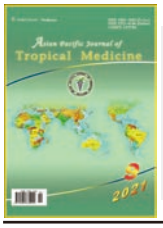

Review Article

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COVID-19-associated mucormycosis and treatments

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ABSTRACT

In the current pandemic, COVID-19 patients with predisposing factors are at an increased risk of mucormycosis, an uncommon angioinvasive infection that is caused by fungi with *Mucor* genus which is mainly found in plants and soil. Mucormycosis development in COVID-19 patient is related to various factors, such as diabetes, immunocompromise and neutropenia. Excessive use of glucocorticoids for the treatment of critically ill COVID-19 patients also leads to opportunistic infections, such as pulmonary aspergillosis. COVID-19 patients with mucormycosis have a very high mortality rate. This review describes the pathogenesis and various treatment approaches for mucormycosis in COVID-19 patients, including medicinal plants, conventional therapies, adjunct and combination therapies.

KEYWORDS: Mucormycosis; COVID-19; Immunosuppression; Pathogenesis; Treatment

1. Introduction

The spread of COVID-19 infection and the associated health issues are serious concerns for the whole world today[1,2]. In current COVID-19 pandemic, mucormycosis has been identified as one of the major opportunistic infections in critically ill COVID-19 patients. This creates an urgent need to understand the molecular mechanism of dual pathology involved in the COVID-19 patients superimposed with fungal infections of rare opportunistic variants. Facts suggest that in critically ill COVID-19 patients, mucormycosis offers an overall mortality rate of 50%, which is triggered by the concomitant use of steroids. The use of steroids to reduce the inflammation of the lungs is a good strategic treatment for COVID-19 patients, but steroids are also reported to reduce the immunity and push up blood sugar levels in both diabetics and non-diabetic patients. This

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drop in immunity may trigger the mucormycosis among critically ill COVID-19 patients. India is one of the countries that is majorly affected with the mucormycosis in critically ill COVID-19 patients. The prevalence of mucormycosis in India is approximately 0.14 cases per 1 000 population, that is 80 times the prevalence of mucormycosis in developed countries. Mucormycosis is an angio-invasive disease that is caused by fungi of the order *Mucorales* like *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella* and *Absidia*[3-5]. However, mucormycosis is an exceedingly rare infection in the general population. It is caused by the exposure to *Mucor* mould that is commonly found in soil, plants, manure, decaying fruits and vegetables[6].

It is ubiquitous and found in the soil and air and even in the nose and mucus of healthy individuals. It frequently affects the lungs, sinuses, orbit and brain. It can be life-threatening in diabetic, severely immunocompromised, cancer and HIV/AIDS patients[7,8]. Mucormycosis is one of the rare fungal infections having a high mortality rate. In addition to the ongoing pandemic crisis, the rise in the number of deadly black fungus or mucormycosis (an epidemic within the corona pandemic) cases have posed a major challenge to the healthcare workers[9,10]. The situation is further complicated due to the emergence of resistance as well as limited efficacy of currently available antifungal drugs for the treatment of this deadly infection[11,12]. Multimodal approach is essential for the successful management and treatment of this dangerous and deadly infection of mucormycosis[13]. Based on the facts over severity of mucormycosis in COVID-19 patients, this present review has been designed to explore the pathogenesis and various treatments against mucormycosis for its successful management.

2. Pathogenesis

2.1. Histology

Mucormycosis (black fungus) is caused by a class of fungi known as *Zygomycetes*[14]. Their hyphae are non-septate and branched at the right angle can easily be visible in H & E stained slides under a low-power light microscope, however, staining with Grocott-Gomori methenamine silver best shows the hyphae in invaded tissues[15]. They are broad wide with thick wall, in contrast to septate and acute angled branching in *Aspergillus* species[16]. Mucormycosis is known as *Mucor circinelloides* and aspergillosis is an uncommon fungal infection that is almost confined to immunocompromised individuals. In COVID-19 patients, the major risk factors for the occurrence of mucormycosis includes diabetes mellitus-type Ⅰ and type Ⅱ, obesity, lympho-hematopoietic malignancies, metabolic syndrome, insulin resistance, fatty liver diseases, chronic alcoholism, hypertension, neutropenia, corticosteroid therapy, allogenic bone marrow transplantation, congenital immunodeficiencies and severe combined immunodeficiency of both humoral and cell mediated type[17].

2.2. Vasculitides

Both *Zygomycetes* and *Aspergillus* cause a non-distinctive suppurative or granulomatous reaction with a predilection to cause invasion of blood vessels (vasculitis) and manifests in thrombosis, vascular necrosis and infarction, leading to severe clinical features[18,19]. Evidence suggests dissemination of *Aspergillus* (white fungus), *Candida* (yellow fungus) and *Mucor* (black fungus) in the setting of neutropenia especially in COVID-19 patients[20,21]. *Aspergillus* and *Mucor* are known to cause the vascular invasion *via* projection of the branching septate hyphae from their fruiting body (conidia)[22,23]. As these organisms gain foot hold on the tissue *via* their hyphae (hold), so they are difficult to dislodge. Similarly, other fungi like *Coccidioides immitis* and *Histoplasma capsulatum* may lead to pulmonary disease resembling that of *Mycobacterium tuberculosis* with granulomatous inflammation[24]. Surprisingly, fungi do not have a propensity for vascular invasion, and *Pneumocystis pneumonia* is not typically accompanied by vascular changes but common in immunocompromised individuals[25]. *Candida* infections are typically superficial and have Gram-positive budding cells with pseudo hyphae, while actinomycosis organism (*Actinomyces*) are typically long filamentous Gram-positive bacilli[26,27]. At times open wounds may be contaminated by *Clostridium perfringens* which are large Gram-positive rods producing gas gangrene[28]. These fungi must be excluded by histology and tissue culture in appropriate media if required[29].

2.3. Rhino-cerebral and pulmonary mucormycosis

Patients suffering from the fungal infection typically have symptoms of stuffy and bleeding nose, swelling of and pain in the eyes, drooping of eyelids, fixed and dilated pupil, ophthalmoplegia, blurred and loss of vision[30]. There could be black patches of skin around the nose. Most of the COVID-19 patients arrive late to get medical attention, so it becomes difficult to treat mucormycosis, and finally the patient suffers from loss of vision. In such condition, immediate surgery to remove the eye is recommended, in order to stop the spreading of infection further into the brain[31]. In a current study, retrobulbar injection of amphotericin B is recommended as an adjunctive treatment modality to prevent exenteration[15]. Reports suggest strain of COVID-19 appears to be virulent, and blood sugars soaring is remarkably higher in young individuals that are suffering from the mucormycosis[32]. As *Zygomycetes*

mainly prevails in the nasal cavity or sinuses, which is also the site favoured by RNA coronaviruses, so they may interact with each other which may facilitate the fungi to spread directly to the brain, orbit and other head and neck structures[33]. Evidence suggests observation of fulminant invasive rhino cerebral mucormycosis in young diabetic patients with ketoacidosis[34]. Even diffuse military type of pulmonary involvement or cavitary lesions are also detected under radiological examination[35]. Similarly, invasive aspergillosis is also reported to be present exclusively in the immunosuppressed patients, which may cause necrotising pneumonia with possibility of dissemination to the brain[36]. As *Aspergillus* resides in crypts of tonsils in normal person, they may migrate to bronchi causing allergic bronchopulmonary aspergillosis with type Ⅰ hypersensitivity and IgE antibodies against *Aspergillus* and eosinophilia in blood smear in some asthmatic patients[37]. It is observed that unhygienic oral practices in the children and adolescents may exacerbate such cases even in non-immunocompromised individuals. *Aspergilloma* (fungal ball) may develop in ectatic bronchi or lung cyst or post-tubercular cavities predisposing to infection and haemoptysis[38]. Similar *Aspergillus* infection and bacterial suppuration are also reported in a new-born baby involving the ethmoidal sinus with bony sequestrum formation[39]. In certain geographical areas, a small number of endemic fungal infections are also observed in the immunocompetent individuals. For example, *Histoplasma capsulatum* (a dimorphic fungus) is highly prevalent in the Mississippi river valley, that often presents as flu like illness and manifests in granulomatous lesion like tuberculosis[40]. Similar tropism has been observed with *Coccidioides immitis* and *Blastomyces dermatitidis* in the southern U.S[41].

3. Potential of medicinal plants–based drugs against mucormycosis

Essential oils from the different parts of the aromatic medicinal plants have been reported to exhibit moderate to excellent anti-fungal activity. For example, the essential oil from the *Ocimum gratissimum* plant exhibits good fungicidal activity against all *Candida* species[42–45]. Oil of *Melaleuca alternifolia* commonly known as tea tree oil exerts synergistic effect in combination with nystatin, fluconazole, amphotericin B against different species of *Candida*[46]. A study by Chhonker *et al.* reported the potential of chitosan-amphotericin-B combination to treat the fungal keratitis[47]. However, various other classes of phytochemicals such as flavonoids, phenolic compounds, coumarins, xanthones, lignans, triterpenes, saponins and alkaloids isolated from various medicinal plants have also been reported to exhibit antifungal activity[48].

4. Conventional therapy against mucormycosis

Efficacious therapeutic algorithms and the use of different adjunctive and supportive therapies based on the co-morbid ailments or chronic disease status are necessary to improve the treatment outcome and survival rate in patients. In the second wave of COVID-19, the severity and the incidence of this deadly fungal infection is surprising and it poses a challenge to the health community. The antifungal treatment alone is ineffective due to vascular thrombosis and an extensive ischemic necrosis barrier, preventing antifungal agents' entry in adequate concentrations. Therefore, radical debridement of infected and necrotic tissue with drainage of infected paranasal sinuses should be performed as soon as possible to minimize the fungal load in the tissue. In addition, sinus lavage by amphotericin B during functional endoscopic sinus surgery with extensive debridement of involved sinuses can be associated with better results[15]. Health workers in the task force are instructed to take utmost importance to control the blood sugar level, reduce steroid intake and discontinue any therapy involving immunomodulatory drugs, especially those recovered from or infected with COVID-19. Unfortunately, few reports have made strong prescriptions or therapeutic regimens for this infection. ESCMID/ECMM guidelines recommend standard protocols for the effective management of mucormycosis[49]. Treatment using steroids in patients with COVID-19 along with other comorbidities like haematological malignancies, and diabetes creates a perfect environment for this fungal growth, and it leads to exponential increase in the risk of mucormycosis. Patients who are post COVID-19 with uncontrolled diabetes are the main targets for mucormycosis, and the rapid correction of metabolic abnormalities is mandatory[49].

Clinical evidence reports that using *Sodium bicarbonate* with insulin is associated with better therapeutic outcome for its ability to prevent the *Mucorales* from invading the host tissue. It has been reported that delaying the therapy (with amphotericin B) for this fungal infection for 5 days results in two-fold increase in mortality with 82% compared to 48% who started treatment immediately in case of the haematological malignancy patients. So, there is a correlation between the importance of early diagnosis and treatment pattern in COVID-19 recovered patients (that are prone to mucormycosis)[50].

Corticosteroids and other immunosuppressive drugs should be titrated properly and replaced by other effective pharmacological agents, if possible, to manage the condition of the patient. *In–vitro* studies report that mucormycosis is resistant to most of the antifungal agents including voriconazole, fluconazole and itraconazole. Surprisingly, there is no validated minimum inhibitory concentration (MIC) breakpoints presented for any of the antifungal agents for the management of mucormycosis. Optimal dose for antifungal agents including triazoles such as posaconazole and isavuconazole is yet

to be validated, and requires definitive, prospective, and controlled clinical judgments[50].

4.1. Surgical treatment of the mucormycosis

Facts suggests using the aggressive surgical debridement approach in the treatment of rhinocerebral mucormycosis. Traditionally the external or transantral approach has been considered as classical approach. Endoscopic sinus surgery (ESS) is an effective method for radical resection. A study reported use of ESS in the treatment of nine rhinocerebral mucormycosis patients, of which the six patients underwent only ESS, whereas the remaining three patients underwent combined treatment of ESS with transantral procedure. Study revealed that the treatment of rhinocerebral mucormycosis with ESS alone or in combination with traditional surgical procedures offers the benefit of lower operative morbidity and higher operative accuracy[51].

4.2. Polyenes: Amphotericin B (AMB)

AMB is the primary drug of choice and the most effective drug reported so far against 524 clinical isolates of *Mucorales* except for some species of *Cuminghamela* and *Apophysomyces*[49]. Lipid formulations of AMB like liposomal AMB (LAMB) and AMB lipid complex have better therapeutic index than conventional AMB. These are recommended by ESCMID/ECMM in the dose range of 5 mg/kg/day to 10 mg/kg/day as a first line therapy for mucormycosis especially in case of CNS infection, but this recommendation has been revisited based on French mycosis clinical trial report[52]. A prospective, uncontrolled French mycosis study reported that 12 weeks treatment of patients using 10 mg/kg/day of LAMB in combination with surgery seems to be beneficial with a good response rate (45%)[52,53]. However, study also revealed that 40% of patients with high dose of LAMB exhibits renal impairment with notable increase in serum creatinine level after the therapy, whereas some patients reported electrolyte imbalance. These results alarmed the health workers and warranted for further clinical trials and dictation of dose reduction. Relatively high AMB MIC value supports the use of high dose of AMB to achieve clearance of fungus from tissues and the efficacy of LAMB was also found to be dose-dependant[54]. There seems to be a better correlation between AMB and treatment outcomes in patients with mucormycosis.

4.3. Triazoles: Posaconazole

Posaconazole acts by depleting ergosterol from the fungal cell. Triazoles plays a significant role in the management of difficult-to-treat mucormycosis. Antifungal activity of these drugs varies from one species to another. Serum concentrations higher than 4 000 mg/mL are required for suppressing the growth of *Rhizopus* species with an MIC of 2 mg/mL, as it is the most common agent causing mucormycosis. It is available as oral suspension with a dose range of 200 mg and should be administered 3 to 4 times daily. This drug should be administered for several months if needed. It should be taken with food rich in fat to enhance its bioavailability, but this administration has its own drawbacks based on the condition of critically ill patients of COVID-19 and many therapeutic failures are reported due to drug absorption problems. In order to overcome its pharmacokinetic (PK) disadvantages and to enhance the bioavailability, several formulation scientists and pharmaceutical companies formulated different dosage forms including tablets and Ⅳ injections[55]. Tablet dosage form appears to be better with optimal PK and pharmacodynamics parameters. ECIL-6 guidelines recommend the use of posconazole as salvage or maintenance therapy while ESCMID/ECMM recommends its use as first line therapy[54,56].

This drug is considered as the first line only in the clinical cases where AMB is absolutely contraindicated while some clinical studies suggested using isovucanzole in this situation. It is also used as a salvage therapy especially in patients unresponsive or intolerant to LAMB[57,58]. As per the clinical case reports, posoconazole oral suspension as salvage therapy was well tolerated with only minimal gastrointestinal side effects and the response rate was 61% and 70%, respectively[56]. Therapeutic drug monitoring is suggested for this drug therapy because of its fluctuating PK and PD parameters. In rare clinical cases Ⅳ formulation of posaconazole with beta cyclodextrin has been administered. Controversies still exist for combinational therapy of posaconazole and caspofungin as they are advised as salvage treatment by ECIL-6[56,57].

4.4. Isovuconazole

Isovuconazole is a recently approved triazole with wide spectrum of antifungal activity and plays a noticeable role against mucorales[56]. It is considered as an alternative to AMB and is used as first line treatment in mucormycosis based on an open label clinical trial report[57]. This drug should be administered for several months if needed. Effects of isovuconazole were compared with the conventional AMB and fortunately the results were similar and encouraging. But the trial has the limitation of small sample size and external control matching. This drug is available as oral and Ⅳ formulations and has many PK and PD advantages like linear kinetics, no need of therapeutic drug monitoring, less drug interactions, less toxicity and excellent oral bioavailability[55]. None of the adverse effects like hepatotoxicity, nephrotoxicity, QT prolongation or ocular toxicity has been reported for the isovuconazole. Several clinical reports have shown the dose-dependant effect of this drug as in the

case of posaconazole and this drug can be used as a salvage therapy in heavily immunocompromised mucormycosis patients including those cases with failure of posaconazole therapy[55,58]. The major concern about this drug is that some recent clinical reports concluded the breakthrough of mucormycosis and other fungal attacks in patients receiving this drug as prophylaxis or for treatment. There is also a report of cross tolerance where patients exposed to prolonged prophylaxis with posaconazole develop breakthrough mucormycosis and are resistant to isovuconazole and all this information is stated in the regulatory studies of this drug. Hence these alarming reports should be considered while treating the patients, especially immunocompromised patients[58].

4.5. New antifungal agents

4.5.1. VT1161–investigational drug

It is a fungal CYP51 inhibitor and possesses prominent action against different mucorales. *In–vivo* preclinical data supports the therapeutic activity of VT1161 as it increases the survival rate of neutropenic mice with mucormycosis and additional studies are in the limelight to confirm the efficacy of this molecule and this is considered as an asset for the therapeutic management of mucormycosis[59].

4.5.2. Fosmanogepix; APX001A (formerly E1210)

This drug targets Gwt1, a step in the glycosylphosphatidyl inositol post translational modification pathway of surface proteins in the fungi, which is proved to be effective in protecting the immunosuppressed mice from *Rhizopus* infection and it is under clinical trial phase for approval process[60].

4.5.3. Hemofungin

This is also a novel agent that inhibits the *in–vitro* growth of several fungi including *Rhizopus* and it inhibits the final step of heme biosynthesis[61,62].

4.6. Adjunct and combinational therapy

4.6.1. Deferasirox

Preclinical reports showed supporting evidence about the use of deferasirox. It is an iron chelator. A prospective, randomised, clinical study in patients reported higher mortality rate after treatment with deferasirox (DFX). Hence ECIL-6 and SCMID/ECMM recommended not to use DFX in patients with mucormycosis[60]. But many recent clinical trial reports showed that DFX is beneficial as an adjunct therapy in patient with diabetes. Combination of LAMB with DFX is reported to be synergistically improved 80% survival rate when compared with monotherapy and placebo. Several exploratory studies about the adjunct DFX therapy for mucormycosis are still ongoing[51,63].

4.6.2. Granulocyte macrophage colony stimulating factor (GMCSF) and interferon

In–vitro assays and preclinical data support the use of GMCSF and INF in the management of mucormycosis because these molecules possess the ability to enhance the immune response. But there is no clinical evidence about their therapeutic strategies[64].

4.6.3. Echinocandins

This drug targets the enzyme expressed by Mucorales especially *Rhizopus oryzae*. Enhanced exposure of beta glycans on the fungal surface results in immune stimulation is also considered as another mechanism for therapeutic action. Combination therapy with other antifungal agents has been reviewed as a means to improve the treatment outcomes of mucormycosis in COVID-19 recovered patients.

However, most clinical outcomes data evaluating combination therapy are from case series and case reports, and the majority of comparative data derives from *in–vitro* models and animal studies[65]. The high morbidity and mortality of COVID-19 associated mucormycosis, demands for combination therapy for suppression of severity of disease. This treatment approach would improve the patient's condition and provide better management of infection. Based on the dosage formulation and safety profile, facts suggests some drug combinations as most appropriate regimens for mucormycosis treatment, such as: echinocandins and polyenes; echinocandins and AMB; Caspofungin and amphotericin B lipid complex; Anidulafungi and liposomal amphotericin B; posaconazole and AMB; posaconazole and DFX, hyperbaric oxygen and AMB, GMCSF and lipid formulations of amphotericin B; and Interferon γ and lipid formulations of amphotericin B[66].

5. Comorbidity associated mucormycosis

Diabetes mellitus was an independent risk factor for rhino-orbital-cerebral mucormycosis in a meta-analysis of 600 series with 851 cases. The most common species isolated was *Rhizopus* species, with an overall mortality of 46%. A case of COVID-19 with rhino-orbital mucormycosis coinfection associated with ketoacidosis was reported in a patient with recent-onset diabetes mellitus[67]. Pathogenic mechanisms involved in fungal aggressiveness include decreased phagocytic activity, accessible amounts of iron due to the displacement of protons by transferrin in diabetic ketoacidosis and fungal heme oxygenase, which promotes iron absorption for its metabolism[68]. In a case of severe COVID-19 associated with

fungal coinfection, cell counts revealed that there was a progressive increase in white blood cell count and neutrophils while lymphocytes progressively decreased[69,70].

It is hypothesised that SARS-CoV-2 infection may affect $CD4^+$ and $CD8^+$ T-cells, which are highly involved in the pathological process of COVID-19 infection[71,72]. It has been shown that in severe COVID-19 cases, there is a reduction in the absolute number of lymphocytes and T-cells, which is associated with the worst outcomes. Mucorales-specific T-cells ($CD4^+$ and $CD8^+$) produce cytokines such as interleukin (IL)-4, IL-10, IL-17 and interferon-gamma (IFN-γ) that damage the fungal hyphae[73,74]. Such specific T-cells were seen only in patients affected by invasive mucormycosis, and they concluded that they could be a useful surrogate diagnostic marker of an invasive fungal disease[75]. It might be speculated that lymphopenia could increase the risk of developing invasive mucormycosis, while the recovery of lymphocyte count could improve the adaptive immune system and induce the production of Mucorales-specific T-cells, which might have a role in controlling the invasive infection[76]. Alterations in cell-mediated immunity, such as chemotaxis, phagocytosis, and cytokine secretion were shown in type Ⅰ and type Ⅱ diabetes[77].

Individuals with diabetes have been described to have alterations in innate immune system components. Natural killer cell activity is reduced in individuals with diabetes, and more pro-inflammatory M1 macrophages are present[78]. Furthermore, T-cell activity is skewed. Disease severity in patients is due to not only the viral infection but also the host response. Elevated glucose levels may also suppress the antiviral response. In the context of COVID-19, severe disease progression is described by a delay in IFN-γ response with a prolonged hyperinflammatory state and lower CD4 and CD8 cell numbers[79]. Regardless of the involvement of the endothelial cells, the initial delay in IFN-γ response together with the hyperinflammatory response in individuals with diabetes may exacerbate the 'cytokine storm' and increase COVID-19 severity[80]. Increased vascular lesions, endothelial inflammation and vasoconstriction associated with endothelial dysfunction put individuals with diabetes at a greater risk for endothelitis in several organs. Change of vascular tone towards more vasoconstrictions may lead to subsequent organ ischaemia, tissue oedema and a procoagulant state[81]. This may explain the thromboembolic episodes observed in these cases. Finally, dysregulated immune cell populations and activity observed in individuals with diabetes play a critical role in aggravating the severity[82]. The mean duration between the diagnosis of COVID-19 and the development of symptoms of mucormycosis was (15.6±9.6) days. Control of hyperglycaemia, early treatment with liposomal amphotericin B and surgery are essential for the successful management of mucormycosis[67]. Thus, the use of glucocorticoids in mild COVID-19 cases (without hypoxaemia) or the utilisation of higher doses of glucocorticoids should be avoided[83]. Further, in the absence of a clear benefit, drugs targeting immune pathways such as tocilizumab should be discouraged. For the successful management of mucormycosis, a high index of clinical suspicion, low threshold for diagnosis in patients with risk factors, neuroimaging, and specific diagnostic tests with a coordinated effort from a multidisciplinary team including ophthalmology, otorhinolaryngology, infectious diseases, neurosurgery, critical care, microbiology and pathology department are crucial. A delay of even 6 days in initiating treatment doubles the 30-day mortality from 35% to 66%[67]. Patients with mucormycosis and their responses to antifungal agents are hosts and sites dependant. This is very crucial in this pandemic because many patients have multiple morbidities especially diabetes, immunocompromised, haematological malignancies and stem cell transplant recipients. Hence host dependant variation in drug treatment success should always be considered in the prognosis and management of patients with mucormycosis. To be efficacious in therapeutic intervention, several clinical trials and pharmacovigilance are the need for the successful management of mucormycosis[84].

6. Conclusions

The present review was intended to explore the pathogenesis and various treatment approaches against mucormycosis in COVID-19 patients. The current review highlights the histology of mucormycosis that including the pathogenesis of vasculitis, rhino-cerebral and pulmonary mucormycosis and relation between SARS and COVID-19. This review describes various therapeutic approaches against mucormycosis, including medicinal plants-based drugs, conventional therapy, and adjunct and combinational therapies to avoid mucormycosis associated complication in COVID-19 critically ill patients. This study concludes and suggests that further clinical trials and pharmacovigilance studies are needed for the successful management of mucormycosis in COVID-19 patients using therapeutic intervention.

Conflicts of interest statement

The authors declare no conflict of interest.

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Authors' contributions

V.S., N.K.F., S.F., H.K.D., D.U.M., M.S., R.B.N., S.C., K.V.S. and S.A.K. developed the date curation and theoretical formalism. V.S., N.K.F., S.F., Y.S.W., U.K., K.S., R.M. and V.K.S. contributed writing review and editing. V.S., N.K.F. and S.F. authors contributed to the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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