

The linkage between the second wave of COVID-19 and the severity of mucormycosis in India

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ABSTRACT

The whole world was fighting the danger of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) since 2019. The SARS-CoV-2 virus was mutating with great speed, and putting new challenges in front of the world. In India, the whole healthcare system was engaged in tackling the second wave of COVID-19 as a result of virus mutation. Additionally, a fungal co-infection, mucormycosis started to invade the COVID-19 patients. Mucormycosis is an acute infection, caused by an opportunistic fungus, mostly attacks the immunosuppressed, diabetic, and neutropenia patients. The other causes of infection include inappropriate use of immunosuppressive drugs, entry of *Mucorales* through open wounds, cancer, acquired immune deficiency syndrome, organ transplant, and malnutrition. In the recent mucormycosis outbreak in India, all the mucormycosis cases included eyesight damage, facial deformities, and even death in critical conditions. These reported mucormycosis cases in India were mostly diabetes, which were treated with immunosuppressive drugs. The mucormycosis fungus was probably invading the recovered, or near to recovery the second wave COVID-19 patients. In this review, we discussed the important risk factors responsible for the sudden outbreak of mucormycosis, and its severity linked to second wave COVID-19 patients in India.

1. INTRODUCTION

In entire India, COVID-19 cases due to double mutant severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus were jumping up in an uncontrolled manner, and the country was also imagining the fear of third COVID-19 wave. In inclusion to these calamities, India was also facing the rising cases of COVID-19 linked mysterious infection “mucormycosis” creating significantly more complications in COVID-19 patients [1–7].

In the year 2021, during the second wave of COVID-19 (SWCOVID-19), 10–100 number of the COVID-19 patients in India were getting infected with fungal co-infection mucormycosis, causing eye damage, facial deformities, blindness, and further death in severe conditions like diabetes [8–10]. News media reported the various cases of mucormycosis among the SWCOVID-19 patients from Pune, Gujarat, Ahmedabad, Madhya Pradesh, Odisha, Karnataka, Uttarakhand, Telangana, Madhya

Pradesh, and Bihar [11,12]. With this inclusion, total number of cases was rising continuously in India [13–20] (Table 1).

Mucormycosis is an acute angio-invasive infection [21–23] causing embolism and death of tissues [24,25]. In most of the cases, the infection progresses as a nosocomial infection [26–34]. Mucormycosis fungus enters inside the body through environmental routes by inhalation [35–38] and captures the broad range of immunologically compromised, and immunocompetent traumatic wound patients [39–41]. Mucormycosis is caused by a group of opportunistic mold “mucoromycetes” [42], belonging

Table 1: Rising mucormycosis cases in India during the second wave of COVID-19 diseases.

Date	Number of mucormycosis cases
May-21-2021	8,848
May-26-2021	11,717
May-28-2021	14,872
June-07-2021	28,252

Source of data [16–18,20].

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to the order “Mucorales,” subphylum mucoromycotina (formerly known as class zygomycetes) [41,43]. The reported number of genera and species of mucormycosis causing infections to humans are 11 and 27, respectively, of which *Rhizopus rhizome* or, *Mucor lichtheimia*, *Apophysomyces*, *Cunninghamella*, *Saksenaea*, *Cokeromyces*, *Actinomucor*, and *Syncephalastrum* species are usually over the globe [21,22,41,44]. The *Rhizopus* spp were predominant in most mucormycosis infections in India. Although, *Apophysomyces elegans*, *Anabaena variabilis*, and *Rhizopus homothallic* were also increasing along with atypical species like *Mucor irregularis* and *Thamnostylum lucknowense* [45,46]. Mucormycosis is categorized into cerebral, cutaneous, rhino-cerebral, gastrointestinal, pulmonary, and disseminated type based on appeared anatomic localization, and clinical symptoms which are uncommon and rare [21,41,47,48].

The causative agent of mucormycosis is omnipresent fungi predominant in dust, decaying matter which causes infrequent opportunistic communicable disease within a very short time [33]. In mucormycosis, infection macrophages and neutrophils perform an important task in the host defense process [49–52]. When their activity gets diminished, spores germinate inside the host [53]. After the entry of fungus, spore germination gets retarded by phagocytic activity of macrophages by killing the hyphae [49]. In a normal host, during the development of infection, neutrophilic cells are attracted toward hyphae by the chemotaxis process and, attaches to it, and prevents the spread of infection. In diabetic patients, neutrophils activity gets hampered, and the long-term neutropenic condition is responsible for the evolution of disease [49].

During the SWCOVID-19-linked mucormycosis (SWCOVID-19), the mortality rate of mucormycosis patients was nearly 50% [7]. In earlier reports, death percent owing to mucormycosis in India was mentioned between 28% and 52% [22,54–59]. In a computer-model-based study, 14 mucormycosis cases per 100,000 individuals in India were evaluated [59], showing the death percent 38.2 per year [58,60]. The figures provided by this model shown ubiquity of mucormycosis in India was almost 70% greater than the global data per 100,000 persons [58]. Chander *et al.* [61] mentioned the altogether mortality rate of mucormycosis can be diversified by the status of the case, kind of fungal attack, affected part of the body, and adequate antifungal treatment along with surgical intervention [61]. The important reason for the death of mucormycosis-infected patients was late diagnosis [62], and old of age patients. The involvement of the head and trunk increases the number of deaths of mucormycosis [63]. It was reported, altogether death rate can fall up to 40% with antifungal treatment, and surgical debridement [64].

In this paper, we have discussed the most possible causes of mucormycosis co-infection and its severity linked to the second wave of COVID-19 patients in India.

2. RISK FACTORS FOR MUCORMYCOSIS CO-INFECTION

Mucormycosis is an opportunistic fungal infection that is generally non-pathogenic in immunocompetent persons [65,66], except in

severe diabetes condition [41]. The danger of this infection is more in patients with diabetes mellitus, immunosuppressed [64,67–72], neutropenic condition [68,71,73], cancer, previously open wound *Mucorales* infection [73], renal failure, organ transplant, under immunosuppressive therapy, cirrhosis, acquired immune deficiency syndrome, iron overload patients, and voriconazole treatment [41,21,22,74] (Fig. 1). Some reports also mentioned infection of mucormycosis to some atypical areas of the body like: breast [75], ear [22], heart [76,77], and bone infection [78,79].

2.1. Mucormycosis and Diabetes

In the recent outbreak of mucormycosis in India among the SW-COVID-19 patients, diabetes mellitus was one of the important risk factors responsible for an increased number of cases [19,80–84]. According to the various reports, globally, among the fungal infection cases in COVID-19 recovered patients, 94% was Diabetes mellitus, and of this 71% cases was from India [5,19]. Diabetic mellitus and diabetes ketoacidosis are the frequent cause of rhino-orbital or rhino-cerebral mucormycosis [85–90], whereas the neutropenic condition of the patients is the reason for pulmonary mucormycosis [91,92]. In the Indian diabetic population pulmonary mucormycosis is the second commonest type of invasion [51,91,93], then cutaneous [22,59] and renal mucormycosis [60]. The available reports also shown, uncontrolled diabetic mellitus is the main risk factor responsible for mucormycosis infection [51,59,94–96]. These patients particularly progress into rhino-orbital mucormycosis, and rarely develop pulmonary and disseminated mucormycosis [97–99]. In a diabetic patient, fungal spores enter through the sinus, and process up to the periorbital region, face, and brain [47]. In Rhino-orbital mucormycosis infection, primary symptoms are either sinusitis or periorbital cellulitis [101], which involves trouble in eyes and face, numbness of the face, followed by conjunctival suffusion, blurry eyesight, and swelling on soft tissue [97,102,103], and blindness. Kasper *et al.* [100] reported in diabetes acidosis and non-ketoacidosis patients, there is a direct connection between high sugar concentrations with mucormycosis infection.

Various study reports have been published regarding the mechanism of establishment of mucormycosis infection in diabetes mellitus cases. In these patients, neutrophils activity gets reduced [50], and also patient becomes deficient in CD4 cells [104,105]. Low activity of cytokine and malfunction of polymorphonuclear cells (PMNC) may be linked with deficiency of CD4 cells [104,106]. In an individual with diabetes mellitus, triggering of microbial infection reduces the secretion of interleukin (IL)-1 & IL-6 by mononuclear cells and monocytes, which is linked to an inherent fault in the cells [106,107]. Although, according to other reports, in diabetes mellitus cases, glycation results in inhibition of production of IL-10, gamma interferon, and tumor necrosis factor. In these patients, increased glucose-6-phosphate level boosts the apoptosis of PMNC which results in a reduction in number, and their transfer through endothelial cell [107]. In diabetes ketoacidosis condition, acidosis of patient interrupts transferrin-ion binding-mechanism, which increases the number of unbound irons, and is responsible for the growth of fungi [108,109].

2.2. The Link between Mucormycosis Infection and SWCOVID-19

COVID-19 is a disease caused by the SARS-CoV-2 virus, showing a broad range of medical complications, which spreads from human–human by respiratory droplets [110]. SARS-CoV-2 virus infects the pulmonary tissues causing alveolar-interstitial lesion, which may be responsible for more susceptibility of COVID-19 patients to mucormycosis co-infection. In such cases, primarily portal of entry of fungus is through nasal route and lung airways [78,111].

During the SWCOVID-19, mucormycosis outbreak in India, all the cases of mucormycosis co-infection were COVID-19 recovered, or near to recovery patients. In COVID-19 disease, immune system of the patient gets weakened on account of virus replication and lung damage, furthermore uncontrolled diabetes mellitus, use of immunosuppressive drugs [80–83,112], comorbidity, and malnutrition also contribute to it (Fig. 1). Therefore, the vulnerability of mucormycosis co-infection is more in the case of COVID-19 disease [113], which is potentially responsible for further health complications, and also death in many cases [114]. It was found that among the 10%–30% of co-infections in hospitalized and critically ill COVID-19 patients, the fungus was ten times more frequent causative agent [115]. The greater risk factors for mucormycosis fungal co-infection in COVID-19 patients was owing to: use of immunosuppressive medications, lack of a diagnostic specific test for the incidence of fungal infections in COVID-19 patients [116], diabetes, hematologic malignancies, prolonged neutropenia, allogeneic hematopoietic stem cell transplantation, solid organ transplant [117], and long-term lymphopenia [113,118].

In COVID-19 disease, replication of virus triggers plenty of cytokines called “cytokine storm,” showing an inflammatory reaction, and extensive damage to the lung [112,119]. Such immunosuppressive state of immune system leads to an uncontrolled reduction in CD4+ and CD8+ cells [19,119–122], B-lymphocytes, and natural killer cells [123,124]. It was also reported that, SARS-CoV-2 infection also decreases the monocytes, eosinophils, and basophils count in patients [125,126]. Such acute lung tissue damage may be prone to secondary infections after the outset of COVID-19 disease [121,127–129].

In COVID-19 in diabetic patients, the mortality can be directly linked with diabetes mellitus. In SARS-CoV-2 infection, there is increased activity of angiotensin-converting enzyme-2-receptors present on pancreatic islet cells, as well as an excess of cytokines secretions generates insulin resistance creating hyperglycemic condition [130].

In COVID-19 patients, iron metabolism is also altered [131]. In severe COVID-19 cases, ferritin level increases, which conducts extra intracellular iron, generating reactive oxygen which damages the tissue. Because of severe infection and diabetic acidoketosis, cytokines particularly IL-6 activate ferritin production, which results in intracellular iron overload [131], and creates an acidic stage, responsible for the risk of mucormycosis [132].

2.3. Mucormycosis and Therapeutic Drug in COVID-19 Disease

During the SWCOVID-19, most of the COVID-19 patients in India were treated with steroids (Tocilizumab), antiviral drugs (Remdesivir), antiparasitic drug (Ivermectin), and antibiotics

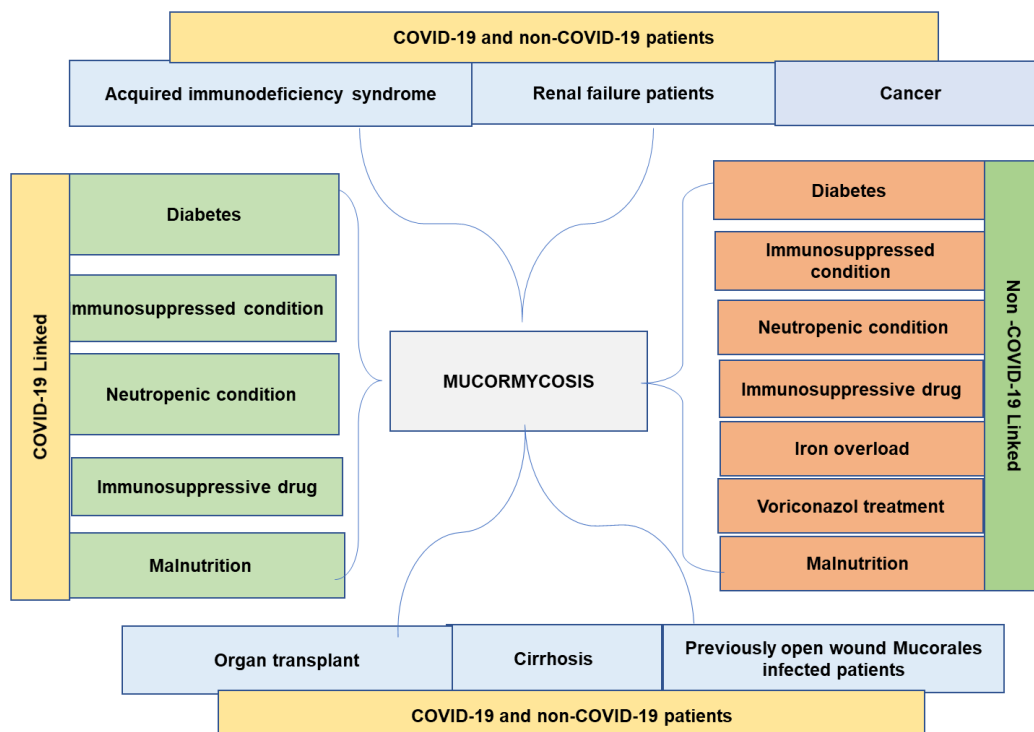


Figure 1: Important factors responsible for mucormycosis infection in COVID-19 and non-COVID-19 patients.

(Azithromycin, Doxycycline); which were also the important cause of mucormycosis [81,113,133]. The steroidal drug and antiviral drugs suppress the immune system of patients during the treatment. The steroidal drugs increase the susceptibility of patients to mucormycosis infection [134], by reducing the activity of macrophages and neutrophils [86], there upon is an important link between COVID-19 disease and mucormycosis co-infection.

Steroids were broadly used in many COVID-19 pneumonia cases, but their efficacy for this disease has been inconsistent [135]. In case of acute pneumonia, sepsis, or critical illness, the hypothalamic–pituitary–adrenal axis gets activated and gives the inflammatory reaction. Steroidal drugs suppress the hypothalamic–pituitary–adrenal axis and develop a hypercortisolism producing endogenous cortisol [136], which reduces lung damage by controlling the various inflammatory responses [135]. In COVID-19 patients, this drug prevents the damage of the lung by reducing the inflammation but increases the blood sugar in both diabetic and non-diabetic, and immunologically weak patients.

In case the high dose of steroid induces hypercortisolemia condition, which liberates corticotropin-releasing hormone and adrenocorticotrophic hormone, causes succeeding hypocortisolemic state [137]. According to one report, the overall mortality rate of mucormycosis was 50%, and this was probably due to the use of the steroidal drug to save critical COVID-19 patients. In the case of COVID-19 diseased patients, therefore appropriate steroid doses are important [114,138].

Antiviral medicines are also used to treat COVID-19 patients. Antiviral medicine like ritonavir inhibits cytochrome P450 3A4 (CYP3A4) strongly, and thereupon during the treatment, there may be chances of incidence of Adrenal insufficiency [139]. Adrenal insufficiency is linked with depleted function of natural killer cells which is important for recognizing infectious agents, and may be responsible for mucormycosis co-infection. During the treatment, sudden termination of steroidal drug which is particularly associated with ritonavir could be dangerous for intensive care unit's cases as it promotes hypocortisolemic state. Even so another blend of treatments like hydroxychloroquine, antiviral could create a hypocortisolemic state [139].

2.4. Mucormycosis and Malnutrition

Malnutrition is also one of the factors for opportunistic co-infections. Earlier work mentioned in literature suggests that patients who stay longer in an intensive care unit (ICU) develop a loss of appetite. In COVID-19, malnutrition gets provoked during the long-time hospital stay in ICU, responsible for the slow recovery of patients [140]. Therefore, nutritional deficiencies have been noticed over all the stages of COVID-19, especially in serious patients [141].

2.5. Mucormycosis and Other Risk Factors

According to a news report in late May 2021, excessive use of food supplement zinc may also be one of the factors for mucormycosis co-infection in India [142,143]. Zinc is a supplement used to boost immunity in nutrient-deficient patients. But there is no proof that zinc prevents or treats COVID-19 [144]. Further investigation is required to support this data.

3. DISCUSSION

During the SWCOVID-19 in India, COVID-19 patients were started to acquire a deadly opportunistic fungal infection called mucormycosis. The number of mucormycosis cases was increasing with great speed in 28 states of India, of which 86% were history of COVID-19, and 62.3% were history of diabetes [20], exhibiting symptoms of visual changes, nasal stuffiness, facial fullness, headache, blindness, and even death of the patients [10,80].

There were several factors that increased the extremity of mucormycosis in COVID-19 patients than non-COVID-19 patients [145–147]. The main factors responsible for this infection in near recovery and recovered COVID-19 patients were diabetes mellitus and diabetes ketoacidosis [20,80–84,148], critical illness, long-term ventilation, hospital stay [135,139], treatment with the immunosuppressive steroidal drug, an antiviral drug, and other drugs [80,112,135,139]. During the COVID-19 infection, increased viral load in patients elevates the activity of cytokines, called “cytokine storm” which comprehend the danger and projection of the disease [149]. This cytokine supplies inflammatory monocytes with the elevated synthesis of inflammatory cytokines like IL-6 [150]. This inflammation-causing cells enter into the lungs and cause lung injury which is responsible for trouble in lung function of COVID-19 cases [151]. In such COVID-19 patients, susceptibility to opportunistic fungal co-infections like mucormycosis increases.

Patients with uncontrolled diabetes, chances of mucormycosis fungal infections are high [5,20]. In case of uncontrolled diabetes, increased sugar level of patients supports the growth of fungus by at least three channels; (1) hyper glycation of iron-sequencing proteins, (2) overexpression of mammalian cell receptor (glucose regulate protein GRP78) which binds to Mucormycosis fungus, (3) evocation of poorly distinguished fault in phagocytosis [100].

During the COVID-19 disease, treatment with immunosuppressive steroidal drugs prevents lung inflammation by hampering the function of macrophages and neutrophils, but these drugs also suppress the natural immune defense mechanism of patients [85,135]. Therefore, diabetes mellitus and inappropriate dose of steroids were the most important link for the risk of mucormycosis in India [81]. During the long-time hospital stay, the condition of ventilators for adequate oxygen supply also increases the susceptibility of COVID-19 patients towards this opportunistic fungal co-infection mucormycosis (Fig. 2).

During the SWCOVID-19, the new variant was more infective [152] than the previous variants of COVID-19. Along with this severe lung damage due to overexpression of immune system, diabetic condition of the patients, use of immunosuppressive drugs (Fig. 2), hospital environment, and condition of a ventilator have increased the rise in susceptibility and mortality of mucormycosis cases in India. The other factors that may also be responsible for mucormycosis in SWCOVID-19 patients were malnutrition, excessive use of zinc supplements (further study is required).

To prevent the outbreak of mucormycosis, the Government of India issued some guidelines for screening, diagnosis, and management of mucormycosis [153]. All India Institute of Medical Science (AIIMS) doctors advised homecare patients not to take antiviral drug [154]. The Union Health Ministry and Family Welfares'

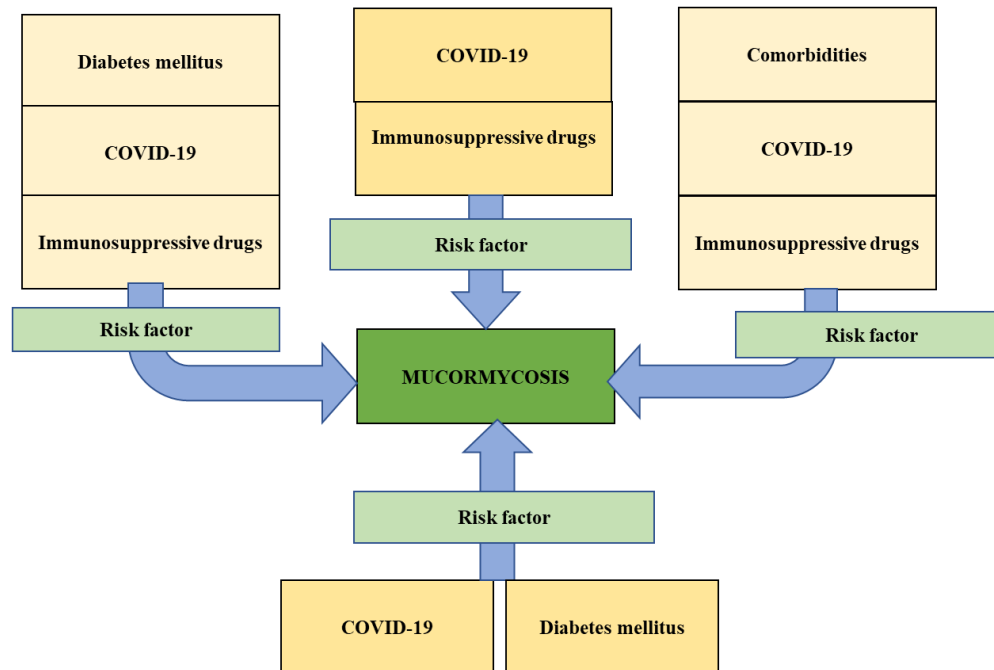


Figure 2: A risk factor in mucormycosis disease.

Directorate General of Health Services (DGHS) had issued the guidelines to stop the use of Ivermectin and doxycycline in COVID-19 patients [155], and also removed Ivermectin, azithromycin, doxycycline, zinc, favipiravir, and plasma therapy from recommendation list [156,157].

4. CONCLUSION

Mucormycosis is an opportunistic fungal infection. The rising cases of COVID-19 linked mucormycosis in many states of India may be related to one or more factors. In SWCOVID-19 disease, severity of infection was more than the earlier COVID-19 disease, which was one of the causes for opportunistic infections like mucormycosis. Secondly, the COVID-19 sufferer who had uncontrolled diabetes mellitus, hypertension, and comorbidity was more prone to mucormycosis infection due to various hyper mechanisms in patients. Thirdly, treatment with immunosuppressive steroidal drugs in critically ill COVID-19, and other COVID-19 patients was one of the reasons for mucormycosis co-infection. To prevent these complications, unnecessary use of steroidal drug should be avoided. In the case of critically ill COVID-19 patients, the right dose and duration of steroidal drug should be used. The other drugs in COVID-19 treatments also contribute to immunosuppressive condition among COVID-19 patients, and mucormycosis infection. The diabetes mellitus COVID-19 patients already suffer from lots of complications due to COVID-19 disease, and treatment with inappropriate steroidal dose and other drugs further suppresses the immune system of patients during the recovery. These were the major links for life-threatening mucormycosis infection in India. Apart from this, malnutrition in under-recovery and recovered COVID-19 patients is very common, which weakens the immune system, can also be the reason for mucormycosis co-infection.

All the above factors are linked with each other for the severity of mucormycosis in SWCOVID-19 patients than non-COVID-19 patients. AIIMS and DGHS have issued various guidelines to prevent the new SWCOVID-19 patients from the danger of mucormycosis co-infection. However, already infected and suspected mucormycosis cases can be protected by: early diagnosis of fungus, an adequate dose of the antifungal drug (Amphotericin B) and other drugs, control over the hyperglycemic condition, maintaining oxygen level of patients, and proper diet.

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6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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8. CONFLICT OF INTEREST

There is no conflict of interest.

9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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