COVID-19-Associated Mucormycosis (CAM): An Updated Evidence Mapping

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Abstract: Mucormycosis, a serious and rare fungal infection, has recently been reported in COVID-19 patients worldwide. This study aims to map all the emerging evidence on the COVID-19-associated mucormycosis (CAM) with a special focus on clinical presentation, treatment modalities, and patient outcomes. An extensive literature search was performed in MEDLINE (Ovid), Embase (Ovid), Cochrane COVID-19 Study Register, and WHO COVID-19 database till 9 June 2021. The primary outcome was to summarize the clinical presentation, treatment modalities, and patient outcomes of CAM. Data were summarized using descriptive statistics and presented in tabular form. This evidence mapping was based on a total of 167 CAM patients with a mean age of 51 ± 14.62 years, and 56.28% of them were male. Diabetes mellitus (73.65% (n = 123)), hypertension (22.75% (n = 38)), and renal failure (10.77% (n = 18)) were the most common co-morbidities among CAM patients. The most common symptoms observed in CAM patients were facial pain, ptosis, proptosis, visual acuity, and vision loss. Survival was higher in patients who underwent both medical and surgical management (64.96%). Overall mortality among CAM patients was found to be 38.32%. In conclusion, this study found a high incidence of CAM with a high mortality rate. Optimal glycemic control and early identification of mucormycosis should be the priority to reduce the morbidity and mortality related to CAM.

Keywords: COVID-19; diabetes; epidemiology; evidence; mortality; mucormycosis; mycoses; public health

1. Introduction

The coronavirus disease (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 228 million people globally, with about 4.7 million deaths as of 21 September 2021 [1]. The novel COVID-19 strains that have emerged this year are more severe variants of the disease and have resulted in higher intensive care unit (ICU) admissions, need for mechanical ventilation, and mortality [2,3]. This, consequently, has increased the burden on healthcare systems globally [4].

COVID-19 patients often have several comorbidities, including diabetes [5]. Ample evidence has found patients with comorbidities to be at higher risk of ICU admissions and mortality [5–7]. Study findings by Liu et al. from Wuhan Union Hospital found a more intense...
level of lymphocytopenia and cytokine storm in patients with severe COVID-19 compared to that in patients with mild disease [8]. Despite the colossal impact of this pandemic gripping the world, there are limited treatment options for it. COVID-19 patients in severe or critical stages (admitted to ICUs) are prescribed high doses of steroids as a life-saving measure [9]. Steroids suppress the immune system (decrease in CD4 + T and CD8 + T cells) to fight against the inflammation caused by the virus, thereby creating a favorable environment for other opportunistic infections [9,10]. This can make the immunocompromised COVID-19 patients more susceptible to a range of viral, bacterial, fungal, and other microbial co-infections [11]. Multiple studies have confirmed that patients with severe COVID-19 admitted to ICUs have a high occurrence of secondary infections and relatively infrequent bacterial co-infection [12–14].

Mucormycosis, a serious and rare fungal infection, has occurred concurrently in COVID-19 patients globally [15]. COVID-19-associated mucormycosis (CAM) notably created havoc in the second wave of COVID-19 in India. Mucormycosis, also known as black fungus, is an invasive fungal infection most commonly caused by species of the genus Rhizopus [16]. Other species causing this fungal infection include those belonging to the genera Apophysomyces, Absidia, Mucor, and others. Amongst the various types of mucormycosis, rhino-orbital-cerebral is the most common one [17]. Risk factors associated with the development of fungal infection among COVID-19 patients include diabetes, neutropenia, hematological malignancy, stem cell transplant recipients, patients receiving corticosteroid treatment, and individuals in the immunocompromised state [18,19]. Mucormycosis is associated with a high risk of all-cause mortality (54%), with mortality depending on body site infected, fungus type, and the patient’s overall condition [20].

This deadly fungal infection is clinically challenging and expensive to treat and puts a high toll on public health and a humanitarian and economic burden on individuals and healthcare systems [21,22]. Low- and middle-income countries such as India witnessed a massive number of CAM cases in the second wave of COVID-19, leading to a collapse of the health system in the midst of the pandemic. The Indian government (state governments) declared mucormycosis as an outbreak in May 2021 [23]. Evidence from previous published studies was based on fewer cases and limited information [24,25].

Presently, more detailed evidence on the clinical presentation, treatment modalities, and patient outcomes is required. The preliminary search for mapping existing evidence was performed on 25 May 2021, in Epistemonikos, the international prospective register of systematic reviews (PROSPERO), Open Science Framework (OSF), Cochrane Library, and Jonna Briggs Institute (JBI) Evidence Synthesis, and no previous evidence mapping was identified. Therefore, we conducted this study with an objective to map all the emerging evidence on the CAM with a particular focus on each minute detail of clinical presentation, treatment modalities, and patient outcomes.

2. Materials and Methods

The proposed study was developed by adhering to the JBI methodology for evidence mapping and is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Scoping Reviews (PRISMA-ScR) [26,27]. Compliance with the PRISMA-ScR is presented in Supplementary Table S1.

Furthermore, this review was conducted by adhering to our protocol registered prospectively at OSF with an identification number (osf.io/438sm) and published as a preprint at the Preprint Server for Health Sciences (medRxiv) [28]. There were slight deviations from the protocol; firstly, the critical appraisal was skipped as it is not mandatory as per the JBI guidelines. The second deviation was the inclusion of suspected COVID-19 cases with confirmed mucormycosis, as patients developed mucormycosis after recovery from COVID-19.
2.1. Eligibility Criteria

2.1.1. PCC Elements

According to the JBI reviewer’s manual, the following PCC (Population, Concept, and Context) elements were used for this review.

(a) Participants: patients with confirmed COVID-19 (RT-PCR) and mucormycosis (either histologically or microbiologically confirmed) based on the definition of Centers for Disease Control and Prevention were included in the study. We also included studies with suspected COVID-19 patients (based on the included studies assessment) who had confirmed mucormycosis.

(b) Concept and context: this review included all studies that described the clinical presentation, treatment modalities, and patient outcomes of CAM.

2.1.2. Types of Sources

We included analytical observational studies (cohort, case–control) and descriptive observational studies (case report, case series, cross-sectional).

2.1.3. Exclusion Criteria

(a) Non-English language studies;
(b) studies with no confirmed mucormycosis; and
(c) systematic reviews, narrative reviews, editorials, opinions, and study protocols were excluded.

2.2. Information Sources and Search Strategy

A three-step search strategy was utilized to identify published, unpublished, or ongoing studies with no language restrictions. An initial limited search was undertaken in MEDLINE (Ovid), followed by analyzing the text words in the title and abstract and the index terms assigned to the articles. Slightly modified Ovid Expert Searches for COVID-19 were combined with keywords and index terms related to mucormycosis to perform the searches in MEDLINE (Ovid) [29] and Embase (Ovid) [30] (Appendix A).

On 9 June 2021, we conducted a second search in MEDLINE (Ovid), Embase (Ovid), Cochrane COVID-19 Study Register, and the World Health Organization (WHO) COVID-19 database.

Complete search strategies are presented in Supplementary Table S2 for each database with their respective hits. Third, the manual search of reference lists of all included studies and relevant systematic reviews was screened for any potentially eligible studies. Citation tracking was also performed for all the included articles.

2.3. Selection Process

Two independent reviewers (S.H. and H.B.) screened all the retrieved articles against the eligibility criteria. We included all those articles describing the mucormycosis case (diagnosed either based on histopathology, culture, or stain) in COVID-19-positive patients.

In the initial screening phase, articles were selected based on the title and abstract scanning. In the second phase, full-text screening was performed for the final inclusion of articles. Any confusion regarding study inclusion was resolved by discussion with the third reviewer (M.K.). A detailed description of the study selection process is shown using the PRISMA flow diagram in Figure 1.
2.4. Data Extraction

Two reviewers (S.H. and H.B.) independently extracted the data in a pre-designed data extraction template. The following information was extracted from all the eligible studies qualified for inclusion: study author, year of publication, country, study design, demographic characteristics of the population (age and sex), sample size, comorbidities, treatment for COVID-19, symptoms of mucormycosis, diagnosis of mucormycosis, identification of fungal species, treatment for mucormycosis, and patient outcomes. The included studies are described using descriptive statistics and presented in a tabular form.

3. Results

A total of 209 articles were identified by searching the selected sources. After removing duplicates, only 92 articles were found to be unique. After the full-text screening, 37 studies [31–67] qualified for inclusion in this evidence mapping study. Four additional articles [68–71] were identified by hand search during bibliography screening and citation tracking. Finally, a total of 41 articles were included in this review [31–71]. Refer to Supplementary Table S3 for the list of articles excluded during full-text screening with reason.
3.1. Studies Characteristics

Out of 41 studies, the majority of studies (n = 15) were from India with 82 mucormycosis cases, 9 studies with 9 cases of mucormycosis were from the USA, while only 3 studies were from Iran but with 17 mucormycosis cases. Most of the included studies were case reports (n = 27) followed by case series (n = 9), and the rest were of other study designs. Diabetes mellitus (73.65% (n = 123)), hypertension (22.75% (n = 38)), and renal failure (10.77% (n = 18)) were the most common co-morbidities among CAM patients. Diabetic ketoacidosis was observed in one-tenth of the diabetic patients.

3.2. Clinical Presentation

This evidence mapping was based on a total of 167 CAM patients with a mean age of 51 ± 14.62 years, of which 56.28% of them were male. COVID-19 was confirmed through the RT-PCR test in approximately three-fourth (74%) of the included studies.

The majority of the patients (76.04%) were treated using steroids, while only 11.64% of patients were treated with remdesivir to manage COVID-19. Most patients who developed mucormycosis had severe (based on included studies’ categorization) or critical COVID-19 (defined based on ICU status/mechanical ventilation).

Twenty-nine (17.57%) patients had concurrent CAM, while the remaining patients were diagnosed with CAM after an average of 19.24 days. Mucormycosis was diagnosed using stain (24 studies), culture (26 studies), or histopathology (30 studies), and nine studies diagnosed mucormycosis using all three diagnostic techniques. The Rhizopus species were the most common fungal species infecting CAM patients (13.77%).

Facial pain, ptosis, proptosis, visual acuity, and vision loss were the most common symptoms observed in CAM patients. Rhino-orbital (16%) followed by rhino-orbital-cerebral (11.3%) mucormycosis was the most common form of mucormycosis found in CAM patients (Table 1).

3.3. Treatment Modalities and Outcomes

Liposomal amphotericin B in various doses (5 mg/kg/day) was the most commonly used drug for managing mucormycosis infection in 158 patients (35 studies). Adjunct surgery was performed on 142 patients, and surgical debridement was the most common surgical procedure performed. Only 23 CAM patients were managed without surgery, and most of them (18 CAM patients) died between 7 to 62 days after the diagnosis of mucormycosis.

Survival was higher in patients who underwent both medical and surgical management (64.96%) than in CAM patients who underwent medical management only (21.73%). Overall mortality among CAM patients in the included studies was 38.32% (n = 64). The patients died between 6 to 90 days after mucormycosis diagnosis (Table 2).
Table 1. Summary of study characteristics and anamnestic, diagnostic, and treatment features of COVID-19-associated mucormycosis (CAM) cases.

| Study                        | Country | Design | n  | Age (years) | COVID-19 Confirm. | COVID-19 Severity | Onset (days) | Comorbidities | COVID-19 Treatment | Clinical Features | Region | Diagnosis | Stain | Cult. | Cultiv. | Histo. | Species |
|------------------------------|---------|--------|----|-------------|-------------------|-------------------|--------------|---------------|-------------------|-------------------|---------|-----------|-------|-------|--------|--------|---------|
| Alekseyev et al. 2021 [31]  | USA     | Case report | 1 | M | RT-PCR | NR | NR | Yes | No | No | No | DKA | Yes (name NS) | HCQ | NS | No | No | Yes | NS |
| Arana et al. 2021 [32]      | Spain   | Case report | 1 | M | RT-PCR | Severe (requiring non-invasive mechanical ventilation) | 7 | Yes | Yes | No | Yes | ESKD | Dexame-thasone 6 mg daily for 10 days | Ceftriaxone, azithro-mycin, Fever, headache and left malar region swelling | Rhinosi-nus | No | Yes | No | Rhizopus/Rhizopus oryzae |
| Ashour et al. 2021 [33]     | Egypt   | Case series 6 | M/F: 3/3 | 54.66 | RT-PCR (2); NR (4) | Critical (n = 1) on ventilation, NR (n = 5) | Not clear | Yes (100%) | No | No | No | CKD (12.5%) | NR | Ophthalmoplegia (66%), conjunctival che-mosis (33%), eyelid edema (33%), facial edema (33%) | Rhino-or-bital-cerebral (100%) | No | Yes | Yes | NS |
| Bayram et al. 2021 [34]     | Turkey/Case series 11 | M/F: 9/2 | 73.1 ± 7.7 years (range: 61–88 years) | Moderate (FiO2: 28%) | 21 | Yes | Yes | No | No | No | ESKD | Prednisone 20 mg | HCQ, azithromycin, lopinavir/ritonavir, tocilizumab | Pain and increase in right limb diameter | Musculo-skeletal | No | Yes | No | Lichtheimia ramosa |
| Bellanger et al. 2021 [35]  | France  | Case report | 1 | M | RT-PCR | Severe (ICU) | 21 | No | No | No | No | No | Remdesivir (200 mg × 1, then 100 mg daily), supportive care | Cavitary pneumonia with pleural effusion | Pulmonary mucormyco-sis/cavitary | Yes | No | Yes | Rhizopus/Rhizopus species |
| Dallalzadeh et al. 2021 [36]| USA     | Case report | 1 | M | RT-PCR | Severe (ICU, ventilation) | 6 | Yes | No | No | No | Ketosisis | Dexame-thasone | CCP (COVID-19 convalescent plasma) | NR | No | Yes | Yes | Rhizopus/Rhizopus species |
| El-Kohly et al. 2021 [37]   | Egypt   | Cross-sectional | 28 | M/F: 19/17 | 52.92 ± 11.30 | RT-PCR | Mixed (n = 11), moderate (n = 13), severe (n = 12) | 17.82 ± 2.97 | Yes (27.8%) | Yes (17%) | Yes (8%) | No | CKD (8%) | Yes (name NS) lant, and vitamins (name NS) | Anterior, anticoagu-lant, and vitamins (name NS) | Sinusosal (100%), orbital (93%), cerebral (29%), and palatine (33%) | Yes | Yes | Yes | Mucor species |
| Everett et al. 2020 [70]    | Germany | Case series 2 | F | 52.5 | RT-PCR | Critical (n = 2 on ventilation) | NR | No | No | No | Obesity, liver cirrhosis | Yes | NR | NR | NR | No | No | Yes | Yes | Mucor species |
| Garg et al. 2021 [39]       | India   | Case report | 1 | M | RT-PCR | Severe (84% SpO2) | 21 | Yes | Yes | No | No | ESEf, Is-chemic cardiac- myopathy, venous thrombosis | Dexame-thasone (6 mg, on day 1 and 100 mg on days 2–5), suppor-tive care | Cavitary pneumonia with pleural effusion | Pulmonary mucormyco-sis/cavitary | Yes | No | Yes | Rhizopus/Rhizopus species |
| Hanley et al. 2020 (Autopsy) [40] | UK | Case series 1 | M | 22 | RT-PCR | Critical (mechanical ventilation, vaso-pressor, ICU) | Concurrent | NR | NR | NR | NR | Frank necrotic-hem-orrhagic pan-creatitis, renal failure | NR | NR | NR | Yes | No | Yes | NR |
| Johnsons et al. 2021 [41]  | USA     | Case report | 1 | M | RT-PCR | Critical (ICU, ventilation) | 19 | Yes | Yes | No | No | IV dexame-thasone (6 mg daily for 10 days) | IV remdesivir (200 mg 1, then 100 mg daily) | Pain | NR | No | Yes | Rhizopus/Rhizopus oryzae |

Note: RT-PCR = Reverse Transcription Polymerase Chain Reaction; NR = Not Reported; NS = Not Specified; DM = Diabetes Mellitus; HTN = Hypertension; Asthma = Asthma; CAD = Coronary Artery Disease; DKA = Diabetic Ketoacidosis; ESKD = End Stage Kidney Disease; CCPR = COVID-19 convalescent plasma; IV = Intravenous; BAL = Bronchoalveolar Lavage.
| Authors | Year | Country | Study Type | Sex | Age | Sample Size | Test | Disease Severity | Concurrent Infections | Mortality | Treatment 1 | Treatment 2 | Treatment 3 | Other Findings | Comments |
|---------|------|---------|------------|-----|-----|-------------|------|------------------|----------------------|----------|-------------|-------------|-------------|---------------|----------|
| Karimi et al. | 2021 | Iran | Case report | F | 61 | 1 | RT-PCR | Severe | No | No  | NR | Yes | NR | Remdesivir, interferon alpha | Rhino-orbital |
| Kanwar et al. | 2021 | USA | Case report | M | 56 | 1 | RT-PCR | Severe | No | No  | No | NR | Methylprednisolone | Tocilizumab | Necrotizing pneumonia with empyema | Pulmonary mucormycosis |
| Karimi-Galougah et al. | 2021 | Iran | Case report | M | 86 | 1 | Throat swab | Severe (ICU) | No | No  | No | NR | Methylprednisolone | Oseltamivir | Remdesivir, interferon alpha | Hemifacial pain, proptosis, frozen eye, complete loss of vision, and fixed mydriasis | Rhino-orbital |
| Khatri et al. | 2021 | USA | Case report | M | 68 | 1 | Suspected | Critical | No | No  | NR | Methylprednisolone | Predisone (for gout) | CCP | Purplish skin discoloration with fluctuant swelling | Mucorales/NS |
| Khan et al. | 2021 | USA | Case report | F | 44 | 1 | RT-PCR | Critical (ICU, ventilation) | Yes | No  | NR | Remdesivir 100 mg IV daily | NR | NR | Pneumonia and empyema | No |
| Krishna et al. | 2021 | India | Case report | M | 34 | 1 | RT-PCR | Severe | Yes | No  | No | NR | Methylprednisolone (30 mg IV twice a day) | Tocilizumab | Necrotizing pneumonia with empyema | No |
| Krishna et al. | 2021 | UK | Case report (autopsy) | M | 22 | 1 | RT-PCR | Severe (mechanical ventilation) | No | No  | No | NR | NR | NR | Swelling pain over the first quadrant teeth | NR |
| Maiti et al. | 2021 | India | Case report | M | 38 | 1 | RT-PCR | Severe (ICU) | No | No  | NR | Methylprednisolone (80 mg/day) | Oseltamivir (75 mg twice daily), interferon alpha (4 mg twice daily) | NR | NR | Swelling and pain in the left eye | Mucorales/NS |
| Mehta et al. | 2020 | India | Case report | M | 60 | 1 | RT-PCR | Critical (ICU, ventilation) | No | No  | NR | Methylprednisolone (40 mg twice daily) and dexamethasone (4 mg twice daily) | Oseltamivir (75 mg twice daily), interferon alpha (4 mg twice daily) | Bilateral lid edema with right eye prominence, febrile, breathless, and hypoxic | Mucorales/un-specified |
| Mekonnen et al. | 2021 | USA | Case report | M | 60 | 1 | Suspected | Severe (mechanical ventilation, ICU) | Yes | Yes | No | NR | Methylprednisolone (40 mg twice daily) and dexamethasone (40 mg twice daily) | Oseltamivir (75 mg twice daily), interferon alpha (4 mg twice daily) | Bilateral lid edema with right eye prominence, febrile, breathless, and hypoxic | Mucorales/un-specified |
| Meshram et al. | 2021 | India | Case report (renal transplant recipients) | M | 47; 25 | 2 | Suspected | Mild | No | No  | NR | NR | NR | NR | Swelling over the face and black nasal discharge (50%), fever, cough, and black expectoration (50%) | Mucorales/un-specified |
| Mishra et al. | 2020 | India | Case series | M/F: 9/1 | 55.8 | 10 | MIF: 9/1 | Suspected | Mixed (n = 3); moderate (n = 6); severe (n = 1) | Yes | Yes | No | AKI | Dexamethasone | CCP | Proptosis, erythema and edema of the eye, orbital cellulitis, facial swelling, headache, proptosis, oedema of the extraocular muscles, orbital cellulitis and conjunctival chemosis | Yes |
| Moorothy et al. | 2021 | India | Case series | M/F: 1/4 | 54.6, 35–73 (mean, range) | 17 | M/F: 1/4 | Suspected | 62.2 Average age | Yes | Yes | No | CKD (20%) | Remdesivir (50%) | Eye pain, facial pain and nasal block | Sinusitis alone (n = 3), rhino-orbital (n = 6), rhino-orbital-cerebral (n = 5), rhino-cerebral (n = 3) |
| Nehara et al. | 2021 | India | Case series | M/F: 1/4 | 62.2 Average age | 5 | M/F: 1/4 | Suspected | 62.2 Average age | Yes | Yes | No | Yes (20%) | Dexamethasone | Oxygen supplementation, intravenous meropenem, remdesivir (40%), subcutaneous enoxaparin, tablet azithromycin, severe headache, diminished vision, chemical, mild proptosis, complete ophthalmoplegia, blackish discharge from the nasal cavity, and black crust on the hard palate | Yes |

**Notes:**
- M: Male, F: Female
- NR: Not reported
- AKI: Acute kidney injury
- CCP: Convalescent plasma
- CKD: Chronic kidney disease
- NS: Not specified
| Pakdel et al. 2021 [53] | Iran | Cross-sectional | 15 | M: 8, F: 7 | Median age: 52 (14-71) | RT-PCR | Severe (34%) | Median: 7 (1-37) | Yes (87%) | Yes (46%) | Yes (13%) | No | Ketaocidosis (6%) | Dexamethasone (46%) | Yes (7%) | Unilateral periorbital pain and edema (73%), eyelid ptosis (73%), acute vision loss (73%), proptosis (73%), unilateral facial edema (60%), cranial nerve palsy (60%), headache (33%), fever (27%), nasal blockage (13%), and ear pain (7%) | Mixed (rhinobortal (47%); sino-orbital (33%), isolated orbital movement (13%) and others) | Yes | No | Yes | NS |
|------------------------|------|----------------|----|------------|-----------------|--------|-------------|----------------|-----------|---------|---------|----|-----------------|-----------------|---------|-------------------|-----------------|---------------|--------|--------|---|---|
| Pasero et al. 2020 [54] | Italy (renal transplant) | Case report | 1 | M 66 | RT-PCR | Critical (ICU) | 14 | No | Yes | No | No | Renal failure No | HCQ5, lopinavir, ritonavir | NS | NS | Yes | Yes | No | Rhizopus/Rhizopus species |
| Paudi et al. 2021 [55] | Brazil | Case report | 1 | F 50 | Suspected | Mild | 8 | Yes | No | No | No | No | Hydrocortisone/NS | Deep ulcerated lesion located at the center of the hard palate | Yes | No | Yes | Yes | Yes | Mucorales/unspecified |
| Placki et al. 2020 [56] | USA | Case report | 1 | M 49 | RT-PCR | Critical | 14 | No | No | No | No | No | Dexamethasone | Remdesivir, tocilizumab | No | No | Yes | No | Yes | Rhizopus/Rhizopus species |
| Rabagliati et al. 2021 [57] | Chile | Retrospective cohort | 1 | M 55 | Suspected | Critical (ICU) | Not specified | Yes | Yes | No | Yes | No | Atrial fibrillation | 812 mg prednisone equivalent | No | NS | No | No | No | Rhizopus/Rhizopus microsporum |
| Rao et al. 2021 [58] | India | Case report | 1 | M 66 | Suspected | NR | No | No | No | No | No | No | Systematic steroids | NS | NS | No | Yes | No | Fungal hyphae |
| Ravani et al. 2021 [59] | India | Retrospective cohort | 8 | NR | NR | RT-PCR | NR | 60 | Yes (100%) | NR | NR | NR | Dexamethasone | NR | Deminination of vision (46/60 in 91% of patients) and ophthalmoplegia (77%), orbital NR cellulitis (67%), pansinusitis (77%) | No | No | No | Yes | NS | Rhinoro-orbito-cerebral |
| Revanavar et al. 2021 [60] | India | Case report | 1 | F | NR | RT-PCR | Mild | Not specified | Yes | No | No | No | No | NR | NR | Left-sided facial pain, complete ptosis and fever, tenderness of all sinuses on left side, ophthalmoplegia (left eye), left eye visual acuity | NS | No | Yes | Yes | Rhizopus/Rhizopus species |
| Saldanha et al. 2021 [61] | India | Case report | 1 | F | 32 | RT-PCR | Not specified | Concurrent | Yes | No | No | No | No | NR | NR | Left eye complete ptosis and left facial pain, visual acuity (left eye) | NS | No | Yes | Yes | NS | Rhinoro-orbito-cerebral (n = 4), Mucorales (n = 2) |
| Sarkar et al. 2021 [62] | India | Case series | 6 | M: 4, F: 2 | 44 | RT-PCR | Critical (n = 6) | Concurrent | Yes | No | No | No | No | Ketaocidosis | Dexamethasone | Remdesivir (84%) | Visual acuity (100%) | Rhinoro-orbito-cerebral (n = 1) | Yes | Yes | No | NS |
| Satish et al. 2021 [63] | India | Case series | 11 | NR | NR | RT-PCR | Mixed (mild (n = 2); moderate (n = 3); severe (n = 4); asymptomatic (n = 2) | NR | Yes (100%) | Yes (50%) | No | Yes (16.6%) | Diabetic ketoacidosis (50%) | Intravenous methylprednisolone/dexamethasone/oral prednisolone (84%) | No | Pain, redness, and periocular swelling, drooping of eyelids, limitation of ocular movements, and painful loss of vision | Rhinoro-orbito-cerebral | Yes | No | Yes | NS |
| Sen et al. 2021 [64] | India | Retrospective cohort | 19 | M 65 ± 12 (range 46 to 73) years | RT-PCR | Severe | NR | Yes (100%) | Yes (50%) | No | Yes (16.6%) | Diabetic ketoacidosis (50%) | Intravenous methylprednisolone/dexamethasone/oral prednisolone (84%) | No | Pain, redness, and periocular swelling, drooping of eyelids, limitation of ocular movements, and painful loss of vision | Rhinoro-orbito-cerebral | Yes | No | Yes | NS | Mucorales/unspecified |
|    | Gender | Age | Test | Disease Severity | Concomitant Conditions | Treatment | Neurological Signs | Infectious Agent |
|----|--------|-----|------|------------------|------------------------|-----------|-------------------|-----------------|
| 1  | F      | 40  | RT-PCR | Mild             | No                     | No        | No                | No              | 8 mg/day | Remdesivir 200 mg on day 1 followed by 100 mg daily for 4 days, and IV levofloxacin (500 mg/day) | Bilateral visual loss, periorbital pain, and visual acuity | Rhinocerebral | No | No | No |
| 2  | M      | 54  | RT-PCR | NR              | Yes                    | No         | No                | No              | 8 mg/day | Remdesivir 200 mg on day 1 followed by 100 mg daily for 4 days, IV levofloxacin (500 mg/day) | Left orbital pain and periorbital swelling together with progressive vision loss | Rhinocerebral | No | No | No |
| 3  | F      | 24  | RT-PCR | Critical (ICU)   | Concurrent             | Yes        | No                | No              | NA       | Ketoacidosis, renal failure | Left lid swelling and maxillary hypoesthesia, left hypereemic conjunctiva, and an opaque cornea | Rhinocerebral | Yes | No | No | Lasiobacter (Abigailia) species |
| 4  | F      | 33  | Suspected | Critical (ICU)   | Concurrent             | Yes        | Yes               | No              | No       | Ketoacidosis, renal failure | Remdesivir, CCP | Eye ptosis | Yes | No | No |
| 5  | M      | 53  | RT-PCR | Critical (ICU)   | Concurrent             | No         | No                | No              | Prednisolone Tocilizumab | Fungal pneumonia with effusion | Rhinocerebral | No | No | Yes | Rhizopus/Rhizopus microsporus |

CAD: coronary artery disease; DM: diabetes mellitus; ESRD: end-stage renal disease; F: female; HCQs: hydroxychloroquine; HTN: hypertension; ICU: intensive care unit; IV: intravenous; M: male; NR: not reported; NS: not specified; RT-PCR: reverse-transcriptase polymerase chain reaction; USA: United States of America. * No separate outcomes reported for mucormycosis (n = 28).
Table 2. Treatment details and patient outcomes.

| Study (Author, Year) | Country | Treatment | Surgical Management | Patient Outcome * |
|----------------------|---------|-----------|---------------------|------------------|
| Alekseyev et al. 2021 [31] | USA | Amphotericin B (LAmB 5 mg/kg/day), isavuconazole, and subsequently posaconazole | Yes | Lived |
| Arana et al. 2021 [32] | Spain | Amphotericin B (LAmB 5 mg/kg/day) together with isavuconazole 200 mg/8 h for 24 days | Yes (surgical debridement) | Lived |
| Ashour et al. 2021 [33] | Egypt | Amphotericin B | Yes (surgical debridement (n = 4)) | Lived (67%), Died (33%) |
| Bayram et al. 2021 [34] | Turkey | Amphotericin B, voriconazole | Yes (all patients: endoscopic sinus surgery with extensive debridement) | Lived (36%), Died (64%) |
| Bellanger et al. 2021 [35] | France | Amphotericin B (LAmB 5 mg/kg/day) | No | Died |
| El-Kohly et al. 2021 * [38] | Egypt | Amphotericin B; voriconazole; posaconazole | Yes (endoscopic debridement (n = 27)) | Lived (64%), Died (36%), Died (100%) |
| Evert et al. 2020 [70] | Germany | LAmB/isavuconazole | No | Died |
| Garg et al. 2021 [39] | India | Amphotericin B (LAmB 5 mg/kg/day) | No | Died |
| Hanley et al. 2020 [40] | UK | Amphotericin B (LAmB 400 mg/day) | Yes (no tracheostomy, and percutaneous endoscopic gastrostomy) | Lived |
| Junior et al. 2020 [37] | Brazil | Amphotericin B (LAmB 5 mg/kg/day) | No | Died |
| Kanwar et al. 2021 [42] | USA | Amphotericin B (LAmB 5 mg/kg/day) | No | Died |
| Kartini-Galough et al. 2021 [43] | Iran | Amphotericin B + posaconazole | Yes (endonasal endoscopic debridement of necrotic tissue, right eye exenteration) | Lived |
| Khan et al. 2021 [44] | USA | Amphotericin B (LAmB 5 mg/kg/day) | No | Died |
| Khan et al. 2020 [71] | India | Amphotericin B (LAmB 5 mg/kg/day) | No | Died |
| Krishna et al. 2021 [45] | UK | Caspofungin | No | Died |
| Krishna et al. 2021 [46] | India | Amphotericin B 300 mg/day, tobramycin and fluconazole | Yes (debridement) | Lived |
| Mehta et al. 2020 [48] | India | Amphotericin B | No | Died |
| Mekonnen et al. 2021. [49] | USA | Amphotericin B + caspofungin/posaconazole | Yes (sinus debridement) | Died |
| Meshram et al. 2021 [50] | India | Amphotericin B | Yes (maxillectomy) | Died |
| Mishra et al. 2021 [68] | India | Amphotericin B | Yes (all patients (mixed or any single surgery): functional endoscopic sinus surgery, endoscopic maxillectomy, local debridement) | Lived (50%), Died (40%), Lost to follow-up (10%) |
| Moorthy et al. 2021 [51] | India | Amphotericin B (5 mg/kg/day) | Yes (FESS (n = 17), maxillectomy(n = 11), exenteration (n = 11)) | Died (35.29%) |
| Metha et al. 2021 [52] | India | Amphotericin B (LAmB 5 mg/kg/day), posaconazole | No | Lived (60%), Died (40%), Died (47%) |
| Pakdel et al. 2021 [53] | Iran | Amphotericin B (LAmB 5 mg/kg/day), oral posaconazole | Yes (sinus debridement (n = 12); orbital exenteration (n = 5); palatal debridement (n = 2)) | Died |
| Pasero et al. 2020 [54] | Italy | Amphotericin B/posaconazole | No | Died |
| Pauli et al. 2021 [55] | Brazil | Amphotericin B | Yes (debridement) | Died |
| Placik et al. 2020 [56] | USA | Amphotericin B | Yes (resection) | Died |
| Rabagliati et al. 2021 [57] | Chile | Amphotericin B (LAmB) | No | Died |
| Rao et al. 2021 [58] | India | Amphotericin B (LAmB) | Yes (endoscopic sinus surgery) | NR |
| Authors          | Country | Treatment | Surgery                  | Outcome |
|------------------|---------|-----------|--------------------------|---------|
| Ravani et al. 2021 [59] | India   | Amphotericin B (LAmB 5 mg/kg/day) | Yes (sinus debridement; n = 18) | Lived (94%), Died (6%) |
| Revannavar et al. 2021 [60] | India   | Amphotericin B | Yes (endoscopic sinus surgery) | Lived |
| Saldanha et al. 2021 [61] | India   | Amphotericin B (25 mg/day) | Yes (endoscopic sinus surgery) | Lived |
| Sarkar et al. 2021 [62] | India   | Amphotericin B | Yes (maxillectomy (n = 3), debridement (n = 1)) | Died |
| Satish et al. 2021 [69] | India   | Amphotericin B | Yes (all patients: surgical debridement) | No data |
| Sen et al. 2021 [63] | India   | Amphotericin B (LAmB)+ voriconazole/posaconazole | Yes (exenteration (n = 2), sinus debridement (n = 3)) | Lived |
| Vessi et al. 2021 [64] | Iran     | Amphotericin B (4 mg/kg/day) | Yes (surgical debridement) | Died |
| Waizel-Haiat et al. 2021 [65] | Mexico   | Amphotericin B | No | Died |
| Werthman-Ehrenreich et al. 2021 [66] | USA     | Amphotericin B | Yes (sinus debridement) | Died |
| Zurl et al. 2021 [67] | Austria  | No | No | Died |

AMB: amphotericin B; IV: intravenous; LAmB: liposomal amphotericin B; NR: not reported; UK: United Kingdom; USA: United States of America. * No separate outcomes were reported for mucormycosis (n = 28).
4. Discussion

To the best of our knowledge, this is the most comprehensive and up-to-date evidence mapping aimed to explore the published and unpublished evidence on the clinical presentation, treatment modalities, and patient outcomes of CAM. The current body of evidence was based on the 41 studies that met our inclusion criteria and discussed the association of COVID-19 with mucormycosis.

Mucormycosis is a rare opportunistic infection, and COVID-19 patients are at risk of developing mucormycosis because of pre-compromised immune systems. A growing body of evidence supports that comorbidities (diabetes, transplantation, malignancies) and medications (steroids) make the patients more vulnerable to CAM [5–7]. A recent case report found an invasive pulmonary mucormycosis case in a patient after a short course of steroids [72]. Likewise, Pan et al. found mucormycosis in a patient with AIDS receiving short-term systemic steroids [73]. In our study, we found that COVID-19 patients with comorbidities had a higher occurrence of mucormycosis.

Around 50% of CAM cases in our study were reported from India. A possible reason for this could be the deadly COVID-19 delta variant wave infecting around half a million people every day in recent months and a high prevalence of diabetes mellitus in CAM patients [74]. Diabetes mellitus is a predisposing factor for the development of mucormycosis [75,76]. The potential mechanism behind this could be the aggravation of the inflammatory state due to hyperglycemia and activation of antiviral immunity [77]. The risk of developing CAM increases significantly in patients with diabetic ketoacidosis, where Mucorales use free iron levels in the serum for pathogenesis [78].

In our study, the number of male mucormycosis patients was twice the number of female patients. These findings are aligned with a previously published study by Roden et al. [79] that found mucormycosis in 65% of male patients.

Rhino-orbital and rhino-orbital-cerebral were the most common forms of mucormycosis observed in this study. In both forms of infection, the fungus invades the nasal mucosa and orbital wall and leads to the occurrence of symptoms such as facial pain, vision loss, proptosis, apoptosis, and ophthalmoplegia [80,81]. CAM patients who underwent both surgical and medical management had a better survival rate than those with medical management alone. Published studies from different parts of the world have also found better outcomes in mucormycosis patients who underwent combined surgical and medical management [82,83]. However, despite the best management of CAM patients, the overall mortality was high, suggesting the need for the early identification of cases.

Our study findings suggest that clinical practitioners (intensivists and their teams) should be alerted about the increased possibility of CAM in critically ill COVID-19 patients; therefore, they should act proactively and monitor for potential fungal and bacterial co-infections and secondary infections among the COVID-19 cohorts, especially the immunocompromised and diabetic patients [84]. Moreover, these findings call drug regulators and health systems, especially in low- and lower-middle-income countries, to implement strict policies for steroid stewardship.

4.1. Limitations

Like every study, this evidence mapping has few limitations. Firstly, we could not differentiate the outcome based on glycemic-controlled status due to the lack of information on the glycosylated hemoglobin value of the CAM patients with diabetes in the included studies. Secondly, there was variability in the definition of severity of COVID-19 in the included studies. Lastly, limited information (fungal species identified, RT-PCR result) in a few included studies was also a drawback.

4.2. Strengths

The major strength of this review was a large number of exhaustive literature searches in major databases, a protocol-oriented approach, most up-to-date evidence with sound
methodology, and the capture of each minute detail of 167 CAM patients to make this review a one-stop source of information for CAM.

5. Conclusions

This evidence mapping found a high incidence of CAM with a high mortality rate. Therefore, clinicians should cautiously use the steroids using the risk–benefit analysis approach. Optimal glycemic control and early identification of mucormycosis should be the priority to reduce the morbidity and mortality related to CAM.

Supplementary Materials: The following are available online at www.mdpi.com/article/10.3390/ijerph181910340/s1, Table S1: PRISMA-ScR checklist, Table S2: Search strategy, Table S3: List of excluded articles.

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Institutional Review Board Statement: The study was exempted from ethical approval due to its observational nature and the use of publicly accessible data.

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Data Availability Statement: The data that support the findings of this study are available from the corresponding author (S.H. or M.K.) upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. MEDLINE® ALL <1946 to 8 June 2021> (Ovid).

| #  | Search String                                                                 | No. of Results |
|----|------------------------------------------------------------------------------|----------------|
| 1  | exp Coronavirus/                                                             | 77,269         |
| 2  | exp Coronavirus Infections/                                                 | 94,303         |
|    | (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus* or “Kawasaki like paediatric inflammatory multisystem syndrome” or “Kawasaki like pediatric inflammatory multisystem syndrome” or “PIMS-TS” or “Kawa-COVID-19” or “MIS-C” or “multisystem inflammatory syndrome in children” or pediatric multisystem inflammatory disease).mp. | 159,987         |
| 4  | (or/1–3) and ((20191* or 202*).dp. or 20190101:20301231.(ep.).) (147001)     | 147,001        |
| 5  | 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel * or dromedary* or equine or corona or coronal or covedence* or coveden or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCoV or zoonotic or avian influenza or H1N1 or H5N1 or IBV or H7N7 or coccidiosis*).mp. | 54,231         |
| 6  | (or pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov* or sars*).mp. or exp pneumonia/) and Wuhan.mp. | 5278           |
|    | (2019-ncov or ncv or ncov19 or ncov 2019 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sars-cov-2 or SARS-2-nCoV or SARS-2-Cov or Sars-COV-19 or Sars-coronavirus2 or Sars 2 coronavirus* or Severe Acute Respiratory Syndrome-CoV-2 or SARS-like coronavirus* or coronavirus or 2019-nCoV or covid-19 or covid 2019 or ((nvel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemic*2)) or ((covid or covid19 or covid 19 or SARS-CoV-2) and pandemic*2) or (coronavirus* and pneumonia*).mp. | 144,923        |
|    | (COVID-19 or SARS-CoV-2).rx,px,ox,zn. or (COVID-19 or COVID-19 serotherapy or ORF7b protein, SARS-CoV-2 or ORF6 protein, SARS-CoV-2 or ORF8 protein, SARS-CoV-2 or pediatric multisystem inflammatory disease, COVID-19 related or envelope protein, SARS-CoV-2 or SARS-like coronavirus* or coronavirus or 2019-nCoV or covid-19 or covid 2019 or ((nvel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemic*2)) or ((covid or covid19 or covid 19 or SARS-CoV-2) and pandemic*2) or (coronavirus* and pneumonia*).mp. | 8460           |
| 8  | SARS-CoV-2 or ORF7a protein, SARS-CoV-2 or spike protein, SARS-CoV-2 or ORF3a protein, SARS-CoV-2 or COVID-19 drug treatment or severe acute respiratory syndrome coronavirus 2 or membrane protein, SARS-CoV-2 or ORF1ab polyprotein, SARS-CoV-2 or nucleocapsid protein, Coronavirus or COVID-19 vaccine or COVID-19 diagnostic testing).os,ps,rs,rs. | 3407           |
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