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# Impact of Diabetes on the Risk and Outcomes of Mucormycosis in COVID-19 Patients: A Systematic Review and Meta-Analysis.

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**KEYWORDS**
COVID-19
Diabetes Mellitus
Mortality
Mucormycosis
Risk Factors Steroids

**ABSTRACT:**

**Introduction**: The COVID-19 pandemic has precipitated a surge in secondary infections, notably mucormycosis, particularly among individuals with diabetes mellitus. This review explores the impact of diabetes on the prevalence and outcomes of COVID-19-associated mucormycosis (CAM), with a focus on mortality and the compounding role of corticosteroid therapy.

**Objectives**: The present study aimed to systematically evaluate the impact of diabetes mellitus on the prevalence and mortality of COVID-19-associated mucormycosis (CAM), and to assess the modifying role of corticosteroid therapy.

**Methods**: This systematic review and meta-analysis were conducted following the PRISMA guidelines and registered in PROSPERO (ID: CRD42024590439). A comprehensive search of PubMed, Cochrane Library, and EBSCOhost up to September 23, 2024, identified 750 records. Sixteen studies meeting the inclusion criteria were included. Data were extracted on prevalence, mortality, steroid use, and hypertension, and analyzed using a random-effects model. Heterogeneity and publication bias were assessed using $I^2$ statistics and Egger's test.

**Results**: A total of 16 studies were included in this review. Diabetes mellitus emerged as the most common comorbidity among COVID-19 patients with mucormycosis, indicating a strong association with increased CAM risk. The meta-analysis revealed a significant pooled estimate for diabetes (intercept = 84.2, $p < 0.001$), with moderate heterogeneity ($I^2 = 60.96\%$). Publication bias assessments, including Egger's regression and Kendall's Tau, indicated no significant bias. The analyses on steroid use and hypertension also demonstrated significant associations with CAM, though with substantial heterogeneity ($I^2 > 90\%$). Overall, the findings underscore diabetes and steroid therapy as major contributors to CAM prevalence and adverse outcomes.

**Conclusions**: This study highlights the crucial importance of strict glycemic control and cautious corticosteroid use in diabetic patients with COVID-19 to minimize CAM risk. Public health strategies should prioritize early screening and tailored management. Future research should explore biological mechanisms and alternative therapies to reduce CAM incidence.

**Introduction:** The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has led to unprecedented global health challenges since its emergence in late 2019. The virus primarily spreads through respiratory droplets and close contact, resulting in a wide spectrum of clinical manifestations, from asymptomatic cases to severe respiratory illness and death.1 As of June 2023, over 760 million cases and 6.9 million deaths have been reported

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worldwide, underscoring the profound impact of COVID-19 on public health systems.[1,2]

Amidst the pandemic, there has been a notable increase in secondary infections, particularly mucormycosis. Mucormycosis, also known as zygomycosis, is a rare but serious fungal infection caused by molds belonging to the order Mucorales.[1,2] These molds are ubiquitous in the environment, and infections typically occur when spores are inhaled or enter the body through skin breaches. The disease predominantly affects immune-compromised individuals, including those with uncontrolled diabetes mellitus, leading to conditions such as rhino-orbital-cerebral mucormycosis, which can be life-threatening if not promptly treated. [2,3]

The intersection of COVID-19 and mucormycosis has emerged as a significant concern, particularly in regions with a high prevalence of diabetes. The management of severe COVID-19 often involves the use of corticosteroids to mitigate hyper inflammatory responses. However, corticosteroid therapy can suppress the immune system and elevate blood glucose levels, increasing susceptibility to opportunistic infections like mucormycosis.[3] This is especially critical for patients with pre-existing diabetes, as the combination of immunosuppression and hyperglycaemia creates an environment conducive to fungal proliferation. [1-3]

India has reported a disproportionately high incidence of COVID-19-associated mucormycosis (CAM), with prevalence rates estimated at approximately 0.14 cases per 1,000 population, about 80 times higher than those observed in developed countries.[3-6] This alarming trend is largely attributed to the country's substantial burden of diabetes and the extensive use of corticosteroids in COVID-19 treatment protocols. The convergence of these factors has led to severe outbreaks of CAM, posing significant challenges to healthcare systems already strained by the pandemic. [4-9]

Given the critical interplay between COVID-19, diabetes, and mucormycosis, this systematic review and meta-analysis aim to elucidate the impact of diabetes on the prevalence and clinical outcomes of CAM. By synthesizing data from multiple studies, we seek to address the following questions:

1. Prevalence: What is the prevalence of mucormycosis in COVID-19 patients with diabetes compared to those without diabetes?

2. Clinical Outcomes: What are the clinical outcomes and mortality rates of CAM in diabetic versus non-diabetic patients?

Addressing these questions is essential for understanding the role of diabetes as a risk factor for CAM and its influence on patient outcomes, including mortality rates, intensive care unit admissions, and the necessity for surgical interventions. The insights gained will be pivotal in developing targeted treatment strategies and informing public health policies to mitigate the impact of CAM, particularly in high-risk populations.

**Objectives**

This study aimed to evaluate the impact of diabetes mellitus on the prevalence and clinical outcomes of COVID-19-associated mucormycosis (CAM), with a particular focus on mortality and the additional influence of corticosteroid therapy. Specifically, this systematic review and meta-analysis sought to determine the prevalence of mucormycosis among COVID-19 patients with diabetes compared to those without diabetes, assess differences in clinical outcomes and mortality rates, and examine how corticosteroid use may further compound the risk of developing CAM in this vulnerable population.

**Methods**

The current study was conducted according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.

Data Sources

The data sources for this systematic review and meta-analysis, registered in PROSPERO (ID: CRD42024590439), were selected from three primary databases: PubMed, Cochrane Library, and EBSCOhost. These databases were chosen to ensure a comprehensive range of peer-reviewed articles addressing the intersection of COVID-19, mucormycosis, and diabetes. A defined search strategy was employed, combining relevant terms such as “COVID-19,” “mucormycosis,” and “diabetes” to identify and retrieve pertinent studies. All publications available up to September 23, 2024, were included to ensure the review incorporated the most recent data, with no restrictions on the publication start

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date to allow for the broadest possible inclusion of studies. The review was limited to English-language, peer-reviewed studies only, and the bibliographies of seven related meta-analyses identified during the search were examined for potential additional studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] criteria were adhered to throughout the conduct of this systematic review.

Systematic review was adopted to follow the PICO criteria (Table 1).

Table 1 - Description of the PICO (P = Population, I = Intervention, C = Comparison, O = Outcome) elements

| Component | Description |
|---|---|
| **Population (P)** | Patients diagnosed with COVID-19 infection, with or without diabetes mellitus |
| **Intervention (I)** | Presence of diabetes mellitus (and/or use of corticosteroids in diabetic patients) |
| **Comparison (C)** | COVID-19 patients without diabetes (and/or without steroid exposure) |
| **Outcome (O)** | Prevalence of mucormycosis (CAM), clinical outcomes including mortality rates and need for intensive interventions |

Study Selection

Inclusion Criteria:

- Studies involving individuals diagnosed with COVID-19.
- Studies reporting cases of mucormycosis developing during or after COVID-19 infection.
- Studies including patients with or without diabetes mellitus.
- Clinical trials, randomized clinical trials, and observational studies.

Exclusion Criteria:

- Studies unrelated to COVID-19-associated mucormycosis or diabetes.
- Case reports, editorials, and commentaries.
- Reviews without original data.

Two independent reviewers [AS, MW] assessed the titles and abstracts of the initial articles, applying inclusion and exclusion criteria to identify eligible studies. Full-text reviews were conducted for studies identified as potentially eligible, with any disagreements resolved by consensus. This process ensured the selection of studies meeting the specified population (COVID-19 patients with diabetes and/or mucormycosis) and methodological requirements, refining the selection to only those studies relevant to the review's focus. The process of searching and retrieving information is depicted as PRISMA in (Figure 1).

Data Extraction

Data extraction for this systematic review followed standardized guidelines to ensure accuracy, consistency, and data quality. Studies selected for inclusion, based on predefined criteria, underwent a comprehensive screening process where titles and abstracts were first reviewed to identify relevant studies, followed by full-text assessments to confirm eligibility. Extracted data included key study characteristics (e.g., study design, setting), participant demographics (e.g., age, sex, diabetes status), outcomes (e.g., incidence of mucormycosis, mortality rates), and intervention details (e.g., treatment strategies). To ensure consistency, data were systematically extracted using a standardized data extraction form and recorded in a data management system. The detailed data extraction sheet is added as (Table 2). This form was designed to accurately capture all relevant information, allowing for consistent study comparisons. Multiple reviewers assessed Data quality and validity independently, applying agreed-upon guidelines to each study. Any discrepancies in data extraction were resolved through consensus discussions, and, if necessary, a third reviewer was consulted. This approach helped maintain the integrity of the data collection process, providing a reliable foundation for subsequent analysis and interpretation.

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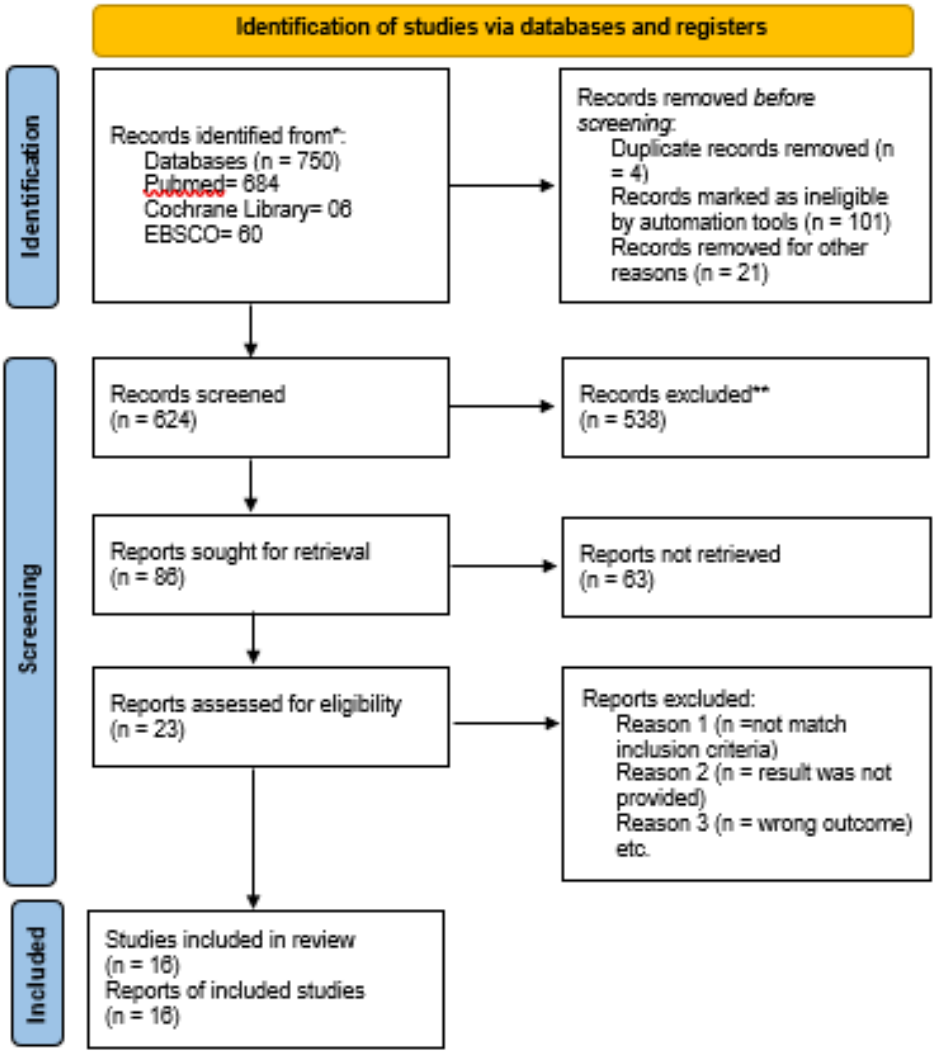


Figure: 1 PRISMA chart for selection of the studies by different databases.

Table 2. Extraction table of all included articles

| S. No. | First author | place of the study | study design | Patients (n) | Male/ female (n) | Diabetes mellitus (n} | other comorbidities | steroid use(n) | Mortality (n) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Ansari et al(2023)[11] | KAHER's KLE VK Institute of Dental Sciences, Balagavi, India | observational hospital-based study | 76 | 72/4 | 71 | Renal Disease- 2, MI- 1 | All patients | 1 |
| 2 | Grewal et al(2022)[12] | University college of medical sciences, New Delhi, India | retrospective observational study | 46 | 29/17 | 46 | HTN-42 | 0 | not specified |

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|---|---|---|---|---|---|---|---|---|---|
| 3 | Vijapur et al (2022)[13] | Karnataka Institute of Medical Sciences, Hubli, Karnataka, India. | retrospective, observational study | 60 | 43/17 | 60 | HTN-5, IHD-2, HIV-1, cavernous sinus thrombosis-1, and hepatitis-1 | 31 | not specified |
| 4 | Goel et al (2023)[14] | Tertiary care hospital in Bhopal, India. | observational, pilot study | 30 | 24/6 | 27 | major organ disease (6) | 18 | not specified |
| 5 | Yadav et al (2022)[15] | Tertiary-care center in Northern India | Retrospective, observational, record-based study. | 220 | 22/10( out of 32 who had corneal manifestations) | 29 | 32(corneal manifestations) | 19 | 6 |
| 6 | Chakravarty et al (2022)[16] | SS Hospital, Institute of Medical Sciences (IMS), Banaras Hindu University (BHU), Varanasi, India. | Observational study | 208 | 136/72 | 200 | CKD-8, HTN-61, HIV1-2 | 131 | 68 |
| 7 | Sree Lakshmi et al (2022)[17] | Gandhi Medical College/Hospital, Musheerabad, Padmarao Nagar, Secunderabad, Telangana | prospective observational study | 200 | 132/68 | 162 | HTN-70 | 172 | 31 |
| 8 | Mani et al(2022)[18] | tertiary care center in Thanjavur, Tamil Nadu, India. | Retrospective observational cross-sectional study | 89 | 70/19 | 86 | Not specified | 82 | 3 |
| 9 | Kulkarni et al (2022)[19] | hospital in Pune, India | Observational study | 49 | 35/14 | 40 | HTN-18,Dyslipidemia-5, Ischemic Stroke: 45, Intracerebral Haemorrhage-3, Subarachnoid Haemorrhage- 1 | not specified | 25 |
| 10 | Dubey et al (2021)[20] | tertiary care referral-based institute in Eastern India | Observational study | 55 | 35/20 | 55 | not specified | 33 | not specified |
| 11 | Ramaswami et al (2021)[21] | All India Institute of Medical Sciences, New Delhi. | retrospective, single-center, observational study | 70 | 42/28 | 49 | HTN-17,CAD-04, CKD-06 | 49 | 16 |
| 12 | Avatef Fazeli M et al (2021)[22] | Imam Khomeini Hospital, Kermanshah, Iran | retrospective observational study | 12 | 05/7 | 10 | HTN-07,IHD-4, CKD-2 | 9 | 8 |
| 13 | Sen M et al (2021)[23] | 102 treatment centers in 22 states and union territories of India. | retrospective, multicentric, non-interventional observational study | 2826 | 1993/833 | 2194 | HTN-690,CKD-88, Asthma-17,Chronic sinusitis-18, Cardiovascular disorder: 16 | 2073 | 305 |
| 14 | N. Bayram et al(2021)[24] | Kayseri City Training and Research Hospital, Kayseri, Turkey | Prospective observational clinical study | 11 | 9/2 | 8 | CRF-3,ARF-2, myelodysplastic syndrome-1 | 11 | 7 |

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 15 | Sharma S et al (2021)[25] | Sawai Man Singh Medical College and Hospital, Jaipur, India | Prospective observational study | 23 | 15/8 | 21 | HTN-14,RF-1 | 23 | 0 |
| 16 | Singh A et al (2023)[26] | Lala Lajpat Rai Memorial (LLRM) Medical College, Meerut. | Retrospective observational study. | 56 | 38/18 | 43 | HTN-8,CKD-2, COPD-1, Hypothyroidism -1, Malignancy-4 | 45 | 15 |

Table 2: Data extraction sheet of all the selected articles. HTN- hypertension, COPD- chronic obstructive pulmonary disease, CRF- chronic renal failure, CKD- chronic kidney disease, RF- renal failure, ARF- acute renal failure, IHD- ischemic heart disease, CAD- Coronary Artery Disease, MI- myocardial infarction, HIV1- human immunodeficiency virus 1

**Results**

Following the PRISMA guidelines, our systematic review began with 750 records identified from three databases: PubMed (684), Cochrane Library (6), and EBSCO (60). After removing 4 duplicate records, 101 ineligible records by automation, and 21 records for other reasons, 624 records were screened. A total of 538 records were excluded during the initial screening, leaving 86 reports for further review. Of these, 63 reports could not be retrieved, and 23 were assessed for eligibility. Finally, 16 studies met the inclusion criteria and were included in the review, focusing on the association of diabetes and steroid use with mucormycosis in COVID-19 patients.

Finally, in this systematic review of 16 observational studies, diabetes mellitus was a prevalent comorbidity among COVID-19 patients with mucormycosis, indicating a strong association between diabetes and the increased risk of mucormycosis. Across the studies, the majority of patients with mucormycosis had pre-existing diabetes, suggesting that hyperglycaemia might play a critical role in susceptibility to this infection. Steroid use was documented in most studies, highlighting its potential contribution to disease progression by exacerbating immunosuppression and hyperglycemia. Mortality data showed variable outcomes, but studies consistently noted higher mortality rates among patients with both diabetes and steroid use. [11-26]

Meta-analysis

The meta-analysis on diabetes used a random-effects model with 16 studies.[11-26] The intercept was estimated at 84.2, with a standard error (SE) of 2.91, resulting in a Z-value of 28.9 and a highly significant p-value ($p < 0.001$). The 95% confidence interval (CI) for the intercept ranged from 78.514 to 89.919.[27-30] The illustrations of the meta-analysis and publication bias on diabetes are shown in (Figures 2A and B).

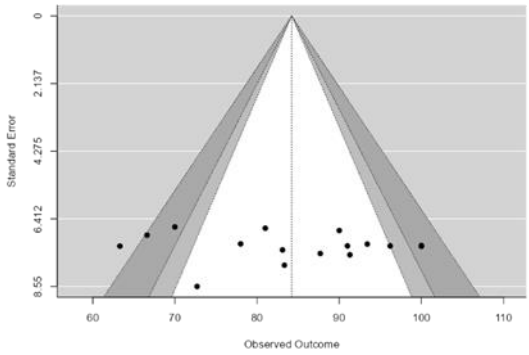


Figure 2A: Forest Plot of Diabetes-Related Risk Factors for Mucormycosis in COVID-19 Patients

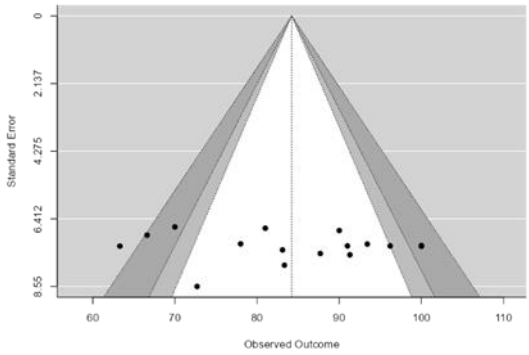


Figure 2B: Funnel Plot of Diabetes-Related Risk Factors for Mucormycosis in COVID-19 Patients

For heterogeneity, the Tau was 9.073, with $Tau^2$ estimated at 82.3212 (SE = 49.4119), indicating substantial variability among the studies. The $I^2$ statistic was 60.96%, suggesting moderate heterogeneity, while $H^2$ was calculated at 2.561. The degrees of freedom (df) were 15, with a Q statistic of 38.567 and a highly

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significant p-value ($p < 0.001$), affirming heterogeneity in the results. [27-30]

Publication bias assessment showed a Fail-Safe N of 12,674 ($p < 0.001$), which indicates that a significant number of studies would be needed to overturn the findings. Kendall's Tau was 0.092 ($p = 0.620$), and Egger's regression yielded a value of 0.149 ($p = 0.881$), suggesting no significant publication bias. [27-30]

The equivalence test, using Two One-Sided Tests, was non-significant with a Z-value of 28.774 ($p = 1.000$) against equivalence bounds of -0.500 and 0.500 at an alpha level of 0.05. However, the null hypothesis test was highly significant ($Z = 28.946$, $p < 0.001$), indicating that the observed effect is statistically different from zero. This suggests that the effect is significantly different from zero, but not statistically equivalent to zero.[27-30]

The mortality meta-analysis publication bias assessment indicated a Fail-Safe N of 622 ($p < 0.001$), Kendall's Tau of 0.229 ($p = 0.303$), and a significant Egger's regression result of 2.190 ($p = 0.029$). The equivalence test was non-significant, with a Z-value of 3.832 ($p = 1.000$), and null hypothesis testing was significant ($Z = 3.907$, $p = 0.0000933$). The confidence intervals for the TOST ranged from 15.011 to 36.836, and for the null hypothesis, from 12.920 to 38.927. The observed effect was statistically different from zero but not equivalent to zero.[27-30] The illustrations of the meta-analysis and publication bias of mortality are shown in (Figures 3A and B).

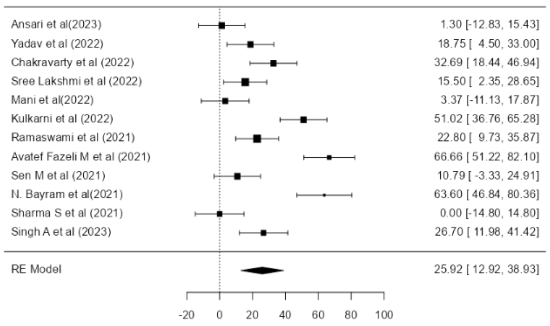


Figure 3A: Forest Plot of Mortality-Related Risk Factors for Mucormycosis in COVID-19 Patients

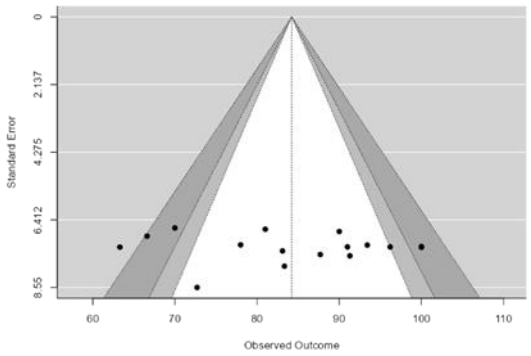


Figure 3B: Funnel Plot of Mortality-Related Risk Factors for Mucormycosis in COVID-19 Patients

The meta-analysis on hypertension (HTN) utilized a random-effects model with ten studies ($k = 10$), yielding an estimated intercept of 38.2, significant at $p<0.001$, with a confidence interval ranging from 22.628 to 53.734. High heterogeneity was observed, with a $tau^2$ value of 577.3924 and an $I^2$ of 91.76%, indicating substantial variability across studies. Publication bias was assessed, showing no significant bias with Egger's test ($p = 0.229$) and Kendall's tau ($p = 0.216$). The equivalence test was non-significant ($p = 1.000$), suggesting the observed effect differs significantly from zero but lacks statistical equivalence to zero, as supported by the null hypothesis test ($Z = 4.812$, $p = 0.0000015$). The illustrations of the meta-analysis and publication bias of hypertension are shown in (Figures 4A and B).

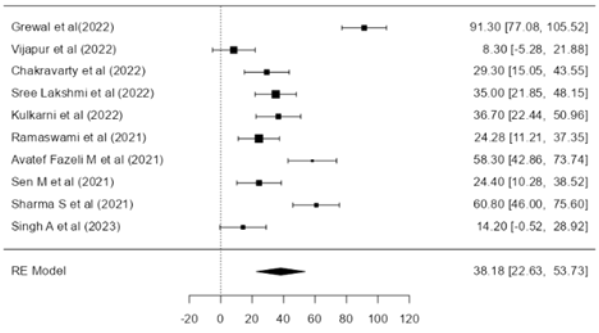


Figure 4A: Forest Plot of Hypertension-Related Risk Factors for Mucormycosis in COVID-19 Patients

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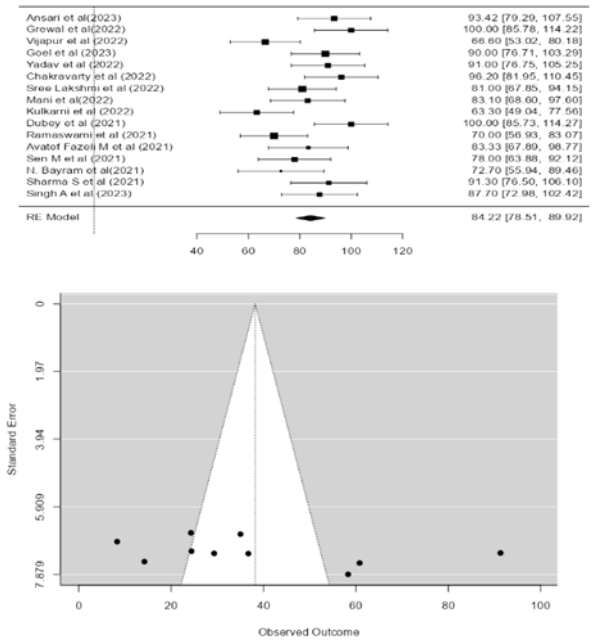


Figure 4B: Funnel Plot of Publication Bias in the Association between Hypertension and Mucormycosis Outcomes in COVID-19 Patients

Using a random-effects model across 16 studies (k = 16), the meta-analysis on steroid use reported an intercept estimate of 71.4, which was highly significant at $p<0.001$ with a confidence interval from 59.357 to 83.407. The illustrations of the meta-analysis and publication bias of steroid use are shown in (Figures 5A and B). Substantial heterogeneity was indicated by a tau² of 548.9187 and an $I^2$ of 91.24%. Publication bias tests were mostly non-significant (e.g., Egger's test p = 0.237). The equivalence test was non-significant (p = 1.000), while the null hypothesis test confirmed the effect significantly differs from zero, with strong statistical support (Z = 11.635, p ≈ 0).

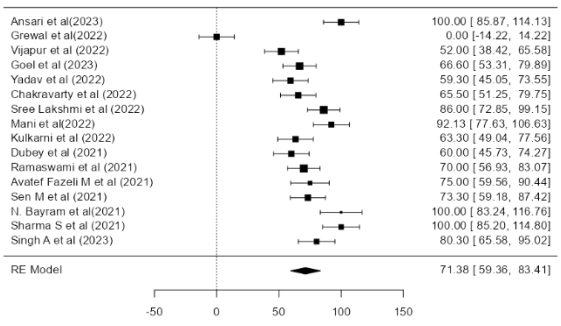


Figure 5A: Forest Plot of Steroid use -Related Risk Factors for Mucormycosis in COVID-19 Patients

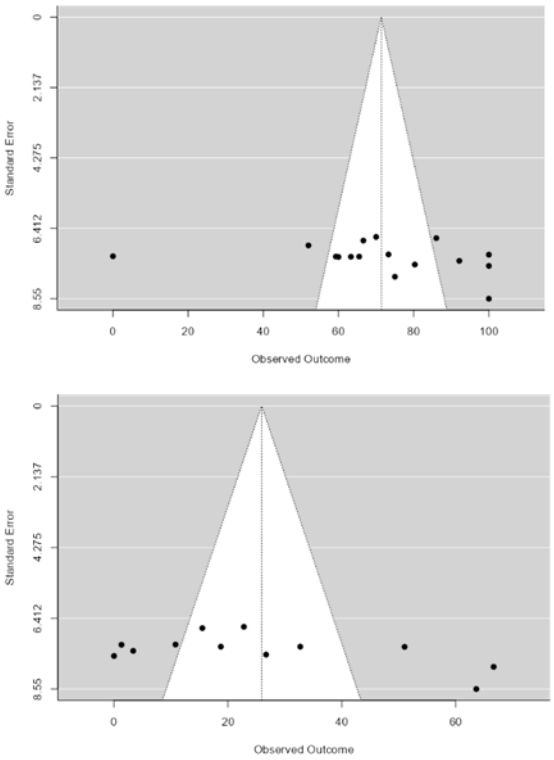


Figure 5B: Funnel Plot of Publication Bias in the Association between Steroid use and Mucormycosis Outcomes in COVID-19 Patients

Quality assessment

In the systematic review, the Newcastle-Ottawa Scale (NOS) [31] was used to assess the quality of the included studies. NOS is a commonly utilized tool for evaluating the quality of non-randomized studies, focusing on three core areas: selection, comparability, and outcome. Each study included in the meta-analysis was scored across these categories to determine its methodological strength.

The selection criteria evaluated the representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of exposure, ensuring that studies had a reliable basis for participant grouping. Additionally, it examined whether the outcome of interest (mucormycosis incidence) was absent at the study's onset, maintaining clarity in exposure-outcome relationships. The comparability criterion involved examining how well studies controlled for confounding variables through design or analysis, with studies receiving up to two points for demonstrating strong comparability between groups. Lastly, the outcome

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assessment focused on the adequacy of follow-up and the methods used to determine outcomes, with points awarded for robust follow-up times and clear outcome measurement. The detailed Quality assessment is added as (Table 3).

In this review, most studies scored consistently in selection and outcome assessment but varied in comparability, which is critical for controlling the impact of confounding factors, particularly diabetes, on mucormycosis outcomes in COVID-19 patients. Studies achieving higher NOS scores reflect a lower risk of bias and a more reliable contribution to the meta-analysis conclusions.

**Discussion**

This systematic review and meta-analysis aimed to clarify the impact of diabetes on the risk and outcomes of mucormycosis in COVID-19 patients. The analysis identified a strong association between diabetes and the increased risk of developing mucormycosis among COVID-19 patients, especially when steroid therapy was used. These findings underscore the importance of diabetes as a critical risk factor for COVID-19-associated mucormycosis, aligning with studies that suggest a compounded risk due to hyperglycaemia, which creates an immunocompromised environment favourable for fungal infections.

The findings of this review support the conclusions of previous studies that identified diabetes as a major risk factor for mucormycosis among COVID-19 patients. For instance, one study [(7)] found that diabetic COVID-19 patients were significantly more susceptible to mucormycosis, particularly when treated with corticosteroids. The hyperglycaemic environment in diabetic patients, compounded by COVID-19-induced immune deregulation, creates conditions conducive to fungal proliferation. The role of steroids in worsening these outcomes has been documented in a study,[(32)] which observed that steroid therapy exacerbated hyperglycaemia and impaired immune function, both of which contribute to fungal growth in diabetic patients.

Some studies, however, report different findings, particularly among non-diabetic COVID-19 patients. A study[(33)] demonstrated that non-diabetic COVID-19 patients receiving steroid therapy did develop mucormycosis but at notably lower rates than diabetic patients. This suggests that diabetes itself, independent of steroid use, may be a more critical factor in mucormycosis susceptibility. The study[(34)] further supports this notion, showing that while steroid use did contribute to mucormycosis development, diabetic patients were disproportionately affected, even when adjusting for steroid dosage and duration. Together, these findings highlight diabetes as a prominent risk factor, suggesting that its impact on mucormycosis risk extends beyond the effects of corticosteroid therapy alone.

Interestingly, some studies included in this review observed comparable mortality rates in diabetic and non-diabetic COVID-19 patients with mucormycosis, contrary to our findings.[(36)] A study [(25)] noted that while diabetes increases mucormycosis susceptibility, other factors, such as underlying comorbidities, access to medical care, and early diagnosis, may influence outcomes. This disparity in mortality rates suggests that while diabetes elevates mucormycosis risk, its impact on outcomes might be modified by these additional factors. A study [(35)] found that prolonged or high-dosage steroid use, in conjunction with uncontrolled diabetes, substantially increased mortality risk, indicating that both the severity and management of diabetes are pivotal in determining clinical outcomes.

**Conclusion**

Strengths and Limitations

This study's strength lies in its comprehensive approach, incorporating data from various databases and analyzing multiple observational studies that evaluated COVID-19 patients with and without diabetes. The systematic approach enabled an objective examination of mucormycosis prevalence, clinical outcomes, and mortality, particularly concerning diabetes and steroid use. By utilizing stringent inclusion and exclusion criteria, we ensured that only studies meeting specific methodological standards were included, thus enhancing the validity and reliability of the findings.

However, the study also has some limitations. First, the reliance on observational data means the findings primarily illustrate associations rather than causative relationships. Additionally, heterogeneity among studies in terms of sample sizes, geographic locations, and treatment regimens posed challenges for uniformity, which could impact the generalizability of our results.

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For example, while the reviewed studies indicate that diabetes and steroid use contribute to mucormycosis risk, it is difficult to isolate each factor's impact precisely. The lack of control trials and variability in diabetes management across studies may also influence observed outcomes, potentially limiting broader applicability. Another limitation is the inclusion of only English-language studies, which may exclude relevant findings published in other languages, especially from countries with high mucormycosis rates. Finally, data gaps in some studies, such as incomplete mortality reporting, may have impacted the assessment of clinical outcomes.

Implications for Public Health

This study underscores the importance of vigilant monitoring of diabetic COVID-19 patients, especially those undergoing steroid treatment, to reduce the risk of mucormycosis. Given the observed association between diabetes and poor outcomes, public health initiatives should prioritize early screening for mucormycosis symptoms in diabetic COVID-19 patients, particularly in regions with high fungal infection rates. Additionally, these findings highlight the need for caution in prescribing corticosteroids to diabetic COVID-19 patients and suggest that alternative management strategies should be considered to mitigate the risk of opportunistic infections. Improved awareness and early intervention strategies may help prevent adverse outcomes in high-risk populations.

Future Research and Conclusion

Future research should focus on exploring the mechanisms by which diabetes predisposes COVID-19 patients to mucormycosis and the impact of different steroid regimens on infection risk. Randomized controlled trials evaluating alternative treatments to corticosteroids for diabetic COVID-19 patients would help identify safer therapeutic options. Research is also needed to determine the potential benefits of routine glucose monitoring and strict glycaemic control in reducing mucormycosis incidence among COVID-19 patients.

In conclusion, this systematic review demonstrates a strong association between diabetes and the risk of mucormycosis in COVID-19 patients, with steroid use further compounding this risk. The findings emphasize the importance of diabetes management in preventing COVID-19-associated mucormycosis and suggest that more cautious steroid use could reduce adverse outcomes in diabetic populations. Ultimately, these results contribute to the evidence supporting targeted approaches for at-risk populations to improve patient outcomes and reduce the burden of mucormycosis in COVID-19 contexts.

**Conflict of interest**

The Authors have no conflict of interest.

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Table 3: Quality assessment of all studies by Newcastle-Ottawa scale (NOS)

| S. No. | Study | Item & score | | | | | | | | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Representativeness of the exposed cohort （1） | Selection of the non-exposed cohort (1) | Ascertainment of exposure（1） | Demonstration that outcome of interest was not present at start of study (1) | Compare ability of cohorts on the basis of the design or analysis (2) | Assessment of outcome (1) | Was follow up long enough for outcomes to occur (1) | Adequacy of follow up of cohorts (1) | |
| 1 | Ansari et al(2023) [11] | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| 2 | Grewal et al(2022)[12] | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| 3 | Vijapur et al (2022)[13] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 4 | Goel et al (2023)[14] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 5 | Yadav et al (2022)[15] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 5 |
| 6 | Chakravarty et al (2022)[16] | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| 7 | Sree Lakshmi et al (2022)[17] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 8 | Mani et al(2022)[18] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 9 | Kulkarni et al (2022)[19] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |

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|---|---|---|---|---|---|---|---|---|---|---|
| 10 | Dubey et al (2021)[20] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 11 | Ramaswami et al (2021)[21] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 12 | Avatef Fazeli M et al (2021)[22] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 13 | Sen M et al (2021)[23] | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 5 |
| 14 | N. Bayram et al(2021)[24] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 15 | Sharma S et al (2021)[25] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |
| 16 | Singh A et al (2023)[26] | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 6 |