



Various Treatment Modalities in COVID-19 Associated Facial Mucormycosis and the Need for its Surgical Management: A Systematic Review

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Received: 9 February 2022 / Accepted: 20 February 2023
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Abstract

Introduction Mucormycosis emerged as a wildfire in post-covid-19 infected patients. Most frequently involved sites of mucormycosis are rhino-orbital, rhino-sinusal and rhino-orbito-cerebral. The hallmark sign of mucormycosis is tissue necrosis, which is often a late sign. The fatality rate of mucormycosis is 46% globally. Despite early aggressive combined surgical and medical therapy, the prognosis of mucormycosis is poor.

Methods We searched the electronic database of PubMed, web of science, Embase, Scopus and Google Scholar from Jan 2020 until December 2021 using keywords. We retrieved all the granular details of original research articles, case reports/series of patients with rhino-orbito-cerebral mucormycosis (ROCM), and COVID-19 reported worldwide. Subsequently, we analyzed the patient characteristics, associated comorbidities, location of mucormycosis, treatment given and its outcome in people with COVID-19. (Prospero registration—CRD42021256830, June 4, 2021).

Results Overall, 544 rhino-orbito-cerebral mucormycosis patients were included in our review with a history of Covid-19 infection. Out of which 410 patients had diabetes mellitus which has proven to be major contributing immunocompromised disease. Other diseases like hypertension, chronic kidney diseases, hypothyroidism, etc., were also attributed as an immunocompromised disease causing increased number of covid associated mucormycosis cases. We found out that total number of patients alive after taking only antifungal drug treatment were 25 in number, whereas total number of patients alive when antifungal drugs were combined with surgical intervention were 428 which was significantly higher.

Conclusion Our systematic review concluded that surgical debridement should be performed whenever feasible in parallel to antifungal treatment in order to reduce the mortality rate of COVID-19 associated rhino-orbito-cerebral mucormycosis patients.

Keywords Rhino-orbito-cerebral mucormycosis · Covid associated rhino-orbito-cerebral mucormycosis · Covid associated mucormycosis · Mortality · Treatment

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Introduction

Originally, mucormycosis was described by Paltauf in 1885, as an infection from nonseptate, broad, branching hyphae typical of molds. However, the first recorded human infection with Mucorales was a case of pulmonary mucormycosis reported by Sluyter in 1847. In 1943, Gregory described mucormycosis as the syndrome of acute orbital mucormycosis characterized by uncontrolled diabetes, unilateral internal and external ophthalmoplegia, proptosis, meningoencephalitis, and rapid death [1].

Mucormycosis previously known as zygomycosis was initially found rarely in the population. It is an angio-invasive disease caused by group of fungi called mucormycetes. It is known to spread by ubiquitous fungi commonly found in soil, fallen leaves, compost, animal dung and air which can be inhaled, causing infection of the lungs, sinuses and extend into brain and eyes or it can also enter the body through a cut or an open wound. Mucormycosis is not a contagious disease, it is known to effect people who are immunocompromised.

According to worldometers 2022 (Jan 14, 2022), SARS-CoV-2 has affected 222 Countries and Territories around the world and has reported a total of 320,959,141 confirmed cases of the coronavirus COVID-19 that originated from Wuhan, China, and a death toll of 5,539,206 deaths around the globe [2]. While the ‘third wave’ of SARS-CoV-2 and its variants-mediated COVID-19 continue to affect the global population, the deadly rise of myriads of manifestations and complications and, specifically, the rise of fatal fungal

infection, the mucormycosis, has put the lives of COVID-19 patients further at high risk [3, 4]. Currently, India is having the second largest Covid-19 affected population in the world with more than 36,582,129 cases as on Jan 14, 2022 [2]. It is recorded in various studies that treatment of COVID-19 infection might have led to the sudden surge. In India, more than 45,432 cases and 4252 deaths due to mucormycosis have been reported as on July 15, 2021, either among COVID-19 infected patients or in patients who had recovered from COVID-19 with Rhino-cerebral mucormycosis (77.6%) being the most common variant. Covid-19 associated mucormycosis (CAM) is reported to develop in patients with uncontrolled diabetes mellitus, immunosuppression by steroids, prolonged ICU stay, comorbidities like post-transplant/malignancy, or patients on Voriconazole therapy.

An epidemiological survey conducted about two decades ago suggested that mucormycosis, if left untreated, could be fatal, with mortality rate rising as high as up to 54%. [5] Since there was almost no instance of COVID-19 associated

Fig. 1 PRISMA flowchart.

Note: *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. <https://doi.org/10.1136/bmj.n71>. For more information, visit: <http://www.prisma-statement.org/>

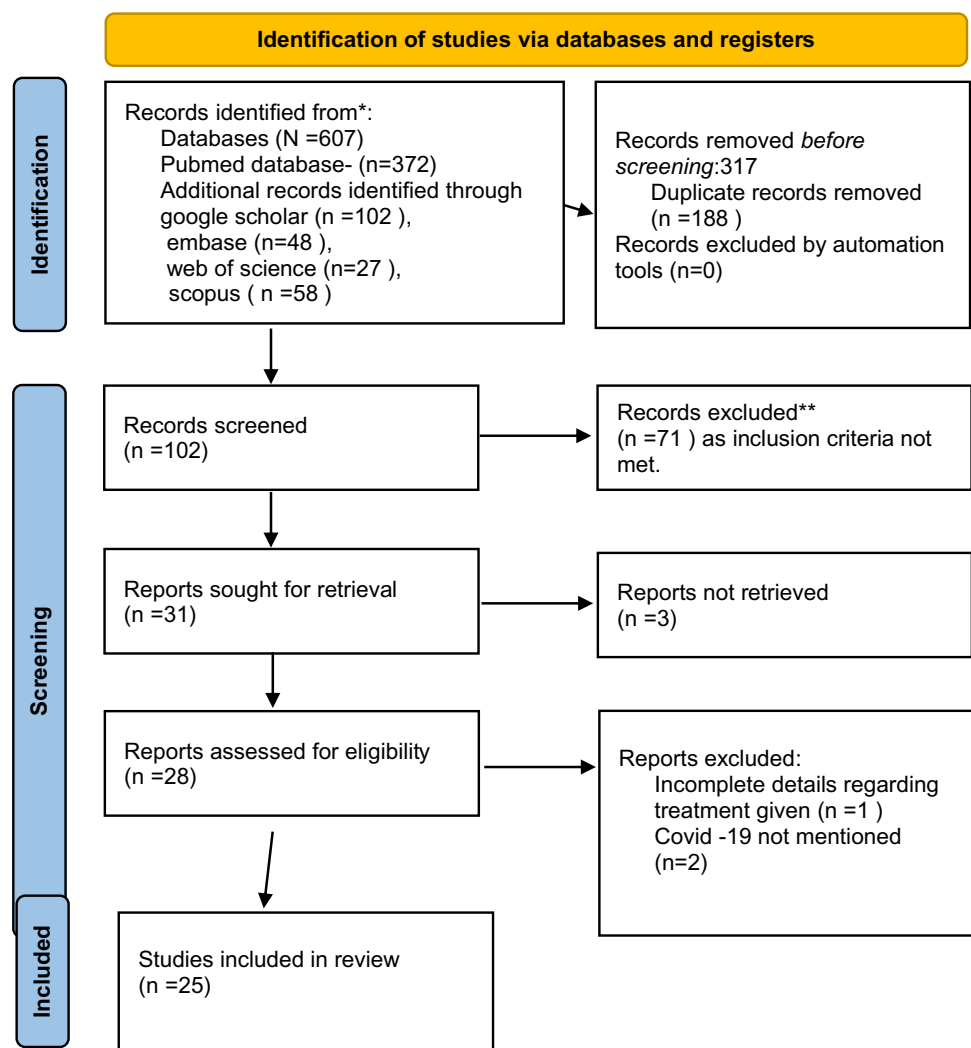


Table 1 Data extraction sheet

| Author and year | No. of patients | Male | Female | Demographic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|--------------------------------|-----------------|------|--------|------------------|------|---|---|---|---|---|--------|
| 1 Riad 2021. [7] | 7 | 5 | 2 | Egypt | ROCM | Dm-6 Chronic htm-1 Cvs disease-1 Stable angina-1 | Biopsy -4 Rtper positive for mucorales -2, CBCT, CULTURE | LAmB-all patients | Surgical debridement (FESS)-5 | Alive-7 | |
| 2 Abha Kumari 2021. [8] | 20 | 11 | 9 | India | ROCM | DM-16 | HPE, PNS | Liposomal Amphotericin at 3-5 mg/kg/day (over a period of 3-4 weeks) for a targeted cumulative dose of 4-5 g Intravenous Liposomal Amphotericin-B =20 (100%) Oral Posaconazole (on discharge)c 8 (100)c | 20 (100%) patients underwent endoscopic debridement, 4 (20%) orbital decompression and 1 (5%) maxillectomy with orbital exenteration = 1 patient (5%) | Successful 14 (70%) Discharge from hospital 8 (40%) Stable, but not yet discharged 6 (30%) Death 6 (30%) | |
| 3 BAYRAM 2021. [9] | 11 | 9 | 2 | Kayseri City | ROM | DM-8 CHRONIC RENAL FAILURE-3 MYELODYSPLASTICSYN-DROME-1 | LCB and KOH mount, SDA CULTURE, CT, MRI | amphotericin B | FESS- 11, Systemic, and retrobulbar amphotericin B SECONDARY SURGICAL DEBRIDEMENT-8 patients | DEAD-7 | |
| 4 Barman2021. [10] | 5 | 3 | 2 | New Delhi | Room | DM-3 HTN-2 IGA NEPHROPATHY-1 HYPOTHYROIDISM -1 | HPE and fungal KOH mount | Inj. Liposomal amphotericin B, syr Posaconazole ON DISCHARGE | FESS-5 RT EYE EXENTERATION -1 | ALIVE ALL | |
| 5 Hardeva Ram Nehara 2021 [11] | 5 | 1 | 4 | NORTH WEST INDIA | ROCM | T2DM-5 HTN-4 ASTHMA-1 | LCB & KOH mount | Liposomal amphotericin B antibiotics, Inotropes, | DEBRIDEMENT-1 patient | Dead-2 Alive-3 | |

Table 1 (continued)

| Author and year | No. of patients | Male | Female | Demographic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|---------------------------------|-----------------|------|--------|-------------|------|--|---|--|---|---|--------|
| 6 Sunil Kumar Pippal, 2021 [12] | 80 | 55 | 25 | MP, INDIA | ROCM | Controlled diabetes-22 patients Uncontrolled diabetes-50 patients Hypertension-60 patients. All patients with hypertension also had Diabetes mellitus Chronic kidney disease- | KOH mount and fungal culture | intravenous amphotericin and oral posaconazole all patients | FESS with debridement 58 patients, orbital exenteration 06, orbital decompression 10, maxillectomy 27, operated outside 12 patients, 10 patients required readmission | All alive | |
| 7 Ravi Meher, 2021 [13] | 134 patients | 85 | 46 | India | Room | DM-124 | DNE WITH FUNGAL KOH STAIN-ING, LCB stain mount, CECT, MRI | Injection Liposomal Amphotericin B, Posaconazole and Voriconazole | Surgical intervention included Endoscopic approaches, Open approaches and combined approaches. The various surgeries conducted were Functional Endoscopic Sinus Surgery (FESS), total and partial maxillectomy, endoscopic orbital clearance and open exenteration. orbital exenterations = 20 patients were performed. Open maxillectomies = 32 patients | Recovered = 124 Died = 7 | |
| 8 Mohammed A. Alamin 2021. [16] | 1 | 1 | 0 | INDIA | ROCM | DM TYPE 2 | Tissue and blood culture, CT, MRI | liposomal amphotericin B and later to Oral posaconazole on discharge | FESS | Outpatient follow-ups and scheduled eye enucleation for total eye blindness. ALIVE | |

Table 1 (continued)

| Author and year | No. of patients | Male | Female | Demographic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|--------------------------|-----------------|------|--------|-------------|-------|---|---|--|---|---|--------|
| 9 Salil Mehta2020 [17] | 1 | 0 | 1 | INDIA | ROCM | DM HTN | NASAL BIOPSY, SDA Culture, MRI | Amphotericin B (0.5 mg/kg/day) meropenem (1 gm thrice daily) and vancomycin (1 g twice daily)with the addition of amphotericin B (0.5 mg/kg/day) | | DEAD ON DAY 6 | |
| 10 Alfshawy 2021. [18] | 21 | 14 | 7 | Egypt | ROCM | On admission DM-19/21, 3/21- DIABETIS KETOACIDOSIS | CULTURE | 17/21 (81%) patients received amphotericin B either alone or in combination, 3 (14.3%) received itraconazole, and 2 (9.5%) received voriconazole, ONLY LAMB -7 | SURGERY DONE WITHIN 24 HRS AND ALIVE-5/5 Within 48 h and alive-3/5 72 h and alive-2/2 > 72 h and alive -0/2 No surgery and alive- 4/7 | Mortality was 7/21 (33.3%), 5 of them (71.4%) had rhinocerebral disease | |
| 11 Ritu Arora1 2021 [19] | 60 | 45 | 15 | Room | India | DM-49 Newly dm-10 therefore DM-59 Hypertension 14-Coronary artery disease-6 Thyroid dysfunction-4 Chronic kidney disease-2 Stroke-1 | Direct microscopy using KOH mount, DNE, CECT, MRI | IV amphotericin B liposomal- all patients | Functional endoscopic sinus surgery (FESS)= 10 patients. In 2 cases FESS was combined with maxillectomy and orbital exenteration. Transcutaneous retrobulbar amphotericin B injection. The remaining 48 patients were planned for radical sinus debridement | ALL alive | |

Table 1 (continued)

| Author and year | No. of patients | Male | Female | Demographic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|---|-----------------|------|--------|-------------|-------------|--------------|----------------------------------|---|--|---|--------|
| 12 ESWARAN, 2021. [20] | 1 | 1 | 0 | INDIA | ROCM | DIABETES | MRI, CT BRAIN, CT -PNS, KOH, H/P | Liposomal Amphotericin B Injection, LATER BY POSACOA-ZOLE | Aggressive surgical debridement with frontal craniectomy, maxillectomy and right orbital evisceration and left endoscopic orbital decompression. Maxillectomy and Right Frontal craniectomy with Debridement and repair with Titanium mesh | ALIVE | |
| 13 Aastha Maini a, 2021. [21] | 1 | 1 | 0 | INDIA | ROCM | NONE | DNE, MRI, | Inj. Amphotericin B 300 mg/day, eyedrops Tobramycin BD and Nepalact TDS | Surgical debridement was planned under general anesthesia FESS DONE. Lateral canthotomy and inferior cantholysis was done | ALIVE | |
| 14 Akshay Gopinathan Nair a,b,c,d, Namrata G. Adulkare, Lynn D'Cunhaa, Priyanka R. Raoa, Renuka A. Bradoof, Maneesh2021. [22] | 13 | 9 | 4 | India | ROCM | 13-DM | KOH mount,SDA CULTURE, CT, MRI | All patients underwent endoscopic sinus debridement surgery and received systemic amphotericin-B therapy = 127 patients. Five patients (5/13; 38.4%) received retrobulbar amphotericin-B injections | All patients underwent endoscopic sinus debridement surgery The globe could be salvaged in 4 patients. In all, 8 of the involved orbits had to be exenterated | Life salvage was possible in 100% of the cases; globe salvage was possible in 42.8% (6/14 eyes) | |

Table 1 (continued)

| Author and year | No. of patients | Male | Female | Demo-graphic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|-----------------------------|-----------------|------|--------|--------------|--|--|-------------------------------------|--|---|--|--------|
| 15 Farzad Pakdel 2021. [23] | 15 | 10 | 5 | Iran | ROM 7 (47) SOM 5 (33) OM 2 (13) SM 1(7) | 13 patients (86%) had diabetes mellitus 7 HAD DM + HTN, ASTHMA – 2 HYPOTHYROIDISM=1 CVS RELATED =2 ,STEROID USAGE=7 | Biopsy-proven mucormycosis, CT, MRI | Six patients (40%) received combined antifungal therapy and none that received combined antifungal therapy died Amphotericin B 15 Patients (100%) Posaconazole 4 patients (27%) Caspofungin 3 patients (20%) Combined therapy 6 patients (40%) | Five patients (33%) underwent orbital exenteration, Improved 1 (7) Exenterated 5 (33) Non-exenterated blind frozen eye 8 (53) Non-exenterated seeing eye 1 (7) | Seven (47%) patients died from mucormycosis. Died 7 (47) Survived 8 (53) | |
| 16 Polou 2021. [24] | 1 | 1 | 0 | Honduras | ROCM | HTN | KOH,SDA CULTURE, MRI, CT | Antifungal treatment with amphotericin B (deoxycholate), with 1000 mg (1 g) of cumulative dose | During surgery, part of the right maxilla, malar bone and orbit floor were removed, along with tissue debridement FESS + MAX-ILLEC-TOMY + ORBITAL EXENTERATION | Alive | |

Table 1 (continued)

| Author and year | No. of patients | Male | Female | Demographic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|-------------------------------|-----------------|------|--------|-------------|---|-----------------------|---|------------------------------|---|---|--------|
| 17 Pradeep Pradhan 2021. [25] | 46 | 40 | 6 | INDIA | 33(71.7%) were affected with rhino-orbital mucormycosis and 10 were rhino-cerebral mucormycosis. Two patients were found to affect the paranasal sinuses and one had isolated involvement of the mandible | 44 DM, 41-STEROID USE | KOH mount, CT, MRI, DNE | Systemic amphotericin B = 46 | FESS = 46 Majorities of the patients (78.30%) underwent a combined surgical approach for complete clearance of the disease | Four patients with rhino-orbital involvement and 5 patients with rhino-cerebral mucormycosis have died during their treatment in the ward | |
| 18 SAAD,2021. [26] | 1 | 1 | 0 | EGYPT | ROCM | Immunocompetent | CT, MRI, MRV | AMPHOTERICIN B | HEMIMAXILLECTOMY +LT EYE EXENTERATION | DIED 5 DAYS AFTER ALT RECONSTRUCTION | |
| 19 Saldana et al. [27] | 1 | 0 | 1 | India | ROCM | DM | KOH MOUNT, CT, MRI | Amph B | FESS | Alive | |
| 20 Yogendra mishra 2021. [28] | 32 | 17 | 15 | INDIA | ROCM | DM = 28 STEROID = 30 | Confirmed with microscopy 29/32 (90.6%), histopathology 27/32 (84.3%) and by culture in 27/32 (34.7%) cases | Lamb = 32 | In 30/32 (93.3%) patients, endoscopic debridement of sinuses was done. During the entire duration of study 4/32 (12.5%) patients did not survive, 5 (15.6%) | In our study 4/32 (12.5%) patients did not survive in the study period of seven weeks. Survivors-27. Dead-3 | |

Table 1 (continued)

| Author and year | No. of patients | Male | Female | Demographic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|-----------------------------|-----------------|------|--------|-------------|---------------------|--|--|---|---|---|--------|
| 21 Yudhvir singh 2021. [29] | 13 | 10 | 3 | India | Rhino-orbital 13/14 | DM=7 HTN=7 ASTHMA=1 NEUTROPE-NIA=1 15HYPOTHY-ROIDISM=2 | CT, MRI | Liposomal amphotericin B=11 LamB+POS=2 | Surgical intervention-3 patients | Surgical intervention and alive-2/3 Surgical intervention and dead 1/3 3/10 o surgery but alive No surgery and dead -7 | |
| 22 MOORTHY 2021. [30] | 18 | 15 | 3 | INDIA | ROCM | DM-16 STEROID INTAKE=16 | KOH mount | Liposomal Amphotericin B | FESS =17, MAXILLECTOMY -11 EXENTERATION -7 | ALIVE -11 DECEASED -6 | |
| 23 Ekta et al . [31] | 1 | 1 | 0 | INDIA | ROCM | INDUCED DM post- COVID-19 infection | rhinoscopy and nasal swab sample culture, MRI, LCB STAIN | liposomal amphotericin B (L-AMIB) 5 mg/kg | FESS, Triple intervention" was carried out – craniotomy and stereotactic excision of granuloma by a neurosurgeon, orbital exenteration by an oculoplasty surgeon, and repeat sinuses irrigation by an otolaryngologist in similar order in the same sitting | ALIVE | |

Table 1 (continued)

| Author and year | No. of patients | Male | Female | Demographic | Site | Risk factors | Method of diagnosis | Treatment | Surgical treatment | Survival rate | REMARK |
|---------------------|-----------------|------|--------|-------------|----------------------------------|--------------|-----------------------------|--|--------------------|--|--|
| 24 Dave et al. [32] | 58 | 44 | 14 | ROCM | INDIA | DM-43 | HPE, CT, MRI | Intravenous liposomal Amphotericin B followed by oral Posaconazole | 58 (100%patients) | Sinus debridement = 58 patients (100%) Orbital exenteration = 22 patients (38%) Debridement of orbital necrotic tissue = 3 patients (5%) orbital irrigation with amphotericin B TRAMB = 1 patient (2%) Died on 46 day | Alive = 35 patients (60%) Mortality = 23 patients (34%) |
| 25 Rana 2021. [33] | 1 | 1 | 0 | NEW DELHI | PULMONARY WITH SINUS INVOLVEMENT | DM -1 | Biopsy, DNE, KOH MOUNT, MRI | Amphotericin B | Fess | | |

Total = 544

Male = 380

Female = 164

mucormycosis throughout the first wave of SARS-CoV-2, questions arise about the factors and elements that may have instigated or caused this sudden surge of mucormycosis, particularly during the second wave. Types of mucormycosis include Rhino-orbito-cerebral mucormycosis (ROCM), Pulmonary mucormycosis, Gastrointestinal mucormycosis, Cutaneous mucormycosis, Disseminated mucormycosis. In this review, we aim at contemplating the best treatment modality available for the management of facial mucormycosis.

Methods

A systematic literature search was conducted in the electronic database of PubMed, Scopus, web of science, Embase and google scholar from January 2020 until December 2021 using keyword “covid-19 associated mucormycosis”, “rhino-orbital mucormycosis”, “rhinocerebral mucormycosis”, “rhino-orbito-cerebral mucormycosis”, “facial mucormycosis”, “rocm”, “mortality rate”, “treatment”, “covid-19”, “cam”, “pandemic”, “management”, “treatment”, “resection”, “amphotericin”, “maxillectomy”, “exenteration”, “endoscopic surgery”, “fess”, “drug therapy”, “liposomal amphotericin b”, “mortality”, “death rate”, “outcome”, “quality of life”.

Selection Criteria

Other references cited in the retrieved reports were also reviewed, and if relevant were included in our review. The studies considered relevant to our review were thoroughly examined, and a set of criteria were applied for their selection and inclusion in this systematic review (Fig. 1). The abstracts and full texts were read and classified to select only those that provided the information necessary for our review by two independent authors SS and SC. They were also sorted according to the potential risk of any type of bias.

This research was approved by the institutional ethics committee and conducted in accordance with preferred reporting items for Systematic Review and Meta-analysis (PRISMA) to answer the following questions:

What are the different treatment modalities available for COVID-19 associated mucormycosis patients? What are the outcomes of each treatment modality in treatment of COVID-19 associated mucormycosis patients? Whether patient has any comorbidities along with COVID-19

infection? What is the mortality rate of COVID-19 associated mucormycosis?

The studies were selected according to the inclusion and exclusion criteria. The inclusion criteria were English-language reports and randomized clinical trials (RCT), reviews of RCTs, case series retrospective study, prospective study and cohort studies. Inclusion criteria were patient with a history of COVID-19 infection who developed mucormycosis of facial bones and paranasal sinus which were then assessed for different treatment modalities used for the management and their outcome. Exclusion criteria selected were non-covid associated mucormycosis patients and patients with mucormycosis involvement other than in head and neck region. Animal studies were excluded.

Details of all the cases that reported mucormycosis in people with COVID-19 so far were retrieved by two authors SC and SS. In addition, the bibliographies of included studies were hand searched to identify potentially eligible studies that were not captured by electronic search. Characteristics of each patient were collected on excel sheet and analyzed on various endpoints and outcomes. Two authors independently checked the veracity of data. In case of any missing or unclear information, the study was excluded from the review.

Data Extraction

Two authors namely SC and SS extracted the data from the full text article and entered in tabular form which contains all descriptive variables namely author and year, number of patients, male, female, demographic site, risk factors, method of diagnosis, treatment, surgical treatment and survival rate (Table 1). The data accumulated from the Excel sheet (Table 1) were analyzed using qualitative data analysis. A narrative synthesis was formed from the extracted data findings and was presented in tabular form and categorized into five major categories:

(i) infection site(s); (ii) predisposing risk factors or underlying conditions; (iii) method(s) of diagnosis;

(iv) details of antifungal therapy (including types of antifungal, dose and treatment duration), endoscopic debridement as well as surgical and/or adjunctive therapy; and (v) patient outcomes, recovery from infection and their mortality. If any of these categories were not fulfilled by an individual chosen study, that study was omitted from further evaluation. Summary of all findings were tabulated in separate tables for data syntheses. The methodological quality

Table 2 Medical history of patients with COVID-19 associated facial mucormycosis

| S.No | Name | Medical history | | | | | | | | | | | | |
|------|-----------------------------|-----------------|-----|--|----------------|---|--------|---------|----------------|-------|-------------|------------------|--|----|
| | | DM | HTN | Kidney | AIRWAY RELATED | OTHERS | HTN+DM | Thyroid | LIVER DIS-EASE | HEART | STEROID USE | | | |
| 1 | Riad et al [7] | 6 | 1 | | | | | | | | | Stable angina 1 | | |
| 2 | Kumari et al. [8] | 16 | | | | | | | | | | | | |
| 3 | Baryam et al. [9] | 8 | | Chronic renal failure 3 acute renal failure 2 | | Myelodysplastic syndrome 1 | | | | | | | | |
| 4 | Barman et al. [10] | 1 | 2 | IgA nephropathy 1 | | | | | 2 | | | Hypothyroidism 1 | | |
| 5 | Nehra et al [11] | 3 | | | | | | | 2 | | | | | |
| 6 | Pippal et al [12] | 12 | | 1 CKD | | | | | 60 | | | | | |
| 7 | Meher et al. [13] | 124 | | | | | | | | | | | | |
| 8 | Alamin et al. [16] | 1 | 0 | 0 | | 0 | | | 0 | | | 0 | | |
| 9 | Mehta et al. [17] | | | | | | | | 1 | | | | | |
| 10 | Alfishawy et al [18] | 19 | 7 | ckd-2 | Asthma-3 | | | | | | | Hypothyroidism-1 | | |
| 11 | Arora et al [19] | 59 | 14 | | | Chronic bronchitis -1 benign prostatic hyperplasia-1 carcinoma breast-1 | | | | | | 4 | cvs-8 Coronary artery disease 6 stroke 1 | 1 |
| 12 | Esawaran et al. [20] | 1 | | | | | | | | | | | | |
| 13 | Maine et al. [21] | 0 | 0 | 0 | | 0 | | | 0 | | | | | |
| 14 | Nair et al. [22] | 13 | | | | | | | | | | | | |
| 15 | Farzad et al [23] | 6 | | | 2-ASTHMA | | | | 7 | | | | | 7 |
| 16 | Poulou et al. [24] | 0 | 1 | 0 | | 0 | | | 0 | | | 0 | | |
| 17 | Pradeep Pradhan et al. [25] | 44 | | | | | | | | | | | | 41 |
| 18 | Saad et al. [26] | 0 | 0 | 0 | | 0 | | | 0 | | | 0 | | 0 |
| 19 | Saldana et al. [27] | 1 | | | | | | | | | | | | |
| 20 | Yogendra Mishra et al. [28] | 28 | 0 | 0 | | 0 | | | 0 | | | 0 | | 0 |
| 21 | Yudhvir Singh et al. [29] | 7 | 7 | | ASTHMA = 1 | NEUTROPENIA = 1 | | | | | | | | 30 |
| 22 | Moorthy et al. [30] | 16 | | | | | | | | | | | | |
| 23 | Sahu Ekta et al. [31] | 1 | | | | | | | | | | | | 16 |

Table 2 (continued)

| S.No | Name | Medical history | | | | | | | | | | | | | | |
|-------------------------|------------------|-----------------|-----|--------|----------------|--------|---------|---------|----------------|-------|-------------|--|--|--|--|--|
| | | DM | HTN | Kidney | AIRWAY RELATED | OTHERS | HTN +DM | Thyroid | LIVER DIS-EASE | HEART | STEROID USE | | | | | |
| 24 | Dave et al. [32] | | | | | | | | | | 43 | | | | | |
| 25 | Rana et al. [33] | | | | | | | | | | 1 | | | | | |
| Total DM = 410 patients | | | | | | | | | | | | | | | | |
| HTN-32 patients | | | | | | | | | | | | | | | | |
| CKD -6 | | | | | | | | | | | | | | | | |
| Acute renal failure - 3 | | | | | | | | | | | | | | | | |
| IgA nephropathy 1 | | | | | | | | | | | | | | | | |
| ASTHMA = 6 | | | | | | | | | | | | | | | | |
| HTN + DM = 72 | | | | | | | | | | | | | | | | |
| HYPOTHYROIDISM = 9 | | | | | | | | | | | | | | | | |
| H/O STEROID USE = 95 | | | | | | | | | | | | | | | | |
| CVS -18 | | | | | | | | | | | | | | | | |

of the selected studies was evaluated using the Jonna Briggs Institute (JBI) critical appraisal tool. ROB 2.0 was used to assess risk of bias. Two independent contributors (SC and SS) assessed the quality of included studies and any discrepancies were resolved by discussion with third reviewer PW. Sensitivity analysis was not performed.

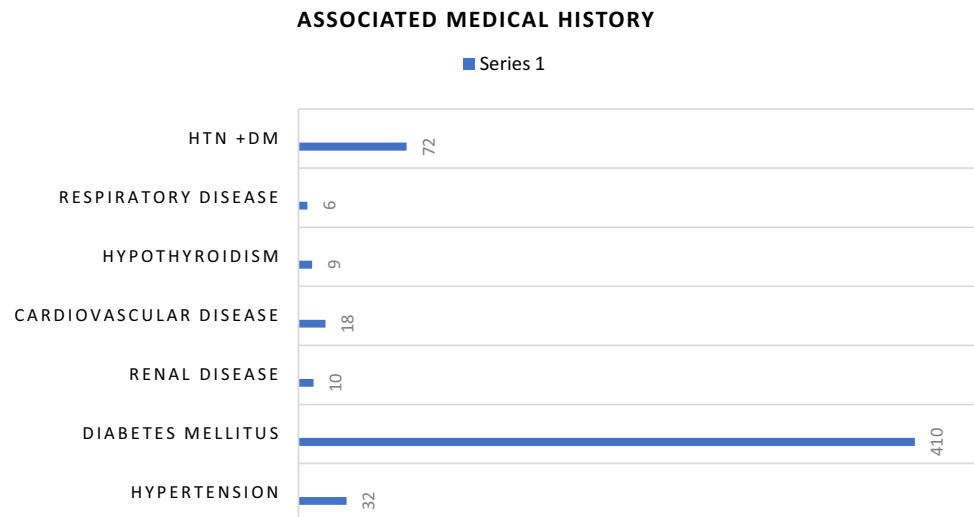
Results

On performing a systematic search, records were identified through various databases among which 372 records were identified through PubMed database and a total of 235 records were identified through Additional records involving google scholar (102 records), Embase (48 records), web of science (27 records) and Scopus (58 records). Before screening, 188 duplicate records were omitted as a part of the review. On further screening, 71 studies were removed for not abiding with the chosen inclusion criteria. Selected 31 studies were further screened, out of which 3 of them could not be retrieved. Total of 28 reports were assessed for eligibility, due to lack of complete information 3 studies were further removed.(flowchart 1).

We used the RoB 2.0 tool to assess risk of bias for each of the included studies. A summary of these assessments is provided in (Table 5). In terms of overall risk of bias, there were no concerns about risk of bias for all chosen studies.

In all, there were 25 studies abiding with preformed inclusion and exclusion criteria among which a total of 544 rhino-orbito-cerebral mucormycosis patients with a history of COVID-19 infection were taken in reference. There were 380 men and 164 women included. Population included in this review were majorly from Indian cities (19 studies) followed by Egypt (3 studies), Iran (1 study), kanseri city (1 study) and Honduras city (1 study). The diagnosis of mucormycosis was reached by performing either of the following tests; KOH staining, diagnostic nasal endoscopy, histopathology, lactophenol cotton blue stain. Often, CT, CECT, MRI radiological diagnosis were done along with the biopsy to understand the extent of the lesion. On evaluation COVID-19 associated mucormycosis patients, it was observed that maximum number of patients were suffering from Diabetes Mellitus which was seen in 410 patients, along with other diseases like hypertension in 32 patients, chronic kidney diseases in 3 patients, renal diseases in 10 patients, cardiovascular diseases in 18 patients, hypothyroidism in 9 patient, respiratory diseases in 6 patients, hypertension along with diabetes mellitus were reported in 72 patients. (Table 2) (Fig. 2).

Various treatment modalities were used for the management of COVID-19 associated rhino-orbito-cerebral

Fig. 2 Associated Medical History

mucormycosis patients among which a few of them were treated by using only antifungal drugs either alone or in combination with other antifungal drugs. The common antifungal drugs used were Amphotericin B (Amph-b), Liposomal Amphotericin B (LAMB), Posaconazole (POS), Itraconazole (ITC), Voriconazole, Caspofungin, vancomycin, meropenem, etc. Majority of patients were treated with Liposomal Amphotericin B (345 patients) followed by Amphotericin B in (79 patients), voriconazole (6 patients), itraconazole (3 patients). Combined antifungal drug therapy included treatment with liposomal amphotericin B with Posaconazole in 8 patients, Amphotericin B with Posaconazole in 3 patients, amphotericin B with Posaconazole and caspofungin in 2 patients, amphotericin B with caspofungin in 2 patients and meropenem with vancomycin were used in 2 patients. As part of surgical debridement, majority of patients underwent Functional endoscopic sinus surgery (FESS) done in 486 patients as form of primary intervention. Along with FESS patient with extensive lesion underwent maxillectomy (77 patients), orbital exenteration (87 patients), orbital decompression (11 patients) depending on the extent of the infection. It was found that combination therapy of antifungal drug along with surgical debridement helped saving many lives (Table 3) (Fig. 3). Out of 544 patients, there were 90 deaths reported and 1 patient was lost to follow-up. In patients who were only on drug therapy it was found that 14 of them could not be saved, whereas 25 patients only on antifungal drug therapy recovered. In the chosen publications for this review article, 428 patients recovered who underwent

surgical debridement along with antifungal drugs whereas 76 patients were deceased. (Table 4) (Fig. 4).

Discussion

In our systematic review, we finalized 25 studies/case reports/case series which included population majorly from Indian origin. There were few studies noted from Egypt, Iran, Kanseri city, etc. We looked upon cases of Covid associated rhino-orbito-cerebral mucormycosis. Our main intention was to evaluate the efficacy of various treatment modalities whether in combination or alone in reducing mortality rate of patients with rhino-orbito-cerebral mucormycosis associated with COVID-19 infection.

Total number of patients evaluated in this review were 544 patients out of which 380 were male and 164 were female. Majority of patients had history of immunosuppressed disease, majorly being associated with Diabetes mellitus, which was observed within 410 patients. There were also reported cases of newly developed diabetes mellitus post-COVID-19 infection. Other associated immunocompromised diseases involved hypertension (32 patients), chronic kidney diseases (6 patients), cardiovascular diseases (18 patients), hypothyroidism (9 patients), nephropathy, pneumonitis, etc.(Fig. 2).

Out of the chosen twenty five such studies, Gupta et al [6] reported 8 patients with hypertension, three with no

Table 3 Treatment modalities

| S.No | NAME | AMPHO-TERICIN B | LIPO-SOMAL AMPHO-TERICIN B | POSACONAZOLE | VORICONAZOLE | ITRACONAZOLE | CASPOFUNGIN | VANCOMYCIN | MEROPENEM | OTHER | FESS | MAXILECTOMY | ORBITAL EXENTERATION | ORBITAL DECOMPRESSION |
|------|--|-----------------|----------------------------|-------------------------|--------------|--------------|-------------|------------|---|-------|------|-------------|----------------------|-----------------------|
| 1 | Riad 2021. [7] | 7 | | | | | | | | | 5 | | | |
| 2 | Abha Kumari 2021. [8] | 20 | | DISCHARGE MEDICATION | | | | | | | 20 | 1 | 4 | |
| 3 | BAYRAM 2021. [9] | 11 | | | | | | | | | 11 | | | |
| 4 | Barman 2021. [10] | 5 | | DISCHARGE MEDICATION | | | | | | | 5 | | 1 | |
| 5 | Hardeva Ram Nehara 2021 [11] | 5 | | DISCHARGE MEDICATION -1 | | | | | Given along with meropenem and vancomycin | | 1 | | 1 | |
| 6 | Sunil Kumar Pippal, 2021 [12] | - | | DISCHARGE MEDICATION | | | - | | | | 58 | 27 | 6 | 10 |
| 7 | Ravi Meher, 2021 [13] | 125 | | DISCHARGE MEDICATION | 6 | | | | | | 99 | 32 | 20 | |
| 8 | Mohammed A. Alamin 2021. [16] | 1 | | DISCHARGE MEDICATION | | | | | | | 1 | | | |
| 9 | Salil Mehta2020 [17] | 1 | | | | | | | WITH VANCOMYCON AND MEROPENEM | | | | | |
| 10 | Alfishawy 2021. [18] | 5 | 4 | DISCHARGE MEDICATION | | 3 | | | Lamb + POS =6 | | 14 | | | |
| 11 | Ritu Arora [2021 [19] | 60 | | | | | | | | | 60 | 1 | 1 | |
| 12 | ESWARAN,2021. [20] | 1 | | DISCHARGE MEDICATION | | | | | | | 1 | 1 | 1 | 1 |
| 13 | Asstha Maini a,2021. [21] | 1 | | | | | | | | | | | | |
| 14 | Akshay Gopinathan Nair a,b,c,d, Namrata G. Adulkare, Lynn D'Cunhaa, Priyanka R. Raoa, Renuka A. Bradoof, Maneesh2021. [22] | 8 | 5 | DISCHARGE MEDICATION | | | | | IV FLUCONAZOLE | | 13 | | 8 | |
| 15 | Farzad PakdelI 2021. [23] | 15 | | | | | | | COMBINED ANTI-FUNGAL THERAPY FOLLOWED AMB+ POS =3 AMB+ POC + CASPO-FUNGIN =2 AMB+ CASPO-FUNGIN =1 | | 12 | 2 | 5 | |
| 16 | Polou 2021. [24] | 1 | | | | | | | | | 1 | +1 | +1 | |
| 17 | Pradeep Pradhan 2021. [25] | 46 | | | | | | | | | 46 | | 8 | |
| 18 | SAAD,2021 . [26] | 1 | | | | | | | | | 1 | +1 | +1 | |
| 19 | Saldana et al. [27] | 1 | | | | | | | | | 1 | | | |

Table 3 (continued)

| S.No | NAME | AMPHO-TERICIN B | LIPO-SOMAL AMPHO-TERICIN B | POSACONAZOLE | VORI-CONAZOLE | ITRA-CONAZOLE | CASPO-FUNGIN | VANCO-MYCIN | MERO-PENEM | OTHER | FESS | MAXIL-LECTOMY | ORBITAL EXENTERATION | ORBITAL DECOMPRESSION |
|------|----------------------------|-----------------|----------------------------|----------------------|---------------|---------------|--------------|-------------|------------|-------|------|---------------|----------------------|-----------------------|
| 20 | Yogendra mishra 2021. [28] | | 32 | | | | | | | | 30 | | | |
| 21 | Yudhvir singh 2021. [29] | | 11 | LaMB + POS = 2 | | | | | | | 30 | | | |
| 22 | MOORTHY 2021. [30] | | 18 | | | | | | | | 17 | 11 | 7 | |
| 23 | Ekta et al. [31] | | 1 | DISCHARGE MEDICATION | | | | | | | 1 | | 1 | |
| 24 | Dave et al. [32] | | 58 | | | | | | | | 58 | | +22 | |
| 25 | RANA et al | 1 | | | | | | | | | 1 | | | |

AMPH B – 179

LIPOSOMAL AMPH B – 345

FESS = 486

MAXILLECTOMY = 77

ORBITAL EXENTERATION = 87

ORBITAL DECOMPRESSION = 11

POSACONAZOLE USED AS DISCHARGE MEDICATION = 274

LAMPH B + POS = 8

AMB + POS = 3

AMB + POC + CASPOFUNGIN = 2

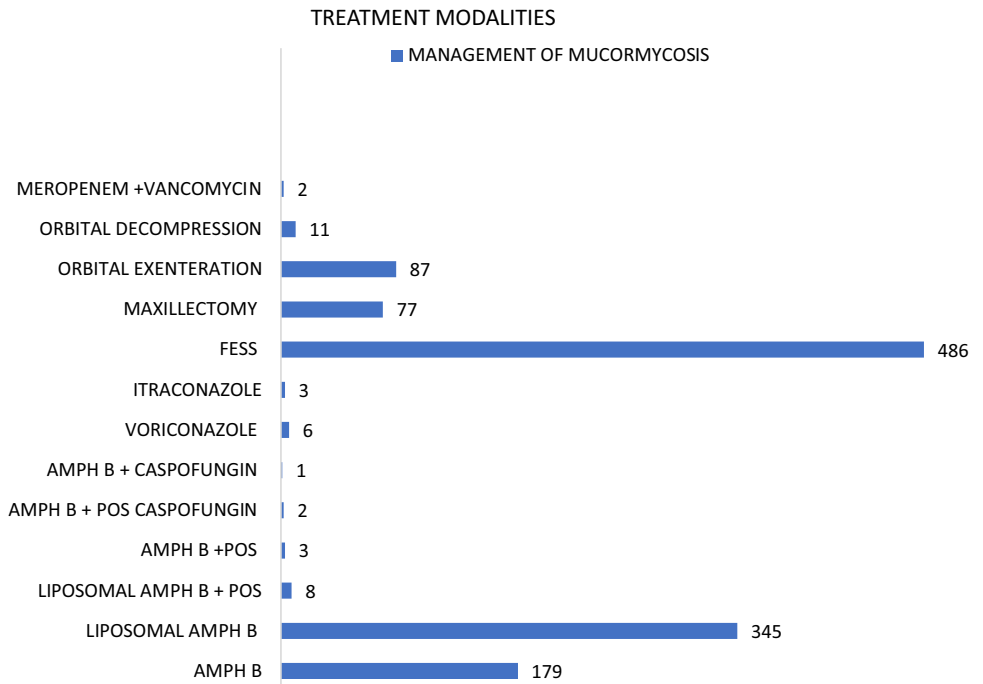
AMB + CASPOFUNGIN = 1

VORICONAZOLE 6

ITRACONAZOLE = 3

MEROPENEM AND VANCOMYCIN = 2

Fig. 3 Outcome of various treatment modalities



medical history. Riad et al [7] reported 3 patients with cardiovascular diseases which included angina, Hypertension along with 6 patients suffering from Diabetes Mellitus. Kumari Abha [8] et al. mentioned 3 patients of chronic kidney disease and 1 suffering from liver diseases rest 16 patients suffering from Diabetes Mellitus. Bayram et al. [9] reported 3 patients suffering from chronic kidney disease, 1 with myelodysplastic syndrome. Barman et al [10] reported patients with hypertension 1 hyperthyroidism 1, diabetes mellitus 8 patients. Nehra et al [11] reported 4 patients with hypertension and 6 with diabetes mellitus .

According to study conducted by pippal et al [12] out of 80 rhino-orbito-cerebral mucormycosis infected patients 72 patients were known diabetic, 60 patients had diabetes mellitus along with hypertension. In their study at the end of four-month follow-up period, there were no deaths reported. 72.5% patients involved were treated with antifungal drugs along with FESS and surgical debridement.

Meher et al [13] in their study evaluated 131 COVID-19 associated out of which 85 patients were known case of diabetes mellitus. They reported use of antifungal drug therapy in 106 patients, voriconazole was used in 5 patients, maxillectomy in 32 patients, orbital exenteration in 20 patients and FESS surgical debridement was done in 99 patients. They reported 7 deaths in their study.

The number of days between COVID-19 infection and development of mucormycosis were not clearly mentioned in the chosen articles. It is said that oxygen therapy, corticosteroid abuse for the treatment of COVID-19 infection

acts as a causative factor in development of mucormycosis. In a data of 465 cases of mucormycosis without COVID-19 infection in India, Patel et al. has shown that rhino-orbital presentation was the most common (67.7%), followed by pulmonary (13.3%) and cutaneous type (10.5%) [14]. Diagnosis of mucormycosis was clinically dependent on the basis of common symptoms according to the 1950 Smith and Krichner criteria for the clinical diagnosis of mucormycosis is still considered to be gold standard and includes. [15]:

- (i) Black, necrotic turbinate’s easily mistaken for dried, crusted blood,
- (ii) Blood-tinged nasal discharge and facial pain, both on the same side,
- (iii) Soft peri-orbital or peri-nasal swelling with discoloration and induration,
- (iv) Ptosis of the eyelid, proptosis of the eyeball and complete ophthalmoplegia and,
- (v) Multiple cranial nerve palsies unrelated to documented lesions.

Clinical examination was followed by KOH stain, Lactophenol cotton blue (LCB) mount, and Diagnostic Nasal Endoscopy. Radiological support was taken from CECT and MRI. It was observed that majority of mucormycosis infected patients were treated using combination therapy of antifungal drugs. Oral Posaconazole was majorly prescribed as discharge medication or as a second line of drug if patient

Table 4 Outcome of various treatment modalities

| S.No | Name | Drug | | Surgery + Drug | | Dead | Alive |
|------|-----------------------------|------|-------|----------------|-------|------|--------------------------|
| | | Dead | Alive | Dead | Alive | | |
| 1 | Riad et al [7] | | 2 | | 5 | | 7 |
| 2 | Kumari et al. [8] | | | 6 | 14 | 6 | 14 |
| 3 | Baryam et al. [9] | | | 7 | 4 | 7 | 4 |
| 4 | Barman et al. [10] | | | | 5 | | 5 |
| 5 | Nehra et al [11] | 2 | 2 | | 1 | 2 | 3 |
| 6 | Pippal et al. [12] | | 15 | | 65 | 0 | 80 |
| 7 | Meher et al [13] | | | 7 | 124 | 7 | 124 |
| 8 | Alamin et al. [16] | | | | 1 | | 1 |
| 9 | Mehta et al. [17] | 1 | | | | 1 | |
| 10 | Alfishawy et al. [18] | 3 | 3 | 5 | 10 | 8 | 13 |
| 11 | Arora et al. [19] | | | | 60 | | 60 |
| 12 | ESAWARAN [20] | | | 0 | 1 | 0 | 1 |
| 13 | Maine et al. [21] | | | | 1 | | 1 |
| 14 | Nair et al. [22] | | | | 13 | | 13 |
| 15 | Farzad et al. [23] | 1 | | 6 | 8 | 7 | 8 |
| 16 | Poulou et al. [24] | | | | 1 | | 1 |
| 17 | Pradeep Pradhan et al. [25] | | | 9 | 37 | 9 | 37 |
| 18 | Saad et al. [26] | | | 1 | | 1 | |
| 19 | Saldana et al. [27] | | | | 1 | | 1 |
| 20 | Yogendra Mishra et al. [28] | | | 4 | 28 | 4 | 28 |
| 21 | Yudhvir Singh et al. [29] | 7 | 3 | 1 | 2 | 8 | 5 |
| 22 | Moorthy et al. [30] | | | 6 | 11 | 6 | 11 (1 Lost to follow-up) |
| 23 | Sahu Ekta e al [31] | | | | 1 | | 1 |
| 24 | Dave et al. [32] | | | 23 | 35 | 23 | 35 |
| 25 | Rana et al. [33] | | | 1 | | 1 | |
| | TOTAL | 14 | 25 | 76 | 428 | 90 | 453 |

Total patient—544 patients

Alive 453

Dead—90

Lost to follow-up-1

Surgery + drug alive = 428

Surgery + drug dead = 76

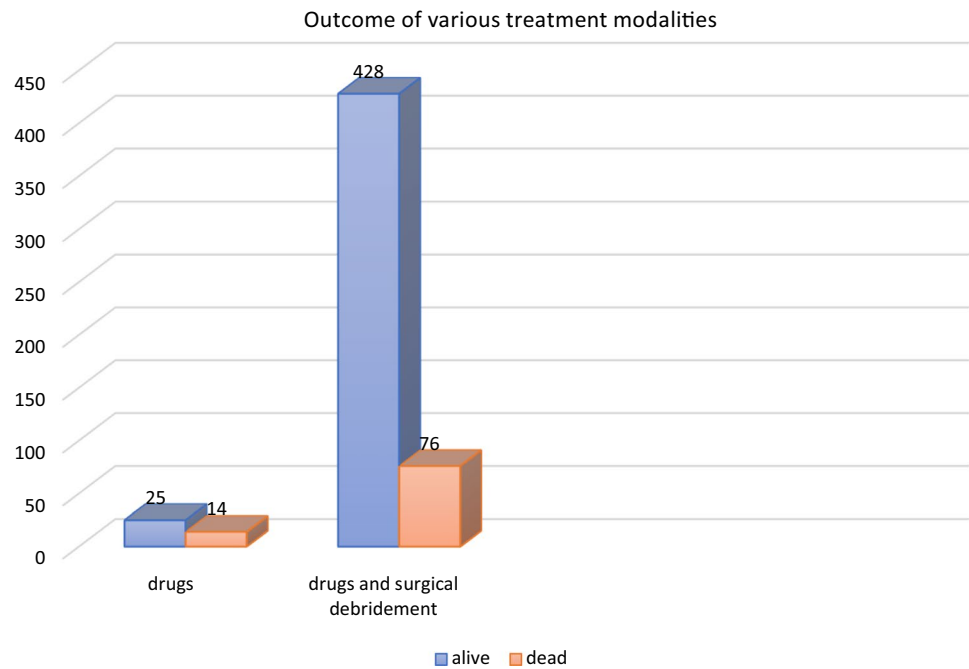
Drug alive = 25

Drug dead = 14

is allergic to amphotericin B or has developed acute kidney infection on having amphotericin-B. Oral Posaconazole as a discharge medication was given to 274 patients. Patients were treated by either using one antifungal drug or as a combined antifungal drug therapy approach. Various combinations followed were Amphotericin B with caspofungin in 1 patient, Amphotericin B with Posaconazole in 3 patients, Amphotericin B with Posaconazole and caspofungin in 2 patients, meropenem with vancomycin in 2 patients, liposomal amphotericin B infusion with Posaconazole in 8

patients. Majority of patients were treated with either liposomal amphotericin B at 5–10 mg/kg/bw observed in 345 patients or were given Amphotericin B only observed in 179 patients. Other antifungal drugs used were voriconazole in 6 patients, itraconazole in 3 patients.

Surgical management included Functional endoscopic sinus surgery which was done in majority of the cases (486 patients). The approach used for treatment of mucormycosis was to go as invasive as possible in first attempt depending on the extent of the lesion. This approach

Fig. 4 Treatment modalities

seemed to be the most effective and hence decreasing the mortality rate, but quality of life was questioned upon. There were procedures like maxillectomy (77 patients), orbital exenteration (87 patients) and orbital decompression (11 patients) done as a form of surgical management. Even though these procedures add to decreased quality of life but surely gives reasons to believe that early antifungal drug therapy along with invasive surgical management has reduced mortality rate in such patients.

It was found that infected rhino-orbito-cerebral COVID-19 associated mucormycosis population who were treated with only antifungal drug therapy out of which only 25 patients recovered whereas 14 were reported dead. In patients who were treated with both antifungal drug therapy along with surgical debridement, there was evident increase in chances of survival observed with alive patients being 428 and 76 patients could not be saved. (Fig. 4)

Limitations of this review were limited follow-up period of the patients and limited data of interval between diagnosis, surgical intervention and its outcome. There was no clear mention of the mortality rate in the chosen studies; hence, it could not be determined.

Conclusion

Our review concluded that surgical debridement should be performed whenever feasible in parallel to antifungal treatment. The drug of choice is liposomal amphotericin B (5–10 mg/kg/bw qDay infuse IV at rate of 2.5 mg/kg/hr). In case of renal failure, posaconazole or Isavuconazole was shown to be effective as well as for maintenance therapy. If a patient is intolerant to liposomal amphotericin B, its dose can be reduced, but should stay ≥ 5 mg/kg bodyweight. In case of extensive disease, rapid progression, or poor general condition, the addition of Isavuconazole or posaconazole can be considered. Treatment should be continued until resolution of initially indicative findings on imaging and reconstitution of host immune system. Hence, early surgical debridement along with antifungal drugs is proven to be beneficial and gives a better outcome in management of rhino-orbital mucormycosis patients.

Differences between protocol and review: in our protocol, duration of hospital stays in days was one of the detrimental category which was not evident in all the studies hence that category was omitted as one of the factors.

Table 5 Risk of bias

| S.No | Study | Bias arising from the randomization process | Bias arising from the timing of identification and recruitment of individual participant in relation to timing of randomization (CRCT only) | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported result | Overall risk of bias (selection) | Overall risk of bias (consumption) |
|------|---|---|---|--|----------------------------------|------------------------------------|--|----------------------------------|------------------------------------|
| 1 | Riad 2021. [7] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 2 | Abha Kumari 2021. [8] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 3 | BAYRAM 2021. [9] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 4 | Barman 2021. [10] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 5 | Hardeva Ram Nehara 2021 [11] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 6 | Sunil Kumar Pippal, 2021 [12] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 7 | Ravi Meher, 2021 [13] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 8 | Mohammed A. Alamin 2021. [16] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 9 | Satli Mehta 2020 [17] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 10 | Alfishawy 2021. [18] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 11 | Ritu Arora 2021 [19] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 12 | ESWARAN, 2021. [20] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 13 | Aastha Maini a, 2021. [21] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 14 | Akshay Gopinathan Nair a,b,c,d, Namrata G. Adulkare, Lynn D'Cunhaa, Priyanka R. Raoa, Renuka A. Bradoof, Maneesh 2021. [22] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 15 | Farzad Pakdel 2021. [23] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 16 | Polou 2021. [24] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 17 | Pradeep Pradhan 2021. [25] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 18 | SAAD, 2021 . [26] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

Table 5 (continued)

| S.No | Study | Bias arising from the randomization process | Bias arising from the timing of identification and recruitment of individual participant in relation to timing of randomization (CRCT only) | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported result | Overall risk of bias (selection) | Overall risk of bias (consumption) |
|------|----------------------------|---|---|--|----------------------------------|------------------------------------|--|----------------------------------|------------------------------------|
| 19 | Saldana et al. [27] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 20 | Yogendra mishra 2021. [28] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 21 | Yudhvir singh 2021. [29] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 22 | MOORTHY 2021. [30] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 23 | Ekta et al. [31] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 24 | Dave et al. [32] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| 25 | Rana 2021.[33] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

Funding The authors received no financial support for the research, authorship and/or publication of this article.

Declarations

Conflict of interest We hereby declare that we have no conflict of interest, related to this article titled “Various treatment modalities in COVID-19 associated facial mucormycosis and the need for its surgical management–A systematic review”.

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