Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Systematic review

COVID-19–associated mucormycosis: a systematic review and meta-analysis of 958 cases

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ABSTRACT

Background: Mucormycosis, a rare fungal infection, has shown an increase in the number of reported cases during the COVID-19 pandemic.
Objectives: To provide a comprehensive insight into the characteristics of COVID-19–associated mucormycosis, through a systematic review and meta-analysis.
Methods of data synthesis: Demographic information and clinical features were documented for each patient. Logistic regression analysis was used to predict the risk of mortality.
Data sources: PubMed, Scopus, Web of Science, Cochrane, CINAHL, Ovid MEDLINE, and FungiSCOPE.
Study eligibility criteria: Studies reporting individual-level information in patients with adult COVID-19–associated mucormycosis (CAM) between 1 January 2020 and 28 December 2022.
Participants: Adults who developed mucormycosis during or after COVID-19.
Interventions: Patients with and without individual clinical variables were compared.
Assessment of risk of bias: Quality assessment was performed based on the National Institutes of Health quality assessment tool for case series studies.
Results: Nine hundred fifty-eight individual cases reported from 45 countries were eligible. 88.1% (844/958) were reported from low- or middle-income countries. Corticosteroid use for COVID-19 (78.5%, 619/789) and diabetes (77.9%, 738/948) were common. Diabetic ketoacidosis ($p < 0.001$), history of malignancy ($p < 0.001$), underlying pulmonary (p 0.017), or renal disease ($p < 0.001$), obesity ($p < 0.001$), hypertension (p 0.040), age (>65 years) (p 0.001), *Aspergillus* coinfection (p 0.037), and tocilizumab use during COVID-19 (p 0.018) increased the mortality. CAM occurred on an average of 22 days after COVID-19 and 8 days after hospitalization. Diagnosis of mucormycosis in patients with *Aspergillus* coinfection and pulmonary mucormycosis was made on average 15.4 days (range, 0–35 days) and 14.0 days (range, 0–53 days) after hospitalization, respectively. Cutaneous mucormycosis accounted for <1% of the cases. The overall mortality rate was 38.9% (303/780).
Conclusion: Mortality of CAM was high, and most reports were from low- or middle-income countries. We detected novel risk factors for CAM, such as older age, specific comorbidities, *Aspergillus* coinfection, and tocilizumab use, in addition to the previously identified factors. **Laşin Özbek, Clin Microbiol Infect 2023;29:722**

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Introduction

COVID-19 caused by the SARS-CoV-2 was declared a pandemic on 11 March 2020 [1], approximately 2 months after its first detection in Wuhan, China [2]. Soon after, fungal coinfections, namely aspergillosis, candidiasis, and mucormycosis, started to emerge, particularly in patients with acute respiratory failure admitted to intensive care units (ICUs) requiring invasive ventilation [3,4]. At first, only rarely described, mucormycosis has been increasingly reported in patients with a current or past COVID-19 infection in early 2021 during the pandemic, particularly in India [5–7]. In India, where rates of mucormycosis have been generally high because of environmental exposure and host susceptibility patterns, the prevalence was shown to double in late 2020 compared with the previous year [8,9]. Overall, most COVID-19–associated mucormycosis (CAM) cases were reported in India, with at least 14 872 cases until May 2021 [10,11].

Mucormycosis is caused by fungi of the order Mucorales, which are ubiquitous in the environment [12]. Mucorales cause severe, rapidly progressive infections mostly in immunocompromised hosts, associated with life-changing morbidities and high mortality. Risk factors for mucormycosis include diabetes mellitus, haematological malignancies, solid organ transplantation, iron overload, neutropenia, and prolonged glucocorticoid use, all resulting in impaired immune function [13]. In the background of COVID-19, the risk of mucormycosis is increased because of the use of corticosteroids in addition to the uncontrolled hyperglycemic state and hyperferritinemia accompanying the viral infection [14]. Mucorales can cause infections at various anatomical sites, with associated signs and symptoms. Mucormycosis is a medical emergency that requires immediate initiation of systemic antifungals and adjunctive surgery [10,15].

With the continuing rise in CAM cases, there is a need for a comprehensive study investigating the demographic details, risk factors, disease characteristics, and outcomes of CAM. This study aimed to provide a comprehensive overview of the most common underlying conditions, causative fungal pathogens, the clinical management of mucormycosis in patients with COVID-19, and predictors of mortality in respective patients through the analysis of the cases reported between January 2020 and December 2022, to serve as a guide for health care professionals in the clinical management and prevention.

Methods

Search strategy

A preliminary scoping review was conducted to determine the key search terms and variables to obtain. A systematic search of PubMed, Scopus, Web of Science, Cochrane, CINAHL, and Ovid MEDLINE databases was performed for studies published between 1 January 2020 and 28 December 2022. The search terms included “COVID-19” AND “mucormycosis”. The detailed search strategy is presented in Table S1. Selected publications were managed using the reference manager Endnote (version X7, Clarivate Analytics [formerly Thomson Reuters], Philadelphia, PA, USA). Additional unpublished cases were identified in the FungiSCOPE registry (PMID 28730644). Collaborators within the network were invited via email or through posts on social media to contribute to cases diagnosed at the respective times (see Collaborators section). Anonymized patient data were provided using a data sheet or by documenting the case in the FungiSCOPE online questionnaire (Questback). Cases were validated by the FungiSCOPE team (D.S.) and evaluated for inclusion by the lead authors (L.Ö. and U.T.).

Selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used for reporting this systematic review and meta-analysis [16]. Studies that met the following criteria were included: (a) patients (>18 years old) who acquired mucormycosis during or after COVID-19 are presented; and (b) who had individual patient data available. Articles were excluded if (a) full text was unavailable, (b) unrelated to CAM, or (c) patient-level data were not provided. Manuscripts were subject to a triple-blind review by the authors for inclusion (L.Ö., U.T., M.M., B.H.E., S.N.B., S.A., and B.Ö.). Additionally, eligible articles were identified by citation chaining. Variables of interest were extracted for each case with a triple-blind check to create a consistent dataset (L.Ö., U.T., M.M., B.H.E., S.N.B., S.A., and B.Ö.). The eligible articles were subject to quality assessment based on the National Institutes of Health Quality Assessment Tool for Case Series Studies, and poorly graded studies were excluded (Tables S2 and S3) [17]. The grading was blind-reviewed (L.Ö., U.T., M.M., B.H.E., S.N.B., S.A., and B.Ö.), and disagreements were resolved jointly by the lead authors.

Data retrieval

If the diabetic control status was not specified in the article, patients with HbA1c levels >6.5% were considered diabetic, and HbA1c >8% was categorized as uncontrolled. HbA1c levels between 7% and 8% were considered to be associated with poorly controlled diabetes. For patients whose severity of COVID-19 was not specified in the article, the severity of COVID-19 was determined according to National Institutes of Health guidelines [18]. All cumulative corticosteroid doses were converted to dexamethasone equivalents [19].

The protocol of this study was registered with PROSPERO (CRD42022315423).

Statistical analysis

Statistical analysis was performed using Stata 16.0 software (Stata Corp, College Station, TX, USA). Chi-squared test and *t* test were used in the univariate analysis. Independent determinants of mortality were determined by multivariate logistic regression analysis. A p value of $\leq$0.05 was considered statistically significant.

Results

Our literature search yielded a total of 3877 studies (Fig. 1). A total of 298 studies reported the individual patient data of 902 eligible CAM cases (Table S3). Combined with the 56 cases provided by the collaborators, 958 CAM cases from 45 countries were included in our meta-analysis.

Among the studies included, the countries reporting the most CAM cases overall were India (543/958, 57%), Iran (103/958, 11%), Egypt (61/958, 6%), France (33/958, 3%), and Türkiye (30/958, 3%) (Fig. 2, Table S4). A total of 88.1% (844/958) of the cases were reported from low- and middle-income countries.

The median age of included CAM patients was 53 (range, 18–88 years; interquartile range 43–62 years), and the majority of the patients were men (672/958, 70%). The overall mortality rate was 38.9% (303/780), and the mortality rates varied widely between countries and different infection sites (Fig. 2, Tables S4 and S9). The mean age was higher among the fatal cases compared with the patients who survived (55.5 [standard deviation (SD), 14.5] vs. 51.0 [SD, 12.8]; p 0.001). Age >65 years was associated with increased mortality (91/174 [52.3%] vs. 212/605 [35.0%], p 0.001). Diabetes was the most common comorbidity (738/948 [77.9%]), 5.7% being post–COVID-19 diabetes (Table 1). Of the patients with diabetes, the vast

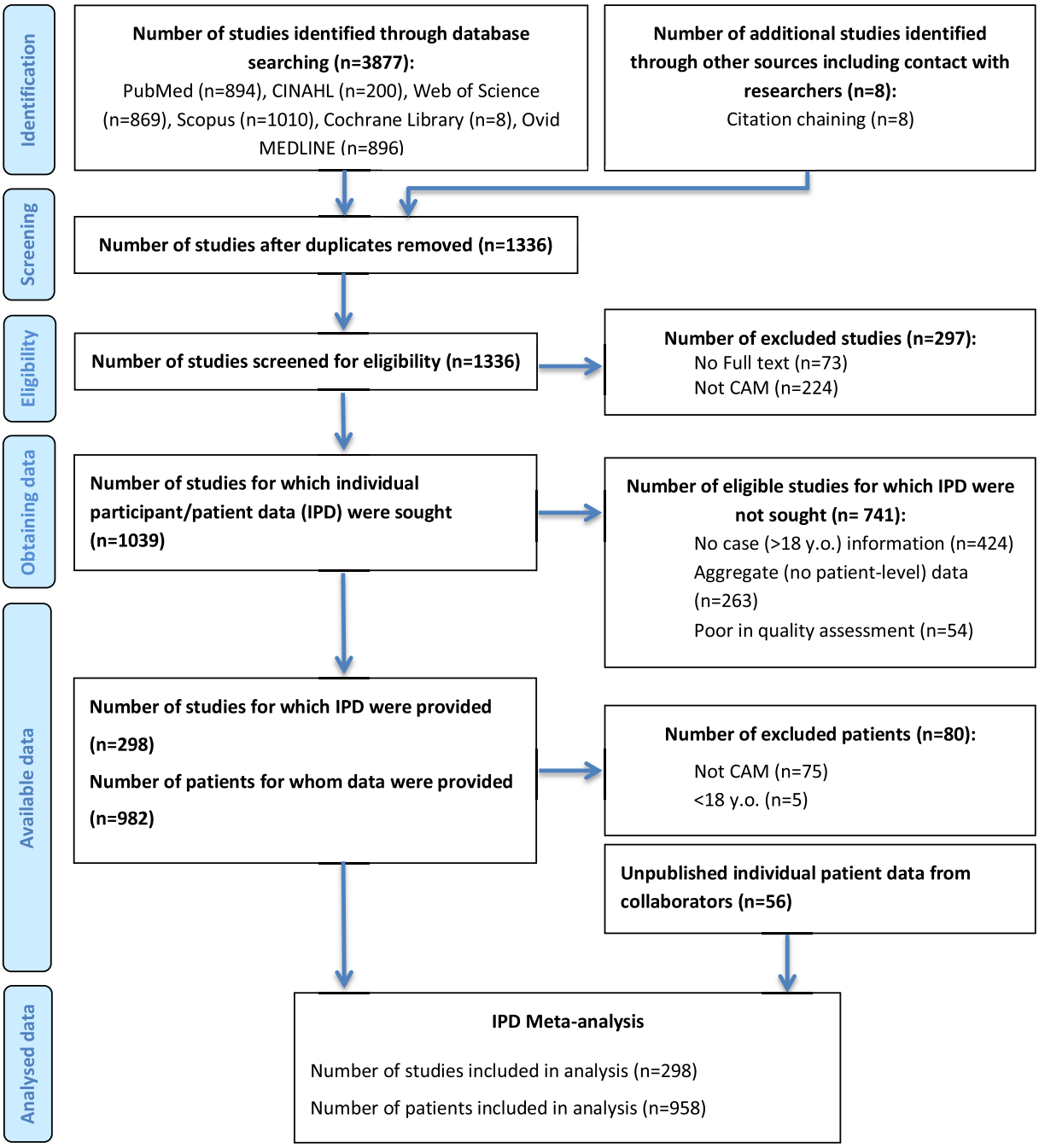

Fig. 1. Flow diagram describing the study selection process according to the PRISMA guidelines.

majority (341/405 [84.2%]) had poorly controlled or uncontrolled diabetes. 9.5% of all patients presented with diabetic ketoacidosis (DKA) (Table 1). Diabetes was equally common in women and men (226/283 women, 79.9% vs. 512/665 men, 77.0%; p 0.331), whereas DKA was significantly more common in women (25/183 women, [13.7%] vs. 36/460 men, [7.8%]; p 0.023). In the univariate analysis, DKA ($p < 0.001$), history of malignancy ($p < 0.001$), underlying pulmonary disease (p 0.017), renal disease ($p < 0.001$), obesity (body mass index >30.0) ($p < 0.001$), and hypertension (p 0.040) were associated with increased mortality (Table 1). In contrast, patients with uncontrolled or poorly controlled diabetes had lower mortality (p 0.006) (Table 1). Details of other comorbidities are presented in Tables S5 and S6.

The severity of COVID-19 was reported for 493 patients; 305 (61.9%) had severe, 86 (17.4%) had moderate, 89 (18.1%) had mild, and 13 (2.6%) had an asymptomatic infection. A total of 49.0% of the patients were admitted to the ICU and 29.4% required mechanical ventilation during COVID-19 (Table 2). In the univariate analysis, severe COVID-19 ($p < 0.001$) and ICU admission ($p < 0.001$) or mechanical ventilation ($p < 0.001$) during COVID-19 were significantly associated with higher mortality (Table 2). Most patients were treated with corticosteroids (78.5%), with dexamethasone being the most commonly used drug (46.6%) (Table 2). The history of corticosteroid use for COVID-19 did not significantly affect survival (Table 2), nor was a high cumulative dose of corticosteroids associated with increased mortality (Table S6). Tocilizumab use for

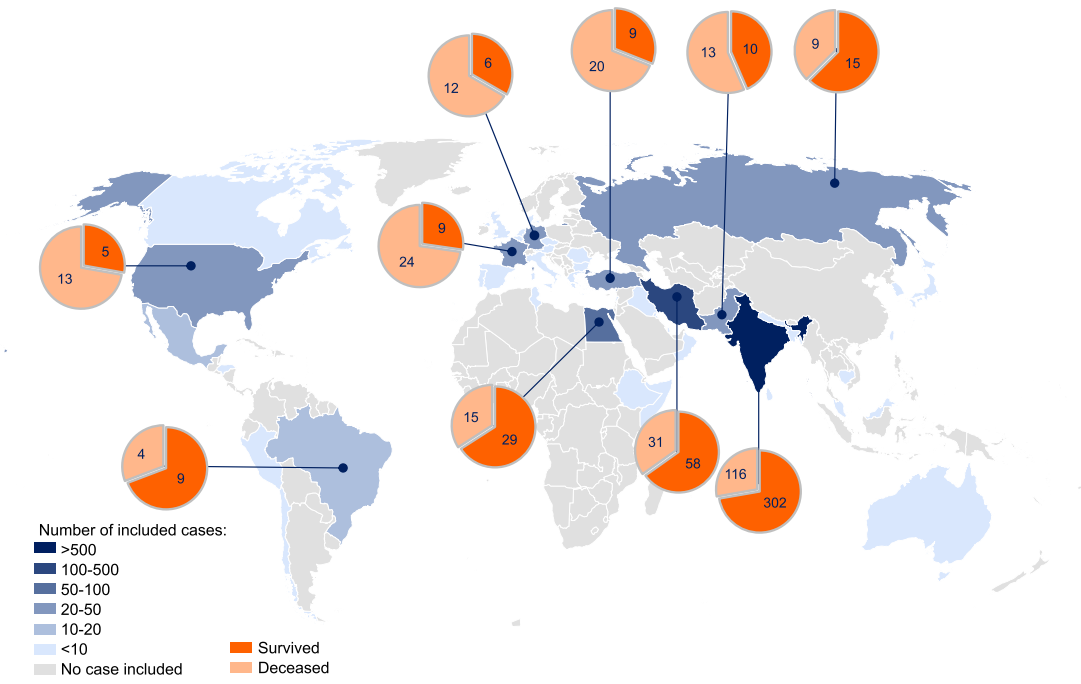

Fig. 2. Global distribution of the 958 CAM cases. The number of cases reported from each country is shown on the geographical heatmap with corresponding shades of blue as indicated in the legend. Pie charts show the number of survived and deceased patients for the top 10 countries reporting the most cases.

Table 1
The frequencies of the comorbidities and the associated rate of mortality

Comorbidities	% of patients with the comorbidity	% Mortality in patients:		p
		With the comorbidity	Without the comorbidity	
Diabetes mellitus	77.9 (738/948)	36.9 (217/588)	44.6 (83/186)	0.060
Post–COVID-19	5.7 (51/889)	29 (9/31)	39.1 (270/691)	0.261
Poorly controlled/uncontrolled	84.2 (341/405)	34.7 (104/300)	51.7 (30/58)	0.003
DKA	9.5 (61/643)	75.5 (40/53)	37.8 (186/492)	<0.001
Hypertension	26.4 (231/876)	44.6 (87/195)	36.3 (194/535)	0.040
Malignancy	4.1 (36/878)	74.3 (26/35)	36.8 (257/698)	<0.001
Hypothyroidism	3.0 (26/875)	37.5 (9/24)	38.5 (272/706)	0.919
Pulmonary disease	5.0 (44/877)	56.1 (23/41)	37.4 (258/690)	0.017
Renal disease	11.2 (97/870)	61.4 (54/88)	34.2 (216/632)	<0.001
Cardiovascular disease	10.7 (94/876)	44.4 (36/81)	37.9 (246/650)	0.250
Neutropenia	1.5 (13/869)	53.9 (7/13)	38.4 (269/701)	0.256
Transplant history	4.6 (40/871)	54.3 (19/35)	38.4 (265/690)	0.060
SOT	4.0 (35/871)	50.0 (15/30)	38.7 (269/695)	0.215
HSCT	0.6 (5/871)	80.0 (4/5)	38.9 (280/720)	0.061
Obesity (BMI > 30.0)	3.7 (32/877)	65.6 (21/32)	37.3 (263/706)	0.001

The percentage and number of occurrences for each variable are indicated. The mortality of patients with and without each comorbidity is given in two separate columns. p value is provided for the chi-squared test of mortality for each variable. Patients with no reported survival outcomes were excluded from the mortality analysis.
BMI, body mass index; DKA, diabetic ketoacidosis; HSCT, haematopoietic stem cell transplantation; SOT, solid organ transplantation.

COVID-19 was associated with increased mortality in the univariate analysis (Table 2).

First symptoms of mucormycosis developed on an average of 22.3 days (range, 0–240 days; SD, 26.8) after the diagnosis of COVID-19, and the mean duration of mucormycosis symptoms before admission was 10.7 days (range, 0–150 days; SD, 16.9). The mean duration between admission and diagnosis of mucormycosis was 8.2 days (range, 0–53 days; SD, 10.4), whereby diagnosis was significantly delayed in patients who passed away (mean, 10.6 days in deceased vs. 4.7 days in patients who survived; p 0.030). Details of the time course are presented in Supplementary Table S7. Overall, in 30.5% (158/518) of the cases, mucormycosis was

Table 2
The clinical features of the patients with COVID-19-associated mucormycosis

Clinical features of CAM	% of patients with the condition	% Mortality in patients:		p
		With the condition	Without the condition	
Severe/critical COVID-19	61.9 (305/493)	57.7 (158/274)	24.6 (41/167)	<0.001
ICU admission for COVID-19	49.0 (209/427)	68.5 (126/184)	27.5 (52/189)	<0.001
Mechanical ventilation for COVID-19	29.4 (126/429)	78.5 (91/116)	29.3 (79/270)	<0.001
Corticosteroids use for COVID-19	78.5 (619/789)	40.6 (218/537)	35.9 (51/142)	0.311
Dexamethasone	46.6 (240/515)	44.8 (98/219)	39.6 (95/240)	0.263
Prednisone	2.5 (13/515)	58.3 (7/12)	41.6 (186/447)	0.247
Prednisolone	6.0 (31/515)	16.1 (5/31)	43.9 (188/428)	0.002
Methylprednisolone	19.0 (98/516)	49.4 (44/89)	40.3 (149/370)	0.116
Hydrocortisone	1.9 (10/515)	90.0 (9/10)	40.1 (180/449)	0.002
Non-steroid immunomodulator use for COVID-19	14.6 (78/535)	50.7 (36/71)	37.0 (150/406)	0.028
Tocilizumab	9.1 (48/530)	55.6 (25/45)	37.4 (161/430)	0.018
Hydroxychloroquine	1.5 (8/522)	37.5 (3/8)	39.2 (180/459)	0.921
Hospital-onset mucormycosis	30.5 (158/518)	61.7 (92/149)	32.5 (95/292)	<0.001
Coinfection with *Aspergillus* sp.	8.5 (63/743)	51.7 (31/60)	37.9 (226/597)	0.037
Infection of the orbits	58.1 (529/911)	37.4 (165/441)	40.8 (124/304)	0.353
Infection of the cerebrum	34.0 (302/889)	44.8 (112/250)	36.1 (171/474)	0.022
Surgical treatment	78.0 (659/845)	26.5 (151/570)	75.3 (125/166)	<0.001
Antifungal treatment	96.3 (847/880)	37.0 (269/727)	79.3 (23/29)	<0.001
Amphotericin B	89.2 (749/840)	36.3 (235/648)	57.8 (41/71)	<0.001
Liposomal AmB	73.5 (536/729)	36.3 (169/465)	51.2 (84/164)	0.001
AmB deoxycholate	14.0 (102/729)	43.6 (41/94)	39.6 (212/535)	0.467
Others	1.1 (8/729)	42.9 (3/7)	40.2 (250/622)	0.886
Posaconazole	22.9 (192/839)	16.8 (31/185)	45.8 (244/533)	<0.001
In-hospital	14.2 (115/808)	25.0 (28/112)	42.5 (246/579)	0.001
Simultaneous with AmB	7.8 (59/753)	31.0 (18/58)	43.6 (252/578)	0.065
Subsequent to AmB	6.6 (50/756)	9.1 (4/44)	44.8 (265/591)	<0.001
Isavuconazole	7.2 (62/864)	44.6 (25/56)	37.9 (260/687)	0.314
Voriconazole	4.3 (37/865)	55.9 (19/34)	37.6 (267/710)	0.032
Fluconazole	2.2 (19/865)	33.3 (1/3)	38.5 (285/741)	0.855
Echinocandins	3.7 (32/865)	59.4 (19/32)	37.5 (267/712)	0.013

The number and percentage of occurrences for each variable are indicated. The mortality of patients with and without each variable is given in two separate columns. p value is provided for the chi-squared test of mortality for each variable. Patients with no reported survival outcomes were excluded from the mortality analysis.
AmB, amphotericin B; ICU, intensive care unit.

diagnosed during hospitalization, whereas in the other cases, patients were either admitted for the first time or discharged and eventually readmitted due to mucormycosis (Table 2). Hospital-onset cases were found to have increased mortality compared with those admitted with signs of mucormycosis (Table 2). The majority of the patients received antifungals and/or underwent surgery, both of which were more common in the surviving group (Table 2). Moreover, the survival rate was higher in patients receiving the combination of antifungals with known *in vitro* activity against mucormycosis and surgery compared with patients who received only antifungals with *in vitro* activity (385/522, 74% vs. 39/133, 29%; $p < 0.001$). Posaconazole therapy was associated with a high survival rate (Table 2). Seeing that some patients were treated with posaconazole after discharge only, in-hospital use of posaconazole was separately analysed and still yielded a high survival rate (Table 2). Although the simultaneous use of amphotericin and posaconazole did not pose an improved survival, subsequent posaconazole use was more frequent in the surviving group (Table 2).

Aspergillus coinfection was seen in 8.5% (63/743) of patients and was associated with higher mortality (Table 2). *Aspergillus* coinfection was significantly more prevalent in cases with hospital-onset, ICU admission, mechanical ventilation, obesity, neutropenia, pulmonary or disseminated mucormycosis, history of

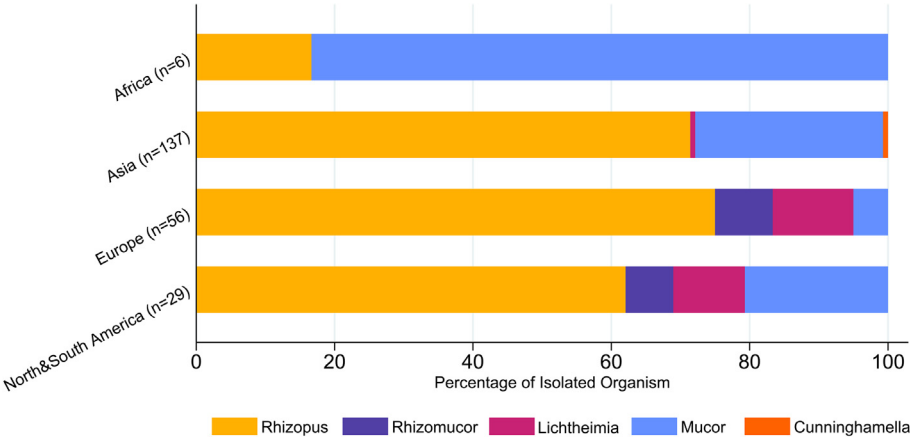

Fig. 3. Genus distribution of the identified pathogens by continents.

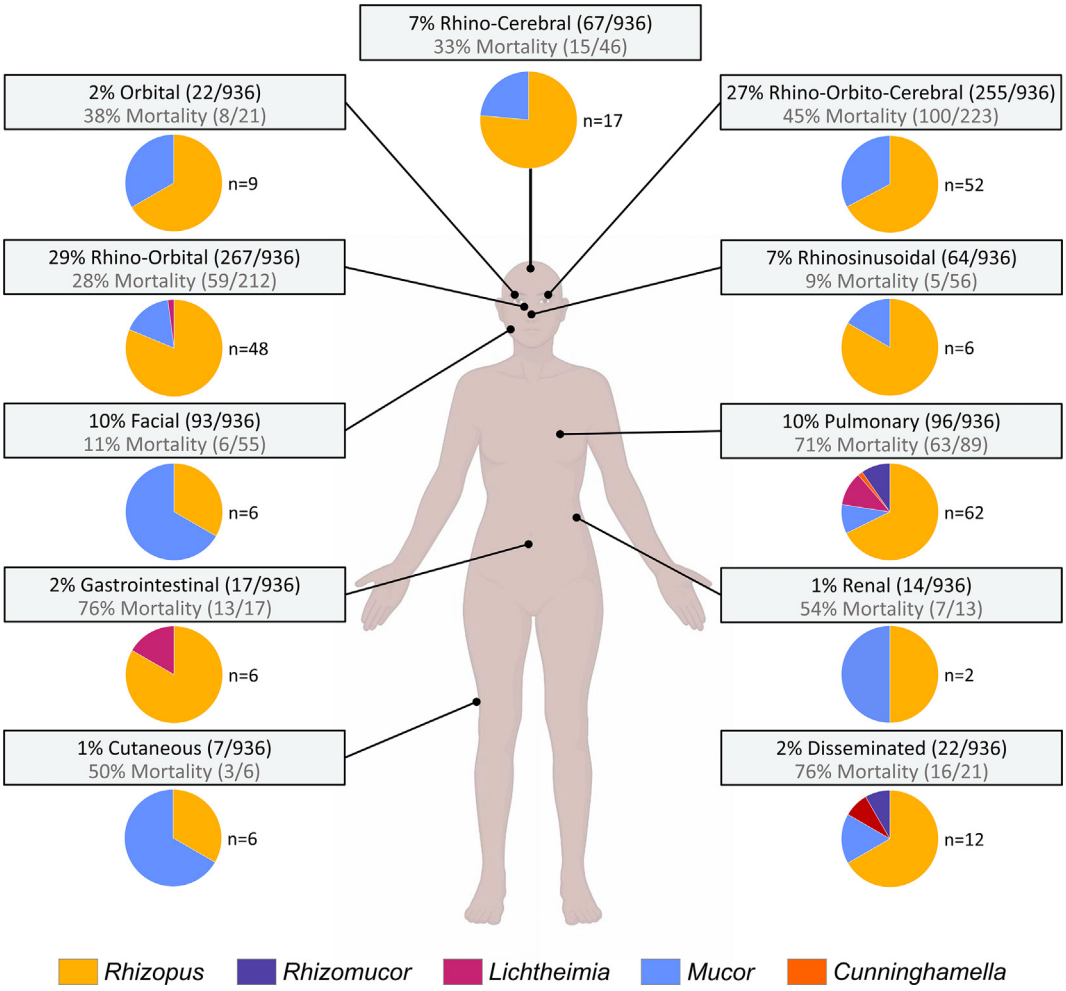

Fig. 4. Mortality rates and distribution of isolated pathogens for each site of mucormycosis. Other sites not shown in the figure are the glottis, mediastinum, breast, lymph node, spleen, vesicle, penis, and musculoskeletal.

malignancy, and COVID-19–related corticosteroid, dexamethasone, hydrocortisone, or tocilizumab use (Table S8). The mean duration of mucormycosis diagnosis was significantly prolonged in the case of coinfection (15.4 days [range, 0–35; SD, 11.5; $n = 10$] in patients with aspergillosis vs. 5.1 days [range 0–24; SD 7.2; $n = 35$] in patients without aspergillosis; p 0.001). Voriconazole, echinocandins, or isavuconazole use was more common among cases with aspergillosis (Table S8).

Information on isolated pathogens was available at the genus level for 233 cases and species level for 124 cases. *Rhizopus* was the most commonly identified genus ($n = 164$, 70.4%). Other genera included *Mucor* ($n = 50$, 21.5%), *Lichtheimia* ($n = 11$, 4.7%), *Rhizomucor* ($n = 7$, 3.0%), and *Cunninghamella* ($n = 1$, 0.4%). The predominantly identified species were *Rhizopus arrhizus* with 52 cases (41.9%) and *Rhizopus microsporus* with 40 cases (32.3%). Univariate mortality analysis revealed that *Rhizomucor* infections were more fatal (100% vs. 49%; p 0.007) and *Mucor* infections were less fatal (35% vs. 55%; p 0.020) (Table S9). The majority of the isolated pathogens in India (74%), Iran (80%), and France (72%), whereas the dominant genus in Egypt (83%) and Turkey (82%) were *Mucor*. *Lichtheimia and Rhizomucor* sp. were isolated predominantly in cases reported from Europe and the Americas (Fig. 3, Table S10).

The most common site of infection was rhino-orbital, followed by rhino-orbito-cerebral and pulmonary mucormycosis (Fig. 4, Table S9). The involvement of orbits and cerebrum was observed in 58.1% and 34.0% of patients, respectively (Table 2). Rhino-orbito-cerebral (p 0.025), pulmonary ($p < 0.001$), gastrointestinal (p 0.001), and disseminated ($p < 0.001$) mucormycosis were associated with increased mortality, whereas rhino-orbital ($p < 0.001$), facial ($p < 0.001$), and rhinosinusoidal ($p < 0.001$) infections were found to be less fatal. *Rhizopus* was the most commonly identified genus from all locations except facial and cutaneous, where *Mucor* was the predominant genus (Fig. 4, Table S11).

Rhino-orbito-cerebral and rhino-orbital mucormycosis were significantly more common in patients with diabetes (Table S12). Less common in patients with diabetes, pulmonary mucormycosis was associated with a history of malignancy, underlying pulmonary disease, ICU admission, or mechanical ventilation (Table S14). Mean time from admission to diagnosis was longer in patients with pulmonary mucormycosis (14.0 days [range, 0–53; SD, 12.5], $n = 19$) than patients with other infection sites (5.8 days [range, 0–35; SD, 8.5], $n = 47$; p 0.003). The history of malignancy increased the likelihood of disseminated as well as pulmonary infection sites, whereas rhino-orbito-cerebral and rhino-orbital mucormycosis were less common in these patients. *Rhizomucor* sp. and *Rhizopus* microsporus was more commonly isolated from pulmonary mucormycosis or patients with malignancy, whereas *Rhizopus arrhizus* were more common in patients with diabetes and rhino-orbito-cerebral mucormycosis (Tables S12, S13, S14, and S15).

Table 3
The predictors of fatality in mucormycosis

	Univariate analysis			Multivariate analysis		
Variable	Odds ratio	95% Confidence interval	p	Odds ratio	95% Confidence interval	p
Age >65 y	2.032	1.445–2.859	<0.001	0.909	0.373–2.213	0.833
Severe COVID-19	2.066	1.612–2.647	<0.001	1.208	0.709–2.057	0.487
Malignancy	4.957	2.287–10.743	<0.001	2.067	0.507–8.415	0.311
Renal disease	3.059	1.932–4.843	<0.001	1.265	0.506–3.161	0.615
Diabetic ketoacidosis	5.062	2.638–9.713	<0.001	6.690	2.326–19.247	<0.001
Hypertension	1.416	1.015–1.975	0.041	2.225	0.963–5.143	0.061
Chronic pulmonary diseases	2.140	1.133–4.040	0.019	0.532	0.158–0.792	0.308
Obesity	3.216	1.526–6.775	0.002	1.838	0.497–6.798	0.362
ICU for COVID-19	5.723	3.665–8.938	<0.001	2.369	2.369–1.333	0.125
MV for COVID-19	8.801	5.261–14.720	<0.001	5.722	1.847–17.719	0.002
Pulmonary mucormycosis	4.599	2.836–9.457	<0.001	4.784	1.737–13.171	0.002
Gastrointestinal mucormycosis	5.337	1.723–16.526	0.004	3.578	0.328–39.033	0.296

Independent risk factors for increased mortality in patients with COVID-19-associated mucormycosis based on the multivariate logistic regression analysis.
ICU, intensive care unit; MV, mechanical ventilation.

In the multivariate logistic regression analysis, factors with an increased mortality risk were DKA, pulmonary mucormycosis, and COVID-19–associated mechanical ventilation (Table 3). The area under the receiver operating characteristic curve was 0.8649.

Discussion

Summary of findings

Our in-depth analysis included 958 COVID-19–associated mucormycosis cases from around the globe. Diabetes and corticosteroid use for the treatment of COVID-19 was the most frequent underlying conditions in this study. Age >65 years, DKA, obesity, hypertension, history of malignancy, and underlying pulmonary or renal diseases were significant predictors of mortality. Despite the vast majority of patients receiving systemic antifungal treatment with surgical intervention in many cases, the overall mortality rate was high at 38.9%. Furthermore, mucormycosis caused by *Rhizomucor* spp., coinfection with *Aspergillus*, and rhino-orbito-cerebral, pulmonary, gastrointestinal, and disseminated mucormycosis were associated with poorer outcomes.

Patient demographics

Patients with COVID-19–associated mucormycosis had a higher average age compared with those in the prepandemic studies [6,20]. With age and comorbidities, the risk of severe COVID-19 increases, which is more likely to be treated with high-dose corticosteroids and associated with admission to the ICU and mechanical ventilation, all well-established risk factors for mucormycosis [7]. Overall mortality rates were lowest in India, where the majority of the cases were reported from. This could be explained by the high number of rhino-orbital mucormycosis cases reported in India, which are associated with better outcomes when compared with pulmonary, gastrointestinal, and disseminated mucormycosis [21–23]. The latter is more frequent in patients who are severely ill with underlying malignancy or other fatal comorbidities, together accounting for high mortality.

Underlying conditions

Uncontrolled diabetes as a well-known risk factor for mucormycosis was not associated with increased mortality in our study. This finding could be attributed to other more fatal underlying conditions giving rise to the infection in nondiabetics. It is crucial to underline that we found a higher percentage of orbital involvement in diabetic patients compared with nondiabetics. This could be substantiated by the angioinvasion of the fungi because of microangiopathic alterations induced by the advanced glycation end products and reactive oxygen species [24]. DKA provides perfect conditions in humans for fungal growth, such as hyperglycemia, hyperferritinemia, and metabolic acidosis [25]. DKA was identified as an independent predictor of increased mortality in our analysis. Obesity mediates the dysregulation of the immune system and thereby increases the risk of fungal infections; it has been identified as another prognostic factor associated with increased mortality in our patient population [24]. In contrast to studies conducted before the pandemic where diabetes, malignancies, and other immunocompromising underlying conditions were the major risk factors for mucormycosis globally [26,27], corticosteroid use was the most common risk factor in our patients. Lack of awareness of the increased risk for developing mucormycosis in the case of overuse of corticosteroids and easy access to the medication that was promoted to prevent severe courses of COVID-19 in India, lead to a high number of mucormycosis cases in the region.

Shifting patterns in mucormycosis during the pandemic

Before the COVID-19 pandemic, *Rhizopus microsporus* was isolated from mucormycosis patients with a frequency of 15% [27]. In our study, *Rhizopus microsporus* accounted for 32% of the cases. This increase is particularly concerning since *R. microsporus* is less susceptible to amphotericin B *in vitro* [28]. Moreover, in our study, *R. microsporus* was isolated more commonly in pulmonary mucormycosis, which was independently associated with higher mortality. However, these findings should be interpreted with caution since the etiological agent was known in only 24% (233/958) of the cases, based on morphological identification in most reports.

Apophysomyces and *Saksenaea* spp. mainly cause cutaneous mucormycosis, mostly in immunocompetent individuals after direct inoculation of the fungus after traumatic injuries [15,27]. As opposed to the higher prevalence in prepandemic studies [29,30], no patients in our cohort presented with skin trauma and cutaneous infections were generally scarce (<1%). Consistently, *Apophysomyces* and *Saksanea* were not isolated from any of the patients. Gastrointestinal mucormycosis, known to be associated with malnutrition and peritoneal dialysis [31,32], was also rare compared with prepandemic studies [26,33]. These results can be explained by our diverse group of patients presenting mostly with immunosuppressive conditions during the pandemic.

Despite the wide range of respiratory complications associated with COVID-19, we did not observe an increased frequency of

pulmonary mucormycosis during the pandemic [34]. This finding suggests that COVID-19 predisposes to mucormycosis through its systemic effects in the body, not through respiratory damage. However, it must be noted that the diagnosis of pulmonary mucormycosis was possibly more challenging in patients with COVID-19 because of overlapping symptoms masking the actual prevalence [7]. Indeed, the diagnosis of pulmonary mucormycosis was significantly delayed in our patients and was associated with higher mortality. One explanation could be that pulmonary lesions might not be accurately identified due to the background of COVID-19 lung damage. Also, the lack of awareness or initial misdiagnosis as pulmonary aspergillosis because of insufficient diagnostics may have been reasons for the delayed diagnosis of mucormycosis and thus, the delay in targeted treatment.

Management of CAM

The time between admission and diagnosis of mucormycosis was significantly shorter in surviving patients than in fatal cases, which was in line with the expectations given the aggressive and invasive nature of Mucorales. Patients with severe comorbidities and pulmonary or disseminated sites of mucormycosis were less likely to undergo surgical treatment, possibly due to the high risks associated with these operations outweighing the benefits. This may explain the poorer outcome in patients who did not undergo surgery. The use of voriconazole and echinocandins, agents with no proven *in vitro* activity against Mucorales associated with breakthrough mucormycosis [35–37], was associated with a lower survival rate in our patients. The increased mortality of patients treated with voriconazole can also be attributed to the presence of *Aspergillus* coinfection or misdiagnosis of pulmonary mucormycosis as aspergillosis, for which voriconazole would be the drug of choice.

Aspergillus and mucorales coinfection

Coinfection with *Aspergillus* was found in 9% of patients, demonstrating a higher frequency compared with prepandemic cases, and coinfection was associated with higher mortality in our study [38,39]. We found the risk factors for *Aspergillus* coinfection to be a history of malignancy, obesity, neutropenia, and the use of corticosteroids, dexamethasone, hydrocortisone, or tocilizumab for COVID-19. Aspergillosis coinfection was associated with ICU stay and mechanical ventilation for the treatment of severe COVID-19. Most cases with coinfections because of *Aspergillus* had pulmonary or disseminated mucormycosis, whereby mucormycosis was always diagnosed after aspergillosis. These findings suggest that aspergillosis is a risk factor for severe mucormycosis in COVID-19 patients admitted to the ICU, particularly in the setting of mechanical ventilation [40]. addition, patients with *Aspergillus* coinfection showed a significant delay in the diagnosis of mucormycosis, most likely due to the challenging differential diagnosis and lack of awareness for mucormycosis complicating aspergillosis.

Limitations

There were several limitations to our study. First, detailed information was not available for all patients for all variables. Second, a great number of patients presented in the literature with aggregate data had to be excluded. Therefore, our study establishes a significant relationship among the infection characteristics based on individual cases rather than establishing a global patient profile epidemiologically. Long follow-ups for surviving patients were usually not available; therefore, thereby we could only use the survival status of the patients as reported at the time of publication. Finally, we do not have a non-CAM control group to identify predisposing factors.

Future directions

Future studies should explore diagnostic algorithms with new techniques to establish mucormycosis diagnosis with high sensitivity and high specificity, bypassing the current obstacles in diagnosis caused by microbiological and imaging challenges. There is also very limited research on the management of CAM as a new entity. Both surgical interventions and medical treatments recommended previously in mucormycosis should be systematically explored in CAM.

Conclusion

CAM has posed a novel threat during the pandemic, especially because the impact of COVID-19 as a potential new risk factor for mucormycosis was unknown, and similarities and differences with mucormycosis before the pandemic had not been evaluated. Besides highlighting the changing characteristics of the infection, analysis of the data from a global patient group included in this study yielded a significant relationship between the underlying conditions, clinical details, and the outcome. With the increasing knowledge about mucormycosis in the setting of COVID-19, tailored clinical management will improve patient outcomes.

Author contributions

ÖE, LÖ, UT, BHE, and MM conducted the preliminary literature review and data analysis. LÖ, UT (introduction, methods, results, discussion); SNB, MH, and SA (introduction, discussion) wrote the initial manuscript. DS coordinated the provision of individual-level data on unpublished cases from our collaborators, validated cases, and supported the initial drafting of the figures. All authors contributed to the eligibility assessment and data extraction, critically reviewed the manuscript and contributed to the intellectual content and interpretation of the data.

Transparency declaration

Conflicts of Interests

The authors declare that they have no conflicts of interest.

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Availability of data

Available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.03.005

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