.4%) from 60 case reports/series studies [20–79] from 17 countries including India (132 cases, 62.85%), Iran (32 cases, 15.23%), Turkey (12 cases, 5.71%), USA (9 cases, 4.28%), Egypt (8 cases, 3.8%), Netherlands (4 cases, 1.9%), Brazil (2 cases, 0.95%), Spain (2 cases, 0.95%), France (1 case, 0.47%), Austria (1 case, 0.47%), Italy (1 case, 0.47%), England (1 case, 0.47%), Nepal (1 case, 0.47%), Pakistan (1 case, 0.47%), Honduras (1 case, 0.47%), Mexico (1 case, 0.47%), and Iraq (1 case, 0.47%)) was retrieved. The study selection process is presented in the PRISMA flowchart (Fig. 1).

Demographics and COVID-19-Related Information

A summary of the 210 CAM patient's characteristics in the overall RMOCM and non-RMOCM categories is presented in Table 1.

The mean age was 51·78 ± 15·03 (range 5–88) years with significant male predominance (155/210: 74%, *P*-value < 0·001). Most patients' mucormycosis diagnosis or symptoms onset was in the COVID-19 active phase (118/210: 56.2%) after recovery (92/210: 43.8%). In addition, COVID-19 was severe/critical and mild/moderate in 58% (105/181) and 42% (76/181), while the disease severity was not reported in 14% (29/210).

Non-RMOCM patients required significantly higher (*P*-value < 0·001) ICU admission (14/22: 63.6%) than RMOCM patients (37/188: 19.6%) and required significantly higher (*P*-value < 0·001) more mechanical ventilation (11/22: 50%) than RMOCM cases (22/188: 11.7%) before mucormycosis development. Also, non-RMOCM cases required significantly (*P*-value:0.003) longer ICU admission (25·09 ± 16·39 days) than RMOCM cases (9·82 ± 7·96 days).

The median of COVID-19 confirmation to mucormycosis infection (diagnosis or symptoms onset) in the RMOCM group was significantly lower (14 (IQR: 14) days) than the non-RMOCM group (21 (IQR: 13) days) with a significant difference (*P*-value:0·007). Early symptoms appeared in 53% (66/125, unknown: 63) and 89.6% (112/125, unknown: 63) of RMOCM cases within 2 weeks and the first month.

Causative Pathogens

Causative Mucorales genera were identified in 19% (40/210) patients. Rhizopus was the predominant fungal species

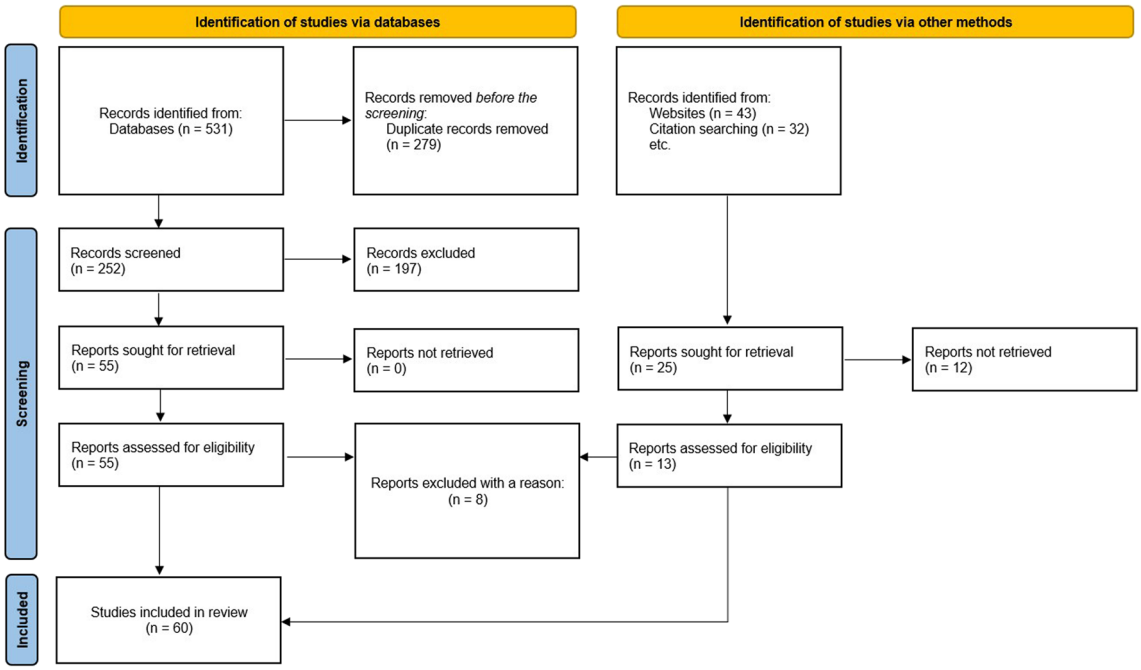

Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flowchart showing the study selection process

identified (33/40:82·5%), followed by Mucor sp. (4/40:10%). Also, Mucor sp. was identified only in RMOCM cases (Table 1).

CAM Manifestations and Clinical and Radiological Presentations

The RMOCM category was the most common manifestation (188/210: 89.52%), and other organ involvement (non-RMOCM) comprised 10.48% (22/210). In the non-RMOCM category, pulmonary involvement was the most observed manifestation (13/210: 6.19%). Figure 2 presents the mucormycosis manifestations in 210 CAM patients based on anatomic site involvement. According to anatomic site involvement, in the RMOCM category, rhino-orbital mucormycosis (76/210: 36.19%) was the most common, followed by rhino-maxillo-orbital mucormycosis (30/210: 14.29%).

Sinus/nasal involvement (183/188: 97.3%) was the most common RMOCM radiological finding, followed by orbital involvement (156/188: 82.5%). The most common radiographic presentation regarding pulmonary mucormycosis was caviatory necrotizing pneumonia (9/13: 69%).

The common RMOCM clinical presentation is presented in Supplementary material Figure S1. Vision loss was the most common clinical presentation (109/188: 58%), followed by orbital/facial pain (79/188: 42%) and maxillary/palatal necrosis/wound (65/188: 34.5%).

Co-Morbidities/Predisposing Factors for CAM Development

The co-morbidities/predisposing factors are provided in Table 1, and the associations between them and different MCR manifestations development are provided in Supplementary material Table S3. The 96.67% (203/210) CAM cases had co-morbidities/predisposing factors other than COVID-19.

Diabetes was the major preexisting co-morbidity overall (171/210: 81.4%). In comparison, it was significantly higher (P-value < 0·001) in RMOCM cases (163/188: 86.7%) with an odds ratio (OR) of 18.29 (P-value < 0·001) as an independent risk factor versus non-RMOCM cases (8/22: 36.4%).

In contrast, ICU admission, wide spectrum antibiotic therapy, and organ transplant were independent risk factors for non-RMOCM versus RMOCM development (OR: 11.64, P-value: 0.012; OR: 5.717, P-value: 0.012; and OR: 16.99, P-value: 0.028). In addition, the use of tocilizumab (P-value < 0.001), renal disease (P-value:0.001), and hematological malignancies (P-value: 0.022) were significantly associated with non-RMOCM. Corticosteroid therapy was the most common predisposing factor (127/185: 68.6%); however, it was not associated with particular disease manifestations.

Treatment and Outcome of CAM

Information on the treatment and outcomes is provided in Table 1. Systemic Amphotericin-B (Amp-B) was used

Table 1 Summary of the characteristics of the 210 patients with COVID-19-associated mucormycosis

	RMOCM (188 cases) *n* (%)	Non-RMOCM (22 cases) Pulmonary, disseminates, gastrointestinal… *n* (%)	*P*-value between RMOCM and non-RMOCM	Overall CAM (210 cases) *n* (%)
Age Mean ± SD Median (IQR)	51.69 ± 14.86 (5–88) Median: 52.5(21)	52.55 ± 16.809 (22–86) Median: 55(24)	0.8	51.78 ± 15.034 (5–88) Median: 53 (21)
Sex	M 135/188: 71.8% F 53/188: 28.2% *P*-value < 0.001	M 20/22: 90.9% F 2/22: 9.1% *P*-value < 0.001	0.54	M 155/210: 73.8% F 55/210: 26.2% *P*-value < 0.001
COVID-19-related information				
Mild to moderate disease	70/159: 44% UKN: 29	6/22: 27.3%	0.136	76/181: 42% UKN: 29
Severe/critical disease	89/159: 56% UKN: 29	16/22: 73%		105/181: 58% UKN: 29
Active COVID-19	102/188: 54.3%	16/22: 72.7%	0.98	118/210: 56.2%
Recovered COVID-19	86/188: 45.7%	6/22: 27.3%		92/210: 43.8%
ICU admission	37/188: 19.6%	14//22: 63.6%	< 0.001	51/210: 24.2%
ICU days Mean ± SD	9.82 ± 7.96 (11 cases)	25.09 ± 16.39 (11 cases)	0.003	17.45 ± 14.806
Mechanical ventilation	22/188:11.7%	11/22:50%	< 0.001	33/210: 15.7%
COVID-19 to mucormycosis infection (days) Mean ± SD Median (IQR)	Mean: 17.84 ± 21.84 Median: 14 (14) (125 cases) UKN: 63	Mean: 23.84 ± 18.42 Median: 21 (13) (19 cases) UKN: 3	0.007	Mean:18.63 ± 21.45 Median: 15 (14) (144 cases) UKN:66
Treatments received for COVID-19				
Corticosteroid	111/163: 68.1% UKN: 25/188:13.3%	16/22: 72.72%	0.66	127/185: 68.6% UKN: 25/210:11.9%
Cumulative glucocorticoid dose[a] (Mean ± SD)				227.81 ± 390.46 (16–1795), 99.07 ± 80.75[b]
Corticosteroid therapy in mild to moderate COVID-19 patients	17/158: 10.69% UKN: 29	3/22: 13.63%	0.68	20/181: 11.04% UKN: 29
Tocilizumab	5/188: 2.7%	8/22: 36.4%	< 0.001	13/210: 6.2%
Remdesivir	31/188: 16.5%	6/22: 27.3%	0.209	37/210: 17.6
Broad spectrum antibiotics therapy	36/188: 19.1%	14/22: 63.6%	< 0.001	50/210: 23.8%
Mucormycosis-related information				
Mycological evidence				
Proven	169/188:89.9%	15/22: 68.2%	0.003	184/210: 87.6%
Probable	19/188: 10.1%	7/22: 31.8%		26/210: 12.4%
Causative pathogen				
Rhizopus spp.	22/27: 81.5%	11/13: 84.6%	0.81	33/40: 82.5%
Mucor spp.	4/27: 14.8%	0%	0.14	4/40: 10%
Lichtheimia spp.	1/27: 3.7%	2/13: 15.4%	0.19	3/40: 7.5%
Comorbidities of CAM				
COVID-19 without diabetes and corticosteroid therapy	9/184: 4.89% UKN: 4	4/22: 18.18%	0.015	13/206: 6.31% UKN: 4
COVID-19 only[c]	6/188: 3.19%	1/22: 4.54%	0.74	7/210: 3.33%
Diabetes-related information				
Diabetes	163/188: 86.7%	8/22: 36.4%	< 0.001	171/210: 81.4%
Controlled	12/153: 7.8% UKN: 10	0% UNK: 3	0.515	12/158: 7.6% UKN: 13
Uncontrolled	141/153: 92.2%	5/5: 100%		146/158: 92.4% UKN: 13
HbA1c[d] (Mean ± SD)				10.33 ± 1.33
Newly diagnosed/new onset	33/163: 20.24%	0	N/A	33/171: 19.3%
DKA	17/163: 10.4%	1/8: 12.5%	0.852	18/171: 10.5%
Other co-morbidities and predisposing factors				

Table 1 (continued)

	RMOCM (188 cases) *n* (%)	Non-RMOCM (22 cases) Pulmonary, disseminates, gastrointestinal… *n* (%)	*P*-value between RMOCM and non-RMOCM	Overall CAM (210 cases) *n* (%)
HTN	52/188: 27.7%	8/22: 36.4	0.393	60/210: 28.6%
Hematological malignancies	6/188: 3.2%	3/22: 13.6%	0.022	9/210: 4.3%
Renal disease	15/188: 8%	7/22: 31.8%	0.001	22/210: 10.5%
Cardiovascular disease	22/188: 11.7%	2/22: 9.1%	0.716	24/210: 11.4%
Organ transplant	5/188: 2.7%	3/22: 13.6%	0.011	8/210: 2.8%
Chemotherapy/immunosuppressive	14/210: 7.4%	4/22: 18.2%	0.089	18/210: 8.6%
Mucormycosis treatments				
Systemic antifungal therapy	186/188: 99% Amp-B: 183/188: 97%	18/22: 82% Amp-B: 16/22: 73%	< 0.001	204/210: 97% Amp-B: 199/210: 95%
Surgical intervention	157/188: 83.5%	9/22: 41%	< 0.001	166/210: 79%
Treatments and outcomes				
Non-survived	66/169: 39% UKN: 19	17/22: 77.3%	< 0.001	83/191: 43.5% UKN: 19
Survived	103/169: 61% UKN: 19	5/22: 22.7%		108/191: 56.5% UKN: 19
Follow-up (days) Mean ± SD	Mean: 99.59 ± 68.02 27 cases	Mean: 68.33 ± 37.53 3 cases	0.445	Mean: 96.47 ± 65.85 30 cases
CAM diagnosis to death (days) Mean ± SD Median (IQR)	27.27 ± 31.15 days (3–180) (37 cases) Median: 22 (24) UKN: 29	14.47 ± 12.46[e] days (2–41) (15 cases) Median:10 (22) UKN: 1	0.332	23.58 ± 27.6 days (2–180) (46 cases) Median:17 (25) UKN: 30
Anatomic site involvement and morbidity in RMOCM patients				
Sinus/nasal involvement	183/188: 97.3%			
Pansinusitis/multiple sinuses involvement	81/188: 43%			
Maxillary involvement	65/188: 34.57%			
Orbital involvement	156/188: 82.5%			
Cerebral involvement	57/188: 30.3%			
Eye exenteration in survivors	29/103: 28.1%			
Eye exenteration in surviving patients with orbital invasion and clear outcome	29/75: 38.7%			
Vision loss	109/188: 58%			
Vision loss in survivors	59/103: 57.2%			
Vision loss in survived patients with orbital invasion and clear outcome	59/75: 78.6%			

RMOCM, rhino-maxillo-orbito-cerebral mucormycosis; *SD*, standard deviation; *IQR*, interquartile range; *UKN*, unknown; *HbA1c*, glycosylated hemoglobin; *DKA*, diabetic ketoacidosis; *HTN*, hypertension; *Amp-B*, amphotericin B

[a]Dose as dexamethasone equivalent. Information was available in only 27/185 patients with glucocorticoid therapy

[b]The cumulative glucocorticoids dose was calculated, while patients who received a very high dose from reference number 34 were excluded

[c]The patients without the following mucormycosis risk factors: diabetes, corticosteroid therapy, ICU admission, hematologic malignancy, organ transplant, immunosuppressive therapy/chemotherapy, and renal disease

[d]Data were available in only 25/171 patients with diabetes mellitus

[e]Cutaneous case was excluded due to inherent differences with other non-RMOCM manifestations

in 95% alone and in combination with another antifungal agent in 10.5% of patients. However, the combination therapy failed to reduce mortality (Table 2). The retrobulbar injection also was performed in 10.9% of RMOCM cases with orbital invasion but could not improve the eye, vision, and life salvage (Supplementary material Table S4). Surgical intervention was undertaken in 83.5% (157/188) of RMOCM cases versus 41% (9/22)

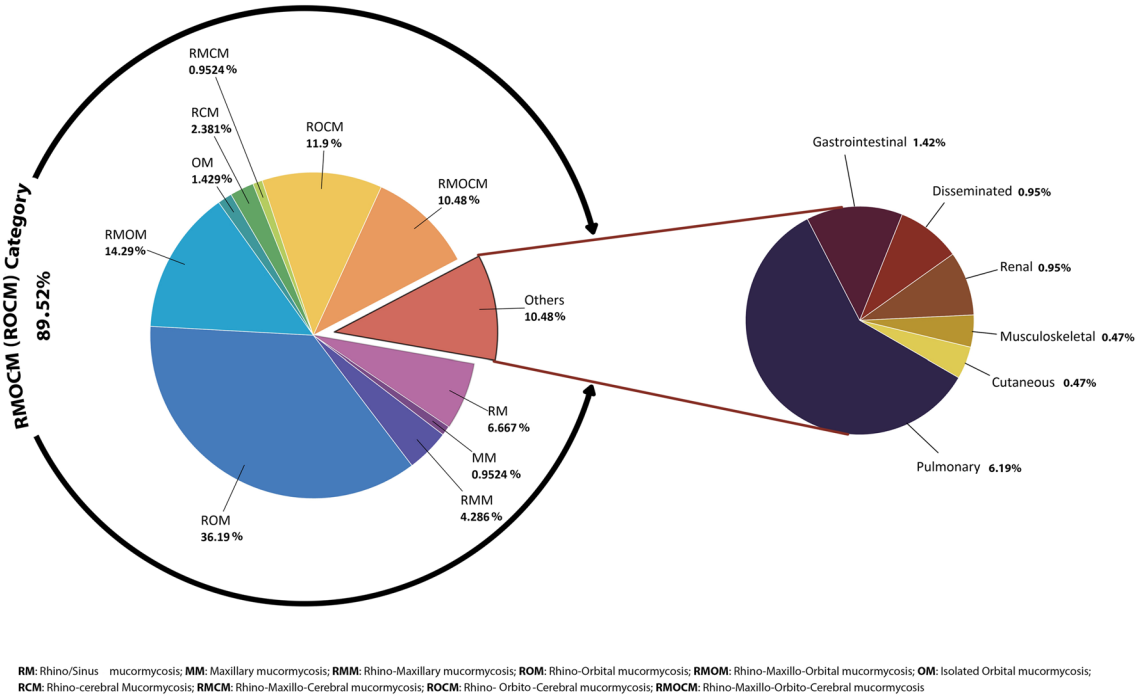

Fig. 2 Mucormycosis manifestations in 210 CAM patients based on anatomic site involvement

in non-RMOCM cases, with a significant difference (*P*-value < 0.001).

Vision loss is the most common morbidity in 57.2% of surviving RMOCM patients, while 78.6% of survivors with orbital invasion lost their vision. Among CAM patients with a clear outcome, mortality was 43.5%, which was significantly higher (*P*-value < 0·001) in non-RMOCM (77.3%) versus RMOCM (39.64%) cases.

Among non-survived patients, the median survival time from the MCR diagnosis or symptom onset was 22 (IQR: 24) days for RMOCM cases versus 10 (IQR: 22) days for non-RMOCM patients. In this regard, Kaplan–Meier survival analysis showed a higher survival probability in RMOCM cases without cerebral involvement compared to cases with cerebral involvement as well as non-RMOCM cases (*P*-value: 0.025 and 0.001, respectively) and also a higher survival chance in RMOCM cases if the patient survives within a month (Fig. 3).

A multivariate analysis of potential mortality risk factors is presented in Table 2. Age over 45 years and severe/critically ill COVID-19 disease were independently associated with increased mortality risk in CAM patients (OR: 2.874, *P*-value: 0.005, and OR: 3.667, *P*-value: < 0.001). ICU admission and mechanical ventilation during COVID-19 treatment also increased the mortality risk (OR: 6.789, *P*-value: < 0.001; and OR: 6.272, *P*-value: < 0.001). Additionally, cerebral and orbital involvement were associated with an increased risk of mortality in RMOCM cases (OR: 3.253, *P*-value < 0.001; and OR: 3.205, *P*-value: 0.013). In contrast, the surgical intervention significantly improved survival in RMOCM cases (OR: 18.922, *P*-value < 0·001). However, despite surgical intervention, cerebral invasion showed higher mortality (OR: 2.755, *P*-value = 0.007).

Risk of Bias Assessment

A total of 36.6%, 33.4%, and 30% of studies were rated as high, moderate, and low bias levels, respectively. An overall quality assessment is provided in supplementary material Figure S2.

Discussion

During the COVID-19 pandemic, the number of mucormycosis cases among SARS-COV-2 infected patients increased dramatically, estimated to be 50-fold higher than before COVID-19 [2], which may indicate a predisposing role of COVID-19 in CAM development through several inflammatory pathways [3, 4••, 8]. COVID-19-induced hyperglycemia can be due to the following reasons: direct viral damage to pancreatic beta cells leading to decreased insulin production [10], increased stress-related cortisol levels [80],

Table 2 Mortality-associated factors in 210 COVID-19-associated mucormycosis (CAM) patients

Mortality risk factors	RMOCM (169 cases)				All CAM (191 cases)			
	Survivors, $n=103$	Non-survivors, $n=66$	Odds ratio (95% CI)	*P*-value	Survivors, $n=108$	Non-survivors, $n=83$	Odds ratio (95% CI)	*P*-value
Demographics[a]								
Age > 45	63 (61.2%)	54 (81.8%)	2.874	0.005	68 (63%)	65 (78.3%)	2.124	0.022
Sex (M)	77 (74.8%)	45 (68.2%)	0.724	0.352	82 (75.9%)	60 (72.3%)	0.827	0.568
CAM reported from India	75 (72.8%)	31 (47%)	0.331	< 0.001	77 (71.3%)	37 (44.6%)	0.324	< 0.001
COVID-19-related factors[a]								
Active COVID-19	56 (54.4%)	41 (62.1%)	0.727	0.32	61 (56.5%)	52 (62.7%)	0.774	0.39
Recovered COVID-19	45 (43.7%)	15 (22.7%)			47 (43.5%)	31 (37.3%)		
Mild to moderate COVID-19	36 (35%)	44 (66.7%)	3.667	< 0.001	46 (42.6%)	20 (24%)	3.22	< 0.001
Severe to critical COVID-19	36 (44.4%)	44 (74.6%)			40 (37%)	56 (67.46%)		
ICU admission	9 (8.7%)	26 (39.4%)	6.789	< 0.001	12 (11.1%)	37 (44.6%)	6.435	< 0.001
Mechanical ventilation	5 (4.9%)	16 (24.2%)	6.272	< 0.001	7 (6.5%)	25 (30.1%)	6.219	< 0.001
Corticosteroid therapy	60 (58.3%)	47 (71.2%)	1.773	0.088	65 (60.2%)	58 (69.9%)	1.535	0.165
Remdesivir	18 (17.5%)	12 (18.2%)	1.049	0.907	21 (19.4%)	15 (18.1%)	0.914	0.81
Comorbidities and predisposing factors[a]								
Diabetes mellitus	89 (86.4%)	57 (86.4%)	0.996	0.993	91 (84.3%)	63 (75.9%)	0.588	0.148
Diabetes and corticosteroids therapy	93 (90.3%)	64 (97%)	3.441	0.099	98 (90.7%)	77 (92.8%)	1.31	0.616
Hematologic malignancy	1 (1%)	3 (4.5%)	4.857	0.136	1 (0.9%)	6 (7.2%)	8.338	0.022
Organ transplant	3 (2.9%)	2 (3%)	1.042	0.965	4 (3.7%)	4 (4.8%)	1.316	0.703
Chemotherapy/ immunosuppressive	5 (4.9%)	7 (10.6%)	2.325	0.156	6 (5.6%)	10 (12%)	2.329	0.108
Orbital involvement	78 (75.7%)	60 (90.9%)	3.205	0.013				
Cerebral involvement	20 (19.4%)	29 (43.9%)	3.253	< 0.001				
Treatment-related factors[b]	(121 cases)	(66 cases)			(126 cases)	(83 cases)		
Surgical intervention	111 (91.7%%)	44 (66.7%)	0.18 18.922	< 0.001	113 (89.7%)	51 (61.4%)	0.183	< 0.001
Combination antifungal therapy	13 (10.7%)	3 (4.5%)	0.396	0.148	15 (11.9%)	7 (8.4%)	0.682	0.424
Retrobulbar injection	8 (6.6%)	9 (13.6%)	2.23	0.11				
Surgical intervention in cases with cerebral involvement[c]	24 (21.6%)	19 (43.2%)	2.755	0.007				

RMOCM, rhino-maxillo-orbito-cerebral mucormycosis

[a]All cases with unclear outcomes and surviving patients without surgical treatment were excluded

[b]All but one patient whose outcome was not reported were analyzed

[c]Only patients who underwent surgical intervention were included in the analysis

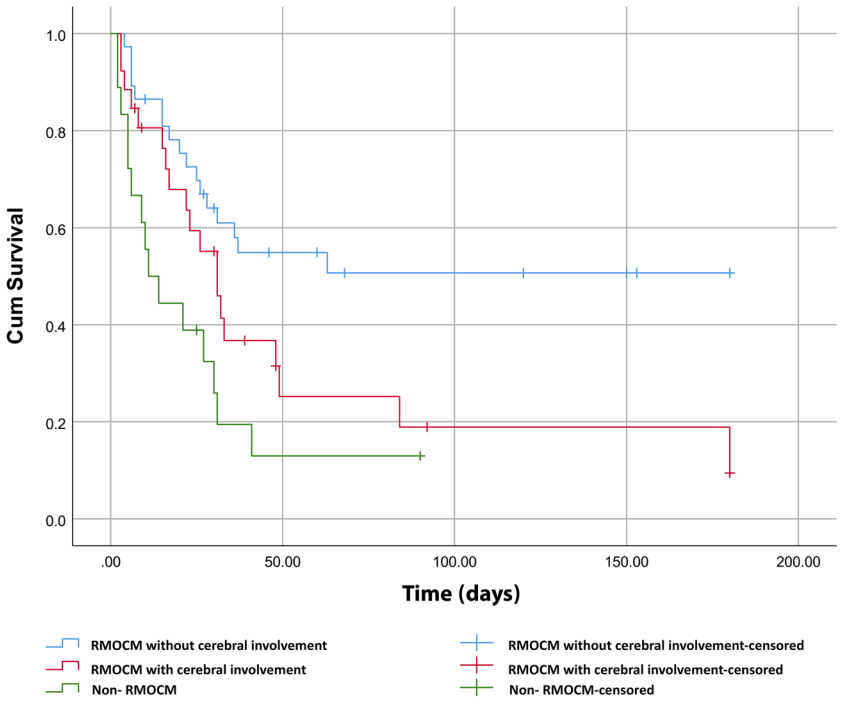

Fig. 3 Kaplan–Meier survival estimation among patients with the outcome and follow-up, comparing **a**) rhino-maxillo-orbito-cerebral mucormycosis without cerebral involvement. **b**) Rhino-maxillo-orbito-cerebral mucormycosis with cerebral involvement. **c**) Non-RMOCM (pulmonary, gastrointestinal, disseminated, renal, musculoskeletal). RMOCM without cerebral involvement (20, events 17). RMOCM with cerebral involvement (7, events 19). Non- RMOCM (3, events 15). RMOCM with cerebral versus without cerebral involvement (Pv:0.025). RMOCM without cerebral involvement versus non-RMOCM (Pv:0.001). RMOCM with cerebral involvement versus non-RMOCM (Pv:0.111)

and inappropriate corticosteroid therapy during COVID-19 management [11]. In addition, COVID-19-induced immunosuppression [12] and phagocytic dysfunctions by extensive corticosteroid therapy [81] fail to stop spore growth. Subsequently, the patient becomes susceptible to fungal infection. Furthermore, most COVID-19 patients show elevated ferritin levels, which leads to disrupted iron homeostasis and iron overload in the body [82]. This, in turn, promotes the growth of Mucorales species and contributes to vascular thrombosis and tissue necrosis [83]. Finally, since endothelial invasion is a crucial step in the pathogenesis of mucormycosis, endothelial damage in COVID-19 patients may serve as an important predisposing factor [84]· Given the above, COVID-19 infection is likely to contribute to CAM development. In the present study, COVID-19 alone (patients without other risk factors) was not identified as a primary risk factor; however, its predisposing role should not be overlooked (Table 1). COVID-19 infection is likely to contribute to CAM development.

In the present study, the RMOCM and non-RMOCM manifestations were 89.52% and 10.48% (Fig. 2), respectively, which is consistent with recent studies [4••, 85], although the RMOCM manifestation was much higher than pre-COVID-19 MCRs (34%). [7, 86• In addition, there was a close association between DM and CAM (81.4%) compared to the pre-COVID-19 period (40%) 7].

The ROCM refers to a range from sino/nasal to cerebral involvement (Fig. 2). Unlike traditional mucormycosis, maxillary involvement was observed in many CAM patients with toothache, tooth mobility, palatal wounds, and bone necrosis [14]. Since clinical presentations of orbital involvement are more pronounced and critical, early disease invasions, especially maxillary involvement, are often overlooked. In the present study, vision loss was the most common clinical presentation. However, facial/orbital pain (43%) and maxillary involvement (35.3%) appeared earlier, indicating their diagnostic value in the early stages.

Diabetes mellitus (DM) is a significant risk factor for COVID-19 and mucormycosis [5–7, 9]. On the other hand, COVID-19 infection and corticosteroid therapy during treatment can lead to dysregulation of blood glucose levels (hyperglycemia) [10, 11, 80] and immunosuppression [12]. Hyperglycemia causes phagocyte dysfunction, impaired chemotaxis, and intracellular killing by oxidative and non-oxidative mechanisms that predispose uncontrolled diabetic patients to mucormycosis [83, 87]. Diabetic ketoacidosis (DKA) disrupts iron homeostasis, leading to an increase in free iron in the blood and impairing phagocyte activity. This condition makes patients more susceptible to mucormycosis [83, 87].

During the COVID-19 outbreak, diabetes became the most critical risk factor [3, 4••, 14, 85, 85•]. We found diabetes is the leading independent risk factor (OR: 18.29) for RMOCM development and with much more weight compared to the pre-COVID-19 period (OR: 2.49) 7] versus non-RMOCM. In addition, in agreement with recent studies, 19.3% of diabetic patients were presented with newly diagnosed/new-onset DM, indicating undiagnosed diabetes or COVID-19/corticosteroid-induced hyperglycemia [14, 85].

Since inappropriate corticosteroid therapy can lead to corticosteroid-induced diabetes in healthy individuals or uncontrolled diabetes in diabetic patients, thereby increasing the mucormycosis risk [13], the corticosteroid predisposing role has recently been highlighted during the COVID-19 epidemic [14]. In the present study, COVID-19-related corticosteroid therapy was the most common predisposing factor (68.6%), which is almost similar to recent findings [4••, 14, 85, 86•, 88], but much higher than before COVID-19. The COVID-19 treatment guidelines recommend corticosteroids use only for patients needing supplemental oxygen and with a maximum of 6 mg/day dexamethasone for up to 10 days [18]. In this analysis, consistent with the previous findings [14, 88], the cumulative dexamethasone-equivalent doses in most patients were much higher than the recommended COVID-19 guidelines (Table 1), which could increase the CAM development risk [14].

The present analysis did not identify corticosteroid therapy as an independent risk factor for CAM. However, steroid-induced diabetes and glycemic dysregulation can be a significant predisposing factor in diabetic patients, particularly when used in inappropriate doses.

Consistent with previous studies [86•, 88], we estimated the mortality rate of COVID-19-associated mucormycosis to be 43.5%, which is similar to the mortality rate of pre-COVID-19 (46%) before the COVID-19 pandemic [7, 14]. However, this estimation should be viewed with skepticism, as most cases have been reported without follow-up or with only limited follow-up. In this regard, the mortality rate in the rest of the world (59.74%) is almost double compared to that of India (32.45%) (see Supplementary Material Table S5). This difference appears to be due to reporting bias and limited cases with clear outcomes in India. Only 14% of patients from India, compared to 57% from the rest of the world, were reported to have clear outcomes. However, the treatment experiences due to the endemic mucormycosis prevalence in India could be the reason for the different results.

The survival time and survival probability of RMOCM patients were significantly higher than those of non-RMOCM patients, particularly in cases of pulmonary and disseminated diseases. This finding is consistent with previous studies [14, 86•]. Possible reasons for the poorer outcome and shorter survival of non-RMOCM compared to RMOCM may include delayed diagnosis and challenges in performing surgical interventions in severe/ critical COVID-19 patients. Survival probability was significantly higher in RMOCM patients without cerebral involvement compared to those with cerebral involvement 3). Cerebral/orbital involvement was associated with an increased risk of mortality. Invasion of the cerebrum in non-survivors with orbital involvement also appears to be the primary cause of death, although it may remain undiagnosed. In general, an aggressive multidisciplinary approach to cases of mucormycosis helps improve outcomes. The three principles of mucormycosis treatment are controlling comorbidity/predisposing factors, administering appropriate and timely antifungal therapy, and performing surgical debridement with clean margins [6, 14, 85, 86•]. CAM is more commonly associated with a hyperglycemic state and inappropriate corticosteroid use. Therefore, it is recommended to strictly control hyperglycemia and discontinue steroid therapy. Due to vascular thrombosis and extensive tissue necrosis, antifungal therapy alone is ineffective [14, 85, 86•]. Regarding the present study, surgical intervention significantly improved outcomes in patients with RMOCM. However, cerebral invasion doubled mortality rates, even with surgical intervention. Therefore, early and thorough removal of necrotic tissue is recommended to prevent the spread of disease to vital structures such as the orbital cavity and cerebrum 20, 85, 86•]. Despite limited reports 23, 88], combination antifungal therapy failed to improve the outcome, which is consistent with previous evidence [6]. The retrobulbar injection was also unable to improve vision, eye, and life salvage in RMOCM patients (Supplementary material Table S4), which contradicts the previous report [35].

There are limitations to conducting the current review. First, the analysis was based on case report/series studies with significant heterogeneity in reporting, as well as reporting and publication biases. Second, many patients were reported with incomplete information. Third, due to the COVID-19 pandemic, limitations in medical services, and the lack of long-term follow-up, the incidence and outcome of CAM cases should be interpreted with caution. Finally, since most contributors were ophthalmic institutions, early non-ophthalmic clinical presentations were likely to have been neglected.

The strengths of our study include a comprehensive review and analysis of the characteristics of a large number of patients worldwide. We have collected detailed information on different manifestations of mucormycosis, including clinical presentations (particularly early symptoms), relevant comorbidities/predisposing factors, relevant parameters, risk factors for mortality, treatments, disease outcomes, and survival rates. These findings contribute to the credibility of our study. An update to the traditional classification of mucormycosis was also introduced, which now includes maxillary involvement. To accurately estimate the incidence, risk factors, and outcomes, further research is suggested to analyze patients with long-term follow-up and compare the CAM with the control group.

Conclusion

Within the limitation of the present study, it seems that the following conclusions can be reached:

1. CAM appears to be multifactorial, mainly due to combinations of COVID-19 with uncontrolled diabetes in RMOCM patients and COVID-19 with ICU admission in non-RMOCM cases.
2. COVID-19 alone is not the leading risk factor in the absence of other risk factors for CAM development.
3. Primary or corticosteroid-induced DM is the leading independent risk factor for RMOCM development (OR: 18.29).
4. ICU admission and antibiotic therapy (mostly in ICU patients) during COVID-19 treatment are major independent risk factors for non-RMOCM development (OR: 11.64, OR: 5.71).
5. CAM is a rare but high-mortality disease (43.5%), especially in pulmonary, disseminated, and cerebral involvement cases.
6. In RMOCM patients, orbital/cerebral involvement has a significant mortality risk (OR: 3.20, and 3.25), and in most survivors, the orbital invasion has life-changing morbidities, so early diagnosis is critical.
7. Control of comorbidities/predisposing factors (especially glycemic control), COVID-19 disease, and evidence-based use of corticosteroids are paramount to prevent CAM development.

Abbreviations CAM: COVID-19-associated mucormycosis; ROCM: Rhino-orbito-cerebral mucormycosis; RMOCM: Rhino-maxillo-orbito-cerebral mucormycosis; MCR: Mucormycosis; DM: Diabetes mellitus; OR: Odds ratio; Amp-B: Amphotericin-B; PRISMA: Preferred reporting items for systematic review and meta-analyses; PROSPERO: International Prospective Register of Systematic Reviews; IQR: Interquartile range

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Data Availability Data used in this study is available on reasonable request from the corresponding author.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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