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# COVID-19 ASSOCIATED MUCORMYCOSIS: A CASE SERIES REPORT AND AN UMBRELLA REVIEW

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**Abstract:** The emerging epidemic of COVID-19 Associated Mucormycosis(CAM) has been recognized as a significant global public health threat. India accounted for majority of the globally detected CAM cases especially during the second wave of the pandemic in 2021. A severe form of invasive CAM called Rhino-orbital-cerebral mucormycosis (ROCM) led to high mortality and morbidity especially in COVID patients with predisposing factors causing immunosuppression such as diabetes mellitus, malignancies, and steroid therapy. This study was carried out to describe the demographic features as well as analyze the comorbidities and outcomes of patients diagnosed with CAM and to provide an umbrella review of published global systematic reviews on CAM with special reference to ROCM. In this case series report, we have noted the findings and outcomes of 12 COVID patients with CAM treated at two different tertiary care hospitals in India. All were males, with an average age of 54.25 years. 66.6% had invasive ROCM and 91.7% had poorly controlled diabetes. All received liposomal amphotericin B, 58.3% underwent surgical interventions and the mortality rate was 33.3%. We also conducted an umbrella review of systematic reviews reported from 2020-2022. PubMed, Embase, Scopus and Google scholar databases and the PRISMA 2020 checklist were used to refine retrieval and review based on our study criteria. Common patterns were noted regarding the predisposing factors and treatment outcomes. Good glycemic control, the regulated use of steroids, proper decontamination of oxygen cylinders and the hospital environment as well as avoidance of overzealous use of steam inhalation have been proposed as important measures to control this epidemic.

**Keywords:** COVID-19, Rhino-Orbital-Cerebral Mucormycosis (ROCM), Diabetes Mellitus (DM).

## Introduction

During the second wave of the COVID-19 pandemic in 2021, an epidemic of COVID-19 Associated Mucormycosis(CAM) emerged as a double whammy especially in immunocompromised patients. A hitherto rare disease before the pandemic, this epidemic of mucormycosis attracted global attention as a major public health catastrophe, especially in countries like India.(Ahmad, 2021; Watanbe et al., 2022). While the general population incidence of mucormycosis is low (0.005–1.7/million

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populations), a surge in such cases were reported with alarmingly high mortality rates of up to 49% and loss of vision in up to 46% of CAM patients (Bhattacharyya et al., 2021; Hoenigel et al.,2022).

Often called by the misnomer 'black fungus", COVID-19-associated mucormycosis became a major public health problem in India with at least 14872 cases as of May 28, 2021. (Raut et al.,2021). COVID-19-associated mucormycosis cases have also been seen outside of India, including in the United States, Pakistan, France, Iran, Mexico, Brazil, and some European countries (Pal et al., 2021). Being a rare infectious disease, mucormycosis had never been nationally notifiable nor reportable in most of the countries in the world. until the second wave of the COVID-19 pandemic that began in winter 2020. In mid-May 2021, due to the expeditious increase in the CAM cases, multiple Indian states declared mucormycosis as a notifiable disease under the Epidemic Diseases Act, 1897 (Hussain et al.,2021).

Mucormycosis is a rare fungal opportunistic disease caused by a group of saprophytic fungi of the order Mucorales. The different clinical types include the rhino-orbital-cerebral mucormycosis (ROCM), pulmonary, gastrointestinal, cutaneous, renal, and disseminated mucormycosis (Serris et al., 2019). The agents of mucormycosis are angioinvasive with infarction and necrosis of infected tissues considered as the hallmarks of invasive disease (Greenberg et al.,2004). The predisposing risk factors include poorly managed diabetes, hematological malignancies, neutropenia, organ transplantation, trauma, burns, and the use of immunosuppressants such as corticosteroids (Cornely et al.,2019; Hariprasath et al.,2019). Following the RECOVERY trial in July 2020, that demonstrated the benefit of dexamethasone, glucocorticoids have been the standard therapy for severe COVID-19 pneumonia. This may have paved the path for a significant increase in secondary invasive fungal infections in COVID-19 patients. (RECOVERY Collab Group, 2021).

During the second wave of the COVID-19 epidemic in India, several cases of ROCM were encountered in the western and southern parts of India. 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. (Sen et al., 2021). On the other hand, some case reports described the simultaneous diagnosis of mucormycosis with COVID-19 raising the possibility of shared underlying co-morbidities such as diabetes and immunodeficiency for COVID as well as mucormycosis, rather than a causal relationship brought by glucocorticoid treatment for COVID-19. (Werthman-Ehrenreich , 2021).

Although there are several published case reports and case report series and some reviews available on CAM and ROCM from different parts of the world, we found a paucity of global systematic umbrella reviews that provide a comprehensive global status of this condition. As extensive review of systematic literature was unavailable, it prompted us to not only describe a series of case reports but also carry out a review of systematic reviews. In this study we have analyzed the data obtained from 12 proven cases of mucormycosis encountered in two different tertiary care hospitals in India. Additionally, we have carried out an umbrella review of the systematic reviews published on CAM in the last two years.

**Materials and Methods**

This study was a collaborative multicentric project carried out with the following aims and objectives:

The aim was to study the incidence and characteristics of a series of cases of COVID associated mucormycosis in two different tertiary care hospitals in India followed by providing a comprehensive umbrella review of existing systematic global reviews. The objectives for the Case Series included analyzing the demographics of patients with CAM, studying the underlying co-morbidities, and looking at significant associations, treatment, and outcomes. For the umbrella review, the objective was to carry out a well-structured comprehensive review of published reviews using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA 2020) guidelines.

Primary clinical and laboratory data of cases of CAM diagnosed and treated at Jawaharlal Nehru Medical College and Hospital, Belgavi, India and the Mahatma Gandhi Mission Medical College & Hospital, Navi Mumbai, India were compiled and analyzed. The two hospitals are in geographically diverse states of India located in the southern state of Karnataka and the western state of Maharashtra respectively. The data included demographic details, the clinical presentations, co-morbidities, predisposing factors, onset of mucormycosis after COVID diagnosis, treatment, and outcomes. Additionally, we conducted an umbrella review of the systematic reviews published on CAM. The objectives were to obtain secondary data published in reviews and to consolidate global information regarding the number of cases with proven diagnosis of CAM, the mean age of patients, gender percentage positivity, clinical presentations, underlying co-morbidities, treatment modalities, and outcomes including mortality rates.

Three online databases (PubMed, Embase and Scopus) were comprehensively searched using the search terms, [‘Zygomycosis OR Mucormycosis OR ROCM’] AND [COVID-19 OR SARS CoV-2 OR Novel coronavirus]. Two independent reviewers( CP and SU) performed the search and data collection compiling the same in Microsoft excel files. Any differences or conflicts in the selection process were resolved with consensus discussion. Data was captured for 2020 through 2022 and retrieved data was stored in excel files. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA 2020) updated statement was used as a guideline for the umbrella review. (Page et al.,2021)

Only those systematic review papers which included cases of mucormycosis with the following inclusion criteria were considered:

- Concurrent or recent past infection with COVID-19 infections.
- Confirmed diagnosis of mucormycosis based on microscopic visualization or histopathologic examination or positive culture results.
- Proven COVID-19 infections based on e.g., reverse transcription polymerase chain reaction [RTPCR], rapid antigen tests, or serum antibody tests.

Following were the exclusion criteria:

- Case reports or case series or clinical trial-based studies.
- Reviews that included papers that did not clearly state the diagnostic criteria used for COVID-19 or where there may have been only a presumptive diagnosis of COVID-19 and/or mucormycosis without laboratory evidence.
- Reviews which did not follow the PRISMA guidelines.
- If more than one review study came from the same author(s), the bigger study was included based on the assumption that this may have included the earlier smaller study.

For assessing the Risk of Bias, we employed the Joanna Briggs Institute (JBI) Critical Appraisal tools for Systematic Reviews and Research Syntheses. (Aromataris and Munn, 2020). The checklist consists of eleven questions based on the clarity of review question, inclusion criteria, search strategy, adequacy of sources and resources for the search, critical appraisal by two or more reviewers, methods to minimize errors in data, assessment of publication bias, alignment of policy recommendations supported by reported data and appropriateness of directives for new research. Each of these were assessed with a yes, no, unclear, and not applicable responses with an overall appraisal to include, exclude or seek further information. The assessment is presented in Table 2 in the results section.

From all the eligible systematic reviews, the information gathered included study author, year, country, study period or duration, the number of COVID-19 cases, confirmation of COVID-19 diagnosis, confirmation of mucormycosis diagnosis, the number of mucormycosis cases among COVID-19 patients, the presence of comorbidities, the mean age of mucormycosis patients, female (%), clinical symptoms, treatment modalities, and mortality. Any confusion in the data collection process was resolved by discussion with a third reviewer.

Primary data obtained from our case series reports as well as secondary data obtained from the systematic reviews were organized in excel sheets and used to calculate means and percentages. These were further represented using suitable charts and graphs. The percentage values of different parameters were compared between findings of our 12 cases versus those published in other reviews. However due to an enormous difference in the number of cases of our study, i.e., 12 as compared to 7600 in the literature reviews, we did not find suitable statistical tests that could compare the two datasets for significant statistical differences.

**Results and Discussion**

Details of the 12 patients admitted to the hospitals included in the study are compiled in Table 1.

*Table 1: Demographic, clinical and outcome details of the 12 patients of CAM treated at the two tertiary care hospitals included in the study*

| | Age in years/ sex of patient | COVID Associated Mucormycosis (Clinical type) | Co - morbidities | Proven COVID and Mucormycosis diagnosis | Features of CAM seen during or post COVID infection | Treatment | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 63/M | ROCM | DM, HTN | Yes | Post COVID | Maxillectomy with surgical debridement + Liposomal Amphotericin B | Uneventful recovery |
| 2 | 45/M | ROCM | DM | Yes | Post COVID | Left orbital exenteration with, left medial maxillectomy and surgical debridement | Death within 2 weeks following diagnosis, 10 days following surgery |
| 3 | 50/M | ROCM | DM | Yes | Post COVID | Amphotericin B | Moved to a reference hospital-lost to follow up. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 4 | 55/F | ROCM | DM,HTN | Yes | Post COVID | Amphotericin B | Recovered in |
| 5 | 53/M | ROCM | DM, HTN | Yes | Post COVID | Amphotericin B | Recovered in 4 weeks |
| 6 | 50/M | ROCM | HTN | Yes | Post COVID | Amphotericin B | Death due to invasive infection |
| 7 | 60/M | ROCM | DM, HTN | Yes | Post COVID | Amphotericin B | Uneventful recovery |
| 8 | 80/M | ROCM | DM, HTN | Yes | Post COVID | Amphotericin B with oculoplasty. | Death due to invasive infection |
| 9 | 51/M | Invasive Rhinosinusitis | DM, HTN | Yes | Post COVID | Surgical debridement and Amphotericin B. | Uneventful recovery |
| 10 | 56/M | Invasive Rhino-ocular mucormycosis | DM | Yes | Post COVID | Surgical debridement with left orbital decompression and Amphotericin B. | Recovery with residual vision loss |
| 11 | 51/M | Invasive Rhinosinusitis | DM | Yes | Post COVID | Surgical debridement with Amphotericin B | Uneventful recovery |
| 12 | 37/M | Invasive Rhinosinusitis | No co-morbidities | Yes | Post COVID | Surgical debridement with Amphotericin B | Death due to sepsis |

M-male ROCM- Rhino Orbital Cerebral Mucormycosis DM-Diabetes Mellitus HTN- Hypertension

*Figure 1: Mucormycosis in a diabetic patient with characteristic orbital cellulitis, proptosis, and periorbital skin discoloration. Indirect ophthalmoscopy showed the optic disc with blackish discoloration on the disc more on the temporal side with blurred margins and attenuation of retinal vessels with macular folds.*

*(Image credit- Gore, V, Professor of Ophthalmology, M.G.M.Medical College and Hospital, Navi Mumbai, India)*

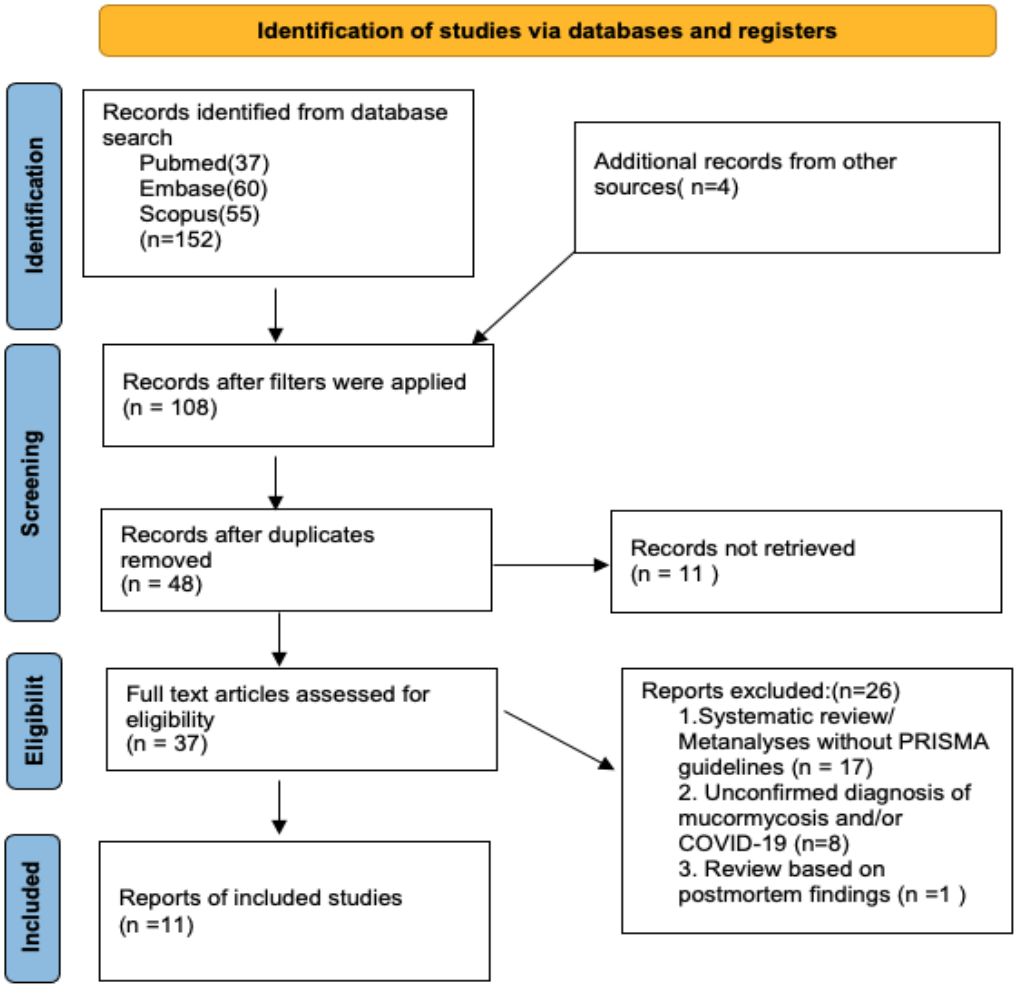


*Figure 2: PRISMA flowchart displaying the study selection process.*

From three search databases 152 review papers and four reports on CAM were identified. As per the PRISMA 2020 guidelines, the papers were further screened based on filters such as the study type and duration. Duplicates and papers that could not be retrieved were removed from the list. Finally based on the inclusion and exclusion criteria, 11 systematic review studies on 7600 proven cases of CAM were eligible for the umbrella review.

As per the JBI critical appraisal tool for Systematic Reviews and Research Syntheses, all the included reviews were of high quality, based on an adequate sample size, adequate description of patients and settings and the systematic review process. The assessment is presented in Table 2.

*Table 2: Risk of Bias assessment of the review studies based on the JBI Critical Appraisal tools for Systematic Reviews and Research Syntheses.*

| Study Author and | Is the review question clearly and | Were the inclusion | Was the search strategy | Were the sources and | Were the criteria for | Was critical appraisal | Were there methods to | Were the methods used | Was the likelihood of publication | Were recommendations for policy and/or practice | Were the specific directives for |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Afal et al., 2022 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Bhattachary a et al., | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Donovan et | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Hoenigl et al., | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Hussain et al.,2021 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Muthu et al., 2022 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

Y-yes, N-no, U-unclear, NA-not applicable

*Table 2 contd.: Risk of Bias assessment of the review studies based on the JBI Critical Appraisal tools for Systematic Reviews and Research Syntheses.*

| Study Author and Publication Year | Is the review question clearly and explicitly | Were the inclusion criteria appropriate for the review | Was the search strategy | Were the sources and resources used | Were the criteria for appraising studies | Was critical appraisal | Were there methods to minimize errors in | Were the methods used to combine | Was the likelihood of publication bias assessed? | Were recommendations for policy and/or practice supported by the reported | Were the specific directives for new research |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nagalli et al., 2022 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Pal et al., 2022 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| SyedAlinaghi et al., 2022 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Watanbe et al., 2022 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Zobairy et al., 2022 | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

Y-yes, N-no, U-unclear, NA-not applicable

*Table 3: Summary of findings of the systematic review articles.*

| Study author and year | Total number and country-wise break down of observational studies; number of patients(n) | Mean Age | Mean % of male patients | Underlying comorbidity | % patients given steroid therapy | CAM type | Treatment given | % Mortality Rate |
|---|---|---|---|---|---|---|---|---|
| SeyedAlinaghi et al.,2021 | Total-31; n=144<br>India-8;n=43<br>USA-7;n=8<br>Egypt-2; n=44<br>Iran-2; n=3<br>UK-2;n=11<br>Turkey-1; n=11<br>China-1; n=10<br>Others-10; 14 | 50.4 years | 75.22% | DM-66.4%<br>HTN-34.3% | Not reported | Not specified | 92%-Amphotericin B<br>Debridement surgery-52% | 33.6% |
| Bhattacharya et al., 2021 | Total-23;n=381<br>India-14;NR<br>Egypt-4;NR<br>Iran, Turkey, Chile, France, Netherlands-1each;NR | 54.6yrs | 78.4% | DM-79%<br>HTN-43.5%<br>CKD-11.4%<br>Malignancy-6.6%<br>CAD-23.5% | 85.75% | ROCM-42.8% | Amphotericin B-93%<br>Surgical debridement-70.9%<br>Orbital Exenteration- 21.2% | 37.3% |
| Hussain et al., 2021 | Total-6; n=223<br>India-4; n=202<br>Turkey-1; n=11<br>Pakistan-1;n=10 | 62.12 years | 65.88% | DM-74.5%<br>HTN-48.44%<br>CKD-17.9%<br>HM-0.89% | 94.3% | Not specified | Amphotericin B: 99.42%<br>Surgical debridement: 73.42% | 29.6% |
| Muthu et al.,2021 | Total-NR; n=275<br>India: n=233<br>Rest of the world-n=42 | 54.45 years | 78.25% | DM-71.3%<br>HM-5.2% | 75.7% | ROM-53.2 %<br>ROCM-23.15 %, Pul-9% | Amphotericin B-88.45%<br>Surgery-68.2% | 49.2 % |
| Nagalli et al.,2021 | Total-36; n= 115<br>India-17; n=57<br>Iran-3;n=18<br>Turkey-1; n=11<br>USA-7; n=9<br>Egypt-1; n=8<br>Others-7; n=12 | 54.9 years | 77.4% | DM-77.1%<br>HTN-29.5%<br>DKA-9.6%<br>CKD-14.3%<br>HM-6.7% | 91.9% | Rhino-sinusal-79.4%<br>ROCM-12.4% | Amphotericin B: 85.9%<br>Surgical debridement-<br>-59.8%<br>Orbital exenteration-14.1% | 48.7% |

*Table 3contd.: Summary of findings of the systematic review articles.*

| Study author and year | Total number and country-wise break down of observational studies; number of patients(n) | Mean age | Mean % of male patients | Underlying comorbidity | % patients given Corticosteroid therapy | CAM type | Treatment given | % Mortality Rate |
|---|---|---|---|---|---|---|---|---|
| Pal et al., 2021 | Total 30; n=99<br>India-14; n=71 cases<br>US-7;n=10<br>Egypt-1;n=6<br>Iran-1;n=3<br>Brazil, Chile- 1 each; n=4<br>Others-5;n=5 | 52.6 years | 78% | DM- 85%<br>HTN-58%<br>CKD-17%<br>No comorbidities 4% | 85% | ROM: 42%<br>ROCM: 24%<br>Pulm-10% | Amphotericin B-95%<br>Surgery-81% | 33% |
| Afzal et al., 2022 | Total 20; n=47<br>India-10; n=15<br>USA-3;n=5<br>Egypt-1;n=10<br>Iran-2;n=6<br>Turkey-1;n=8<br>Iraq, Mexico, Italy-1;n=1each | 56.3 years | 75% | DM-72.9%<br>HTN-20% | 45.83% | ROCM most common | NR | 52% |
| Donovan et al., 2022 | Total 14; n=206<br>India-8;n=140<br>Egypt-3; n=62<br>USA-2;n=3<br>Mexico-1;n=1 | NR | NR | DM-73.3%<br>HTN-34%<br>HM-1.5% | 65% | NR | 61.2%-Amphotericin B,<br>59.2%-surgical debridement | 24.8% |
| Hoenigl et al., 2022 | n=80 cases<br>India-n=42<br>USA-n=8<br>Pakistan-n=5<br>France, Mexico, and Iran-n=4 each<br>Others-n=13 | 55 years | 78% | DM-83%<br>DKA-49%<br>HTN-19%<br>CKD-6%<br>End stage renal disease 9% | 79 % | ROCM-74%<br>Pulmonary-25% | Amphotericin B: 89%<br>Surgical resection-96% | 49% |
| Watanbe et al., 2022 | Total-51; n=2312<br>India-37;n=2039<br>Egypt-7;n=100<br>Iran-3;n=135<br>Others-4;n=38 | 36-63 years | 71.9% | DM-88%<br>HTN-42%<br>CKD-15%<br>Immunosuppression-14%<br>Malignancy-2.6% | 77% | 97%-ROCM,<br>2.7% Rhino-sinusal | Amphotericin B- NR<br>Surgical treatment-83% Orbital exenteration-17% | 29% mortality |
| Zobairy et al.,2022 | Total-18; n=3718<br>India-17; n=3703<br>Iran-1; n=15 | 44.5-58.3 years | 69.7% | DM-89%<br>HTN-37%<br>Cardio-vasds-6%<br>CKD-4% | 79% | ROM-61%<br>ROCM-22% | NR | 24% |

**Discussion**

A hitherto rare disease, mucormycosis had never been nationally notifiable nor globally reportable in most of the countries. However, during the pandemic, COVID associated Mucormycosis(CAM) emerged as as a major public health concern causing high mortality and morbidity in COVID-19 patients as was rightly declared as a nationally notifiable disease by the Indian government, in accordance with the Epidemic Diseases Act of 1897. (Ahmad et al., 2021).

This paper discussion involves the demographic and clinical details including co-morbidities, predisposing factors, and treatment outcomes of the 12 cases of CAM treated at two tertiary care hospitals in two different regions of India. In addition, the umbrella review summarizes important systematic reviews on CAM published between 2020-2022.

## *Patient demographics:*

In our case series consisting of 12 proven cases of CAM from Maharashtra(western India) and Karnataka(southern India) states of India., eight presented as ROCM while three had invasive rhinosinusitis, and one had rhino-ocular mucormycosis. All patients were males and their ages ranged between 37-80 years with a mean age of 54.25 years.

Our patient demographics compare well with the findings of Bhattacharya A et al., Muthu et al., Nagalli S et al. and Hoenigl et al., who reported mean age groups of 54.6, 56.1, 54.9 and 55 years respectively in their reviews. Ten out of the 11 review studies reported a male preponderance ranging from 65.88%-100% while one review did not report the gender percentage.

## *Underlying co-morbidities:*

*A. Diabetes mellitus:*

In our case series, eleven cases (91.6%) had poorly controlled diabetes mellitus (DM) and seven (58.3%) had hypertension (HT). Seven (58.3%) had received steroid therapy and none had malignancies or other immunosuppressive conditions. Four patients (33.3%) had received ventilatory support a few weeks before the onset of mucormycosis. In the systematic review analysis, the associated co-morbidities in CAM cases included DM (78.2%), HT (36.5 %), steroid treatment (78%) and hematological malignancy (3.32%).

Several mechanisms may be at play to explain why and how DM is such a major predisposing factor that leads to CAM.

In general, DM impairs innate as well as adaptive immunity by interfering with phagocytic functions and dendritic cell responses, that are needed to eliminate the pathogens. Additionally, several mechanisms have been implicated in the pathogenesis of CAM in patients with DM:

a) Elevated levels of glucose and iron, as seen during hyperglycemia, diabetic ketoacidosis (DKA), or other forms of acidosis enhance the expression of a glucose-regulated 78 kDa protein (GRP78) which is an essential receptor for vascular invasion by Mucorales. In addition, the expression of the fungal

spore coat protein CotH3 ligand also gets enhanced, leading to lethal rhino orbital/cerebral mucormycosis. (Muthu et al.,2021; Hoenigel et al., 2022).

b) Mucorales produce the toxin mucoricin, which displays structural and functional features of the plant toxin ricin, and is endowed with the ability to induce inflammation, vascular permeability in vitro, and hypovolemic shock and organ necrosis in mouse models of mucormycosis. (Soliman et al., 2021)

c) Another noteworthy point is that the SARS-CoV-2 virus can further lead to diabetes by entering pancreatic islet cells via the Angiotensin-Converting Enzyme 2 (ACE2) protein and by injuring the beta cells. Severe COVID-19 also increases insulin resistance through enhanced secretion of stress hormones (cortisol and others) and cytokines (Affinati et al.,2021). Thus COVID-19 infection may lead to DM and further predispose to CAM.

58.3% of our CAM patients had hypertension as the second most common associated co-morbidity. This concurred well with the observations of Pal et al., and Hussain et al., who respectively reported 58% and 48.44% as the percentage prevalence of hypertension in their studies. In most of the other studies, the percentage prevalence of hypertension was much lower, ranging from 19% to 43.5%, the mean being 36.57 %. Additional research on the association of hypertension with CAM may be needed to see if this association is significant or a chance finding. None of our cases had chronic kidney disease or underlying malignancies.

*B. Steroid therapy:*

Seven out of our 12 cases (58.3%) had been administered steroids during their COVID illness. Of the 11 review articles analyzed, nine papers reported steroid therapy as a preceding event to the occurrence of CAM. The highest percentage of steroid therapy was reported by Hussain et al.,( 94.3%), and Nagalli et al.,(91.9% ). 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. (Watanbe et al., 2022; Recovery Collab Group, 2021). There seems to be conclusive evidence that point towards corticosteroids as an important predisposing factor that can lead to CAM. Glucocorticoids can lead to immunosuppression including impairing the ability of phagocytes to clear infections as well as lead to hyperglycemia, thereby predisposing patients to mucormycosis. (Watanbe et al., 2022; Muthu et al., 2021). Hence corticosteroids should be given with caution and in the right dose and for the right duration as noted in the guidelines.

## *Clinical presentation of CAM:*

% of the 12 cases of CAM in our case series had invasive ROCM, while the remainder had rhinosinusitis. This was higher compared to the data obtained from the 11 review articles wherein the mean incidence of ROCM was found to be 42.19 %. Only seven out of the 11 review studies described the breakdown of CAM cases and the incidence of ROCM. In a descending order, the highest incidence was reported by Watanbe et al., (97.3%), followed by Hoenigl et al.,(74%), Bhattacharya et al.,(42.8%), Pal et al., (24%), Muthu et al., (16.83%), and Nagalli et al., (12.4%). These differences may be related to several factors including:

- How early the patients sought medical consultation for the symptoms related to CAM.
- The presence of underlying co-morbidities such as DM,HT, malignancies etc., and steroid therapy which may have led to faster and extensive dissemination of the angioinvasive mucormycetes.
- The inappropriate use of antimicrobial agents (antibacterial and antifungal drugs) that may alter the delicate balance of the mycobiome and microbiome of the nasal and respiratory epithelium (Nguyen et al., 2015).
- The overzealous use of steam inhalation especially in India, may have led to ciliary damage of the respiratory epithelial cells and impaired clearance of inhaled fungal spores.(Muthu et al., 2021)
- The likely contamination of industrial oxygen stored in containers that were used during the acute shortage of oxygen is a factor which is discussed but not proven.(Muthu et al., 2021)

### *Treatment and outcomes:*

All our patients were given liposomal amphotericin B, majority of our patients (58.3%) underwent surgical interventions such as debridement and two underwent orbital exenteration. Mortality rate in our case series was 33.3%. Among the 11 systematic reviews analyzed, eight had compiled information regarding the use of amphotericin B, nine noted surgical or endoscopic interventions and three noted orbital exenteration carried out for the patients. The patients receiving amphotericin B ranged between 61.2% to 99.42 % with a mean percentage of 88.02%. Surgical or endoscopic procedures were carried out for 59.2%-96% cases, with a mean of 75.62 % receiving surgical treatment. The mortality rate was reported in 10 of the 11 reviews and ranged from 24.8%-52%. The mean mortality percentage was 37.7%. This was slightly more than the 33.3% mortality rate seen in our case series. In our case series, 25% underwent orbital exenteration while in the review analysis, the percentage of cases undergoing exenteration ranged from 14.1% to 21.2%. Systemic antifungal therapy plays a vital role in treating mucormycosis, but endoscopic or surgical debridement is crucial to improving outcomes in CAM patients. The invasive procedure of exenteration is indicated especially when the invasion has extended intracranially and should be considered for actively infected orbit with a blind, immobile eye. However, given that the physical psycho-social consequences of losing an eye and vision are significant, the efforts should be in place to salvage the eye to the greatest extent possible. Thus, our study and the review analysis reiterate the fact that CAM cases can be associated with significant morbidity and mortality and need to be diagnosed and managed promptly.

### *Strengths of the study:*

Our study presents our own experience with CAM and provides an umbrella review of 11 other reviews from across the world. Using the PRISMA 2020 guidelines and the JBMI tool has led to an organized inclusion of systematic reviews for our umbrella review while keeping the study biases to a minimum. Population size studied was good and all reviews included cases that were proven cases based on laboratory evidence for COVID-19 as well as for mucormycosis. Most important clinical correlations were covered.

### *Limitations of the study:*

The limitations of our study are that we could review only 11 systematic reviews based on our inclusion criteria of including those that followed the PRISMA 2020 guidelines. As a result, it is possible that we would have missed out studying the details of several cases of CAM reported by different authors across the world and that this umbrella review draws conclusions from only a few of such systematic reviews. Additional features that we would have like to include in the study would have been correlating the status of glycemic control considering the HbA1C level and the severity of the CAM as well as the dose and duration of steroid treatment correlated with the severity of CAM. As these pieces of information were not available uniformly in all the reviews, these could not be studied.

## Conclusion

COVID-19-associated mucormycosis can be a serious complication of severe COVID-19, particularly in patients with uncontrolled diabetes. Based on our study we conclude that poorly controlled diabetes and steroid therapy are the main factors that predispose COVID-19 patients for this severe complication leading to poor and sometimes fatal outcomes. A high index of suspicion and team effort among clinicians and diagnosticians is needed for the early diagnosis of CAM and timely interventions. Good control of underlying conditions like diabetes and hypertension as well as the judicious use of steroid therapy should be prioritized. Aggressive therapy combining systemic antifungal agents along with targeted surgical interventions are quintessential for the improved outcomes leading to low mortality and morbidity rates. Other preventive measures proposed are proper sanitization and handling of oxygen gas cylinders, proper decontamination of the hospital environment and the avoidance of overzealous use of steam inhalation.

The future studies can be geared towards analyzing the trends of CAM following possible future pandemics of COVID-19. It will be additionally noteworthy to study the correlation of specific strains of the COVID-19 virus with the severity and outcome of CAM.

## Declaration of Interest Statement

The authors declare that there is no conflict of interest.

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