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MINI REVIEW ARTICLE

COVID-19-associated-mucormycosis: possible role of free iron uptake and immunosuppression

Tahani Tabassum[1] · Yusha Araf[2] · Abu Tayab Moin[3] · Tanjim Ishraq Rahaman[4] · Mohammad Jakir Hosen[2]

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Abstract

COVID-19-associated-mucormycosis, commonly referred to as the "Black Fungus," is a rare secondary fungal infection in COVID-19 patients prompted by a group of mucor molds. Association of this rare fungal infection with SARS-CoV-2 infection has been declared as an endemic in India, with minor cases in several other countries around the globe. Although the fungal infection is not contagious like the viral infection, the causative fungal agent is omnipresent. Infection displays an overall mortality rate of around 50%, with many other secondary side effects posing a potential threat in exacerbating COVID-19 mortality rates. In this review, we have accessed the role of free iron availability in COVID-19 patients that might correlate to the pathogenesis of the causative fungal agent. Besides, we have analyzed the negative consequences of using immunosuppressive drugs in encouraging this opportunistic fungal infection.

Keywords Mucormycosis · COVID-19 · *Rhizopus oryzae* · Free iron · Hyperferritinemia · Pathogenesis

Introduction

The pandemic coronavirus disease (COVID-19), caused by the highly contagious severe acute respiratory syndrome (SARS-CoV-2) virus, has had a catastrophic effect on the world demographics, resulting in more than 4.8 million deaths worldwide [1]. Even though substantial clinical advancements have been ascertained, the second wave of the virus has recently wreaked havoc on several countries, emerging as the most consistent and consequential global health crisis. Recently, some countries, prominently India, have reported overwhelming numbers of deadly secondary fungal infections in COVID-19 patients. As of May 25, India had reported around 11,700 cases of COVID-19-associated-mucormycosis and declared this disease as an endemic [2], while minor cases of this infection have also been reported in Pakistan Bangladesh, Nepal, Russia, Uruguay, Chile, and Iran [3–9]. The secondary fungal infection usually is rare in immunocompetent hosts. However, it can be deadly if the fungal agent invades immunocompromised hosts or patients with pre-occurring comorbid conditions that increase their susceptibility to such opportunistic infections [10].

Moreover, some COVID-19 patients are currently being treated with steroids or prescribed broad-spectrum antibiotics. Such medicaments are known further to weaken the immune defense mechanism of the patient, increasing susceptibility to other secondary infections [10, 11]. The exact pathogenesis of this fungal infection in COVID-19 patients is yet explored and needs to be accessed to undertake any potential crisis that the disease might inflict.

Tahani Tabassum and Yusha Araf contributed equally to this work.

✉ Mohammad Jakir Hosen
jakir-gen@sust.edu

Tahani Tabassum
tahanitabassum0506@gmail.com

Yusha Araf
yusha.araf@gmail.com

1 Biotechnology Program, Department of Mathematics and Natural Sciences, School of Data and Sciences, Brac University, Dhaka, Bangladesh

2 Department of Genetic Engineering and Biotechnology, School of Life Sciences, Shahjalal University of Science and Technology, Sylhet, Bangladesh

3 Department of Genetic Engineering and Biotechnology, Faculty of Biological Sciences, University of Chittagong, Chattogram, Bangladesh

4 Department of Biotechnology and Genetic Engineering, Faculty of Life Sciences, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj, Bangladesh

Black fungus and its causative agent

Mucormycosis is a rare, aggressive, opportunistic infection caused by the group of mucor molds "mucoromycetes" belonging to the order "Mucorales" [12]. The most common causative agents for the infection are the *Rhizopus, Lichtheimia, Apophysomyces, Mucor*, and *Rhizomucor* species, whereas occasionally is caused by *Cunninghamella* and *Saksenaea* species [13]. The deadly fungal infection can be categorized based on the involvement of the gastrointestinal system, cerebral, nervous system, urogenital system, or the skin. However, the fatal category is the rhino-orbital-cerebral (ROC) and pulmonary involvements [10].

Currently, acute invasive cases of ROC mucormycosis have been reported in COVID-19 patients, and this association between two infections is referred to as the "black fungus." The typical clinical manifestations of this infection are necrosis of the palate or paranasal sinuses that approaches the intra-cranial structures generating symptoms like swelling of the face, nasal and sinus congestion, headache, facial pain, visual disturbances, and black lesion on the nasal bridge or upper part of the mouth that deciphers the name black fungus [14].

Among the family Mucoraceae, the *Rhizopus oryzae* is the most common agent responsible for nearly 90% of ROC mucormycosis in humans. This rapidly growing saprophytic filamentous fungus is ubiquitous in the environment and demonstrates an overall mortality rate of 50% [10, 15]. The fungi promptly release many sporangiospores into the atmosphere and primarily enter the human body through the respiratory system [12]. Besides, it can be ingested through swallowing spores associated with rotten contaminated organic food or through open wounds. However, these routes of ingestion are rare. Nevertheless, the inhalation of the sporangiospores does not cause disease within immunocompetent hosts, as the host neutrophils and phagocytes generate oxidative metabolites and cationic peptides to inhibit fungal spore proliferation [16–18]. In immunocompromised individuals, especially in cases of hyperglycemia and low pH, phagocytes are rendered dysfunctional in terms of intracellular killing and chemotaxis, enhancing susceptibility to this deadly fungal infection [19].

Pathogenesis of *Rhizopus oryzae*

Interactions between the *R. oryzae* and vascular endothelial cells are prominent in fungal pathogenesis. Following paranasal inhalation, *R. oryzae* spores germinate into coenocytic hyphae that initially proliferate in the sinuses and disseminate to the orbit and the brain, primarily through angioinvasion [20]. The fungal spores specifically adhere to the laminin and type IV collagen on the extracellular protein matrixes of the basement membranes separating endothelial cells from underlying stroma [21]. Recently, the glucose-regulated protein 78 (GRP78) receptor was involved in the fungal penetration of endothelial cells [22]. This adherence with the endothelial cells lining the blood vessels mediates fungus endocytosis that facilitates angioinvasion, resulting in vessel thrombosis, hematogenous dissemination, and subsequent tissue necrosis [23]. Another recent transcriptome analysis shows activation of the platelet-derived growth factor (PDGF) pathway in *R. oryzae* pathology, suggesting that PDGF receptors might also facilitate the fungal endothelial invasion [24] and subsequent host cellular injury.

Role of iron in *R. oryzae* pathology

One of the virulence factors that enable Mucorales to cause disease is acquiring iron from the host [20]. Iron is a crucial micronutrient that is indispensable for fungal metabolic processes, cell growth, and development. The fungus *R. oryzae* has demonstrated poor growth in normal serum unless an exogenous iron source is provided [25, 26]. Similarly, iron starvation strategies are reported to induce apoptosis in *R. oryzae* [27]. In mammalian hosts, iron sequestration within carrier proteins such as transferrin, ferritin, lactoferrin limits the availability of free iron as a natural strategic defense mechanism against *R. oryzae* [25, 26].

Regardless, the fungus has several unique iron-assimilation mechanisms; one prominent mechanism is the release of high-affinity iron permeases (Fig. 1) [28]. These high-affinity iron permeases are part of an integral reductive system, constituting redundant surface reductases that reduce the ferric ion into a more soluble ferrous form. Part of this reductive system is a copper oxidase-ferrous permease complex that captures those soluble ferrous ions, making those available for fungal acquisition (Fig. 1) [28–30]. Recent data shows the gene encoding high-affinity iron permease (FTR1) is overexpressed by *R. oryzae* during murine infection, implying the role of such permeases in enhancing fungal iron uptake [31]. Besides, the fungus may secrete siderophores, low molecular weight iron chelators, such as rhizoferrin, or utilize xenosiderophores such as Deferoxamine that enhances iron uptake (Fig. 1) [20, 32]. Genomic analysis of *R. oryzae* identified 13 siderophore permeases that might serve as siderophore receptors [33]. Rhizoferrin may supply iron to the *R. oryzae* through an energy-dependent receptor-mediated pathway, but the exact mechanism of whether this siderophore releases iron extracellularly or is internalized

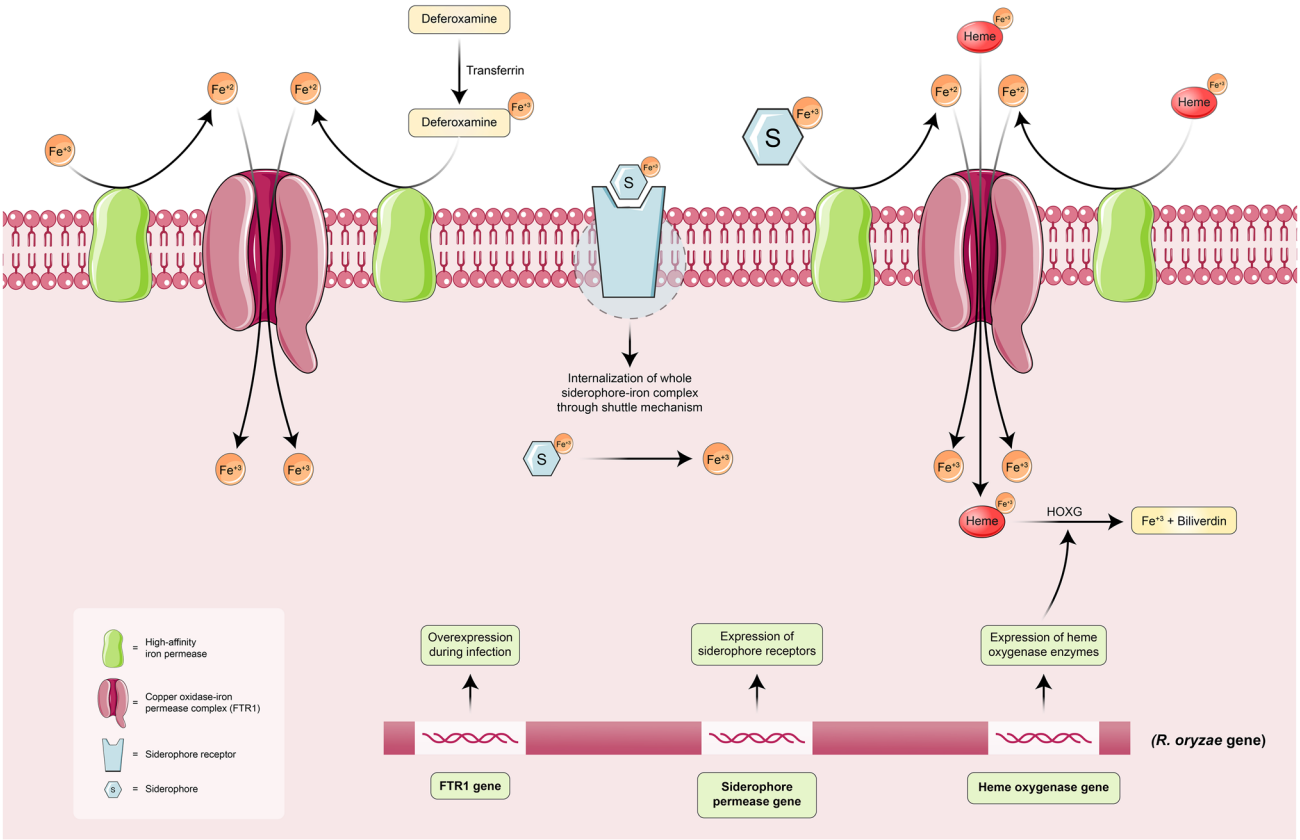

Fig. 1 Different mechanisms utilized by Mucorales to obtain iron from the host. High-affinity iron permeases on the cytoplasmic membrane can convert the less soluble ferric ion into more soluble ferrous ions, followed by their internalization through the copper oxidase-iron permease (FTR1) complex. The complex oxidizes the ferrous form into the ferric form required to properly utilize the ion in intracellular processes. A xenosiderophore, Deferoxamine, may strip Fe^{3+} ion from host transferrin and produce ferrioxamine (Deferoxamine-Fe^{3+} complex) that is reduced into ferrous ion and internalized by FTR1 complex. Other endogenous siderophores are synthesized by the fungus chelate iron extracellularly, and the whole complex may be internalized through a shuttle mechanism. Alternatively, the siderophore-iron complexes may be reduced through membrane permeases to generate Fe^{2+} ions, followed by internalization by the FTR1 complex. The angioinvasive nature of the infection also reveals that heme can be a potential source of iron. The heme-Fe^{3+} complex may be entirely internalized and then acted on by the heme oxygenases intracellularly or reduced on the surface to generate Fe^{2+} ions to be taken in by the FTR1 complex. Overexpression of the *FTR1* gene during infection correlates to the requirement of this complex in internalizing all the extracellular ferrous ions and some iron chelator complexes

before releasing iron is not known yet [32, 34]. Two more recently introduced iron chelators are Deferiprone (act as bidentate chelator) and Deferasirox (act as tridentate chelator). Although both of these chelators have displayed significant depletion of iron levels in clinical practices [35–37], these have not been reported to increase susceptibility to mucormycosis [38, 39]. Besides, these two new chelators do not act as xenosiderophores as the fungal iron uptake system cannot detach iron from them. Their higher affinity for iron forms much stable chemical structure indifferent to fungal iron uptake systems. Another reason might be the lower molecular masses of these chelators limit their access to fungal iron uptake systems [39].

Moreover, the genomic analysis of *R. oryzae* revealed two homologs of heme oxygenase [33], enabling the fungus to obtain iron from host hemoglobin and explain their angioinvasive nature. Genomic analysis of *R. oryzae* depicts a reduced efficiency of utilizing heme as an iron source when the copy number of the *FTR1* gene is reduced [31], suggesting that FTR1 may serve as a membrane permease enabling uptake of extracellular heme and its subsequent intracellular degradation through heme oxygenases to generate free iron (Fig. 1).

Correlation with COVID pathology

Generation of free iron

Hyperferritinemia is a crucial diagnostic and prognostic laboratory biomarker in COVID-19 infection [40–45]. Increased serum ferritin is a common manifestation in

COVID-19 inflammatory reactions and can also contribute to the development of cytokine storms [46]. Hyperferritinemia and inflammation are the primary mediators of COVID-19 associated dysregulation of iron homeostasis [47]. Apart from being an active secretion during inflammation, hyperferritinemia induces hepatic cell death [48], and apoptosis releases the intracellularly stored free irons and serum ferritin to the cell exterior. The stored serum ferritin from hepatocytes on release loses part of the inner iron content, releasing extremely high levels of free iron (Fig. 2) [49].

Consequently, the high incidence of hyperferritinemia is consistent with the emergence of enhanced levels of free iron in COVID-19 patients [50] that R. oryzae might utilize for fungal proliferation and growth. Similarly, inflammation-induced imbalance of iron regulatory hormone hepcidin may elevate free iron levels in COVID-19 patients (Fig. 2) [51]. Another key pathogenic strategy of SARS-CoV-2 that might ensure iron availability for *R. oryzae* pathogenesis is to attack the 1-beta chain of hemoglobin that initiates dissociation of porphyrins from iron and rapid discharge of elevated amounts of iron into circulation (Fig. 2) [52].

Suppression of the immune system

Although the host immune system plays a crucial role in SARS-CoV-2 virus suppression, the excessive release of

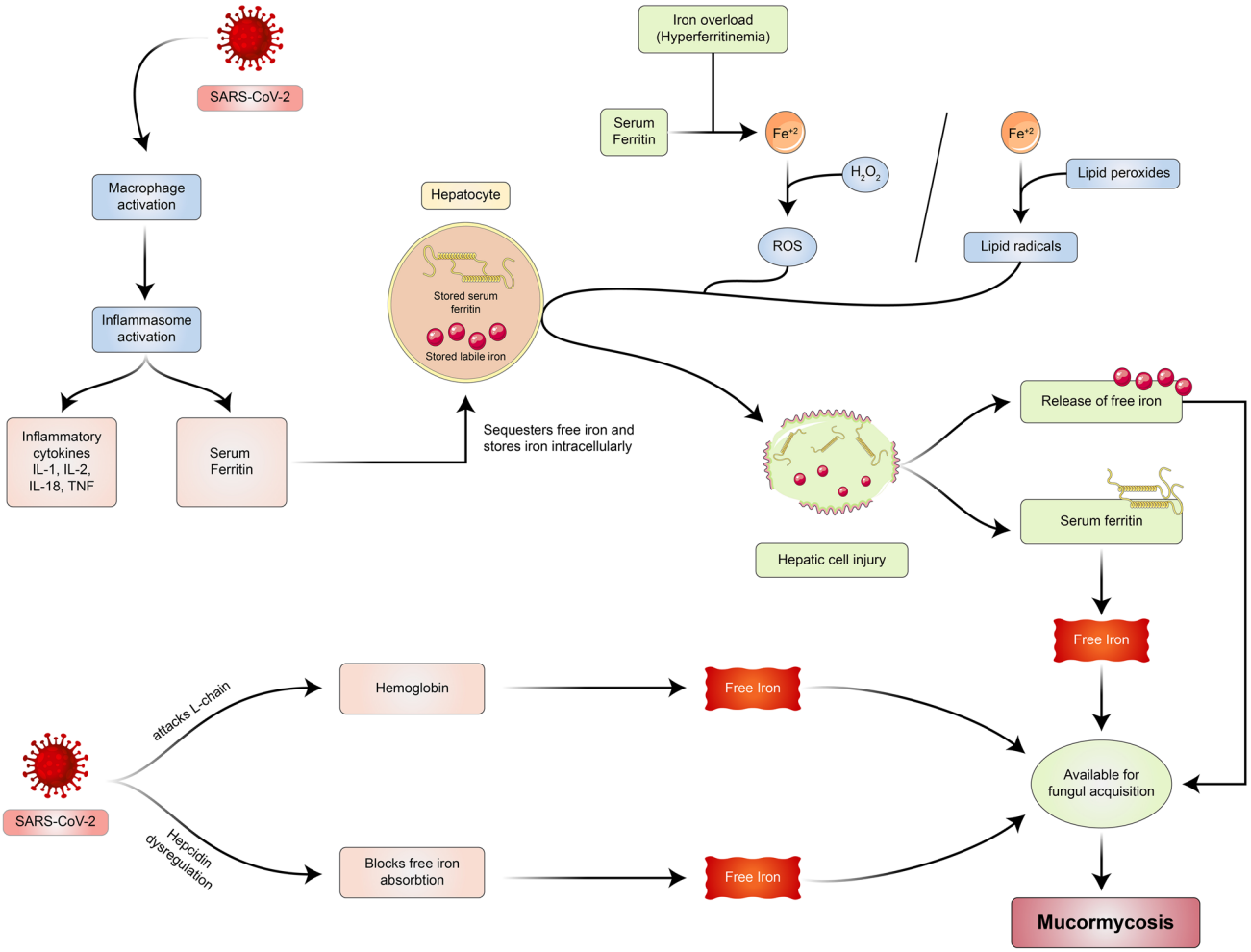

Fig. 2 Higher levels of free iron accumulation during COVID-19 infection. The SARS-CoV-2 virus displays hyperferritinemic syndrome (hyperferritinemia and hyperinflammation). The viral infection activates macrophages, which stimulates the release of elevated cytokine content and serum ferritin. Serum ferritin is advantageous to block secondary fungal infection as it sequesters free iron, resulting in iron starvation for Mucorales. During iron overload, like hyperferritinemia generated in COVID-19 infection, serum ferritin stored in hepatocyte undergoes denaturation in the lysosome, and the Fe^{2+} bound to ferritin is released. The labile Fe^{2+} reacts with hydrogen peroxide (H_2O_2) to generate highly toxic reactive oxygen species (ROS) or lipid peroxides to generate lipid radicals, which induces hepatic cell death and releases the stored labile iron and serum ferritin extracellularly. Moreover, the SARS-CoV-2 virus may attack hemoglobin or induce hepcidin dysregulation, the host's major iron homeostasis regulation hormone. All of these marks free iron availability for fungal acquisition, facilitating mucormycosis in COVID-19 patients

inflammatory and pro-inflammatory mediators aggravates the cytokine storm. It exacerbates COVID-19 induced damage to the host organs [53]. Consequently, several immunosuppressive drugs have become promising agents in treating severe COVID-19 cases, including steroids, anti-cytokine agents, mTOR (mammalian target of Rapamycin) inhibitors, and antimetabolites [54]. These immunosuppressive agents may weaken the patients' immune system, enabling secondary opportunistic infections, including mucormycosis. Besides, steroids are the main reason for drug-induced hyperglycemia [55], one of the significant risk factors for mucormycosis [56].

Moreover, the COVID-19 pathogenesis itself may trigger immune-deprived conditions by entering the immune cells for utilizing its metabolic machinery for viral replication and eliciting subsequent destruction of the immune cells [57]. The viral infection may generate complex immune dysregulation and suppress the immune defense system [58, 59]. Such immune suppression mediated by the virus itself may increase the susceptibility to secondary opportunistic infections, including *R. oryzae* associated mucormycosis.

Conclusion

Rhino-orbital-cerebral mucormycosis is emerging as a deadly secondary infection in COVID-19 that can rapidly upsurge the mortality rates and develop into another significant global concern. This aggressive, opportunistic fungal infection not only displays an overall mortality rate of 50% but also provokes other disabling side effects such as visual impairment or eye loss, which might significantly add to the crippling global debridement this pandemic has incurred on human lives.

Excessive free iron levels are accessible to be utilized by Mucorales and other potential pathogens with chances of creating secondary infection in COVID-19 patients and can lead to fibrosis through redox reaction [60]. Since free iron appears to play a significant role in encouraging fungal proliferation and growth, it is hypothesized that iron depletion or chelation therapy in COVID-19 patients might positively impact controlling this fungal infection. Additionally, iron depletion therapy might also represent a promising therapeutic approach against SARS-CoV-2 replication itself, as studies have demonstrated a positive association between free iron availability and a worse prognosis of other viral infections [61].

The aggressive mycotic ROC mucormycosis infection has a high mortality rate; however, early diagnosis and treatment might facilitate curtailing the mortality rate in COVID-19 patients to some extent. Diagnosis of black fungus is most popularly reliant on the typical clinical presentations such as blackish nasal mucous emission, sinusitis, visual impairment, swelling and pain on only one side of the face with loss of sensation, the node of the orbit, black lesions around the nasal bridge, proptosis, abnormal blood clotting and thrombosis of tissues, and headache. On endoscopic visualization, there might be appearances of dead black tissue mass around the nasal cavity that can be seen even on opening the mouth [11, 62, 63]. Based on clinical suspicion, more specified diagnosis tests such as MRI and CT scan of the nasal cavity, sinuses, or brain are performed to determine lesions' presence and extent [62]. Additionally, histopathological examination of biopsy samples and culturing of the fungal agent can be performed to detect the causative fungal agent [64].

One of the standard features in ROC mucormycosis is the accumulation of fungal debris in the oropharyngeal region that might initiate difficulty in breathing [65]. Besides, COVID-19 patients infected by the fungus may exhibit rapid respiratory function deterioration, including the build-up of excess fluid in the lungs [63]. Since COVID-19 infection also reveals similar patterns of respiratory difficulty, it might be challenging to distinguish the presence of the fungal infection within COVID-19 patients. Upon examining such symptoms, definitive tests must be performed to identify the pathogenic agent through sample culturing.

The group of COVID-19 patients who are more susceptible to mucormycosis, such as patients with diabetes (especially diabetes ketoacidosis), cancer, organ transplant, stem cell transplant, neutropenia, long-term use of steroids, hemochromatosis, skin injury [10, 11, 62, 66], and immunocompromised, must be taken under special consideration. Such comorbid conditions impair the immune defense function, making the patient more prone to getting affected by the fungal agent [63]. Besides, COVID-19 patients who are already taking prescribed broad-spectrum antibiotics or antifungal drugs to combat infections must be brought under special consideration [63], as broad-spectrum antibiotics often disrupt the beneficial microflora and increase the susceptibility of getting attacked by opportunistic infections.

COVID-19 patients with comorbid conditions that stimulate mechanisms to generate iron overload disorder, such as hemochromatosis and beta-thalassemia [67, 68], are at greater risk of getting attacked by the fungus-free iron accumulates within their body. Such patients must be kept in special monitoring to reduce any chances of getting affected by the fungus. Moreover, immunosuppressive drugs, especially steroids, must be regulated appropriately, and proper maintenance and monitoring of blood sugar levels. Patients already taking prescribed steroid medicaments for pre-occurring conditions must be taken special care of due to their weakened immune system and higher chances of getting attacked by the fungus. The appropriate doses and duration of the steroid should be ensured during the treatment and after recovery [69]. Additional steps to enhance their

immune system against this opportunistic infection must also be ensured.

Healthcare practitioners can play a vital role in reducing cases of fungal infection by encouraging the patients to practice safe health and hygiene. Since the fungus is ubiquitously suspended throughout the environment, patients who demonstrate COVID-19 symptoms, those who have recovered from covid-19, and those with compromised immune systems must be aware of the situation. Especially, COVID-19 patients with comorbid conditions that enhance susceptibility to this fungal infection must be cautioned by the healthcare practitioners to practice safe hygiene. Patients with prescribed antibiotics and steroids must also be monitored thoroughly, and the exhibition of any symptoms associated with black fungus must be adequately examined. Healthcare practitioners must be cautious in prescribing antibiotics and steroids throughout the pandemic period while following proper guidelines. Moreover, the testing facilities for the COVID-19 patients must also ensure sterility protocols as experts have suggested that RT-PCR tests that rely on cotton swabs being inserted within the nasal passage of patients might be one of the sources of the fungal infection if the process is not conducted with ensured sterility [70]. However, the association between the two infections is not well-studied, but extensive laboratory studies have to be initiated to unleash the disease pathogenesis and their correlations completely.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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