


# The Past, Present and Future of COVID-19 Associated Mucormycosis: A Rapid Review

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## Abstract

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, which is known for the multiple mutations and forms that have rapidly spread across the world. With the imminent challenges faced by low- and middle-income countries in curbing the public health fallbacks due to limited resources, mucormycosis emerged as a fungal infection associated with high mortality. In this rapid review, we explored MEDLINE, Cochrane, Web of Science, WHO Global Database, and the search engine—Google Scholar for articles listed until July 2021 and presented a narrative synthesis of findings from 39 articles. The epidemiology, causative factors, incidence parameters, pharmacological treatment, and recommendations for low- and middle-income countries are enlisted. This study concludes that a majority of the globally reported COVID-19 associated mucormycosis cases stemmed from India. Individuals receiving systemic corticosteroids or who have a history of diabetes mellitus are more prone to contracting the disease. Public health authorities in LMIC are recommended to strengthen antifungal therapies for COVID-19 associated mucormycosis and to strategize reduction in diabetes mellitus prevalence.

## Keywords

COVID-19, mucormycosis, India, developing countries, public health, fungal infection

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## Introduction

During the time of December 2019, a new virus outbreak occurred in Wuhan City, China. It belonged to a novel member of the coronaviridae family named SARS-CoV-2 (severe acute respiratory coronavirus-2 syndromes) and was responsible for pneumonia-like symptoms.<sup>1</sup> With accelerated exponential spreading capability, this virus emerged as a global pandemic and threat to the life of humans. SARS-CoV-2 is a notorious virus with multiple mutations and forms that have widely spread throughout the world in a short period. Scientists have given the specific designation to these different strains, namely B.1.1.7 lineage (501Y.V1 or VOC 202012/01 or UK variant), P.1 lineage (501Y.V3 or Brazilian variant), B.1.427, and B.1.429 lineages (California or West Coast variants), and B.1.617 lineages (India).<sup>1</sup> The mutations were on the spike protein, and that led to increased transmissibility and disease severity.<sup>2</sup>

The variants, particularly Brazilian variant, B.1.427, and California or West Coast variants, and Indian variants have shown a significant exponential surge in cases and mortality rate.<sup>3</sup> Countries like India and Nepal fall short of health care providers, medical equipment, medications, hospital beds, and sufficient oxygen supply for severe patients. It has been challenging for all medical professionals and the

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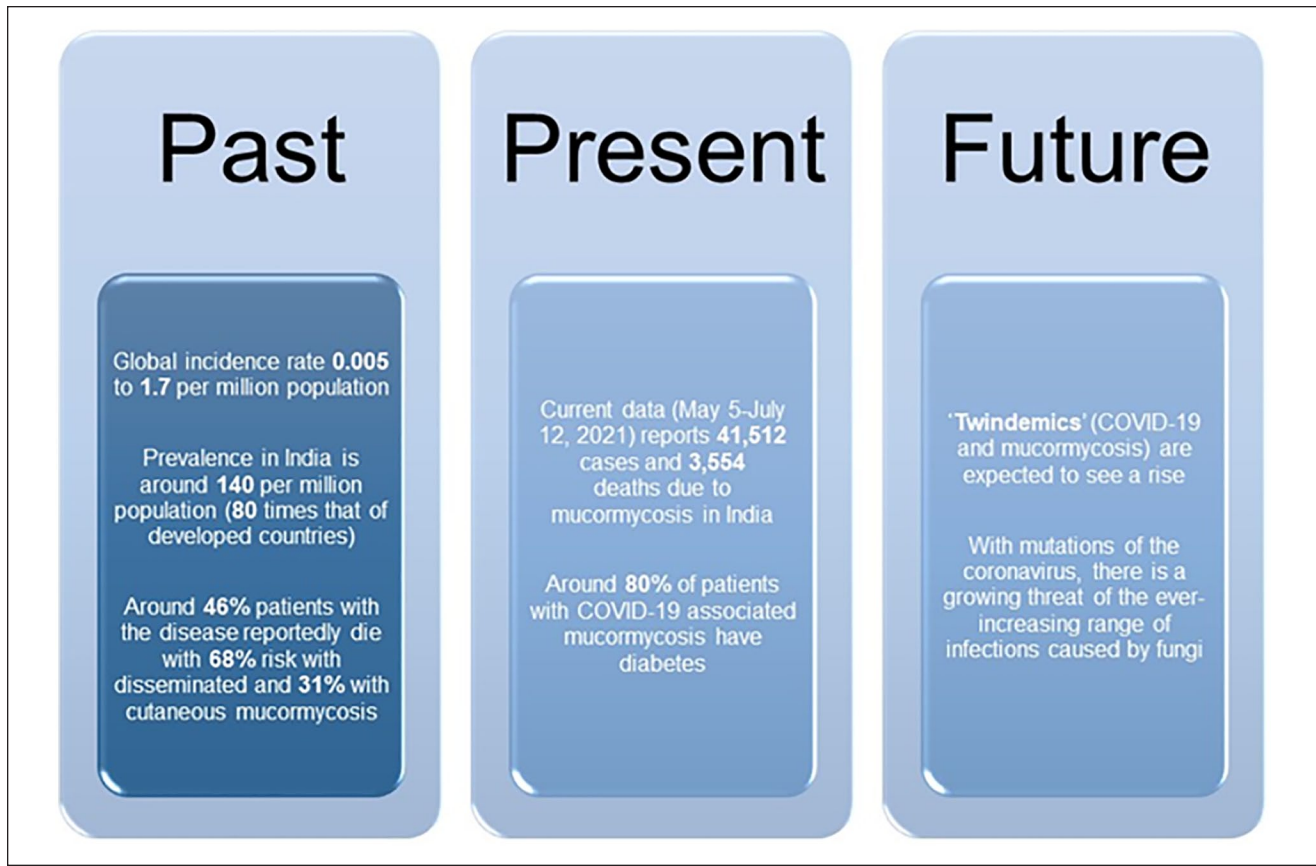
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**Figure 1.** The past, present and future of COVID-19 associated mucormycosis.

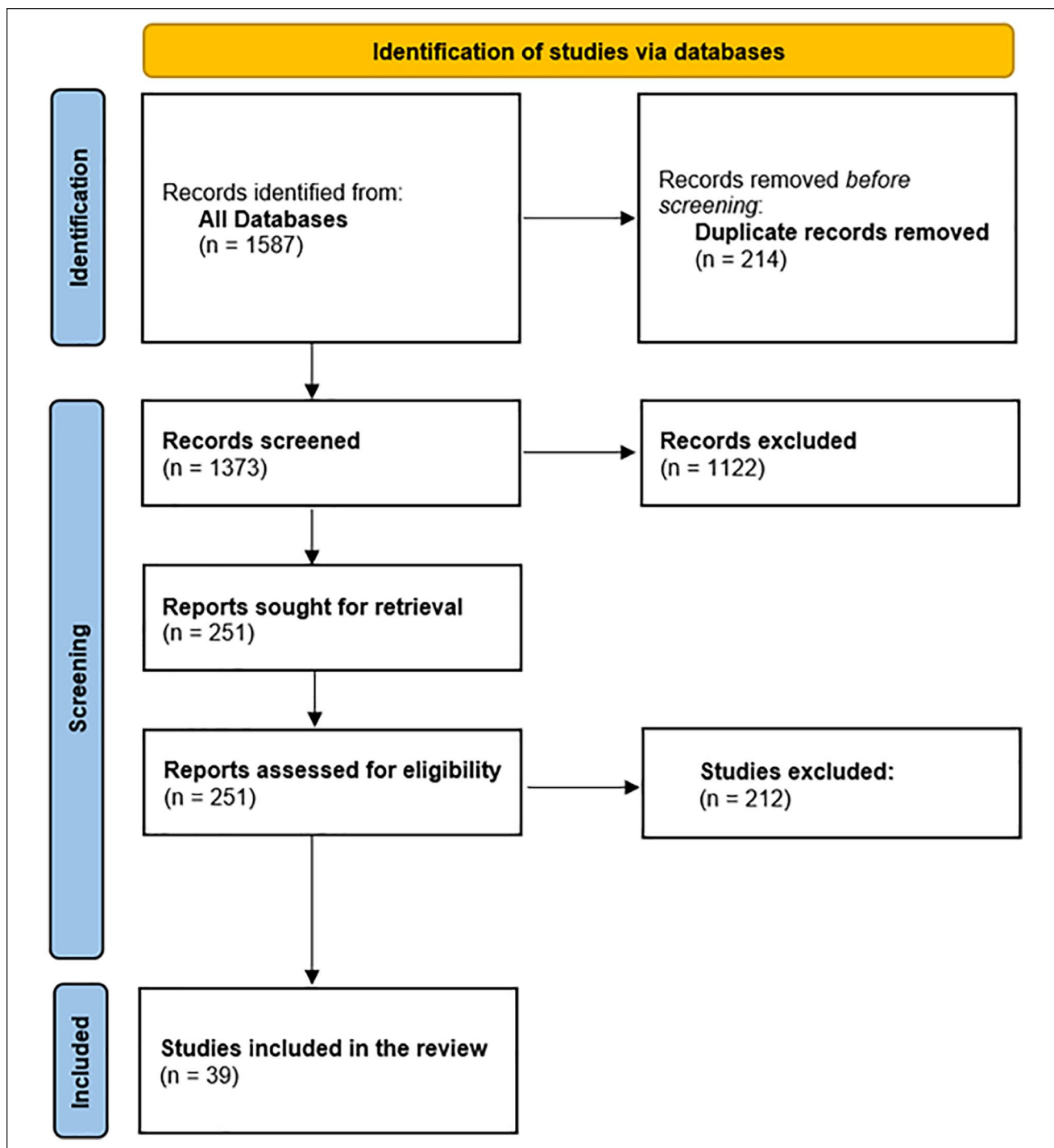
government to develop strategies and plans to overcome the situation. Additionally, with the onset of the second wave, the situation worsened in terms of mortality, morbidity, and hospital stay due to the lack of responsibility and effective strategies from both the government and the general population.<sup>4</sup> Until December 5, 2021, the World Health Organization (WHO) has reported a total of 34.6 million confirmed cases and 0.473 million deaths had occurred so far in India, while a cumulative total of 266 million cases and 5.26 million deaths reported globally.<sup>5</sup>

Mucormycosis has emerged as a rapidly occurring fungal infection with high mortality. It is caused by a group of filamentous molds within the order Mucorales.<sup>6</sup> *Rhizopus* is the most common genus associated with mucormycosis among all Mucorales class, followed by *Mucor* and *Lichtheimia*.<sup>7</sup> These fungi come into contact via inhalation or ingestion of sporangiospores, and they also enter the human body through puncture wounds and trauma.<sup>7</sup> Healthy individuals have sound defense systems with intact mononuclear and polymorphonuclear cells that kill these fungi. Patients with neutropenia or defective phagocytic activity are prone to mucormycosis.<sup>8</sup> Key points about the past, present, and

future are depicted in Figure 1. This paper seeks to rapidly review the epidemiology, causative factors, incidence, and pharmacological treatment of mucormycosis while making recommendations for black fungus (mucormycosis) mitigation in low- and middle-income countries (LMICs).

## Methodology

This study reviewed databases including MEDLINE, Cochrane, Web of Science, WHO Global Database, and the search engine—Google Scholar. We did not apply any restrictions to the data search and included all articles until July 2021. We used a combination of the following search terms using BOOLEAN operators, including “COVID-19,” “mucormycosis,” “LMIC,” “Developing country,” “fungal,” and “mycoses.” There were no language restrictions applied, and any non-English study was translated to English using Google translate. The second and third authors reviewed the databases and search engines, with the first author (ZS) present for any disputes. We did not exclude any study type and manually searched the reference lists of screened studies. All authors searched from data from the included, and the



**Figure 2.** Flow diagram of search process.

primary author (ZS) was present to solve any disagreements for this narrative synthesis of recent findings.

Overall, the search yielded 1587 results. Of these, 214 were duplicates which were removed from the EndNote library (X9) that was used as the bibliographic management software. One thousand three hundred seventy-three studies were screened for titles and abstracts. Two hundred

fifty-one of these screened studies were retrieved with full-texts, of which 39 articles were included (Figure 2).

## Epidemiology

The global prevalence of mucormycosis varies from 0.005 to 1.7 per million population, while the prevalence is

**Table 1.** An Overview of the Forms of Mucormycosis and the Underlying Conditions.

Author (s), Reference	Forms of mucormycosis	Underlying condition(s)
Roden et al, <sup>15</sup> Chadli-Chaieb et al <sup>16</sup>	Rhino-cerebral	Diabetes, ketoacidosis, hematologic malignancy, stem cell transplantation
Bouza et al, <sup>15</sup> Roden et al <sup>17</sup>	Pulmonary	Neutropenia, corticosteroid therapy, chronic renal insufficiency
Petrikkos et al, <sup>18</sup> Adam et al <sup>19</sup>	Cutaneous	Trauma, diabetes
Roden et al <sup>15</sup>	Gastrointestinal	Malnutrition
Bouza et al, <sup>17</sup> Eiser et al <sup>20</sup>	Disseminated disease	Deferoxamine, neutropenia, corticosteroids
Roden et al, <sup>15</sup> Chen et al <sup>21</sup>	Other (central nervous system, endocarditis, etc.)	Various

around 80 times higher, with 0.14 per 1000, in India compared to high-income countries, as of 2020.<sup>9</sup> Notably, India has documented the highest number of mucormycosis cases in the world. However, as the second-largest population in the world with high diabetes mellitus (DM) cases, in addition to being the DM capital of the world, the risk for developing the fungal disease is multifold.<sup>9</sup> A systematic review and meta-analysis of 851 case reports in 2018 documented that the death rate due to mucormycosis in India was 46% among 851 patients.<sup>9,10</sup> Moreover, the case fatality was observed to be higher in patients with disseminated mucormycosis than individuals with cutaneous disease (68% vs 31%).<sup>9,10</sup>

Following the rise of COVID-19 associated with mucormycosis and the Government of India's directive, various Indian states made mucormycosis a notifiable disease in May 2021.<sup>10</sup> The actual burden of fungal disease in other low- and middle-income countries like Pakistan is unknown.<sup>11</sup> However, recent literature suggests that populations across restricted healthcare settings are at high risk for fungal infections such as mucormycosis and candidemia.<sup>9-11</sup> A 2017 report highlighting fungal disease in Bangladesh identifies that deep mycosis is an imperative problem, as evidenced by reports of 16 cases of histoplasmosis.<sup>12</sup> Other systemic mycoses, such as 2 reports of mucormycosis, have been reported to impact human health.<sup>12</sup>

## Causative Factors

*Mucormycosis* is an invasive opportunistic fungal infection mainly affecting the vasculature of the host organism by hyphae.<sup>13</sup> Different predisposing factors such as hematologic malignancy, neutropenia, systemic corticosteroid use, uncontrolled diabetes, chronic renal failure, stem cell transplantation, and immunocompromised state, play a vital role as the risk factors in the development of the disease (Table 1).<sup>14</sup>

Once the fungal spores are inhaled, they penetrate the lungs and activate the first-line defense such as mononuclear and polynuclear phagocytes, which destroy them.<sup>22,23</sup>

In COVID-19 patients, especially with the co-morbid condition of diabetes mellitus, hyperglycemia is often seen with corticosteroid use. Low pH in diabetic ketoacidosis conditions provides a favorable condition for spores to grow. The decreased phagocytic activity of WBC with overuse of steroids causes impairment in WBC migration and phagolysosome fusion, which leaves the patient vulnerable to mucormycosis infection.<sup>10</sup>

Mucormycosis presents with different clinical manifestations like rhino-cerebral manifestation, respiratory manifestation, cutaneous manifestation, gastrointestinal manifestation, disseminated disease, and other manifestations like endocarditis and central nervous system invasion.<sup>17</sup> Mehta and Pandey, in their study, reported that COVID-19 is a culprit of secondary infections due to immune dysregulation because of the widespread use of monoclonal antibodies, broad-spectrum antibiotics, corticosteroid, poor ventilation, and reduced number of T-lymphocytes.<sup>24</sup> COVID-19 patients hospitalized in intensive care units (ICU) usually share the risk factors and increased cytokine storm, which has off-target effects rather than the first-line defense, making the patient susceptible to invasive fungal infection mucormycosis. Additionally, increased inflammation leads to tissue damage.<sup>25,26</sup> COVID-19 patients with mucormycosis were presented in a 101-patient case series where 80% of the patients had diabetes, and 76.3% received corticosteroid treatment.<sup>26</sup> In India's second wave of the COVID-19 pandemic, there is a surge in mucormycosis with clinical manifestations like vision loss, brain abscess, and stroke, increasing the mortality rate in patients with COVID-19. In India, 8848 cases of mucormycosis are documented.<sup>27</sup> 52 deaths were recorded among 1500 cases of mucormycosis in Maharashtra state only.<sup>28</sup>

## Incidence

Since the first case of Mucormycosis reported in 1885 by Paultauf, there has been a massive upsurge in incidence and prevalence globally.<sup>29</sup> The Leading International Fungal Education (LIFE) portal reported an estimated annual

**Table 2.** Estimated Incidence per Million Populations.

Author(s), reference	Country	Incidence per million population
Webb et al <sup>34</sup>	USA	3
Chen et al <sup>36</sup>	Australia	0.6
Mortensen et al <sup>37</sup>	Europe:	
Sabino et al <sup>38</sup>	• Denmark	0.2
	• Portugal	95
Chakrabarti et al <sup>35</sup>	India	140
Torres-Narbona et al <sup>32</sup>	Spain	0.43
Bitar et al <sup>33</sup>	France	0.9

prevalence of mucormycosis to be 910 000 worldwide.<sup>30</sup> The prevalence also varies depending upon the region. Cases in India have been alarmingly high, with 80 times more prevalence than any other country. Out of 910 000 cases in the LIFE portal, 900 000 cases were reported from India.<sup>30</sup> Prakash et al tabulate the annual prevalence of mucormycosis per million populations in various countries, with a mean prevalence of 171 504 in India alone.<sup>30</sup> In the US, a population-based surveillance study conducted in San Francisco, CA, from 1992 to 1993 showed a prevalence of 1.73 cases per million.<sup>29,31</sup> A recent review of 851 cases from January 2000 through January 2017 indicated a higher prevalence of the disease burden in Europe, with rates at 34%, compared to 31% in Asia.<sup>29</sup> The same study showed the burden in North or South America to be 28%, Africa and Australia to be 3% each.<sup>29</sup> This data, however, is likely related to underreporting during this period from Asian Countries. Since this is not a reportable disease and various limitations in the diagnostic process, including difficulty in sample collection, low sensitivity of diagnostic tests, and declining autopsy rates (ie, the standard gold test), the exact burden or prevalence of mucormycosis are not known.<sup>29</sup> Several studies over time have revealed the incidence per million populations as shown in Table 2.<sup>32-38</sup>

A study performed by Roden et al<sup>15</sup> reported among 969 cases studied between 1885 and 2004, the incidence of mucormycosis has increased with each decade. Underlying medical conditions that attributed to this severe infection were a mostly immunocompromised state, malignancies, and transplant patients seen in the developed country whereas uncontrolled DM, CKD, and post-pulmonary tuberculosis in developing countries.<sup>29</sup>

With the upsurge of mucormycosis incidence reported globally during the COVID-19 pandemic, Garg et al presented 8 cases in the United States (3 cases), India (2 cases), Brazil (1 case), Italy (1 case), and the UK (1 case).<sup>39</sup> As of May 22, 2021, the government of India has reported 8848 cases of mucormycosis during the pandemic.<sup>27</sup> Though DM was the predominant risk factor (n=4, 50%) in most countries; extensive corticosteroid use was attributed to India's upsurge during the pandemic.<sup>27,39</sup> A summary of the trends

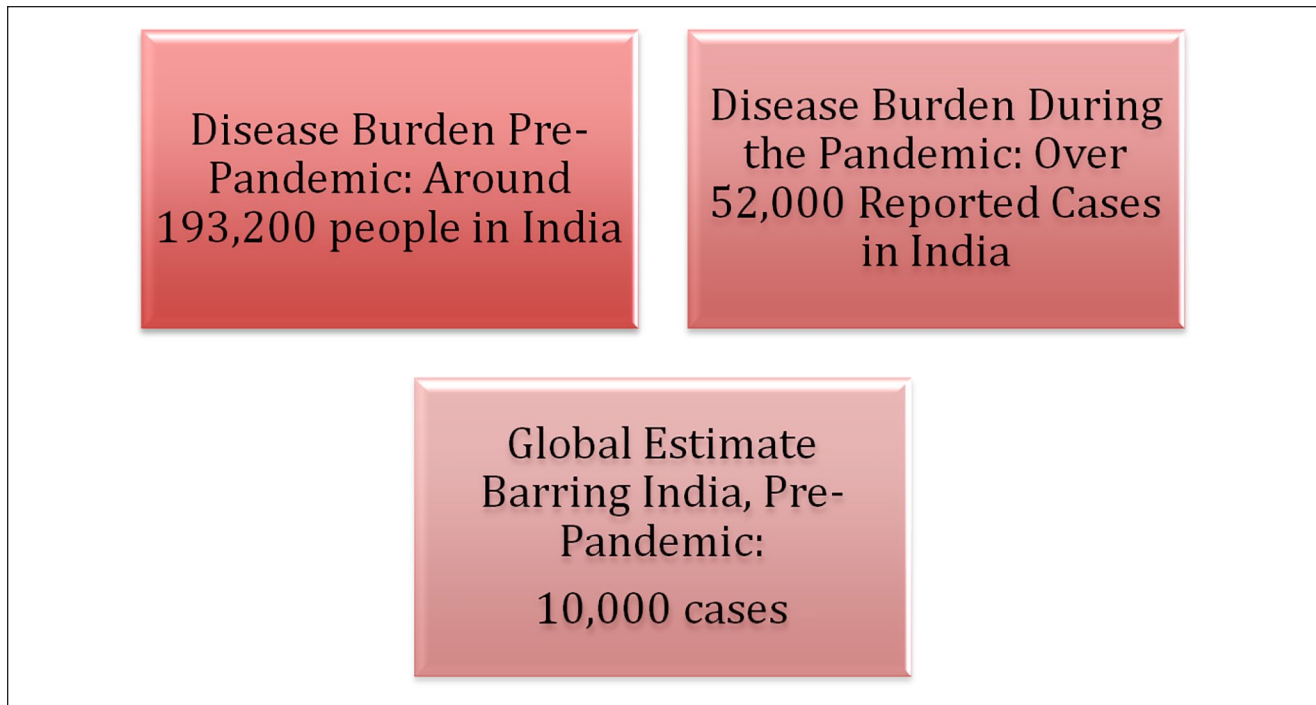
in India pre- and post- the COVID-19 pandemic in addition to global estimates is depicted in Figure 3.

## Pharmacological Treatment

The successful treatment of mucormycosis is always challenging and is based on various approaches, including early diagnosis, discontinuation or reversal of underlying predisposing factors, early and optimal dosage of an active antifungal, and debridement of all the infected tissues.<sup>40</sup> In diabetes mellitus and suspected mucormycosis patients, early and rapid correction of diabetic ketoacidosis is mandatory with judicious use of fluids, sodium bicarbonate, and insulin.<sup>41</sup> Immunosuppressant drugs and Corticosteroids should be tapered abruptly to the lowest possible dose.<sup>42</sup>

Earlier on, amphotericin (Amb) and posaconazole were the only effective antifungal used for mucormycosis. However, recently isavuconazole has been approved for the treatment of mucormycosis, leading to an enlargement of antifungal armamentarium.<sup>43</sup> Liposomal Amb or Amb lipid complex is still the first-line recommended antifungal option for mucormycosis.<sup>44</sup> However, the effective and tolerable dose of Amb is still debatable. The recommended dose, as per ECMM/ESCMID and ECIL-6 guidelines, is 5 mg/kg/day.<sup>44</sup> It should be increased to 10 mg/kg/day for cerebral infections.<sup>44</sup> However, the duration of an antifungal is still a matter of debate and should be determined on underlying conditions and an individual basis; 3 weeks is the proposed duration. Upon clinical and radiological improvement, posaconazole can be started as a consolidation phase.<sup>45</sup> Marty et al conducted a study to evaluate the effectiveness of isavuconazole in mucormycosis patients. The patients were given isavuconazole at a dose of 200 mg (thrice a day) for 2 consecutive days, followed by 200 mg/day until invasive fungal resolution, treatment failure, or 180 days were given to the patients. The results of the trial showed that isavuconazole was well tolerated and was as effective as Amb.<sup>46</sup>

Additionally, surgical debridement is recommended at earlier stages to remove necrotic and healthy infected tissue.<sup>42</sup> Other modalities such as hyperbaric oxygen to



**Figure 3.** Summary trends of mucormycosis cases in India pre- and during the COVID-19 pandemic with global estimates.

provide oxygen-enriched medium and cytokines are administered along with antifungal therapy.

### Recommendations for Low- and Middle-Income Countries

The recommendations for care pertaining to COVID-19 associated mucormycosis must account for the following underlying factors. First, healthcare workers across LMIC ought to aim for better glycemic control for those with diabetes. Second, a well-informed decision on the use of systemic corticosteroids is recommended.<sup>47</sup> Third, the unnecessary usage of antifungals, antibiotics, and other immunomodulators must be halted. Infection prevention and control prevention units at the primary, secondary, and tertiary levels of care across the developing world are key to preventing the environmental spread of the microbe. It is warranted that sterilization and disinfection of the equipment be made when various patients share tracheal tubes, ventilators, or other equipment. The ventilation systems in overpopulated spaces are to eliminate dust or dampness to the best ability of the healthcare center staff. Furthermore, adequate wound management such as taping/securing medical devices such as endotracheal tubes, sterilizing and changing ostomy devices, and refreshing tapes, bandages, and adhesives is necessary. Finally, the public health infrastructure requires proper line management with health facilities at the forefront of the COVID-19 pandemic.

### Conclusion

On the whole, this study finds that a majority of the globally reported COVID-19 associated mucormycosis cases stemmed from India. Moreover, the patients had a history of diabetes mellitus or were receiving systemic corticosteroids. While judicious use of glucocorticoids is necessary amid the COVID-19 pandemic, it is also necessary to acknowledge that many cases across LMIC may not have been reported to healthcare centers and consequently were underrepresented in scientific literature. The line of action for LMIC is to strengthen antifungal therapy to decrease the high mortality rate due to COVID-19 associated mucormycosis, where public health officials strategize reductions of DM prevalence.

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