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REVIEW

Clinical Features and Mortality of COVID-19-Associated Mucormycosis: A Systematic Review and Meta-Analysis

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Abstract The recent increase of COVID-19-associated mucormycosis (CAM) has been commanding global attention. However, basic epidemiologic characteristics have not firmly been established. In this systematic review and meta-analysis, we sought to determine the clinical manifestations, potential risk factors, and outcomes of CAM. Observational studies reporting CAM were searched with PubMed and EMBASE databases in January 2022. We collected data on comorbidities and treatment for COVID-19, and performed a one-group meta-analysis on the frequency of orbital exenteration procedure and mortality of CAM using a random-effect model. Fifty-one observational studies, including a total of 2,312 patients with proven CAM, were identified. Among the 51 studies, 37 were conducted in India, 8 in Egypt, and 6 in other countries. The most common comorbidity was diabetes mellitus (82%). While 57% required oxygenation, 77% received systemic corticosteroids. Among CAM, 97% were rhino-orbital-cerebral (ROCM), and 2.7% were pulmonary mucormycosis. Usual presentations were headache (54%), periorbital swelling/pain (53%), facial swelling/pain (43%), ophthalmoplegia (42%), proptosis

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(41%), and nasal discharge/congestion (36%). Regarding the outcomes, orbital exenteration was performed in 17% (95% CI: 12–21%, I^2 = 83%) of the COVID-19-associated ROCM patients. The mortality of CAM was 29% (95% CI; 22–36%, I^2 = 92%). In conclusion, this systematic review and meta-analysis indicated that the most prevalent type of CAM was ROCM, and most CAM patients had diabetes mellitus and received systemic glucocorticoids. Clinicians in the endemic areas should have a high index of suspicion for this invasive fungal complication of COVID-19 when a diabetic patient who received high-dose systemic glucocorticoids developed rhino-orbital symptoms.

Keywords COVID-19 · Mucormycosis · Glucocorticoids · Diabetes mellitus · Meta-analysis

Introduction

The number of COVID-19 cases complicated by secondary fungal infections has been soaring [1]. This trend has been commanding global attention because secondary infections can result in worse outcomes, as several studies on COVID-19-associated pulmonary aspergillosis (CAPA) have reported higher mortality. Excessive treatments with glucocorticoids and anti-cytokine agents possibly increase the risk of invasive fungal infections [2, 3]. Since the RECOVERY trial demonstrated the mortality benefit of dexamethasone in July 2020, glucocorticoids have been the standard therapy for severe COVID-19 pneumonia [4], possibly leading to the recent noticeable increase of secondary invasive fungal infection [1, 5].

Compared to CAPA, less is known about COVID-19-associated mucormycosis (CAM). Mucormycosis is a fungal infection characterized by infarction and necrosis of host tissues because of its angio-invasive nature of the fungal hyphae [6]. The first case series of CAM in India collected the clinical data between August and December 2020 and indicated the probable relationship between COVID-19 and mucormycosis [7]. This relationship was supported by other reports which described the impact of glucocorticoid therapy for COVID-19 on the subsequent mucormycosis [8, 9]. In contrast, several case reports described the simultaneous diagnosis of mucormycosis with COVID-19 [10, 11]. These cases emphasized the influences of shared background risk factors for both diseases, such as immunodeficiency and diabetes mellitus (DM), rather than the causal relationship brought by glucocorticoid treatment for COVID-19.

Observational studies and reviews of case reports and case series on CAM reported the mortality of 14–30%. However, the actual impact of CAM has not been comprehensively explored as one of the largest observational studies included non-proven mucormycosis as well [12, 13]. Furthermore, whereas rhino-orbital-cerebral mucormycosis (ROCM) and pulmonary mucormycosis had been the major types of the disease before the current pandemic of COVID-19, the difference in clinical characteristics between non-COVID-19 mucormycosis and CAM remain under-investigated. In the present study, we conducted a systematic review and meta-analysis to elucidate the clinical presentations, potential risk factors, and outcomes of CAM, aiming to seize comprehensive pictures of this invasive fungal complication.

Materials and Methods

Data Sources and Search

All prospective, retrospective, and cross-sectional observational studies and case series reporting CAM were searched using a two-level search strategy. First, we conducted a comprehensive literature search of PubMed and Embase databases on January 20, 2022. The search terms included ("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND ("mucor" OR "mucormycosis" OR "zygomycosis"). Second, we performed an additional manual search of secondary sources, including references of initially identified articles, to maximize the completeness of the collection of relevant studies. The search was performed without language restriction.

Study Selection

A study meeting the following criteria was included in the meta-analysis; (1) the study was published in a peer-reviewed journal, (2) the study design was prospective, retrospective, cross-sectional observational study, or case series, (3) the study was reporting mucormycosis cases with past or concurrent COVID-

19 infection, (4) the diagnosis of COVID-19 was confirmed with nucleic acid amplification tests (e.g., reverse transcription polymerase chain reaction [RT-PCR]), rapid antigen tests, or serum antibody tests, (5) the diagnosis of mucormycosis was confirmed by microscopic visualization, histopathologic examination, or culture, in accordance with guidelines [14, 15]. We excluded observational studies that did not clearly state the diagnostic criteria used for COVID-19 or mucormycosis, as well as case reports. When multiple studies from the same authors and the same institutes were detected, smaller (and earlier) studies were omitted because larger studies were assumed to include the cases reported in the smaller studies.

Data Extraction

Two investigators (AW and MS) reviewed the search results separately to select the studies based on the inclusion and exclusion criteria and assessed the eligibility of each study. The full texts of articles were retrieved for eligibility assessment and further analysis after the initial screening with title and abstract. Any discrepancies were resolved by discussion and consensus. The following data were extracted from each eligible study: authors' names, study location, design, setting, observational period, and sample size (the number of CAM). We also collected the following patient characteristics and outcomes: co-morbidities, initial symptoms, the type and extension of mucormycosis, the interval between COVID-19 and the onset of mucormycosis, treatment for COVID-19, intervention for mucormycosis, and the number of deceased patients.

Statistical Analysis

The endpoints of this study were the frequency of endoscopic or surgical intervention, orbital exenteration, and mortality among patients with CAM. We performed a one-group meta-analysis with a random-effects model using the DerSimonian-Laird method. Statistical analyses were executed with OpenMetaAnalyst version 12.11.14 (available at http://www.cebm.brown.edu/openmeta/) [16]. Heterogeneity among studies was evaluated with I^2, more than 50% indicating substantial heterogeneity. This meta-analysis was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [17].

Results

We identified a total of 512 articles through the initial database and subsequent manual searches. After removing duplicated items and screening based on title and abstract, 221 articles were assessed for eligibility. Among these articles, 168 were excluded, including 42 case reports and 14 retrospective studies without clearly stipulated diagnostic criteria for COVID-19 and mucormycosis. In particular, the largest observational study by Sen M et al.[12] (N = 2,826) was excluded because this study included probable/possible cases of CAM as well as microbiologically or histopathologically confirmed CAM; we were unable to extract data of proven CAM separately from their report. Of the remaining 53 studies, we excluded 2 case series [18, 19] because observational studies with larger sample sizes have been published by the same authors. Eventually, 36 observational studies and 15 case series with a total of 2,312 proven CAM cases were included in our meta-analysis [7, 9, 20–68](Fig. 1).

The characteristics of the included studies are summarized in Table 1. Among the selected 51 studies, 37 were conducted in India, 8 in Egypt, 2 in Iran, and 1 in the United Kingdom, Germany, Spain, and the Czech Republic. The observational period of each study varied between January 2020 and August 2021. The median age of the patients ranged from 36 to 63. The percentage of males ranged from 20 to 100%. 2.1% (6/284) were fully vaccinated against SARS-CoV-2. The most common co-morbidity was diabetes 82% (1,853/2,251, [382 patients were newly detected at the time of COVID-19 diagnosis, 61 patients presented with DKA]), followed by hypertension 42% (250/596), chronic kidney diseases 15% (113/735), immunosuppression (i.e., solid organ transplantation, acquired immunodeficiency syndrome, the use of immunosuppressive medications) 14% (97/675), and malignancy 2.6% (10/391). 57% (807/1,420) required oxygen supplementation because of COVID-19 pneumonia, and 12% (89/766) were mechanically ventilated. 77% (1,503/1,949) and 4.7% (23/489) received corticosteroids and tocilizumab, respectively, and 27% (191/699) were admitted

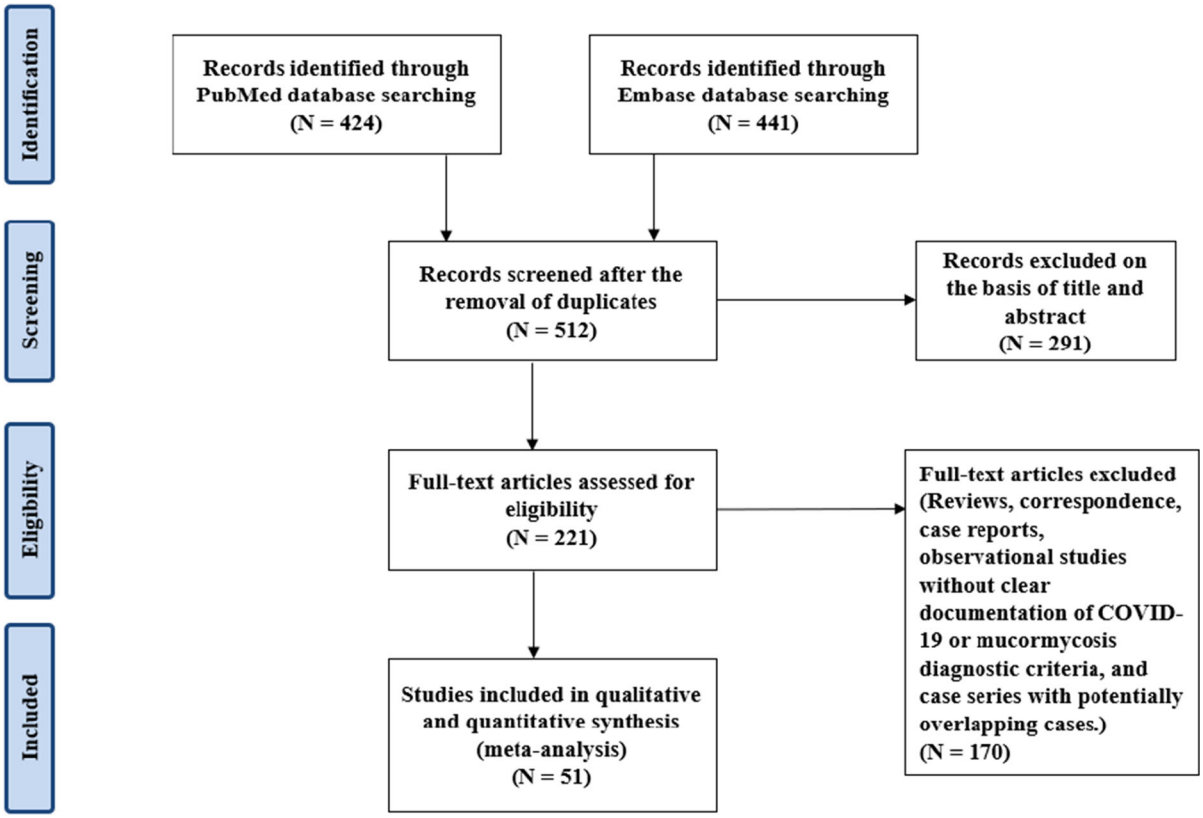


Fig. 1 Flow diagram of study selection

to intensive care units. The median interval between COVID-19 and the onset of initial symptoms of mucormycosis ranged from 10 to 31 days. Concurrent infections with other fungi were observed in 6.1% (24/393) of CAM.

The type of CAM, symptoms, treatments, and outcomes are summarized in Table 2. The most common type of CAM was ROCM 97% (2,242/2,312), followed by pulmonary 2.7% (63/2,312), and others (cutaneous, renal, gastrointestinal, disseminated). Among COVID-19-associated ROCM patients, orbital and intracranial involvement was observed in 50% (731/1,451) and 25% (404/1,638), respectively. The most common presentation was headache 54% (254/474), followed by periorbital swelling or pain 53% (242/460), facial swelling or pain 43% (230/532), ophthalmoplegia 42% (98/236), proptosis 41% (182/447), nasal congestion or discharge 36% (184/515), decreased or loss of vision 31% (181/584), ptosis 28% (78/276), dental pain or loosened teeth 25% (31/124), and palatal discoloration or ulcers 22% (90/404). 83% (95% CI; 78–88%, I^2 = 90%) of CAM patients were endoscopically or surgically treated (Fig. 2a). Orbital exenteration was performed in 17% (95% CI; 12–21%, I^2 = 63%) of ROCM patients (Fig. 2b). The mortality of CAM was 29% (95% CI; 22–36%, I^2 = 92%) (Fig. 2c).

Discussion

This systematic review and meta-analysis identified 2,312 confirmed cases of CAM and provided a comprehensive picture of this disease. ROCM comprised more than 90% of CAM. Diabetes was the most prevalent comorbid condition found in CAM patients. While 57% of the CAM patients had required oxygen therapy for COVID-19 pneumonia, 77% had received corticosteroids. Most mucormycosis was treated endoscopically or surgically, and orbital exenteration was performed on 17% of ROCM patients. The overall mortality of CAM was estimated to be 29%.

Table 1 Study and patients characteristics

Author	Country	Design	Setting	Confirmed CAM, N	Observational period	Age (Mean, SD) [range]	Male, % (N)	Diabetes, % (N)
Moorthy A. [20]	India	Retrospective	Multi-center	17	May 2020–Dec 2020	55 [35–73]	83 (14)	88 (15)
El-Kholy NA. [21]	Egypt	Prospective	Single-center	28	Aug 2020–Dec 2020	53 ± 11	53 (15)	–
Ravani SA. [22]	India	Retrospective	Single-center	31	Sep 2020–Mar 2021	56	65 (20)	94 (30)
Ramaswami A. [23]	India	Retrospective	Single-center	70	Apr 2021–Jun 2021	45 [38–56]	60 (42)	70 (49)
Gupta NK. [24]	India	Retrospective	Single-center	74	Mar 2021–May 2021	52	65 (48)	97 (72)
Mishra Y. [25]	India	Retrospective	Single-center	32	Apr 2021–May 2021	58 ± 9	47 (15)	88 (28)
Kumari A. [26]	India	Retrospective	Single-center	20	Mar 2021–May 2021	54 [35–67]	55 (11)	80 (16)
Gupta DP. [27]	India	Prospective	Single-center	70	Mar 2020–Dec 2020	[20–75]	67 (47)	100 (70)
Patel A. [28]	India	Retrospective	Multi-center	187	Sep 2020–Dec 2020	57 ± 13	80 (150)	60 (113)
Dubey S. [29]	India	Retrospective	Single-center	46	Apr 2021–Jun 2021	53 ± 10	64 (29)	100 (46)
Bhanuprasad K. [30]	India	Prospective	Single-center	132	Jun 2020–Jul 2021	51 ± 12	77 (101)	98 (129)
Selarka L. [31]	India	Prospective	Multi-center	47	Jan 2021–Mar 2021	55 ± 13	75 (35)	77 (36)
Muthu V. [32]	India	Retrospective	Single-center	31	–	53 [48–58]	76 (23)	75 (21)
Pakdel F. [33]	Iran	Cross-sectional	Multi-center	15	Apr 2020–Sep 2020	52 [14–71]	66 (10)	87 (13)
Meawed TE. [34]	India	Cross-sectional	Single-center, ICU	11	Oct 2020–Apr 2021	–	–	–
Zirpe K. [35]	India	Retrospective	Single-center	84	Feb 2021–Jun 2021	49 ± 12	83 (70)	64 (54)
Pal P. [36]	India	Prospective	Single-center	31	May 2021–Jun 2021	53 [20–78]	68 (21)	100 (31)
Pippal SK. [37]	India	Prospective	Single-center	80	May 2021–Aug 2021	–	69 (55)	90 (72)
Ismaiel WF. [38]	Egypt	Retrospective	Single-center	10	–	–	–	–
Avatef Fazeli M. [39]	Iran	Retrospective	Single-center	9	Oct 2020–Nov 2020	59	33 (3)	78 (7)
Goddanti N. [40]	India	Retrospective	Single-center	300	Apr 2021–Jun 2021	49 ± 12	74 (222)	96 (287)
Kulkarni R. [41]	India	Retrospective	Multi-center	49	Dec 2020–Jun 2021	53 ± 11	71 (35)	82 (40)
Dokania V. [42]	India	Prospective	Single-center	21	Apr 2021–Jun 2021	50 ± 14	71 (15)	90 (19)
Nair AG. [43]	India	Retrospective	Multi-center	13	–	36 [20–51]	69 (9)	0 (0)

Table 1 continued

Author	Country	Design	Setting	Confirmed CAM, N	Observational period	Age (Mean, SD) [range]	Male, % (N)	Diabetes, % (N)
Kumar S. [44]	India	Retrospective	Single-center	287	May 2021–Jul 2021	–	79 (227)	80 (229)
Joshi AR. [45]	India	Retrospective	Single-center	25	Mar 2021–Apr 2021	55 ± 13	–	88 (22)
Choksi T. [46]	India	Retrospective	Single-center	73	Mar 2021–May 2021	54 ± 13	66 (48)	74 (48)
Bansai SB. [47]	India	Retrospective	Single-center	11	Feb 2020–May 2021	47 ± 11	100 (11)	64 (7)
Fouad YA. [48]	Egypt	Retrospective	Single-center	26	Apr 2021–Aug 2021	63 [46–70]	54 (14)	96 (25)
Meher R. [49]	Iran	Prospective	Single-center	111	May 2021–Jun 2021	53 ± 12	70 (78)	94 (104)
Guzman-Castro S. [50]	UK	Retrospective	Single-center	6	May 2021	52 [45–57]	83 (5)	83 (5)
Kumar H. [51]	India	Retrospective	Single-center	28	Apr 2021–May 2021	54 [48–59]	79 (22)	75 (21)
Yadav T. [52]	India	Retrospective	Single-center	50	Dec 2020–Jun 2021	50 [28–70]	62 (31)	86 (43)
Meshram HS. [53]	India	Retrospective	Multi-center	61	Nov 2020–Jul 2021	45 [38–54]	89 (54)	49 (30)
Popli H. [54]	India	Retrospective	Single-center	23	Jul 2020–Jun 2021	48 ± 12	57 (13)	78 (18)
Patel DD. [55]	India	Cross-sectional	Single-center	96	Mar 2021–May 2021	49 [21–76]	73 (70)	72 (69)
Sen M. [7]	India	Case series	Single-center	5	Aug 2020–Dec 2020	58	100 (5)	100 (5)
Saidha PK. [9]	India	Case series	Single-center	6	–	[29–68]	66 (4)	100 (5)
Roushdy T. [56]	Egypt	Case series	Single-center	2	Jan 2021–Apr 2021	[59–73]	100 (2)	100 (2)
Sai Krishna D. [57]	India	Case series	Single-center	2	–	[34–50]	100 (2)	100 (2)
Nehara HR. [58]	India	Case series	Single-center	5	–	[33–70]	20 (1)	100 (5)
Singh Y. [59]	India	Case series	Single-center	13	Nov 2020–Jan 2021	[5–75]	85 (11)	62 (8)
Garg R. [60]	India	Case series	Single-center	7	May 2021	[38–70]	71 (5)	100 (7)
Arana C. [61]	Spain	Case series	Single-center	2	–	[48–62]	100 (2)	50 (1)
Barman Roy D. [62]	India	Case series	Single-center	2	–	[39–50]	50 (1)	50 (1)
Ashour MM. [63]	Egypt	Case series	Single-center	6	–	[41–67]	50 (3)	100 (6)
Pal P. [64]	India	Case series	Single-center	10	May 2021–Jun 2021	[28–66]	60 (6)	70 (7)
Riad A. [65]	Czech	Case series	Multi-center	6	Apr 2021–May 2021	[47–68]	71 (5)	83 (5)

Table 1 continued

Author	Country	Design	Setting	Confirmed CAM, N	Observational period	Age (Mean, SD) [range]	Male, % (N)	Diabetes, % (N)
Said Ahmed WM. [66]	Egypt	Case series	Single-center	14	–	[29–77]	71 (10)	100 (14)
Alloush TK. [67]	Egypt	Case series	Single-center	14	May 2021–Jun 2021	[49–82]	64 (9)	93 (!3)
Seidel D. [68]	Germany	Case series	Multi-center	13	Feb 2020–Jun 2021	[30–75]	62 (8)	23 (3)

Author	HTN, % (N)	CKD, % (N)	Immunosuppression, % (N)	Malignancy, % (N)	Hypoxia, % (N)	Mechanical ventilation, % (N)	Corticosteroids treatment, % (N)	ICU admission, % (N)
Moorthy A. [20]	–	–	–	–	–	–	88 (15)	–
El-Kholy NA. [21]	–	–	–	–	–	–	–	–
Ravani SA. [22]	53 (17)	6.3 (2)	–	–	–	–	100 (19)	–
Ramaswami A. [23]	24 (17)	8.6 (6)	2.9 (2)	–	–	–	70 (49)	–
Gupta NK. [24]	–	6.8 (5)	–	1.4 (1)	69 (51)	–	91 (67)	–
Mishra Y. [25]	50 (16)	–	0 (0)	–	69 (22)	–	94 (30)	–
Kumari A. [26]	–	15 (3)	–	–	–	–	80 (16)	–
Gupta DP. [27]	–	–	7.1 (5)	2.9 (2)	–	–	–	–
Patel A. [28]	–	–	1.6 (3)	1.1 (2)	56 (74)	–	78 (146)	31 (58)
Dubey S. [29]	–	–	–	–	72 (33)	0 (0)	52 (24)	–
Bhanuprasad K. [30]	–	5.3 (7)	1.5 (2)	–	14 (19)	2.3 (3)	55 (73)	–
Selarka L. [31]	–	–	–	–	81 (38)	43 (20)	100 (47)	–
Muthu V. [32]	32 (9)	–	–	–	55 (16)	24 (7)	71 (20)	–
Pakdel F. [33]	47 (7)	–	–	13 (2)	60 (9)	6.7 (1)	47 (7)	–
Meawed TE. [34]	–	–	–	–	–	–	–	–
Zirpe K. [35]	37 (31)	3.6 (3)	–	–	68 (57)	–	83 (70)	–
Pal P. [36]	–	–	–	–	–	–	–	–
Pippal SK. [37]	75 (60)	1.3 (1)	–	–	–	–	–	–
Ismaiel WF. [38]	–	–	–	–	–	–	–	–
Avatef Fazeli M. [39]	44 (4)	22 (2)	11 (1)	–	–	13 (1)	100 (7)	25 (2)
Goddanti N. [40]	–	–	–	–	60 (180)	–	79 (237)	–

Table 1 continued

Author	HTN, % (N)	CKD, % (N)	Immunosuppression, % (N)	Malignancy, % (N)	Hypoxia, % (N)	Mechanical ventilation, % (N)	Corticosteroids treatment, % (N)	ICU admission, % (N)
Kulkarni R. [41]	37 (18)	–	–	–	–	–	–	–
Dokania V. [42]	0.5 (1)	–	–	–	–	4.8 (1)	90 (19)	19 (4)
Nair AG. [43]	–	–	–	–	38 (5)	–	54 (7)	–
Kumar S. [44]	–	–	–	–	–	–	90 (257)	23 (66)
Joshi AR. [45]	–	–	8.0 (2)	–	100 (25)	48 (12)	100 (25)	100 (25)
Choksi T. [46]	–	–	–	–	82 (60)	4.1 (3)	98 (58)	–
Bansai SB. [47]	45 (5)	100 (11)	100 (11)	–	36 (4)	0 (0)	36 (4)	–
Fouad YA. [48]	27 (7)	12 (3)	–	–	–	–	77 (20)	–
Meher R. [49]	–	–	–	–	27 (30)	5.4 (6)	60 (67)	5.4 (6)
Guzman-Castro S. [50]	–	–	–	–	50 (3)	33 (2)	100 (6)	–
Kumar H. [51]	–	–	–	–	57 (16)	21 (6)	68 (19)	–
Yadav T. [52]	–	–	2.0 (1)	–	38 (19)	–	44 (22)	–
Meshram HS. [53]	–	100 (61)	100 (61)	–	67 (41)	0 (0)	44 (27)	–
Popli H. [54]	–	–	–	–	–	–	–	–
Patel DD. [55]	40 (38)	2.1 (2)	–	–	73 (70)	6.3 (6)	82 (79)	–
Sen M. [7]	–	–	–	–	–	–	80 (4)	–
Saidha PK. [9]	–	–	–	–	–	–	17 (1)	–
Roushdy T. [56]	100 (2)	–	–	–	–	–	50 (1)	–
Sai Krishna D. [57]	50 (1)	–	–	–	–	–	–	–
Nehara HR. [58]	40 (2)	–	–	–	–	20 (1)	40 (2)	–
Singh Y. [59]	46 (6)	–	15 (2)	23 (3)	85 (11)	69 (9)	77 (10)	77 (10)
Garg R. [60]	–	–	–		29 (2)	0 (0)	100 (7)	0 (0)
Arana C. [61]	100 (2)	100 (2)	100 (2)		100 (2)	0 (0)	100 (2)	50 (1)
Barman Roy D. [62]	–	–	–		0 (0)	0(0)	50 (1)	–
Ashour MM. [63]	–	17 (1)	–		–	–	–	–
Pal P. [64]	–	10 (1)	–		30 (3)	–	80 (8)	–

Table 1 continued

Author	HTN, % (N)	CKD, % (N)	Immunosuppression, % (N)	Malignancy, % (N)	Hypoxia, % (N)	Mechanical ventilation, % (N)	Corticosteroids treatment, % (N)	ICU admission, % (N)
Riad A. [65]	17 (1)	–	–		50 (3)	–	100 (6)	–
Said Ahmed WM. [66]	–	–	–		–	–	–	21 (3)
Alloush TK. [67]	43 (6)	14 (2)	–		100 (14)	0 (0)	93 (13)	–
Seidel D. [68]	–	7.7 (1)	38 (5)		–	79 (11)	79 (11)	79 (11)

Value is shown as mean ± SD or median [range]. The columns of hypoxia, mechanical ventilation, corticosteroids treatment, and ICU admission was the data regarding COVID-19 severity and management. Abbreviations: SD, Standard deviation; HTN, Hypertension; CKD, Chronic kidney disease; ICU, Intensive care units;

The most usual clinical presentation of CAM was ROCM. As for non-COVID-19-associated mucormycosis, pulmonary mucormycosis has frequently been observed in patients with hematologic malignancies or histories of solid organ transplantation, while ROCM has been found primarily in diabetic patients [69, 70]. As more than 80% of the CAM patients had diabetes, the high prevalence of ROCM in CAM may be plausible. Although the reason why ROCM is more prevalent than other types of mucormycosis in diabetic patients is unknown, this interlink appears to be true in CAM as well.

The most common underlying comorbidity in patients with CAM was diabetes. Diabetes has been the most frequent risk factor for non-COVID-19-associated mucormycosis before the COVID-19 outbreak [69, 71]. Due to the lack of a comparison group in this study, we cannot prove that diabetes caused mucormycosis in COVID-19 patients. Nevertheless, the proportion of diabetes in CAM patients was noteworthy. Interestingly, in our meta-analysis, 17% of the patients with hyperglycemia had never been diagnosed with diabetes until the onset of COVID-19. These newly-diagnosed diabetic patients might have developed hyperglycemia as an adverse effect of the glucocorticoids for COVID-19 treatment [72]. Although our data were insufficient to discuss the hypothesis because detailed information on long-term glycemic control such as hemoglobin A1c or changes in blood glucose level after hospitalization was unavailable, further investigations about the relationship between steroid-induced hyperglycemia and mucormycosis are warranted.

More than three-fourths of CAM patients had received corticosteroids for COVID-19. Since the RECOVERY trial showed the mortality benefit of glucocorticoid treatment for severe COVID-19 pneumonia, it has been the standard care for COVID-19 patients requiring oxygen supplementation. As a randomized trial has shown that 12 mg dexamethasone did not improve the outcomes compared to 6 mg [73], the National Institutes of Health guidelines recommend 6 mg of dexamethasone up to 10 days or until hospital discharge for hospitalized adults with COVID-19 who require supplemental oxygen [74]. In our meta-analysis, however, whereas 57% of the patients required oxygen therapy, corticosteroids were administered to 77%. Given the theoretical concern for increased risk of CAM due to hyperglycemia and immunosuppression brought by glucocorticoid therapy, the corticosteroids should be administered with caution.

The majority of CAM patients were endoscopically or surgically treated. While systemic antifungal therapy plays a vital role in treating mucormycosis, endoscopic or surgical debridement is crucial to improving outcomes as well [75]. In particular, 17% of ROCM patients underwent orbital exenteration in this meta-analysis. This invasive procedure may be helpful even for the cases with intracranial spread and should be considered for actively infected orbit with a blind, immobile eye [76]. However, all efforts should be made to preserve the eye because whether orbital exenteration reduces mortality is controversial, and the physical psycho-social consequences are significant [77, 78]. The mortality of the hospitalized patients with COVID-19 varies but seems to be decreasing as

Table 2 Symptoms, treatments, and outcomes of the patients with COVID-19-associated mucormycosis

Author	Days from COVID-19 diagnosis, median [range]	Type of CAM, % (N)	Symptoms, % (N)	Orbital involvement, % (N)	Cranial involvement, % (N)	Endoscopic or surgical procedures, % (N)	Orbital exenteration, % (N)	Mortality, % (N)
Moorthy A	–	ROCM, 100 (17)	Loss of vision, 65 (11)	–	47 (8)	94 (16)	41 (7)	35 (6)
El-Kholy NA	18 ± 3	ROCM, 100 (28)	–	–	–	–	–	–
Ravani SA	–	ROCM, 100 (31)	Ophthalmoplegia, 77 (24), Decreased vision, 94 (29), Proptosis, 26 (8), Eyelid swelling, 29 (9)		–	100 (31)	13 (4)	5.3 (19)
Ramaswami A	20 [13–25]	ROCM, 100 (70)	Orbital pain, 81 (57), Loss of vision, 37 (26), Proptosis, 34 (24), Ptosis, 20 (14), Nasal blockage, 39 (27), Facial pain, 34 (24), Headache, 29 (20), Facial ulcer, 4.3 (3), Facial deviation, 2.9 (2), Oral ulcer, 5.7 (4)	44 (31)	24 (17)	–	–	–
Gupta NK	18	ROCM, 100 (74)	Headache, 45 (33), Dental pain, 27 (20), Visual symptoms, 16 (12), Facial swelling, 11 (8)	20 (15)	4.1 (3)	100 (74)	11 (8)	12 (9)
Mishra Y	11	ROCM, 97 (31), Cutaneous, 3 (1)	Headache, 94 (30), Nasal symptoms, 94 (30), Eye symptoms, 59 (19), Palatal discoloration, 9.4 (3), Cutaneous symptoms, 0.3 (1)	59 (19)	0 (0)	94 (30)	–	13 (4)
Kumari A	[7–15]	ROCM, 100 (20)	Nasal obstruction, 75 (15), Eye swelling, 40 (8), Facial pain, 35 (7), Headache, 35 (7), Proptosis, 50 (10), Ptosis, 10 (2), Vision loss, 5 (1), Ophthalmoplegia, 5 (1), Palatal discolorations, 5 (1)	55 (11)	20 (4)	100 (20)	5 (1)	30 (6)
Gupta DP	–	ROCM, 100 (70)	Periorbital swelling, 53 (37), Facial swelling, 46 (32), Loss of vision, 39 (27), Palatal ulcer, 16 (11), Ptosis, 19 (13), Diplopia, 4.3 (3), Nasal blockage, 7.1 (5)	–	–	59 (41)	33 (23)	5.7 (4)
Patel A	18 [11–27]	ROCM, 86 (167), Pulmonary, 8.6 (16), Renal, 0.5 (1), Disseminated, 2.1 (4)	–	–	24 (44)	70 (131)	–	44 (75)
Dubey S	[7–56]	ROCM, 100 (46)	–	72 (33)	17 (8)	–	–	–
Bhanuprasad K	–	ROCM, 100 (132)	–	70 (93)	30 (39)	–	–	9.8 (13)

Table 2 continued

Author	Days from COVID-19 diagnosis, median [range]	Type of CAM, % (N)	Symptoms, % (N)	Orbital involvement, % (N)	Cranial involvement, % (N)	Endoscopic or surgical procedures, % (N)	Orbital exenteration, % (N)	Mortality, % (N)
Selarka L	12 ± 5	ROCM, 100 (47)	Nasal congestion, 100 (47), Headache, 74 (35), Loss of vision, 26 (12), Facial weakness, 17 (8), Ophthalmoplegia, 19 (9), Proptosis, 2.1 (1)	40 (19)	19 (9)	81 (38)	–	23 (11)
Muthu V	11	ROCM, 83 (24), Pulmonary, 17 (5)	–	–	52 (15)	–	–	–
Pakdel F	7 [1–37]	ROCM, 100 (15)	Periorbital pain, 73 (11), Ptosis, 73 (11), Vision loss, 73 (11), Proptosis, 67 (10), Facial edema, 60 (9), Headache, 33 (5), Fever, 27 (4), Nasal blockage, 13 (2), Ear pain, 6.7 (1)	93 (14)	67 (10)	–	33 (5)	47 (7)
Meawed TE	–	Pulmonary, 100 (11)	–	–	–	–	–	100 (11)
Zirpe K	11	ROCM, 100 (84)	Facial swellings, 21 (18), Eye pain, 33 (28), Headache, 27 (23), Blurred vision, 9.5 (8), Nasal discharge, 14 (12), Proptosis, 3.6 (3), Diplopia, 2.4 (2), Facial palsy, 2.4 (2)	30 (25)	24 (20)	95 (80)	9.5 (8)	15 (13)
Pal P	–	ROCM, 100 (31)	Facial symptoms, 71 (22), Palatal symptoms, 58 (18), Orbital symptoms, 71 (22)	32 (10)	–	100 (31)	32 (10)	26 (8)
Pippal SK	–	ROCM, 100 (80)	–	38 (30)	13 (10)	–	7.5 (6)	–
Ismaiel WF	–	ROCM, 100 (10)	–	–	–	–	–	–
Avatef Fazeli M	[8–50	ROCM, 100 (9)	–	78 (7)	–	100 (9)	–	67 (6)
Goddanti N	–	ROCM, 100 (300)	–	–	–	–	–	–
Kulkarni R	18 [13–25]	ROCM, 85 (48), Pulmonary, 15 (8)	Motor weakness, 76 (34), Altered mental status, 11 (5), Aphasia, 20 (9), Hemianopia, 4.4 (2)	–	100 (49)	–	–	47 (21)
Dokania V	–	ROCM, 100 (21)	Headache/orbital pain, 86 (18), Periorbital swellings, 62 (13), Blurred vision, 24 (5), Ophthalmoplegia, 19 (4), Nasal blockage, 19 (4), Facial numbness, 14 (3), Chemosis, 14 (3), Toothache, 9.5 (2), Palatal ulcer, 9.5 (2)	48 (10)	24 (5)	100 (21)	14 (3)	4.8 (1)
Nair AG	14 [9–22]	ROCM, 100 (13)	–	57 (8)	–	100 (13)	57 (8)	0 (0)

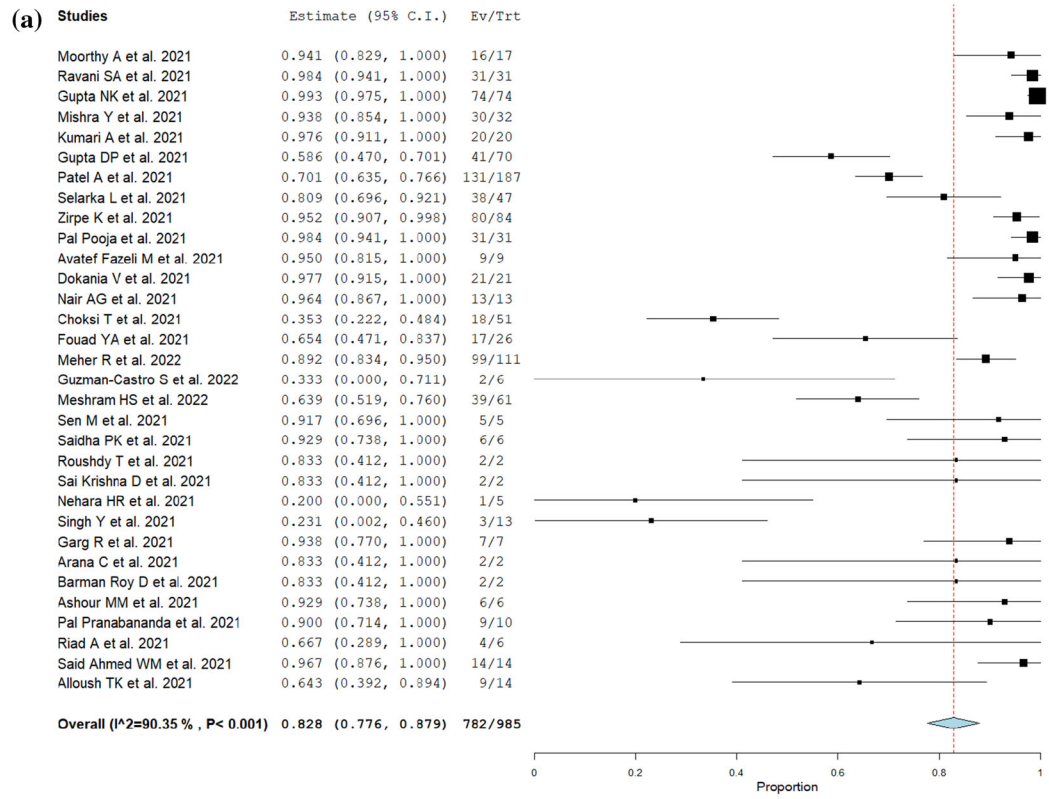
Table 2 continued

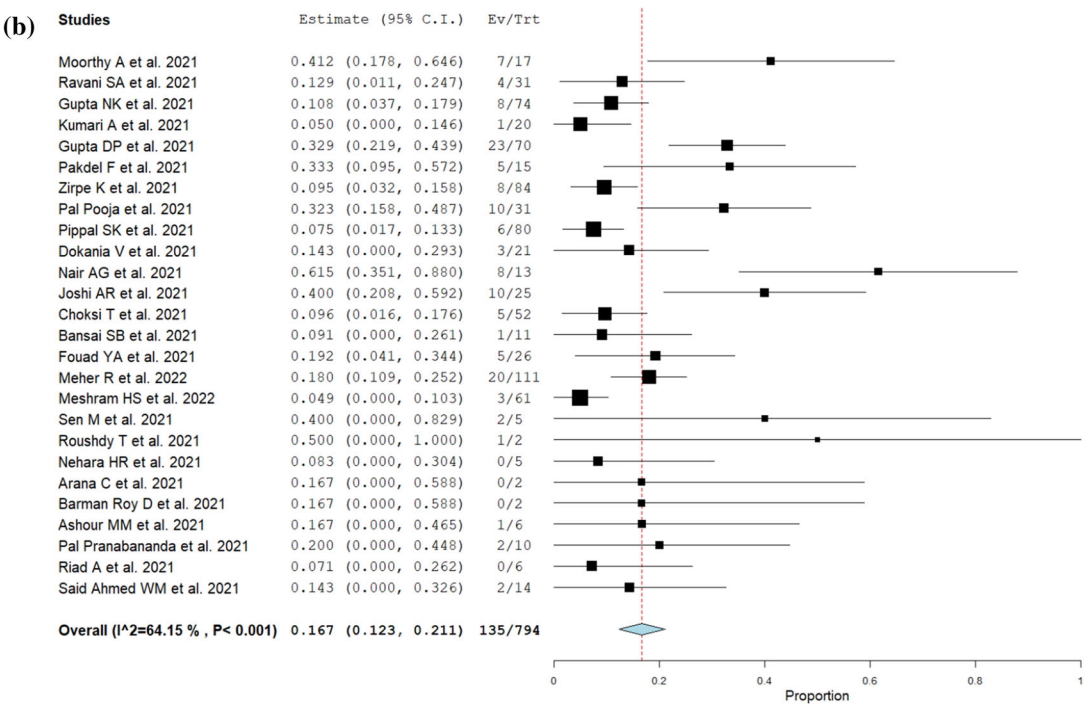
Author	Days from COVID-19 diagnosis, median [range]	Type of CAM, % (N)	Symptoms, % (N)	Orbital involvement, % (N)	Cranial involvement, % (N)	Endoscopic or surgical procedures, % (N)	Orbital exenteration, % (N)	Mortality, % (N)
Kumar S	–	ROCM, 100 (287)	–	36 (102)	21 (60)	–	–	–
Joshi AR	–	ROCM, 100 (25)	–	92 (23)	28 (7)	–	40 (10)	56 (14)
Choksi T	31 ± 20	ROCM, 100 (73)	Ophthalmoplegia, 38 (28), Proptosis, 66 (48), Ptosis, 18 (13), Decreased vision, 16 (12)	93 (68)	8.2 (6)	35 (18)	9.6 (5)	36 (26)
Bansai SB	17 [10–30]	ROCM, 91 (!0), Pulmonary, 9 (1)	Headache, 73 (8), Facial numbness, 36 (4), Facial swelling, 18 (2), Eye pain, 27 (3), Vision loss, 9.1 (1), Hemoptysis, 9.1 (1)	18 (2)	–	–	9.1 (1)	18 (2)
Fouad YA	21 [15–30]	ROCM, 100 (“6)	Facial swelling, 50 (13), Lid swelling, 27 (7), Skin discoloration, 12 (3), Nasal obstruction, 7.7 (2), Decreased vision, 3.8 (1)	–	–	65 (17)	19 (5)	46 (12)
Meher R	19 [10–28]	ROCM, 100 (111)	–	66 (73)	3.6 (4)	89 (99)	18 (20)	5.4 (6)
Guzman-Castro S	15 [8–21]	ROCM, 83 (5), Pulmonary, 17 (1)	Orbital edema, 83 (5), Palatal ulcers, 67 (4), Facial edema, 67 (4), Proptosis, 50 (3), Headache, 50 (3), Dyspnea, 17 (1)	–	–	33 (2)	–	83 (5)
Kumar H	–	ROCM, 86 (24), Pulmonary 14 (4)	–	–	54 (15)	–	–	74 (17)
Yadav T	14 ± 7	ROCM, 100 (50)	–	36 (18)	50 (25)	–	–	–
Meshram HS	–	ROCM, 92 (56), Pulmonary, 8 (5)	Facial swelling, 80 (49), Skin necrosis, 9.8 (6), Paresthesia, 34 (21), Nasal discharge, 30 (18), Epistaxis, 23 (14), Chemosis, 61 (37), Proptosis, 74 (45), Headache, 82 (50), Fever, 28 (17)	36 (15)	14 (6)	64 (39)	4.9 (3)	26 (16)
Popli H	–	ROCM, 100 (23)	–	–	–	–	–	–
Patel DD	–	ROCM, 100 (96)	–	59 (57)	22 (21)	–	–	–
Sen M	14 [0–42]	ROCM, 100 (5)	Ophthalmoplegia, 80 (4), Ptosis, 80 (4), Proptosis, 80 (4), Nasal signs, 60 (3), Palatal eschar, 60 (3)	100 (5)	80 (4)	100 (5)	40 (2)	0 (0)
Saidha PK	[2–3 months]	ROCM, 100 (6)	Facial pain, 83 (5), Loosened teeth, 17 (1), Nasal discharge, 17 (1), Headache, 33 (2)	–	–	100 (6)	–	0 (0)
Roushdy T	[10–14]	ROCM, 100 (2)	Ophthalmoplegia, 100 (2), Chemosis, 100 (2), Ptosis, 100 (2), Proptosis, 100 (2)	100 (2)	100 (2)	100 (2)	50 (1)	0 (0)
Sai Krishna D	–	ROCM, 100 (2)	Facial pain, 100 (2), Toothache, 100 (2)	–	–	100 (2)	–	0 (0)

Table 2 continued

Author	Days from COVID-19 diagnosis, median [range]	Type of CAM, % (N)	Symptoms, % (N)	Orbital involvement, % (N)	Cranial involvement, % (N)	Endoscopic or surgical procedures, % (N)	Orbital exenteration, % (N)	Mortality, % (N)
Nehara HR	[5 days–1 month]	ROCM, 100 (5)	–	80 (4)	0 (0)	20 (1)	0 (0)	40 (2)
Singh Y	[0–16]	ROCM, 92 (12), Pulmonary, 8 (1)	Fever, 38 (5), Epistaxis, 23 (3), Facial pain, 38 (5), Orbital pain, 15 (2)	62 (8)	15 (2)	23 (3)	–	69 (9)
Garg R	–	ROCM, 100 (7)	Facial pain, 100 (7)	29 (2)	0 (0)	100 (7)	–	0 (0)
Arana C	[7–21]	ROCM, 50 (1), Musculoskeletal, 50 (1)	–	–	–	100 (2)	0 (0)	0 (0)
Barman Roy D	–	ROCM, 100 (2)	Facial pain, 50 (1), Decreased vision, 50 (1), Headache, 50 (1)	–	0 (0)	100 (2)	0 (0)	0 (0)
Ashour MM	[2 weeks–2 months]	ROCM, 100 (6)	Chemosis, 17 (1), Ophthalmoplegia, 67 (4), Decreased vision, 67 (4), Proptosis, 33 (2), Facial edema, 17 (1), Palatal ulcers, 33 (2)	100 (6)	33 (2)	100 (6)	17 (1)	33 (2)
Pal P	[5–40]	ROCM, 100 (10)	Headache, 20 (2), Eye swelling. 60 (6), Ophthalmoplegia, 30 (3), Nasal discharge, 10 (1), Skin discoloration, 20 (2), Loss of vision, 40 (4), Loosened teeth, 20 (2)	50 (5)	–	90 (9)	20 (2)	30 (3)
Riad A	[3 days–4 weeks]	ROCM, 100 (7)	Palatal ulcers, 29 (2), Fever, 43 (3), Facial pain, 43 (3)	0 (0)	0 (0)	67 (4)	0 (0)	0 (0)
Said Ahmed WM	–	ROCM, 100 (14)	Palatal ulcers, 100 (14), Loss of vision, 14 (2), Loosened teeth, 14 (2)	21 (3)	–	100 (14)	14 (2)	–
Alloush TK	13 [7–30]	ROCM, 100 (14)	Ptosis, 93 (13), Chemosis, 93 (13), Proptosis, 93 (13), Decreased vision, 100 (14), Ophthalmoplegia, 93 (13), Nasal discharge, 79 (11), Facial pain, 86 (12), Periorbital edema, 71 (10), Palatal ulcers, 64 (9), Headache, 100 (14)	93 (13)	64 (9)	64 (9)	–	21 (3)
Seidel D	10 [0–62]	Pulmonary, 85 (11), ROCM, 8 (1), Gastrointestinal, 8 (1)	–	–	–	–	–	54 (7)

Value is shown as mean ± SD or median [range]. Abbreviations: SD, Standard deviation; CAM, COVID-19-associated mucormycosis; ROCM, Rhino-orbital-cerebral mucormycosis


(a)
Studies
Estimate (95% C.I.)
Ev/Trt
Moorthy A et al. 2021 0.941 (0.829, 1.000) 16/17
Ravani SA et al. 2021 0.984 (0.941, 1.000) 31/31
Gupta NK et al. 2021 0.993 (0.975, 1.000) 74/74
Mishra Y et al. 2021 0.938 (0.854, 1.000) 30/32
Kumari A et al. 2021 0.976 (0.911, 1.000) 20/20
Gupta DP et al. 2021 0.586 (0.470, 0.701) 41/70
Patel A et al. 2021 0.701 (0.635, 0.766) 131/187
Selarka L et al. 2021 0.809 (0.696, 0.921) 38/47
Zirpe K et al. 2021 0.952 (0.907, 0.998) 80/84
Pal Pooja et al. 2021 0.984 (0.941, 1.000) 31/31
Avatef Fazeli M et al. 2021 0.950 (0.815, 1.000) 9/9
Dokania V et al. 2021 0.977 (0.915, 1.000) 21/21
Nair AG et al. 2021 0.964 (0.867, 1.000) 13/13
Choksi T et al. 2021 0.353 (0.222, 0.484) 18/51
Fouad YA et al. 2021 0.654 (0.471, 0.837) 17/26
Meher R et al. 2022 0.892 (0.834, 0.950) 99/111
Guzman-Castro S et al. 2022 0.333 (0.000, 0.711) 2/6
Meshram HS et al. 2022 0.639 (0.519, 0.760) 39/61
Sen M et al. 2021 0.917 (0.696, 1.000) 5/5
Saidha PK et al. 2021 0.929 (0.738, 1.000) 6/6
Roushdy T et al. 2021 0.833 (0.412, 1.000) 2/2
Sai Krishna D et al. 2021 0.833 (0.412, 1.000) 2/2
Nehara HR et al. 2021 0.200 (0.000, 0.551) 1/5
Singh Y et al. 2021 0.231 (0.002, 0.460) 3/13
Garg R et al. 2021 0.938 (0.770, 1.000) 7/7
Arana C et al. 2021 0.833 (0.412, 1.000) 2/2
Barman Roy D et al. 2021 0.833 (0.412, 1.000) 2/2
Ashour MM et al. 2021 0.929 (0.738, 1.000) 6/6
Pal Pranabananda et al. 2021 0.900 (0.714, 1.000) 9/10
Riad A et al. 2021 0.667 (0.289, 1.000) 4/6
Said Ahmed WM et al. 2021 0.967 (0.876, 1.000) 14/14
Alloush TK et al. 2021 0.643 (0.392, 0.894) 9/14
Overall (I^2=90.35 % , P< 0.001) 0.828 (0.776, 0.879) 782/985
0
0.2
0.4
0.6
0.8
1
Proportion


(b)
Studies
Estimate (95% C.I.)
Ev/Trt
Moorthy A et al. 2021 0.412 (0.178, 0.646) 7/17
Ravani SA et al. 2021 0.129 (0.011, 0.247) 4/31
Gupta NK et al. 2021 0.108 (0.037, 0.179) 8/74
Kumari A et al. 2021 0.050 (0.000, 0.146) 1/20
Gupta DP et al. 2021 0.329 (0.219, 0.439) 23/70
Pakdel F et al. 2021 0.333 (0.095, 0.572) 5/15
Zirpe K et al. 2021 0.095 (0.032, 0.158) 8/84
Pal Pooja et al. 2021 0.323 (0.158, 0.487) 10/31
Pippal SK et al. 2021 0.075 (0.017, 0.133) 6/80
Dokania V et al. 2021 0.143 (0.000, 0.293) 3/21
Nair AG et al. 2021 0.615 (0.351, 0.880) 8/13
Joshi AR et al. 2021 0.400 (0.208, 0.592) 10/25
Choksi T et al. 2021 0.096 (0.016, 0.176) 5/52
Bansai SB et al. 2021 0.091 (0.000, 0.261) 1/11
Fouad YA et al. 2021 0.192 (0.041, 0.344) 5/26
Meher R et al. 2022 0.180 (0.109, 0.252) 20/111
Meshram HS et al. 2022 0.049 (0.000, 0.103) 3/61
Sen M et al. 2021 0.400 (0.000, 0.829) 2/5
Roushdy T et al. 2021 0.500 (0.000, 1.000) 1/2
Nehara HR et al. 2021 0.083 (0.000, 0.304) 0/5
Arana C et al. 2021 0.167 (0.000, 0.588) 0/2
Barman Roy D et al. 2021 0.167 (0.000, 0.588) 0/2
Ashour MM et al. 2021 0.167 (0.000, 0.465) 1/6
Pal Pranabananda et al. 2021 0.200 (0.000, 0.448) 2/10
Riad A et al. 2021 0.071 (0.000, 0.262) 0/6
Said Ahmed WM et al. 2021 0.143 (0.000, 0.326) 2/14
Overall (I^2=64.15 % , P< 0.001) 0.167 (0.123, 0.211) 135/794
0
0.2
0.4
0.6
0.8
1
Proportion

◀**Fig. 2** Forrest plots for management and outcomes (random-effect model). **a** Frequency of endoscopic or surgical procedure performed in patients with CAM. **b** Frequency of orbital exenteration performed in patients with COVID-19-associated ROCM. **c** Overall mortality of CAM

the pandemic progresses. According to large observational studies, the mortality of hospitalized COVID-19 patients declined from 30% in early-2020 to 15% in mid-2020 [79]. Observational studies in India, where many CAM studies were conducted, reported the mortality of hospitalized COVID-19 patients of 10% in mid-2020 [80]. Based on our meta-analysis, patients who developed CAM may present worse outcomes than the COVID-19 patients without CAM, although the causal relationship remains unclear. Since early surgical intervention combined with antifungal therapy has been shown to reduce mortality of mucormycosis, healthcare providers should be vigilant with possible clinical manifestations and take swift moves once patients with a history of COVID-19 develop suspicious symptoms.

Several limitations should be noted in our meta-analysis. Firstly, the number of participants in each study was small. Moreover, the study settings varied from ambulatory ophthalmologic clinics to ICUs. These two factors contributed to the substantial heterogeneity of the meta-analysis. Initial

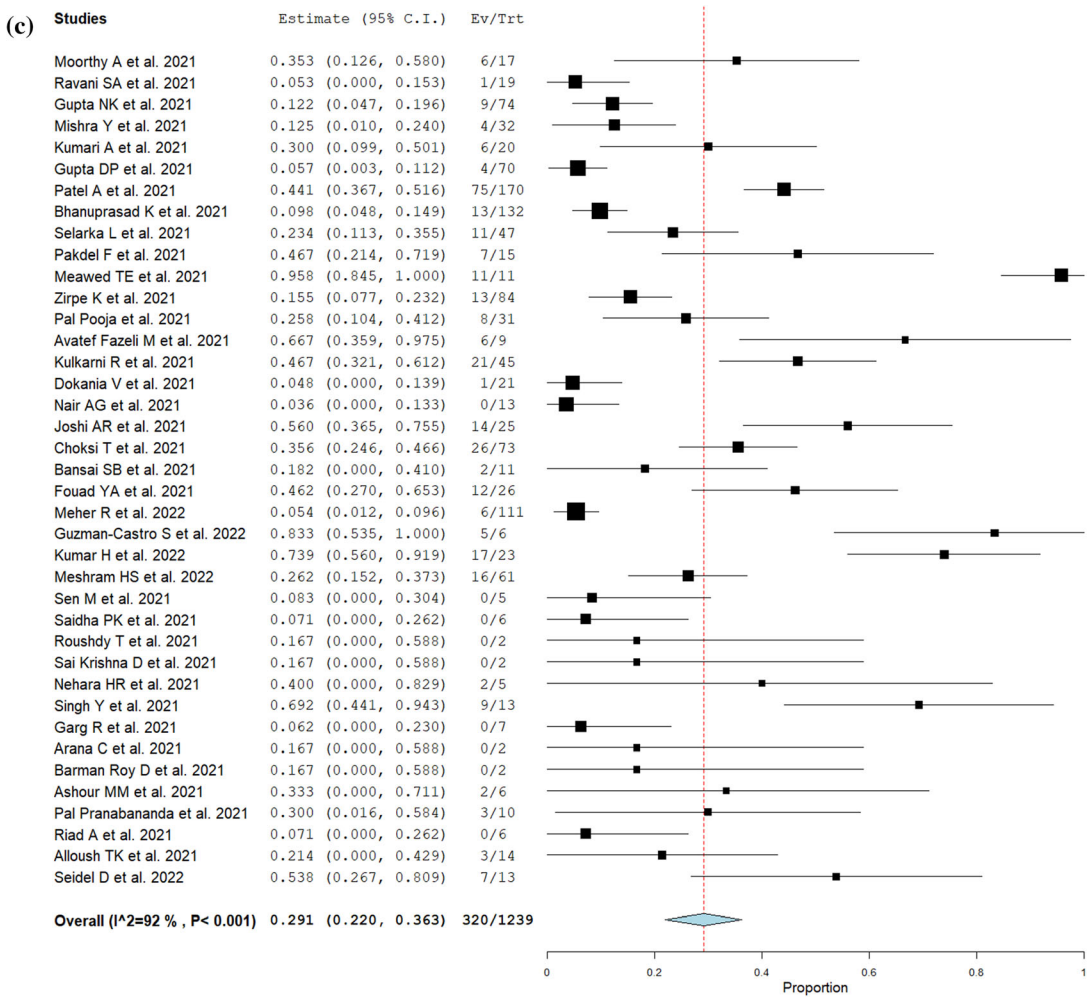


Fig. 2 continued

presentations and mortality could vastly differ from case to case. More focused analysis (e.g., mortality of CAM in ICU) may improve the prediction performance in specific settings. Secondly, because most of the included studies reported on ROCM, applying the results to other types of mucormycosis can be misleading. However, this systematic review revealed that most of the CAM were ROCM. Meticulous observations of those symptoms will be essential to detect the disease early and ameliorate the outcomes. Thirdly, most of the included studies were conducted in India. In western countries, the trend of mucormycosis has been shifting towards malignancy- or transplantation-associated pulmonary mucormycosis [81, 82]. Because diagnosing pulmonary or gastrointestinal mucormycosis is challenging by symptoms, those subtypes might have been under-reported compared to ROCM. Due to such epidemiological differences, our findings may not be generalizable worldwide. Lastly, some data points were unobtainable, such as details on time from glucocorticoid initiation to CAM onset and the glycemic control during hospitalization. Therefore, the relationship between hyperglycemia and immunosuppression due to glucocorticoids on CAM was not conclusive. Extensive, prospective studies will be of help to understand these relationships.

In conclusion, diabetes and glucocorticoid treatment were frequently observed in patients with CAM. CAM may be associated with higher mortality of COVID-19, and around one-fifth of the patients may lose their eyes. Physicians should be aware of those potential risk factors and the typical clinical presentations of CAM. Once CAM is suspected, multidisciplinary approaches with antifungal therapy combined with surgical intervention should be encouraged to improve outcomes.

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