# Supplementary Information (SI)

## Full Title: In-hospital prevalence of mucormycosis amongst COVID-19 and COVID-19 in mucormycosis: a systematic review and meta-analysis

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## List of Contents

# 1. Methods

## 1.1 Literature search: identification and selection of studies

The Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart in **Figure 1** provides details regarding studies included in the systematic review and meta-analysis. The protocol in this study adheres to the MOOSE Checklist (**Supplemental Table 4**) and PRISMA-2020 guidelines (**Supplemental Table 5**). Case studies/series investigating hospitalized COVID-19 patients who either had or developed mucormycosis were reviewed on PubMed and Embase. The reference list of included studies was reviewed for additional case series/studies that could be included. The search was conducted for the period from January 2020 to 7$^{th}$ July 2021 and all relevant studies were included. The search strategy included the following terms: COVID, coronavirus disease 2019, coronavirus, COVID-19, SARS-CoV-2 and mucormycosis, zygomycosis and black fungus. Additional filters were applied to exclude articles that were not full-text and in a language other than English.

**Search strategy**

PubMed: (COVID OR "Coronavirus Disease 2019" OR "Coronavirus" OR "COVID-19" OR "SARS-CoV-2") AND (mucormycosis OR zygomycosis OR "black fungus")

Embase: (COVID OR Coronavirus Disease 2019 OR Coronavirus OR COVID-19 OR SARS-CoV-2) AND (mucormycosis OR zygomycosis OR black fungus).

## 1.2 Inclusion and exclusion criteria

The inclusion criteria consisted of: (a) patients aged ≥18 years; (b) case series of hospitalized, COVID-19 positive patients; (c) groupwise data on COVID-19 patients with and without mucormycosis or mucormyosis with and without COVID-19 were available. The following exclusion criteria were applied: (a) animal studies; (b) duplicated publications; (c) full-text article not available; (d) systematic review, meta-analysis, case conference summary and (e) if all included patients had fungal infections other than mucormycosis.

## 1.3 Data extraction

The titles and abstracts of all studies were screened on Endnote and studies were selected based on the inclusion and exclusion criteria. All remaining articles were screened thoroughly to ensure they fit the eligibility criteria and provided relevant data. This was done independently by two authors experienced in performing a meta-analysis. In case of disagreement, the decision to include or exclude a study was made with consensus. An excel sheet was used to extract all relevant data from each included study. The following data was extracted for the systematic review and meta-analysis: (a) study details: author, title, year of publication, centre/region that included patients are from, time-frame within which data was collected, cohort size, proportion of males and the crude prevalence of patients diagnosed with mucormycosis; (b) patient related details: age (where applicable, mean and standard deviation; data was converted from median and interquartile range (IQR) to mean and standard deviation (SD)), the crude prevalence of comorbidities such as diabetes (controlled and uncontrolled), hypertension, asthma/COPD and obesity, location of mucormycosis infection (rhino-orbital, pulmonary and/or cerebral), length of hospital stay (mean and standard

deviation), in-hospital and all-cause mortality, days between positive COVID-19 test and mucormycosis diagnosis (mean and SD), number of ventilated patients and those receiving mechanical ventilation, mucormycosis related risk factors present amongst included patients (primarily corticosteroid use or diabetes status), corticosteroid use (number of patients receiving corticosteroids, dose and duration), mucormycosis related therapeutics and central nervous system involvement.

Beyond this systematic review and meta-analysis, we also summarised clinical characteristics of mucormycosis in COVID-19 patients from individual case reports. The following data was extracted from the case reports: (a) study details: author, title and year of publication; (b) patient details: age and gender of the patient, presenting complaint, mucormycosis related clinical manifestations, CT and/or MRI findings, COVID severity, mucormycosis related risk factors (primarily corticosteroid use or diabetes status), location of mucormycosis infection, days spent in hospital, days between positive COVID-19 test and mucormycosis diagnosis, mortality and cause of mortality, mechanical ventilation, corticosteroid name, dosage and duration, diabetes status (controlled or uncontrolled), blood glucose, mucormycosis related therapeutics received by the patient and central nervous system involvement.

### 1.4 Quality assessment of included studies

The methodological quality of each study was assessed using the modified Jadad scale. The risk of funding bias was also assessed on a scale of 0-3 (0: a study with low potential for bias; score 1: any conflict of interest declared relating to industry funding outside of the current research publication; score 2: if the study was funded by industry; score 3: a high potential for bias). The methodological quality assessment and funding bias assessment results of all studies included in the meta-analysis can be found in **Supplemental Table 3.**

### 1.5 Statistical analysis

All statistical analyses were performed using STATA (version 13.0, StataCorp LLC, College Station, Texas, USA). Two analyses were conducted – the pooled event rate of mucormycosis amongst hospitalized COVID-19 patients and the pooled event rate of COVID-19 amongst patients with mucormycosis. The “Metaprop” STATA command was used to pool proportions by performing a random-effects meta-analysis of proportions obtained from individual case series. Random effects modelling was performed using DerSimonian and Laird method. To stabilise the variances, Freeman-Tukey Double Arcsine Transformation was applied to calculate the pooled estimates. The heterogeneity was estimated from the inverse-variance fixed-effect model. Heterogeneity was also quantified using the $I^2$ measure. An $I^2$ of 75-100% is considerable heterogeneity, 50-90% is substantial, 30-60% is moderate and 0-40% is low. Forest plots were generated to study the overall effects. A p-value of $<0.05$ is considered statistically significant.

## 2. Expanded Discussion

The current understanding is that COVID-19 patients are more prone to developing fungal infections such as mucormycosis due to compromised immunity, secondary to diabetes and/or clandestine high-dose corticosteroid use (1). Chronically hyperglycaemic patients have a compromised innate and adaptive immunity, resulting in dysfunction of neutrophils, macrophages, and T-cells (2-4). Consequently, diabetic patients are prone to developing infections such as COVID-19 or

mucormycosis. However, the combination of COVID-19 and diabetes increases the chances of patients developing mucormycosis. This is due to the important role of iron metabolism in the pathogenesis of mucormycosis and the increased iron levels in COVID-19 and/or diabetic patients (5). COVID-19 infection induces a hyperinflammatory state, which contributes to increased ferritin levels and thus, increased intracellular iron levels (6, 7). Excessive intracellular iron generates reactive oxygen species leading to tissue damage and a subsequent increase in serum iron levels(8). Diabetic ketoacidosis (DKA) also contributes to increased ferritin levels(9). In addition to this, the spike glycoproteins of the SARS-CoV-2 virus mimics that of hepcidin, a key regulator of iron metabolism(10). As such, SARS-CoV-2 can invade the cytoplasm of cells and disrupt the function of hepcidin(1). These processes contribute to the dysregulation of iron homeostasis and provide grounds for mucormycosis infection(1, 11).

Furthermore, although the pathophysiological mechanism is not fully understood, it is thought that COVID-19 infection may also implicate pancreatic beta cells(12). This causes diabetic patients to develop DKA, thus predisposing them to further infections such as mucormycosis(5).

Patients who have a combination of mucormycosis and COVID-19 experience higher mortality rates compared to patients with COVID-19 alone(13-16). This may be attributed to the aforementioned pathophysiological processes and also to the concurrent, clandestine use of high-dose corticosteroids as a treatment of COVID-19. High dose corticosteroids suppress the immune system and cause drug-induced hyperglycaemia thus exacerbating the pathophysiological processes previously described (13). The infection-related risks of high-dose corticosteroids on the immune system are widely known (17). As such, if a diagnosis of a fungal infection is made, corticosteroids are ceased immediately as seen in several case studies (**Supplemental Table 6**).

Authors from 33 nations collectively analysed existing data to provide recommendations regarding the diagnosis and management of mucormycosis (18). It is recommended that, upon clinical suspicion of infection, appropriate imaging is carried out to ascertain its severity. The first-line treatment is high-dose liposomal amphotericin B, alongside surgical intervention where possible. Intravenous isavuconazole and intravenous or delayed-release tablet posaconazole may also be utilised, however, this is recommended with “moderate strength”(18).

**3. Supplemental Table 1**: Clinical characteristics of patients included in the systematic review and meta-analysis.

| ***Analysis*** | **Prevalence of mucormycosis amongst hospitalised COVID-19 patients** | | | | | | | | | **Prevalence of COVID-19 amongst hospitalised mucormycosis patients** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Case series*** | **Bayran et al[i] (19)** | **Gonzalez et al. (20)** | **Hanley et al. (21)** | **Mulakavalupil et al. (22)** | **Pakdel et al.[i] (23)** | **Patel et al. (24)** | **Rabagliati et al.[ii] (25)** | **Mishra et al.[ix] (26)** | **Selarka et al.[i] (27)** | **Fouad et al. (28)** | **Satish et al. (29)** | **Ravani et al. (30)** | **Patel et al. (24)** |
| *Study ID* | 1a | 2a | 3a | 4a | 5a | 6a | 7a | 8a | 9a | 1b | 2b | 3b | 4b |
| *year* | 2021 | 2020 | 2020 | 2021 | 2021 | 2021 | 2021 | 2021 | 2021 | 2021 | 2021 | 2021 | 2021 |
| *Region* | Turkey | Mexico | UK | Mumbai | Iran | India | Chile | India | India | Egypt | Bangalore | Gujrat | India |
| *Time frame* | 03/20-12/20 | 01/04/20-31/07/20 | 01/03/20-30/04/20 | 03/20-05/21 | 04/20-09/20 | 01/09/20-31/12/20 | 18/05/20-18/07/20 | 12/04/21-31/05/21 | 03/01/21-27/03/21 | 25/03/20-25/09/20 | 03/20-12/20 | 09/20-03/21 | 01/09/20-31/12/20 |
| *Cohort* | 32, 814 | 42 | 10 | 1, 027 | 58 | 12, 096 | 856 | 953 | 2567 | 12 | 25 | 31 | 287 |
| *Prevalence of mucormycosis/COVID-19 (%)[viii]* | 11 (0.0003) | 1 (2.4) | 1 (10) | 0 (0) | 15 (25.9) | 53 (0.44) | 1 (0.11) | 32 (3.35) | 47 (1.8) | 5 (41.7) | 11 (44) | 19 (61.3) | 187 (65.2) |
| *Age mean (SD)* | 73.1 (7.7) | 49.6 (15.1) | 68 (23.2) | NA | 45.7 (46.6) | NA | 61.33 (47.96) | 58.28 (8.57) | 55 (12.8) | 51.2 (16.7) | NA | 56.3 (NA) | 53.4 (17.1) |
| *Male (%)* | 9 (81) | 23 (54.8) | 7 (70) | NA | 10 (66.7) | NA | NA | 15 (46.9) | 35 (74.5) | 6 (50) | 22 (88) | 20 (64.5) | 214 (74.6) |
| | | | | | | **Co-morbidities** | | | | | | | |
| *Diabetes (%)* | 8 (72.2) | 2 (4.8) | NA | 417 (40.6) | 13 (86.7) | NA | 4 (25) | 28 (87.5) | 36 | 10 (83.3) | "majority" | 29 (93.5) | 180 (62.7) |
| *Hypertension (%)* | 7 (63.6) | NA | 4 (40) | NA | 7 (46.7) | NA | 9 (56.3) | 16 (50) | 27 (57.4) | 1 (8.3) | NA | 17 (54.8) | NA |
| *Asthma/COPD (%)* | 1 (9.1) | NA | 3 (30) | NA | NA | NA | 4 (25) | NA | 2 (4.3) | NA | NA | NA | NA |
| *Obesity (%)* | NA | NA | 5 (50) | NA | 1 (6.7) | NA | 3 (18.8) | NA | NA | NA | NA | NA | NA |
| | | | | | | **Infection location** | | | | | | | |
| *Rhino-orbital (%)* | 11 (100) | NA | 0[iii] (0) | 0 (0) | 7 (46.7) | NA | 0 (0) | 32 (100) | 19 (40.4) | 12 (100) | 19 (76) | 31 (100) | 167 (58.2) |
| *Pulmonary (%)* | 0 (0) | NA | 0 (0) | 0 (0) | 0 (0) | NA | 1 (6.25) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 22 (7.7) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Cranial (%)* | 3 (27.3) | NA | 0 (0) | 0 (0) | 10 (66.7) | NA | 1 (6.25) | 0 (0) | 9 (19.1) | 8 (66.7) | 6 (24) | 7 (22.6) | 78 (27.2) |
| **Mucormycosis-related information** | | | | | | | | | | | | | |
| *In-hospital days*[iv] *mean (SD)* | NA | 33.5 (21.3) | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| *Gap*[v] *mean (SD)* | 14.4 (4.3) | NA | NA | MA | 15 (29.4) | NA | 18.5 (NA) | 17.28 (11.36) | NA | NA | NA | NA | NA |
| *Corticosteroids*[vi] *(%)* | 11 (100) | NA | 1 (10) | 915 (89.1) | 7 (46.7) | NA | 15 (93.8) | 30 (93.8) | 47 (100) | 3 (25) | NA | 19 (61.3) | 152 (53) |
| *Therapeutics*[vii] | Anti-fungal, surgical | NA | Anti-fungal | NA | Anti-fungal | NA | Anti-fungal | Anti-fungal, surgical | Anti-fungal, surgical | Anti-fungal, surgical | Anti-fungal, surgical | Anti-fungal, surgical | Anti-fungal, surgical |
| *Mechanical ventilation (%)* | NA | NA | 4 (40) | 283 (27.6) | 1 (6.7) | NA | 14 (87.5) | NA | 20 (42.6) | NA | NA | NA | NA |
| *In-hospital mortality (%)* | 2 (18.2) | 18 (42.9) | 10 (100) | NA | 7 (46.7) | NA | NA | NA | NA | 6 (50) | 0 (0) | 3 (9.7) | NA |
| *All-cause mortality (%)* | 5 (45.5) | NA | NA | NA | NA | NA | 9 (56.3) | 4 (12.5) | 11 (23.4) | NA | 2 (8) | NA | 227 (79.1) |

Abbreviations: NA, not assessed; SD, standard deviation.

[i]Data has only been provided in the context of patients with mucormycosis.

[ii]Data has only been provided in the context of 16 patients who had COVID associated mold infections (of which, only 1 patient had mucormycosis).

[iii]The mucormycosis patient in this study had disseminated infection involving the lungs, hilar lymph nodes, brain and kidney.

[iv]Mean and standard deviation of number of days spent in hospital.

[v]Mean and standard deviation of the gap between a positive COVID-19 diagnosis and mucormycosis diagnosis.

[vi]Number of included patients who received corticosteroids.

[vii]Types of therapeutics used to treat mucormycosis in included patients.

[viii]The prevalence of either mucormycosis amongst COVID-19 patients or COVID-19 amongst mucormycosis patients (depending on the analysis being observed). The prevalence rate in this table was obtained from descriptive statistics.

[ix]all data, except for mean age, has been provided in the context of patients with mucormycosis.

**4. Supplemental Table 2**: Prevalence and standard error of prevalence of mucormycosis amongst COVID-19 patients.

| Study ID | Author (year) | ES | seES | LCI | UCI | WT |
|---|---|---|---|---|---|---|
| **Prevalence of mucormycosis amongst hospitalised COVID-19 patients** | | | | | | |
| **1a** | Bayran et al. | 0.0003 | 0.0055 | 0.00016 | 0.0006 | 23.1 |
| **2a** | Gonzalez et al. | 0.0238 | 0.153 | 0.0006 | 0.125 | 5.3 |
| **3a** | Hanley et al. | 0.1 | 0.308 | 0.0025 | 0.445 | 1.6 |
| **4a** | Mulakavalupil et al. | 0 | 0.031 | 0 | 0.003 | 20.4 |
| **5a** | Pakdel et al. | 0.2586 | 0.130 | 0.152 | 0.390 | 6.7 |
| **6a** | Patel et al. | 0.0044 | 0.009 | 0.003 | 0.005 | 23 |
| **7a** | Rabagliati et al. | 0.0012 | 0.034 | 0.00002 | 0.006 | 20 |
| **8a** | Mishra et al. | 0.033 | 0.032 | 0.023 | 0.047 | 13.9 |
| **9a** | Selarka et al. | 0.018 | 0.02 | 0.013 | 0.024 | 14.6 |
| **Prevalence of COVID-19 amongst hospitalised mucormycosis patients** | | | | | | |
| **1b** | Fouad et al. | 0.42 | 0.28 | 0.15 | 0.72 | 12.8 |
| **2b** | Satish et al. | 0.44 | 0.20 | 0.24 | 0.65 | 20.53 |
| **3b** | Ravani et al. | 0.61 | 0.18 | 0.42 | 0.78 | 23.08 |
| **4b** | Patel et al. | 0.65 | 0.06 | 0.59 | 0.71 | 43.68 |

Abbreviations: ES, Estimated proportion/prevalence; seES, Standard error of ES; LCI, Lower confidence limit for ES; UCI, Upper confidence limit for ES; WT, Study percentage weight.
The estimated prevalence, standard error of estimated prevalence, lower and upper confidence interval and study percentage weight is presented.

**5. Supplemental Table 3**: Modified Jadad analysis and bias analysis results for studies included in the meta-analysis.

| Study ID | 1a | 2a | 3a | 4a | 5a | 6a | 7a | 8a | 9a | 1b | 2b | 3b | 4b |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Was the study randomised** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Was the method of randomisation appropriate (not specified = 0)** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Was the study described as being blinded?** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Was the method of blinding appropriate?** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Was there a description of withdrawals and dropouts?** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| **Was there a clear description of the inclusion/exclusion criteria?** | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| **Was the method used to assess adverse events described?** | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Was the method of statistical analysis described?** | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| **Total MJA score** | 1 | 3 | 2 | 0 | 3 | 1 | 1 | 2 | 1 | 2 | 1 | 3 | 2 |
| **MJA quality assessment** | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low | Low |
| **Funding bias score** | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Abbreviations: MJA, modified Jadad analysis.

Note: modified Jadad analysis could not be carried out for studies included in the systematic review because they were all case series.

Methodological quality assessment using modified Jadad analysis (MJA), a score of 1 indicated “yes” and 0 indicated “no” or “not described”. Note that “adverse events” was interpreted as death of patients included in each study. The quality assessment: low quality (0–3 points) and high quality (4–8 points) levels.

Funding bias assessment: 0 indicated “a low potential for bias”, 1 indicated “conflicts of interest declared related to industry outside of the current publication”, 2 indicated that “the study was funded by industry”, and 3 indicated “a high potential for bias”.

**6. Supplemental Table 4. MOOSE Checklist for meta-analyses of observational studies**

| Item No | Recommendation | Reported on Page No |
|---|---|---|
| | Reporting of background should include | |
| 1 | Problem definition | 3 |
| 2 | Hypothesis statement | 3 |
| 3 | Description of study outcome(s) | 3-4 |
| 4 | Type of exposure or intervention used | NA |
| 5 | Type of study designs used | 3 |
| 6 | Study population | Supplementary information (7-15) |
| | Reporting of search strategy should include | |
| 7 | Qualifications of searchers (e.g., librarians and investigators) | 1 |
| 8 | Search strategy, including time-period included in the synthesis and key words | 3 |
| 9 | Effort to include all available studies, including contact with authors | 15 |
| 10 | Databases and registries searched | 3 |
| 11 | Search software used, name and version, including special features used (eg, explosion) | 3 |
| 12 | Use of hand searching (eg, reference lists of obtained articles) | 3 |
| 13 | List of citations located and those excluded, including justification | 6, 9-13 |
| 14 | Method of addressing articles published in languages other than English | 3 |
| 15 | Method of handling abstracts and unpublished studies | 3 |
| 16 | Description of any contact with authors | NA |
| | Reporting of methods should include | |
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | NA |
| 18 | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 4 |
| 19 | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | 4-5 |
| 20 | Assessment of confounding (eg., comparability of cases and controls in studies where appropriate) | NA |

| | | |
|---|---|---|
| 21 | Assessment of study quality, including blinding of quality assessors, stratification, or regression on possible predictors of study results | 5, Supplementary Information |
| 22 | Assessment of heterogeneity | 5 |
| 23 | Description of statistical methods (eg., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 5 |
| 24 | Provision of appropriate tables and graphics | 14-26 |
| Reporting of results should include | | |
| 25 | Graphic summarizing individual study estimates and overall estimate | 16-17 |
| 26 | Table giving descriptive information for each study included | 19-26 |
| 27 | Results of sensitivity testing (eg, subgroup analysis) | NA |
| 28 | Indication of statistical uncertainty of findings | 6 |

| | | |
|---|---|---|
| Reporting of discussion should include | | |
| 29 | Quantitative assessment of bias (eg., publication bias) | Supplementary Information |
| 30 | Justification for exclusion (eg., exclusion of non-English language citations) | 4, 15 |
| 31 | Assessment of quality of included studies | 5, Supplementary Information |
| Reporting of conclusions should include | | |
| 32 | Consideration of alternative explanations for observed results | 7-8 |
| 33 | Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review) | 8-9 |
| 34 | Guidelines for future research | 7-8 |
| 35 | Disclosure of funding source | 1-2 |

*From*: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

## 7. Supplemental Table 5. PRISMA-2020 Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | 1 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 3 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 3 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 4, SI |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 3, SI |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 3, SI |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 4-5, SI |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 4-5, SI |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 4-5, SI |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 4-5, SI |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 5, SI |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 6, SI |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | NA |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | NA |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 4-5 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 5 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | NA |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | NA |

| | | | |
|---|---|---|---|
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 5 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 5 |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 6 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 6 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 19-26 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | supplementary information |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | 6, 16-17 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | supplementary information |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 6, 16-17 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 6 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | NA |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | NA |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 6 |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 7-8 |
| | 23b | Discuss any limitations of the evidence included in the review. | 8-9 |
| | 23c | Discuss any limitations of the review processes used. | 8-9 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 9, SI |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | NA |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Main Manuscript and SI |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | NA |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 1-2 |
| Competing | 26 | Declare any competing interests of review authors. | 1-2 |

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| interests | | | |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | data used for analyses (19-26) |

SI: supplementary information

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For more information, visit: http://www.prisma-statement.org/

**8. Supplemental Table 6**: Clinical characteristics of individual case reports on mucormyosis in COVID-19 patients.

| **Study ID** | **Author, year** | **Gender age** | **Diabetes status (Blood glucose mg/dl)** | **COVID severity** | **Clinical** manifestations | **Location[ii]** | **Hospital days[iii]** | **Gap[iv]** | **Corticosteroids** | **Therapeutics[vi]** | **Mechanical ventilation[vii]** | **Mortality[viii]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Ahmadikia et al., 2021 (31) | Female 44 | Uncontrolled (230) | NA | toothache, headache, earache, nasal congestion, unilateral facial swelling | Sino-nasal | 18 | 24 | dexamethasone | anti-fungal | NA | no |
| **2** | Alekseyev et al., 2021 (32) | Male 41 | uncontrolled | NA | deep aching pain in nose that radiated down to the throat, odynophagia, black eschar was noted on the palate | Rhino-cerebral | NA | concurrent | NA | anti-fungal, surgical | NA | no |
| **3** | Arana et al., 2021 (33) | male 62 | uncontrolled | severe | fever, headache, and left malar region swelling | Sino-nasal | NA | 7 | dexamethasone, prednisone | anti-fungal, surgical | no | no |
| | | male 48 | NA | moderate | pain, increase in lower right limb diameter | musculoskeletal (right lower limb) | NA | 21 | prednisone | anti-fungal, surgical | NA | no |

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| **4** | Baskar et al., 2021 (34) | male 28 | NA | mild | proptosis of the right eye with conjunctival congestion, chemosis, erythematous and swollen upper and lower eyelids | Sino-nasal | NA | concurrent | NA | anti-fungal, surgical | NA | no |
| **5** | Bellanger et al., 2021 (35) | male 55 | NA | NA | fever | pulmonary | 40 | 13 | NA | anti-fungal | yes | yes |
| **6** | Dallalzadeh et al., 2021 (36) | male 36 | uncontrolled | NA | intraocular pressure of 55 OS, left relative afferent pupillary defect, proptosis, periorbital edema, conjunctival chemosis, optic disc pallor with diffuse vessel attenuation and retinal whitening including the perifovea | rhino-orbital-cerebral | 4 | concurrent | NA | anti-fungal | yes | yes |
| | | male 48 | uncontrolled | NA | right periorbital edema with purulent discharge | rhino-orbital-cerebral | 16 | 6 | dexamethasone | anti-fungal | NA | yes |
| **7** | Garg et al., 2021 (37) | male 55 | uncontrolled | severe | cough, expectoration, burning micturition, ARDS related manifestations | pulmonary | 54 | 21 | dexamethasone | anti-fungal | NA | no |
| **8** | Gonzalez et al., 2020 (20) | male 52 | NA | NA | NA | NA | 4 | NA | NA | surgical | NA | yes |

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| **9** | Hanley et al., 2020 (21) | male 22 | NA | severe | NA | disseminated | 27 | concurrent | NA | anti-fungal | yes | yes |
| **10** | Jain et al., 2021 (38) | female 57 | Uncontrolled (314) | severe | the proximal small bowel was dilated, and the distal ileum was gangrenous with thickened, edematous and indurated mesentery. Ileal gangrene was extending from two feet proximal to the ileocaecal junction to ascending colon; Pulsations of the ileocolic trunk were not palpable | gastrointestinal | ~7 | 25 | methylprednisolone | surgical | NA | yes |
| **11** | Johnson et al., 2021 (39) | male 79 | Uncontrolled (119-228) | severe | hypoxic respiratory failure, bronchoalveolar lavage (BAL) was performed and thick frothy respiratory secretions were seen | pulmonary | 36 | 19 | dexamethasone | anti-fungal | yes | no |
| **12** | Kanwar et al., 2021 (40) | male 56 | NA | severe | generalized fatigue, shortness of breath, hemoptysis | pulmonary | 17 | 16 | methylprednisone | anti-fungal | yes | yes |
| **13** | Karimi-Galougahi et al., 2021 (41) | female 61 | uncontrolled | NA | right hemifacial pain, right hemifacial numbness, decreased visual acuity, chemosis, right-sided | Sino-nasal | NA | 21 | NA | anti-fungal, surgical | NA | no |

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| | | | | | proptosis, frozen eye, complete loss of vision, fixed mydriasis | | | | | | | |
| **14** | Khatri et al., 2021 (42) | male 68 | uncontrolled | NA | purplish skin discolouration with fluctuant swelling in the right axilla, fluid collection along the anterior right upper chest wall, with extensive inflammatory changes in the chest wall and surrounding tissues | the cutaneous, thoracic cavity | 175 | 90 | methylprednisolone | anti-fungal, surgical | yes | yes |
| **15** | Krishna et al., 2021 (43) | male 22 | NA | severe | vasoplegic episodes | pulmonary | 20 | ~20 | NA | NA | yes | yes |
| **16** | Maini et al., 2021 (44) | male 38 | NA | severe | swelling and pain in the left eye, malaise, proptosis, chemosis, periorbital cellulitis, restricted medial gaze, ophthalmoplegia, | sino-orbital | 38 | 18 | Methylprednisolone, dexamethasone | anti-fungal, surgical | NA | no |
| **17** | Mehta et al., 2020 (45) | male 60 | uncontrolled | severe | Unilateral facial swelling, unilateral periorbital facial pain, eyelid oedema, ptosis, proptosis, right orbital cellulitis, acute vision loss | rhino-orbital | 16 | 10 | methylprednisolone dexamethasone | anti-fungal, surgical | yes | yes |

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| **18** | Mekonnen et al., 2021 (15) | male 60 | Uncontrolled (105–143) | severe | Right globe proptosis, oedema of the eyelids and conjunctival chemosis. extensive opacification of right maxillary, ethmoid, and frontal sinuses | rhino-orbital | 31 | 7 | dexamethasone | anti-fungal, surgical | yes | yes |
| **19** | Meshram et al., 2021 (46) | male 47 | controlled | mild | Facial edema, facial tenderness, propotosis, chemosis, no vision, paresthesia, black crusting in nose and palate. | rhino-orbital | 33 | 4 | NA | anti-fungal, surgical | yes | yes |
| | | male 25 | controlled | mild | Bilateral crepitations with bronchial breathing in the middle zone of the right lung. | pulmonary | 29 | 10 | NA | anti-fungal | yes | yes |
| **20** | Monte et al., 2020 (47) | male 86 | NA | severe | melena, severe anaemia, abdominal tenderness | gastrointestinal | 7 | concurrent | hydrocortisone | no | yes | yes |
| **21** | Pasero et al., 2020 (48) | male 66 | NA | severe | Pulmonary infiltrates with an increase of parenchymal thickening of the whole left lung, cavitary lesions in left lung and pleural effusion, opacification of the left maxillary sinus | Sino-pulmonary | 62 | 17 | NA | anti-fungal | yes | yes |

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| **22** | Pauli et al., 2021 (49) | female 50 | Uncontrolled (218) | mild | painful ulcer on hard palate, persistent headache for 3 days | oral | 45 | 8 | hydrocortisone | anti-fungal | NA | no |
| **23** | Placik et al., 2020 (50) | male 49 | NA | severe | Right pneumothorax, bronchopulmonary fistula, necrotic empyema | pulmonary | 21 | 14 | dexamethasone | anti-fungal, surgical | yes | yes |
| **24** | Revannavar et al., 2021 (51) | female "middle-aged" | Uncontrolled (378) | mild | tenderness of all sinuses on the left side, complete internal and external ophthalmoplegia of the left eye, absent left eye direct light reflex, left eye visual acuity of 6/36 | paranasal sinuses | 17 | NA | NA | anti-fungal | NA | no |
| **25** | Sai Krishna et al., 2021 (52) | male 50 | uncontrolled | NA | non-tender, non-erythematous, non-fluctuant swelling in the right malar region with no evidence of any drainage. Intraoral examination revealed a necrotic alveolar region in the right posterior maxillary region and swelling involving the hard palate. | maxilla | NA | NA | NA | anti-fungal, surgical | NA | no |
| **26** | Sargin et al., 2021 (53) | female 56 | Uncontrolled (149) | mild | proptosis in the right eye, restricted eye movements, edema, colour change in the | Rhino-cerebral | 10 | NA | methylprednisolone | surgical, anti-fungal | NA | yes |

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| | | | | | nasal area, dry appearance in nasal area | | | | | | | |
| **27** | Selarka et al., 2021 (54) | male 42 | uncontrolled | NA | tenderness over both maxillary sinuses and an ulcerative eschar at the hard palate | Sino-nasal | 21 | 7 | dexamethasone | surgical, anti-fungal | NA | no |
| **28** | Singh et al., 2021 (55) | male 48 | NA | severe | the abdomen was distended, tense, with rigidity and rebound tenderness suggestive of peritonitis | gastrointestinal | >12 | 19 | methylprednisolone | anti-fungal | no | no |
| **29** | Veisi et al., 2021 (56) | female 40 | NA | severe | progressive bilateral visual loss, periorbital pain, blepharoptosis, ophthalmoplegia, mild proptosis on the right side | rhino-orbital | >90 | NA | dexamethasone | surgical, anti-fungal | no | yes |
| **30** | Waizel-Haiat et al., 2021 (57) | female 24 | Uncontrolled (509) | severe | pain in the left midface region, left lid swelling, with extension to the upper lip and malar region, maxillary hypoesthesia, left proptosis with hyperemic conjunctiva, the opaque cornea | rhino-orbital | NA | concurrent | NA | anti-fungal | yes | yes |
| **31** | Werthman et al., 2021 (58) | female 33 | Uncontrolled (649) | severe | The necrotic palate, necrotic nasal, left eye ptosis, altered mental status, | rhino-orbital | 26 | concurrent | NA | anti-fungal | NA | yes |

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| | | | | | ophthalmoplegia proptosis | | | | | | | |
| **32** | Zurl et al., 2021 (59) | Male 53 | NA | severe | sore throat, parageusia, dysosmia, fever up to 39 °C | pulmonary | 24 | concurrent | prenisolone | Prophylactic anti-fungal | no | yes |

Abbreviation: NA, not assessed.

[i] mucormycosis related clinical manifestation.

[ii] location of mucormycosis infection.

[iii] number of days spent in hospital

[iv] the gap (in days) between a positive COVID-19 diagnosis and mucormycosis diagnosis.

[v] corticosteroid/s used by the patient.

[vi] types of therapeutics used to treat mucormycosis.

[vii] whether the patient received mechanical ventilation.

[viii] yes: the patient died of mucormycosis

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