

**A systematic review on black fungus and its association with uncharted factors in covid-19**

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**Abstract**

**Background:** Mucor mycosis, known as ‘Black Fungus,’ had shown a sudden spurt in the Covid-19 pandemic. By May 2021, over 400,000 cases of Covid-19 had been reported, out of which more than 40,000 cases of Mucor mycosis were seen till June 2021. Rising incidence of Mucor mycosis could be attributed to several factors. Numerous studies have revealed uncontrolled diabetes mellitus, inaccurate corticosteroid therapy, a compromised immune system, malignancy and other crucial variables. Additional factors responsible were prolonged/lack of oxygen supply, low hygiene practice, poor ventilation, secondary infections and malnutrition which are yet to be evaluated.

**Objective:** This systematic review intends to evaluate three factors responsible for Covid-associated rhino-

orbital Mucor mycosis, i.e., prolonged/supplemental oxygen, ventilators and humidifiers.

**Materials and Methods:** An electronic search was done on databases of PubMed, Google Scholar and Europe PMC from 2020 to 28th January 2022 using keywords and 1652 articles were found. All the original observational, retrospective and case-control studies relevant to the systematic review were included. This systematic review is devoid of randomized control trial (RCT) studies. According to the guidelines of PICOS, objectives were set, and PRISMA was prepared. Twenty-three articles were finalized and selected for data extraction.

**Results:** The collective data found that 28.43% of the patients were treated with supplemental oxygen, 5.36% with mechanical ventilators and 5.7% with humidifiers.

Mortality and disease progression rate increased up to 22.45% with above three factors.

**Conclusion:** This systematic review tried to establish a connection between unexplored causes and Mucor mycosis but is yet to be proved by conducting randomized control trials.

**Keywords:** Covid, Humidifiers, Mucor mycosis, Oxygen, Ventilator

### **Introduction**

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) novel strain upended the world's healthcare system. A steady increase in fungal infections occurred during or after COVID, particularly in India during the pandemic. This fungal infection was the black fungus or Mucor mycosis, also known as Zygomycotic.

Mucor mycosis is a severe and rare fungal infection caused by a group of Molds called mucoromycetes. It affects the lungs, skin, gastrointestinal system, central nervous system and paranasal sinuses. Mucor mycosis is classified into six types based on anatomic localization: (1) rhino cerebral, (2) pulmonary, (3) cutaneous, (4) gastrointestinal, (5) disseminated, and (6) uncommon presentations.<sup>1</sup>

Over the world, numerous cases of Mucor mycosis have been described linking it to COVID-19 as Covid-associated Mucor mycosis (CAM). Estimated prevalence of Mucor mycosis was nearly 70 times higher than the global data reported by Epidemiology of Mucor mycosis given by Prakash H Chakrabarti et al.<sup>2</sup>

Many etiological factors for CAM have proven to influence the incidence of mucor mycosis directly. Several host, environmental and microbial variables have been identified. Host factors include immunocompromised states, corticosteroid use, secondary infection, renal illness, malnutrition, cancer, high Body Mass Index (BMI), diabetes and advancing

age. Lack of information by health professionals, oxygen availability, poor hygiene practices, inadequate ventilation, poverty and crowded weather are the environmental variables. Although Mucorales fungi and spores have low intrinsic pathogenicity in healthy people, they can cause a virulent and fulminating infection in immunocompromised hosts.<sup>3</sup>

This systematic review reflects the evidence linking CAM to the risk factors, i.e., the use of supplemental oxygen, ventilators and humidifiers.

A handful of research provided evidence of the unexplored factors causing CAM. The rationale of this systematic review is to link Rhino-Orbital Covid-associated Mucor mycosis (ROCM) with uninvestigated factors like supplemental oxygen, mechanical ventilator or humidifier affecting the disease progression and the mortality rate.

### **Materials and Methods**

The objectives were set according to PICOS guidelines.

P- Population (Post-Covid Mucor mycosis patients = 9401)

I- Intervention (Use of Oxygen therapy, Ventilators, Humidifiers)

C- Comparison (Between these interventions causing mucor mycosis resulting in mortality (22.45%)

O- Outcome (Occurrence of Mucor mycosis due to these above interventions- use of Oxygen therapy (27.35%), Ventilators (5.36%), Humidifiers (5.7%), and contaminated water)

S- Study (Observational, Case control and Retrospective studies, Total=23)

This systematic review was carried out as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A humongous literature search was carried out through the electronic databases of PubMed, Google Scholar, and Europe

PMC, from 2020 to 28th January 2022. Certain and specific mesh words were used in the search string (Table 1).

The entire search summed up to 1652 articles, out of which 23 were included in this systematic review.

Observational, retrospective and case-control studies with the use of all the three parameters were included in this systematic review. General reviews, Letter to the Editor, Short Communications, Case Series and Case Reports, Clinical communications were all excluded from this systematic review.

This systematic review is devoid of Randomized Control Trials (RCTs) based on the use of above interventions.

Data extraction was assessed using potentially eligible articles having full-text. Two investigators independently scanned titles and abstracts to exclude duplicate studies and studies that failed to meet the inclusion criteria. Discrepancies between the above-mentioned investigators were solved by discussion, consensus or arbitration. Gender of the patient was also included in the sample size to help decipher the predilection of CAM, if any.

TOTAL KEYWORDS AND COMBINATIONS USED SINCE 2020 TO 28-01-2022	TOTAL NUMBER OF STUDIES/ARTICLES FOUND		
	PUBMED	GOOGLE SCHOLAR	EUROPE PMC
Oral mucormycosis OR rhino orbital mucormycosis AND post covid	N= 56	N= 560	86
Mechanical ventilators OR ventilators OR ventilation AND oral mucormycosis OR rhino orbital mucormycosis AND post covid	N= 39	N= 226	32
Oral mucormycosis OR rhino orbital mucormycosis AND oxygen AND post covid	N= 6	N= 339	62
Oral mucormycosis OR rhino orbital mucormycosis AND water OR tap water OR contaminated water AND post covid	N= 31	N= 135	13
Oral mucormycosis OR rhino orbital mucormycosis AND humidifier AND post covid	N= 0	N= 63	4
TOTAL	N= 132	N= 1323	197
GRAND TOTAL	N= 1652		

**Table 1:** Literature search based on the above electronic databases

**Results:**

After a thorough literature search and filtering the articles through exclusion criteria, a total of 23 articles were included (PubMed: 09 + Google Scholar: 14 + Europe PMC: 0). The study selection process has been described as below by a PRISMA flowchart (Figure 1).

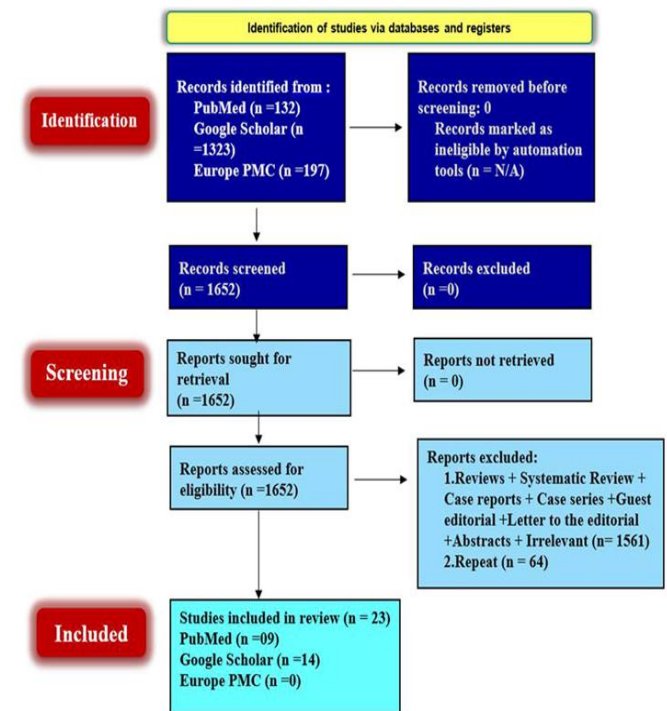


Figure 1: PRISMA Flowchart showing the study selection process

**Discussion**

The global incidence of mucor mycosis ranges from 0.005 to 1.7 per million people, according to the literature given by Jeong W.<sup>4</sup> In India, the second wave of COVID-19 infections resulted in more deaths compared to the first, and B.1.617.2 (Delta) strain was one of the most common strains which was observed among the other strains as studied by Yamini Aiyar.<sup>5</sup> Patients’ co-morbidities, in addition to the issues associated with COVID-19 illness, have also contributed to the development of diseases. Diabetes mellitus, use of

industrial oxygen, compromised oxygen transportation during an emergency, use of steroids to manage COVID-induced cytokine storm, nosocomial fungal exposure due to prolonged hospital stay, ventilators or contaminated oxygen humidifiers, tubing and masks have been proposed as factors contributing to the rise in fungal infections.<sup>6</sup>

### **Role of Oxygen**

Hyperbaric oxygen (HBO) was used as a treatment regimen in CAM, as it suppresses the fungal growth. It usually provides 100% oxygen to patients in chambers through facemasks, hood tents, or endotracheal tubes. In addition to its antifungal activity, it elevates the tissue oxygen levels, increases the tissue healing rate and enhances leukocyte-mediated phagocytosis. It can also significantly boost growth factors, which promote angiogenesis and healing, as found by B.V. John.<sup>7</sup>

Oxygen delivery systems are categorized into low-flow and high-flow systems, as per Hardavella.<sup>8</sup> Whittle Js found that high-flow nasal oxygen was preferred for patients with higher oxygen support requirements. Non-invasive positive pressure ventilation may be associated with a higher risk of nosocomial transmission.<sup>9</sup>

Mucosal erosion caused by forceful steam inhalation or high-flow oxygen has also been identified as a factor that promotes fungus colonization.<sup>10</sup> According to Palanisamy PR, one of the reasons for mucor mycosis was the substitution of industrial oxygen with medical oxygen due to the increasing demand for oxygen cylinders in COVID-19 management.<sup>11</sup> Mordani S postulated that the contamination from industrial oxygen, low-quality oxygen cylinders, low-quality oxygen piping systems and ordinary tap water in ventilators had been blamed for rising cases of mucor mycosis.<sup>12</sup>

Patients who required non-invasive oxygen support or ventilator assistance during their COVID-19 sickness had a significantly greater risk of mortality or orbital exenteration. However few studies where patients had not received supplemental oxygen, showed that uncontrolled hyperglycaemia and hyperglycaemic impact of steroids were probably more significant risk factors for CAM than contaminated oxygen supply. In the study by Mehta S et al, it was believed that poor systemic status and greater levels of immunological impairment were due to the severity of the previous COVID-19 infection.<sup>13</sup>

Zahra Taghinejad said that the requirement for medical oxygen and steroids in an immuno-compromised host might pave the way for fungal infections. Mucor mycosis had been induced by several factors, including diabetes and cortone, which act as immune system modulators. Spread of this illness can be limited by providing oxygen and antifungal medications, as well as re-education of medical workers and individuals about its transmission channels and skin wound care, mainly burn treatment.<sup>14</sup>

Dr. Manjunath et al. suggested that using unwarranted steroids and antibiotics in patients with COVID-19 had been the etiological cause of thromboembolism, which was linked to unclean oxygen administration, changes in cardiopulmonary dynamics and thrombosis.<sup>15</sup>

According to Banerjee M, numerous reasons include industrial oxygen use, tainted masks, excessive vitamins and minerals, zinc supplements, iron consumption and improper steam inhalation practices that cause local nasal mucosa injuries. He also evaluated that higher rates of mucormycosis were related to the SARS-CoV-2 delta mutation and prolonged ICU stays.<sup>16</sup>

Petrikkos G hypothesized that the inhaled spores penetrated the paranasal sinuses and their spread routes

were through blood circulation and anatomical locations, which led to the infection of the rhino orbital or rhino cerebral region.<sup>1</sup>

Afroz F also stated that the treatment with corticosteroids and other immune-modulators, invasive and noninvasive ventilatory supports and other oxygen delivery systems, prolonged hospital stay and comorbidities in the case of COVID-19 were setting the scenarios for opportunistic infections and coinfections with fungus and other pathogens.<sup>17</sup>

In the investigation done by Ravi Meher, there was no correlation between the history of oxygen support and ICU admission and the development of invasive fungal sinusitis or the course of the disease.<sup>18</sup>

According to Satyendra Khichar et al., oxygen therapy is the only proven treatment for COVID-19. There was no evident incidence of CAM among patients in that research who received any oxygen supplementation as a hospital- or home-based respiratory support.<sup>19</sup>

Nandini Passi et al. added that sterile masks and water must be promoted for oxygen humidifiers to reinforce the general "infection prevention and control policy" of healthcare facilities.<sup>20</sup>

Sen et al. culminated that contaminated oxygen was unlikely to cause infection in 43% (1216 of 2818) of the Covid -Associated ROCM cases they studied.<sup>21</sup>

Fahad I Rahman postulated that unclean ventilators and oxygen cylinders caused the fungal outbreak. Some hospitals used ventilators on a shared basis during the second wave.<sup>22</sup>

Archana Ajav Vare had also stated that the prior use of systemic steroids and requirement for oxygen therapy were significant risk factors. During their COVID-19 sickness, patients who required noninvasive oxygen support or ventilator assistance were at significantly elevated risk of mortality or orbital exenteration.

Although prolonged oxygen consumption had been established as a risk factor for CAM, 22 percent of patients did not get any supplementary oxygen suggesting that uncontrolled diabetes and the hyperglycemic effects of steroids were more relevant risk factors for CAM than contaminated oxygen supply.<sup>23</sup>

In a study by Neelam Vaid et al., all hospitalized patients received oxygen during COVID-19 treatment for varied periods, ranging from three to 14 days. 40% of those who contracted mucormycosis died despite rigorous surgical and polyene antifungal treatment. Every patient who passed away from the illness had intracranial involvement.<sup>24</sup>

Aastha stated insufficient evidence to show a causal relationship between oxygen supplementation, steroid usage, and immunosuppressive medicine use in COVID-19 patients. Potential environmental triggers for healthcare-associated mucormycosis, such as air conditioners, polluted ventilation systems or hospital building constructions were not evaluated. Furthermore, the risk factors like using industrial oxygen during the COVID pandemic, using contaminated nebulizer fluids, inline humidifier tubing in ventilator circuits, or using contaminated oxygen delivery systems that were associated with a higher incidence of CAM were not investigated in their study.<sup>25</sup>

Other suggested risk factors, including oxygen therapy, steam inhalation, or protracted steroid therapy were not linked to mucormycosis, according to Lt Col. Rahul Soni et al. The only risk factors were hyperglycaemia and COVID-19 infection, although no association was found between steam inhalation, steroid use, or oxygen therapy.<sup>26</sup>

### **Role of Mechanical Ventilator**

Mechanical ventilation (also known as artificial or assisted ventilation) is a breathing support for people unable to breathe independently. The oxygen therapy can be administered using mechanical ventilation.<sup>27</sup>

Mucor mycosis was linked to a lot of fungal and bacterial secondary illnesses. It could enhance the chance of development and exacerbate opportunistic fungal infections, despite mechanical ventilation, catheter implantation, and immunosuppressive medications, as described by Arman Amin.<sup>28</sup>

Jagtap et al. found that patients on mechanical ventilation and with extended hospital stays were more likely to develop the fungal co-infection.<sup>29</sup>

Cases that required oxygen had a higher mortality rate, with an average of 76.2% in those requiring mechanical ventilation.<sup>30</sup> Patients who stayed in the ward died at a rate of 9.1%, three times higher (35.6%) than those in the ICU (P 0.001). According to Bellani G, the first point to mention was clinical decision-making, whether they require invasive or noninvasive ventilation, which was never consistent, even when dealing with "classic" acute respiratory distress syndrome. In the Lung Safe research (of patients without COVID-19), 15% received noninvasive ventilation during the first two days of enrollment despite satisfying the inclusion criteria for acute respiratory distress syndrome.<sup>31</sup>

Archana Ajay summarized that patients who required NIV during COVID-19 were seven times more likely to have a negative outcome (hazard ratios [HR] = 6.92, 95% CI = 2.9-16.2), but those who got amphotericin-B had a 61% decreased risk (HR = 0.39, 95% CI = 0.16-0.97). As a result, the conclusion was that the present CAM epidemic was mainly found in uncontrolled diabetics, particularly those with ketoacidosis and steroid use. On day 20 of the infection, the cumulative

chance of mortality or orbital exenteration was 38%. Those who required NIV but did not get amphotericin-B were at a high risk of these events, proving that NIV is directly related to mortality rate.<sup>23</sup>

According to Arnaiz-Garcia, COVID-19 patients on mechanical ventilation had a significant prevalence of mucormycosis and a high mortality rate. These results emphasized the requirement for ongoing monitoring of fungi in COVID-19 patients.<sup>32</sup>

As speculated by Am J Respir, an additional factor was the availability of resources, which was a significant concern at the time. The availability of resources had always differed between nations, influencing ICU admission thresholds, assessment of "need" for mechanical ventilation and length of continuing invasive life-supporting therapy.<sup>33</sup>

### **Role of Humidifiers**

One possible explanation for the incommensurate rise in mucormycosis cases in a developing nation is the transmission of the disease through water in oxygen humidifiers. Banerjee M postulated that using polluted water in humidifiers, non-sterile humidifier bottles, and non-medical grade industrial oxygen cylinders might have contributed to the spread of fungi and the rise in fungal diseases.<sup>16</sup>

A study conducted by El-Herte also ascribed fungal growth to humidity. It was found that mucor mycosis positively correlates with humidity.<sup>34</sup> Fungal spores spread more readily when water is utilized in oxygen humidifiers. Another inverse relationship between the concurrent rise in COVID-19 and mucor mycosis was shown here by Rammaert B.<sup>35</sup> Bhogireddy noticed that the filthy oxygen cylinders with masks, the use of contaminated or tap water in humidifiers, the prolonged use of the same mask for more than two patients, the unsanitary delivery of oxygen, or low-quality tubing

systems to these patients at the hospital led to an increase in the incidence of mucormycosis.<sup>36</sup>

According to Vanya Singh, even though fungal spores cannot survive in water, there is a potential that they could spread from high-contact hospital surfaces, such as reusable humidifier bottles.<sup>37</sup> Blood sugar was raised in almost all patients of Aditya Gargava with a history of excessive steroid use & undistilled water in humidifier and nebulization. Uncontrolled blood sugar, excessive use of steroids, undistilled water, poor oral hygiene, and immunocompromised status were the main aggravating factors in the illness of COVID-19 and invasive fungal infections of the paranasal sinus.<sup>38</sup> The possibility of fungus invading lung tissue was proposed in COVID-19 because of airway epithelial injury brought on by oxygen delivery devices, extended use of humidifiers without cleaning, using industrial oxygen, numerous swab tests, and steam inhalation burn injuries which were proposed by Bhuyan A.<sup>39</sup>

Bindu Mulakavalupil et al. conducted research in which they reported using High Flow Nasal Cannula (HFNC) using an inbuilt humidified circuit and no death was registered due to mucor mycosis. Concerns include handling oxygen in an unclean manner or using substandard tubing, contaminated masks, using dirty water in humidifiers, and using the same oxygen mask on more than two patients for a lengthy period.<sup>3</sup> In research proposed by Vaid N et. al., which involved a sample size of 65 patients, out of which 11 patients (17%) were not admitted to the hospital and also did not get oxygen, 23 people were undergoing treatment, and seven died due to intracranial involvement and progression of Mucor mycosis. They have proposed the usage of industrial oxygen, excessive levels of zinc, and hospital-acquired infections caused by infected

humidifiers as the causative factors; however, none of these have been scientifically proven.<sup>24</sup>

Salaheldin Elhamamsy et al reported a case report of humidified oxygen was submitted where it was shown that Hospital care demand had exceeded capacity, which led to insufficient resources for critically ill patients, such as sterile water for humidifying oxygen because non-sterilized water might have colonized with fungus which reported for mucormycosis.<sup>40</sup>

Semridhi Gupta undertook a Single Arm Retrospective Unicentric Clinical Study with 56 post-COVID-19 ROCM patients. Humid working conditions and uncontrolled Diabetes Mellitus (DM) were the primary risk factors for ROCM. The overall mortality rate was 16%. Regarding Patients' occupation; though diversity was seen but most patients were farmers (69%). This could be because this occupation offers calm and humid working circumstances. It was concluded that humid working conditions contributed to a sudden rise of ROCM cases as most were farmers, and the correlation between humidity and fungal growth is well-known.<sup>41</sup>

A study by V. LA FAUCI proved the high rate and kind of microbial contamination of reusable humidifiers used for oxygen therapy. Therefore, these devices could be utilized to propagate potential diseases. Single-use humidifiers could have been replaced to avoid nosocomial pneumonia, proving a lack of microbial contamination.<sup>42</sup>

Mrigesh Bhatia said that oxygenation through a facemask or nasal cannula may have infected the fungi in the upper respiratory tract when a contaminated water humidifier was utilized, but further studies are needed. Clinicians should be careful about the appropriate use of humidifiers for COVID-19 management and ensure aseptic precautions during oxygen support to limit the

risk for mucor mycosis following COVID-19 treatment.

43

### Conclusion

This systematic review presents a compiled summary of all the causes of CAM. Patients with weakened immune systems were shown to have higher illness prevalence. The filthy conditions aided proliferation significantly when sterilization was undermined, and asepsis prevailed.

According to this systematic review, increased mucormycosis is triggered by industrial oxygen, undistilled water in humidifiers, and invasive ventilation. Mucormycosis management should have a multidisciplinary approach since patients with poorly controlled diabetes or a compromised immune system are at a higher risk of infection. Early identification is critical, reversing predisposing variables, and intensive surgical debridement remains the hallmark of treatment for this fatal infection. The limitation of this systematic review is that no literature was found on the interventions in the form of randomized control trials (RCTs), so further studies will be needed. A greater understanding of the mechanism of the illness might lead to novel therapies.

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