Studies that were published all over the world in relation to study
Narrative article
Study with less data.
Literature review
Studies on COVID-19 associated with mucormycosis
Studies were published after 2019 (after attack of COVID-19).
Review articles on mucormycosis
Studies dealing with patients of mucormycosis

Secondary infection of mucormycosis [10].

or has history long-term use of steroids are prone to be affected with
Patient who is already suffering from diabetes, blood disorders, AIDS,
majorly infects sinuses, brain causing headache, epistaxis, fever, etc. [9].

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46% worldwide [7]. Mucormycosis is also known as Zygomycosis and
than other developed countries [6]. The fatality rate of mucormycosis is
population, its prevalence is 0.14 per 1000, which is about 80% higher
rate of mucormycosis globally is 0.005–1.7 per million [5]. In Indian

mood changes, insomnia, and muscle weakness [4]. The incidence
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or has history long-term use of steroids are prone to be affected with
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INTRODUCTION
The pandemic coronavirus disease 2019 (COVID-19) has spread vastly
on a global scale [1,2]. There is no definitive treatment of the disease till
now. However, prevention and symptomatic management is the prime
choice. COVID-19 patients suffer from various secondary infections
such as pneumonia, severe respiratory disease, and heart complication
but super-infections and co-infections in COVID-19 pneumonia are
still under exploration [3]. Secondary infections are more common in
severely ill COVID-19 patients, fungal infections being 10 times more
common [3]. Severe complication of coronavirus disease with secondary
infection with fungus is very dangerous and life threatening to patients.
This is the black fungus disease that is known as mucormycosis. Steroids
and other immunosuppressive drugs are being used in the treatment
of COVID-19 which is resulting into further complications. The side
effects include increased secondary infections, immune modulation,
manifestation of latent diabetes mellitus (DM), dizziness, weight gain,
mood changes, insomnia, and muscle weakness [4]. The incidence
rate of mucormycosis globally is 0.005–17 per million [5]. In Indian
population, its prevalence is 0.14 per 1000, which is about 80% higher
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mostly infects sinuses, brain causing headache, epistaxis, fever, etc. [9].
Patient who is already suffering from diabetes, blood disorders, AIDS,
or has history long-term use of steroids are prone to be affected with
secondary infection of mucormycosis [10].

The objective of systemic review and meta-analysis on mucormycosis
associated with COVID-19 disease this study to provide better
understanding and evaluation of mucormycosis or zygomycosis. It will
help in the better treatment of such fungal infections.

METHODS
This systemic review has been done to know the possible total cases
of mucormycosis associated with novel coronavirus disease all around
the world and specially India. The search of literature was done by the
electronic database of PubMed, Cochrane library, IndMed from the
2019 to 2021, using the search word- COVID-19 and mucormycosis. We
conducted the meta-analysis on the basis of screening and recuperate
all the papers for title and abstract, after that primary selection then
full texts of the conversant studies was perused for the study. The
eligibility criteria were:
• Studies on COVID-19 associated with mucormycosis
• Studies that were published all over the world in related to study
• Studies dealing with patients of mucormycosis
• Studies were published after 2019 (after attack of COVID-19).

We exclude the:
• Review articles on mucormycosis
• Narrative article
• Literature review
• Study with less data.

These were the criteria for selection the studies which were included
in the meta-analysis for better quality. All the data were extracted for
eligible study - author, year of publication, state or country, patient reported with mucormycosis, number of patient suffering from mucormycosis, co-morbidity or history of any kind of disease, COVID positive, management, discussion, and extracted in Tables 1 and 2. Data

| Author                          | Year of publication | Country/state       | Patient reported with mucormycosis                                                                 | No of patients who suffering from mucormycosis | Co morbidity/ past history of any kind of disease | COVID-19 Positive |
|---------------------------------|---------------------|---------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------|-------------------|
| Maini et al. [11]               | 2021                | India (Mumbai), USA | COVID associated with orbital mucormycosis, COVID associated with pulmonary aspergillosis is and possible mucormycosis, and mucormycosis and multiple organ dysfunction syndrome with sequential organ failure assessment t (SOFA) | 38-year-old male patient, 79-year-old male patient | No significant past history, history of diabetes and hypertension (HTN) on | Yes               |
| Johnson et al. [12]             | 2021                | USA                 | COVID associated with rhino orbital mucormycosis, COVID associated with pulmonary Mucormycosis | 66-year-old male patient, 55-year-old male | History of HTN on and urinary tract infection | Yes               |
| Pasero et al. [13]              | December 2020       | Italy               | COVID associated with gastrointestinal mucormycosis (n=23) were associated with mucormycosis (orbital, paranasal) | 60-year-old male patient, 55-year-old male | Patient was diabetic, long standing diabetes with HTN with ischemic heart condition and end stage of renal disease arterial HTN on | Yes               |
| Mehta and Pandey [14]           | September 2020      | India               | COVID with rhino orbital mucormycosis, COVID associated with pulmonary Mucormycosis | 86-year-old male patient, 55-year-old male | 1. (n=21) patients were diabetic. (out of 21), (n=14), patients had history of HTN with DM and n=7 was purely diabetic. 2. (n=1) renal failure 3. (n=1) no history Diabetic | Yes               |
| Garg et al. [15]                | February 2021       | Chandigarh, India   | COVID associated with rhino orbital mucormycosis, COVID associated with pulmonary Mucormycosis | 86-year-old male patient, 55-year-old male | Patient was diabetic, long standing diabetes with HTN with ischemic heart condition and end stage of renal disease arterial HTN on | Yes               |
| Monte Junior et al. [16]        | September 2020      | Saopaulo, Brazil    | COVID associated with gastrointestinal mucormycosis (n=23) were associated with mucormycosis (orbital, paranasal) | 60-year-old male patient, 55-year-old male | Patient was diabetic, long standing diabetes with HTN with ischemic heart condition and end stage of renal disease arterial HTN on | Yes               |
| Sharma et al. [17]              | 2021                | Karnataka, India    | COVID with rhino orbital mucormycosis, COVID associated with pulmonary Mucormycosis | 86-year-old male patient, 55-year-old male | Patient was diabetic, long standing diabetes with HTN with ischemic heart condition and end stage of renal disease arterial HTN on | Yes               |
| Aleskeyev et al. [18]           | April 2021          | USA                 | COVID with cerebral mucormycosis, COVID positive associated with rhino orbital mucormycosis, COVID positive associated with Paranasal Mucormycosis | 41-year-old male patient, 32-year-old female | Middle aged female, DM Uncontrolled diabetes mellitus History of HTN on and asthma Diabetic child | Yes               |
| Revannavar et al. [19]          | April 2021          | Karnataka, India    | COVID with cerebral mucormycosis, COVID positive associated with rhino orbital mucormycosis, COVID positive associated with Paranasal Mucormycosis | 41-year-old male patient, 32-year-old female | Middle aged female, DM Uncontrolled diabetes mellitus History of HTN on and asthma Diabetic child | Yes               |
| Saldanha et al. [20]            | April 2021          | Karnataka, India    | COVID with cerebral mucormycosis, COVID positive associated with rhino orbital mucormycosis, COVID positive associated with Paranasal Mucormycosis | 41-year-old male patient, 32-year-old female | Middle aged female, DM Uncontrolled diabetes mellitus History of HTN on and asthma Diabetic child | Yes               |
| Werthman-Ehrenreich [7]         | 2020                | USA                 | COVID with cerebral mucormycosis, COVID positive associated with rhino orbital mucormycosis, COVID positive associated with Paranasal Mucormycosis | 41-year-old male patient, 32-year-old female | Middle aged female, DM Uncontrolled diabetes mellitus History of HTN on and asthma Diabetic child | Yes               |
| Aljehani et al. [21]            | February, March 2021| Saudi Arabia        | COVID associated with rhino orbital mucormycosis | 86-year-old male patient, 55-year-old male | Patient was diabetic, long standing diabetes with HTN with ischemic heart condition and end stage of renal disease arterial HTN on | Yes               |
| Veisi et al. [22]               | 2021                | Tehran, Iran        | COVID associated with rhino orbital mucormycosis | 86-year-old male patient, 55-year-old male | Patient was diabetic, long standing diabetes with HTN with ischemic heart condition and end stage of renal disease arterial HTN on | Yes               |
| Mekonnen et al. [23]            | 2021                | USA                 | COVID positive with rhino orbital mucormycosis | 86-year-old male patient, 55-year-old male | Patient was diabetic, long standing diabetes with HTN with ischemic heart condition and end stage of renal disease arterial HTN on | Yes               |
| Ahmadikeia et al. [24]          | 2021                | Tehran, Iran        | Influenza with mucormycosis (suspected COVID-19 infection) | 44-year-old female | Poorly controlled diabetes Suspected | Yes               |
| Sen et al. [25]                 | February 2021       | India               | COVID associated with cerebral mucormycosis | (n=6) patients. (47- 74 years old). All male | 1. All 6 patients had history of DM and HTN (n=6) 2. (n=1) purely DM No particular history | All positive. |
| Placki et al. [26]              | October, 2020       | India               | COVID associated with pulmonary mucormycosis, COVID associated with paranasal mucormycosis, COVID associated with sinuses (paranasal) mucormycosis | (n=3) patients. (47- 74 years old). All male | 1. (n=1) Well controlled DM 2. (n=1) DM No particular history 3. (n=1) DM with peptic ulcer | All positive. |
| Sebastian et al. [27]           | February 2021       | India               | COVID associated with pulmonary mucormycosis, COVID associated with sinuses (paranasal) mucormycosis | (n=3) patients. (47- 74 years old). All male | 1. (n=1) Well controlled DM 2. (n=1) DM No particular history 3. (n=1) DM with peptic ulcer | All positive. |
| Bellanger et al. [28]           | 2021                | France              | COVID associated with pulmonary mucormycosis | 1.5-year-old male, 2.60-year-old male, 3.64-year-old male | No significant history Yes. | Yes. |

(Contd...)


Table 1: (Continued)

| Author                  | Year of publication | Country/state | Patient reported with mucormycosis | No of patients who suffering from mucormycosis | Co morbidity/ past history of any kind of disease | COVID-19 Positive |
|-------------------------|---------------------|---------------|------------------------------------|-----------------------------------------------|------------------------------------------------|-------------------|
| Karimi-Galougabi et al. [29] | March 2021          | Iran          | COVID associated with paranasal mucormycosis | (n=8) (11.26%) patients who had no medical history | No particular history | Yes |
| Zarl et al. [30]         | January 2021        | Austria       | COVID associated with pulmonary mucormycosis (auto psy) | (n=5) (3.30%) patients who had no medical history | Acute myeloid leukemia, obesity, depression | Yes |
| Sargin et al. [31]       | February 2021       | Turkey        | COVID associated with rhinocerebral mucormycosis | (n=21) (29.57%) patients who had no medical history | A History of anxiety, hyperglycemia | Yes |
| Hatri et al. [32]        | April 2021          | USA           | COVID associated with pulmonary mucormycosis | (n=10) patients, 1.9 male 2.1 female (The mean age was 55.8 years) | 1. (n=1) Heart transplant, Stage 2 heart failure, DM, HTN, chronic kidney disease. 2. (n=1) DM 3. (n=1) HTN with asthma 4. (n=1) obesity with hypothyroidism 5. (n=1) HTN 6. (n=1) no history. 7. (n=1) DM, asthma, HTN 8. (n=1) HTN were diabetic | Yes |
| Mishra et al. [33]       | May 2021            | India         | COVID associated with rhino orbital mucormycosis | (n=10) patients, 1.9 male 2.1 female (The mean age was 55.8 years) | 1. (n=1) Diabetes with hypothyroidism. 4. (n=1) no past medical history. 5. (n=1) CKD, DM, HTN, hypothyroidism. 6. (n=1) DM with HTN 7. (n=1) CKD. 8. (n=1) DM with CLD. (n=1) Obesity | Yes |
| Waizel-Haiat et al. [34] | February 2021       | Mexico        | COVID associated with rhino orbital mucormycosis | 24 year old female | 1. (n=1) Heart transplant, Stage 2 heart failure, DM, HTN, chronic kidney disease. 2. (n=1) DM 3. (n=1) HTN with asthma 4. (n=1) obesity with hypothyroidism 5. (n=1) HTN 6. (n=1) no history. 7. (n=1) DM, asthma, HTN 8. (n=1) HTN were diabetic | Yes |

COVID-19: Coronavirus disease 2019, DM: Diabetes mellitus, HTN: Hypertension, CKD: Chronic kidney disease, CLD: Chronic liver disease.

of comorbidity are presented in Tables 3 and 4. country wise data are presented in Table 3. Outcomes have been showed in four categories in Table 5. Sex ration is shown in Table 6. All data were thoroughly checked by four reviewers (Figs. 1 and 2).

RESULTS

We have conducted the meta-analysis on 25 articles which were found to related studies from PubMed (n=23), IndMed (n=1), and Cochrane library (n=1). We have presented the search data, on the basis of inclusion, exclusion, title abstract screening, full test screening, and the finally selected articles included for the study. Our total search was 196, 25 were included in meta-analysis, which have mentioned our key search with COVID-19 and mucormycosis. There were total 71 cases found who had presented COVID-19 associated with mucormycosis. In India, there was most of cases were found (n=48) (67.60%), in USA (n=12) cases were found (16.90%), in Iran four cases were found (n=4) (5.63%), in Italy, France, Austria, Saudi Arabia, Mexico, turkey, and brazil each country found one case of COVID 19 associated with mucormycosis. Comorbidity with age variation also presented in schematic format, where only DM was mostly associated as pre disposing factor (29.57%) (n=21). HTN (n=3) (4.22%), HTN with DM (n=21) (29.57%), HTN with asthma (n=2) (2.81%), obesity (n=1) (1.40%), anxiety, and depression (n=1) (1.42%) were also associated as pre disposing factor. There was (n=8) (11.26%) patients who had no medical history. There were almost all cases associated with DM (n=10) with other systemic cause. There was male predominance seen in this study (n=52) (73.29%) female was (n=19) (26.76%). Moreover, the final outcome of each study has been divided in four categories, improvement (n=36) (51.42%), no improvement (n=8) (11.26%), died (n=24) (33.80%), raise complication (n=2) (2.81), and lost follow-up (n=1) (1.40%).

DISCUSSION

Our meta-analysis shows that DM increases the risk of mucormycosis associated with COVID-19, regardless of different study designs, background mucormycosis associated with COVID-19 incidence, or geographic region of the study. The studies reveal that compared with people who do not have diabetes those also were affected by mucormycosis. (29.57%) (n=21). HTN (n=3) (4.22%), HTN with DM (n=21) (29.57%) HTN with asthma (n=2) (2.81%), obesity (n=1) (1.40%), anxiety, and depression (n=1) (1.42%) were also associated as pre disposing factor. There was (n=8) (11.26%) patients who had no medical history. There were almost all cases associated with DM (n=10) with other systemic cause. People with diabetes have an increased risk of developing active mucormycosis associated with COVID-19. Higher increases in risk were seen among male, in populations with high background mucormycosis associated with COVID-19, and in Indian population populations. The mortality rate was (33.80%)
patients with mucormycosis. Heterogeneity of strengths of association may reflect true geographic/ethnic differences in severity of DM, transmission dynamics of mucormycosis associated with COVID-19, and the distribution of effect modifiers such as country, or it may be
Table 3: Country wise studies

| Country   | Patient Population | Percentage | Total patients |
|-----------|--------------------|------------|---------------|
| India     | n=48               | 67.60%     | n=71          |
| USA       | n=12               | 16.90%     |               |
| Iran      | n=4                | 5.63%      |               |
| France    | n=1                | 1.40%      |               |
| Saudi Arabia | n=1          | 1.40%      |               |
| Austria   | n=1                | 1.40%      |               |
| Mexico    | n=1                | 1.40%      |               |
| Italy     | n=1                | 1.40%      |               |
| Turkey    | n=1                | 1.40%      |               |
| Brazil    | n=1                | 1.40%      |               |

Table 4: Co morbidity and age ratio

| Co morbidity and features | Patient population | Percentage | Total patients |
|---------------------------|--------------------|------------|---------------|
| only DM                   | n=21               | 29.57%     | n=71          |
| only HTN                  | n=3                | 4.22%      |               |
| diabetes with HTN         | n=21               | 29.57%     |               |
| HTN UTI                   | n=1                | 1.40%      |               |
| HTN with asthma           | n=2                | 2.81%      |               |
| renal failure             | n=1                | 1.40%      |               |
| DM, HTN, asthma and       | n=1                | 1.40%      |               |
| hyperlipidemia            | n=1                | 1.40%      |               |
| DM with peptic ulcer      | n=1                | 1.40%      |               |
| AML, obesity and depression| n=1            | 1.40%      |               |
| no particular history     | n=8                | 11.26%     |               |
| anxiety with DM           | n=1                | 1.40%      |               |
| HTN, CKD, DM, heart failure| n=1           | 1.40%      |               |
| obesity with hypothyroidism| n=1          | 1.40%      |               |
| DM, HTN, asthma           | n=1                | 1.40%      |               |
| DM, HTN, IHD              | n=1                | 1.40%      |               |
| DM with hypothyroidism    | n=1                | 1.40%      |               |
| CKD, DM, HTN, and         | n=1                | 1.40%      |               |
| hypothyroidism            | n=1                | 1.40%      |               |
| CKD                       | n=1                | 1.40%      |               |
| DM with CLD               | n=1                | 1.40%      |               |
| obesity                   | n=1                | 1.40%      |               |
| DM, HTN, IHD, and         | n=1                | 1.40%      |               |
| renal disease             | n=1                | 1.40%      |               |

DM: Diabetes mellitus, HTN: Hypertension, CKD: Chronic kidney disease, CLD: Chronic liver disease.

Table 5: Outcome

| Category                | Patient Population | Percentage | Total Patients |
|-------------------------|--------------------|------------|---------------|
| No improvement          | n=8                | 11.26%     | n=71          |
| Died                    | n=24               | 33.80%     |               |
| Complication occurs     | n=2                | 2.85%      |               |
| Improvement             | n=36               | 50.70%     |               |
| Lost follow-up          | n=1                | 1.40%      |               |

Table 6: Male and female population

| Gender    | Patient Population | Percentage |
|-----------|--------------------|------------|
| Male      | n=52               | 73.29%     |
| Female    | n=19               | 26.76%     |
| Total     | n=71               |            |

due to differences in study methodology or rigor. Our systematic review identified five additional studies that were HTN, HTN with asthma, and other systemic disease (CKD, CLD, obesity, hypothyroidism, anxiety, and renal failure), that had examined the association of DM and mucormycosis associated with COVID-19 and determined important sources of heterogeneity through rigorous sensitivity analyses.

CONCLUSION

In summary, we found consistent evidence for an increased risk of mucormycosis associated with COVID-19 among people with diabetes despite heterogeneity in study design, geographic area, underlying burden of mucormycosis, assessment of exposure and outcome, and control of potential confounders. Data from these human studies are consistent with emerging information on the biological mechanisms by which hyperglycemia may affect the host immune response to mucormycosis associated with COVID-19. Our findings suggest that fugal controls programs should consider targeting patients with diabetes with COVID-19 for interventions such as active case finding and the treatment of latent DM and, conversely, that efforts to diagnose, detect, and treat DM may have a beneficial impact on fungal control. We also recommend further studies investigating how comorbidity risk varies by type, duration, and severity of mucormycosis associated with COVID-19, for a more thorough understanding of the association that could be translated to a clear public health message.

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AUTHOR’S CONTRIBUTION

Dr. Bikash Biswas: Concept, Study design, collection of data, Statistical analysis, original manuscript writing, writing-review and editing.
Dr. Indrani Pramanik: Statistical drift and writing-review and editing and all over guidance. Dr. Sanjukta Mandal: Data collection. Chart analysis and writing-review and editing. Dr. Poulyam Singh Roy: Data collection. writing-review and editing.

CONFLICT OF INTEREST
There is no conflict of interest.

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