PERSPECTIVE IN MEDICINAL CHEMISTRY

Fungal Infections in COVID-19-Positive Patients: A Lack of Optimal Treatment Options

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1. INTRODUCTION

Starting a few months ago, the coronavirus disease-2019 (COVID-19) has become pandemic and already resulted in more than 25 million confirmed cases worldwide, including over 850,000 associated deaths (https://covid19.who.int/). Older age, hypertension, chronic obstructive pulmonary disease, diabetes and cardiovascular disease are the main risk factors presented for severity and mortality in COVID-19 [1, 2]. Patients with severe COVID-19 infection requiring intensive care may also be challenged to battle against other coexisting infectious agents, such as other respiratory viruses (e.g. influenza), gram-positive and gram-negative bacteria and fungi (both yeasts and filamentous fungi). As an obvious consequence, secondary infections and/or co-infections in the context of COVID-19 patients are important factors affecting hospitalization time, illness severity and mortality [3, 4]. Corroborating this statement, we have witnessed increasing reports on the co-occurrence of respiratory viruses, like influenza epidemics/pandemics, and secondary invasive fungal infections, resulting in poor patient outcome and, consequently, high mortality rates. Therefore, this critical reality demands an urgency for special focus on different aspects of this new disease [5-7].

It has been established that the activation of antiviral immunity in the host tissue of infected patients (in COVID-19-positive patients, lungs are the main affected organs) can provide a desirable environment for the establishment, growth and development of different classes of microorganisms. For instance, a substantial increase of fungal infections (e.g. candidiasis, aspergillosis, cryptococcosis, pneumocystosis, histoplasmosis) has been detected in individuals with active infection caused by the human immunodeficiency virus (HIV), severe flu and COVID-19 [6-8].

Until the present moment, the treatment guidelines for potential co-infections in COVID-19-positive patients follow the original recommendations used to treat co-infections in patients with severe flu. However, this is an empirical inference, since the clinical entities able to cause co-infections are expected to be the same for both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections [5-8]. An early study on COVID-19 infections in China reported that all patients from a Wuhan hospital received empirical antimicrobial treatment, while 93% received antiviral therapy [8]. In another case series from Wuhan experience, it was reported that 76%, 71% and 15% of COVID-19 patients have been also administered with antiviral, antibacterial and antifungal agents, respectively [9]. Since most of the hospitalized COVID-19 patients are under severe medication care, like intubation/mechanical ventilation, they are potentially vulnerable for acquiring hospital infections. Aligned to this assertion, broad-spectrum antibiotics were prescribed in 75% of COVID-19-infected patients who were admitted to intensive care units (ICU) [10].

Relevantly, the incidence of opportunistic fungal infections is dramatically increased in COVID-19 patients with predisposing factors (e.g., diabetes, mechanical ventilation and cytokine storm). On the other hand, due to the complicated medical situations of the COVID-19 patients and the inappropriate collecting of the clinical specimens, the vast majority of fungal infections in this group of patients is misidentified. In fact, researchers around the world have been faced with many challenges regarding both the identification and the diagnosis of fungal infections. Therefore, early diagnosis and appropriate antifungal strategies to treat fungal infections have attracted particular attention to combat these relevant (but yet neglected) illness on a global scale. Moreover, the treatment of fungal infection costs thousands of dollars to both public and private sectors annually, which can be translated into a considerable impact on the economy of the health care systems across the globe. With all this information in mind, the present perspective has focused on summarizing the fungal infections reported in COVID-19-positive patients, with special mention to the current challenges for appropriate antifungal treatment in these particular individuals.

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2. METRIC ANALYSYS

A simple search in the Web of Science (www.webofknowledge.com) and PubMed (http://pubmed.ncbi.nlm.nih.gov/) databases revealed 54 published papers focusing on fungal infections in COVID-19-positive patients. Thirty nine (72.2%) of them described case reports and the isolation/identification of the fungal agents, while 15 (27.8%) were review/opinion papers (Fig. **1A**). The stratification of the publications along the time on this specific knowledge field revealed a rise trend in the number of papers from May to July 2020 compared with March (the month in which the first related paper on this field was published) (Fig. **1B**). Taking into consideration the fungi identified in COVID-19-infected patients, up to now, the following genera were described: *Aspergillus*, *Candida*, *Coccidioides*, *Cryptococcus*, *Mucor*, *Pneumocystis* and *Saccharomyces* (Fig. **1C**). Interestingly, the fungi most commonly associated with COVID-19 infection have been those that commonly colonize the respiratory tract and oropharyngeal mucous membrane, including *Aspergillus* and *Candida*, although many others have been already reported (Fig. **2**).

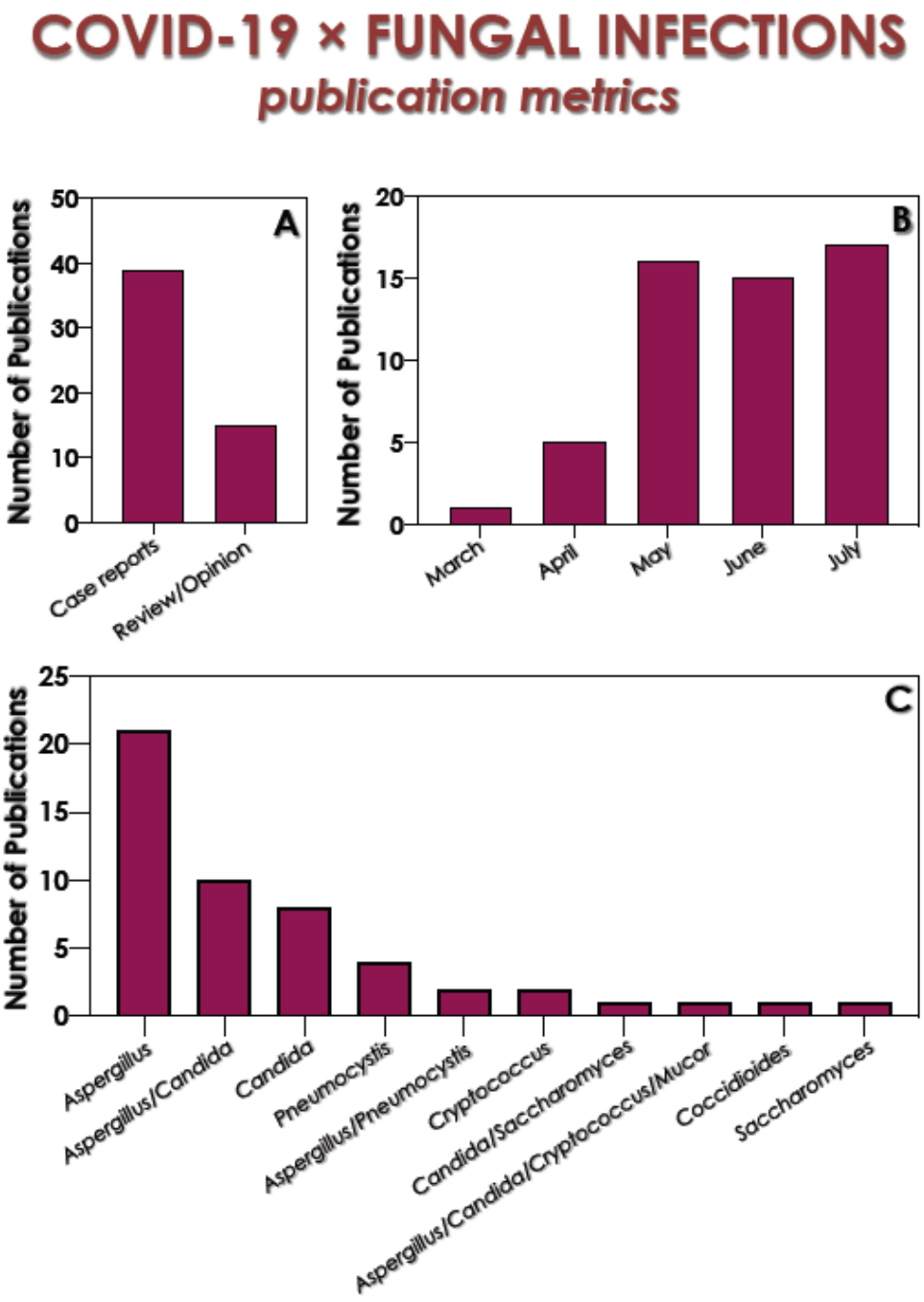

Fig. (1). Metric study showing the number of papers published in 2020 reporting fungal infection in COVID-19-positive patients, taking into account the type of publication (**A**), number of papers along the time (**B**) and the fungal genera responsible for causing co-infections (**C**). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

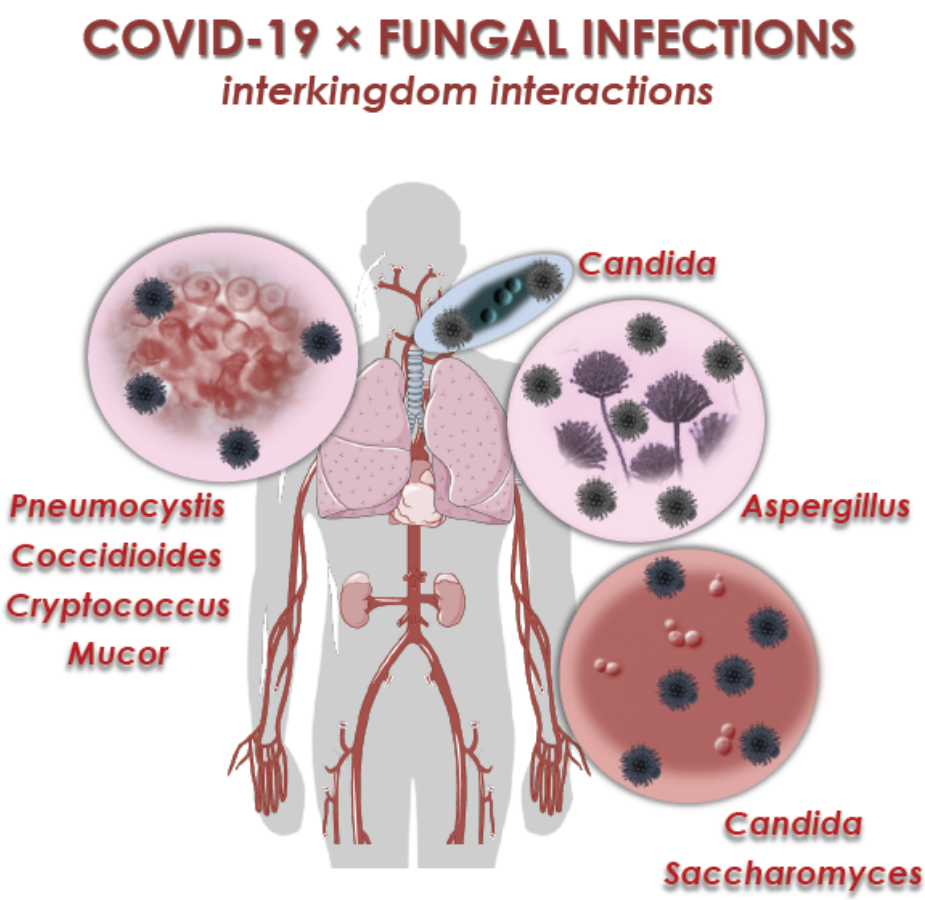

Fig. (2). Fungal genera co-infecting patients with COVID-19 described in the available literature on July 31th, 2020. COVID-19 positive patients developed pulmonary infections caused by *Aspergillus*, *Pneumocystis*, *Coccidioides*, *Cryptococcus* and *Mucor*, while oropharyngeal infections were associated with *Candida* and disseminated infections are related to entry of *Candida* and *Saccharomyces* into the bloodstream. Note that the black spiked circles represent the SARS-CoV-2. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

3. COVID-19 × *ASPERGILLUS*

Like severe flu, COVID-19 progression leads to the manifestation of acute respiratory distress syndrome (ARDS), which predisposes patients to secondary pulmonary aspergillosis. This is an infection caused by *Aspergillus*, a worldwide distributed filamentous fungus. *Aspergillus* spores are typically present in the environment; so, they can easily enter the airway system and, subsequently, they reach the human lung tissue and/or paranasal sinuses by breathing. *Aspergillus* causes a wide range of infection with various clinical manifestations ranging from localized to disseminated diseases. For instance, invasive aspergillosis typically affects severely immunocompromised patients occasionally as a result of organ transplant, cancer treatment (due to the chemotherapy and/or radiotherapy), neutropenia and long-term treatment with corticosteroids. In addition, allergic forms of aspergillosis (e.g., allergic bronchopulmonary aspergillosis - ABPA) are implicated in asthma exacerbation and bronchitis in individuals with hyperactive immune responses as well as in cystic fibrosis patients [11, 12]. Invasive aspergillosis caused by *Aspergillus* species (e.g., *A. fumigatus*, *A. niger*, *A. flavus*, *A. terreus*) carries an overall 30 to 95% mortality rate even if it is early diagnosed and despite antifungal treatment approaches [13].

Some studies from China reported high rates of aspergillosis among COVID-19 patients [9, 14, 15]. A retrospective study from an ICU in Wuhan showed the isolation of *A. flavus* and *A. fumigatus* from respiratory tract secretions in two out of seven (28.6%) patients with hospital acquired pneumonia [16]. In another retrospective study conducted in two hospitals of Wuhan regarding 85 fatal cases of COVID-19, fungal culture from sputum obtained from 9 patients were reported positive in 33.3% of cases with 8 (9.4%), 3 (3.5%) and 2 (2.4%) patients receiving voriconazole, fluconazole and caspofungin [15]. However, in all the studies from China fungal infections were poorly defined and for such reason it appears difficult to make any inference.

European countries such as France, Germany, Belgium and The Netherlands have recently reported high rates of chronic pulmonary aspergillosis among COVID-19-positive patients with a prevalence index of 20-35% [17-26]. A case report from Brazil, which diagnosed a patient infected with *A. penicillioides postmortem,* pointed out the importance of considering invasive pulmonary aspergillosis in patients with underlying severe COVID-19 [27]. An observational study from Pakistan showed that *Aspergillus* spp. were isolated from tracheal aspirates of 39.1% COVID-19-positive patients and, in this fraction, 21.7%

were diagnosed with aspergillosis and 17.4% were only considered colonized [28]. In this scenario, the most commonly used drugs are the new triazoles voriconazole and isavuconazole followed by less common cases treated with liposomal amphotericin B and caspofungin [29]. These findings and other previous reports highlight that many cases may remain undiagnosed, since standard culture methods exhibit limited sensitivity. Consequently, the appropriate therapy is not achieved on time and clinical failure outcomes are usually reported [30]. The Table **1** summarizes studies describing antifungal failure in the treatment of COVID-19 patients co-infected with *Aspergillus* species.

Table 1. Antifungal therapy used to treat *Aspergillus* infection in COVID-19 patients.

Country	Number of patients	Fungal species	Antifungal therapy	Outcome	References
Germany	5	*A. fumigatus*	Two patients received voriconazole, one patient used isavuconazole and two patients received caspofungin followed by voriconazole	4 Deaths 1 Alive	[17]
France	2	*A. fumigatus*	One patient received voriconazole and the other one caspofungin	2 Deaths	[18]
Belgium	6	*A. fumigatus*	Four patients received voriconazole and two others received voriconazole plus isavuconazole	3 Deaths 3 Alives	[19]
France	1	*A. fumigatus*	Voriconazole	Death	[22]
France	1	*A. flavus*	Voriconazole switched to isavuconazole	Death	[23]
Netherlands	6	*A. fumigatus*	Five patients received voriconazole plus anidulafungin and one patient was treated with liposomal amphotericin B	4 Deaths 2 Alives	[24]
Italy	1	*A. fumigatus*	Liposomal amphotericin B	Death	[25]
Germany	2	*A. fumigatus*	Liposomal amphotericin B	2 Deaths	[26]

4. COVID-19 × *CANDIDA*

Fungal infections caused by yeasts can also occur in patients with ARDS, including COVID-19, as a result of impaired immune system functions. Invasive candidiasis is an important health care-associated fungal infection responsible for high mortality rates and it is caused by several opportunistic species belonging to the *Candida* genus, with *Candida albicans* as the most common species [31]. Data from a hospital in Spain pointed out a rising incidence of invasive candidiasis in COVID-19-positive patients, with an associated mortality of 40% [32]. Invasive candidiasis by *C. albicans* was similarly reported in COVID-19 patients requiring critical care in United Kingdom hospitals [3]. A case report from Austria described a secondary catheter-related candidiasis caused by *C. glabrata* successfully treated with caspofungin for 14 days [33]. Likewise, in another published work, *Candida* spp. was one of the most frequently fungi identified in the bloodstream of patients using central venous catheters during COVID-19 pandemic episodes in New York City, USA [34].

According to recent studies, the majority of *Candida* species recovered from COVID-19 patients were isolated from the oropharynx. Oropharyngeal candidiasis is a localized mucous membrane infection, which is characterized by invasion and damage of oral epithelial cells [35]. *Candida* spp. and other yeasts were isolated from the respiratory tract in 21.4% of positive cases of co-infection during the first pandemic of COVID-19 in two hospitals in the United Kingdom [3]. A retrospective study in Italy evaluated the respiratory specimens of hospitalized COVID-19 patients in ICU. The results showed that almost 52% of cultures were positive for bacteria and fungi (*C. albicans* and *C. glabrata*) [36]. Additionally, in a study conducted in Iran, the authors reported that *C. albicans* was the most frequent fungus followed by other species isolated from oral lesion of COVID-19-positive patients suffering from oropharyngeal candidiasis. Interestingly, those *Candida* isolates were susceptible to all tested antifungal drugs [37].

5. COVID-19 × *SACCHAROMYCES*

Invasive infection by *Saccharomyces cerevisiae* was reported in two COVID-19 patients hospitalized in ICU after receiving prophylactic supplementation containing *Saccharomyces* [38]. Initially, both patients were immediately treated with anidulafungin; however, after conclusive identification of species and antifungal performing susceptibility testing, the treatment was changed to fluconazole [34]. First suspected as candidiasis, Amorim dos Santos and co-workers [39] reported a patient with secondary mucosal lesions caused by *S. cerevisiae* resulting from the treatments for COVID-19 or due to the deterioration of the host immune system. The patient received a combination treatment including intravenous fluconazole (for 10 days), oral nystatin (for 30 days) treatment, chlorhexidine digluconate (0.12%) mouth rinses and daily prescription of 1% hydrogen peroxide.

6. COVID-19 × *PNEUMOCYSTIS*

Pneumocystis pneumonia, one of the most common associated opportunistic fungal infections in acquired immunodeficiency syndrome (AIDS) patients, has long been associated with other immunodeficiency states as well [40]. Because COVID-19 and *Pneumocystis* pneumonia may present common clinical features, this fungal infection is often undiagnosed [40]. A case report from the USA described a patient with COVID-19 and pneumonia due to *Pneumocystis* [41]. Surprisingly, the patient did not have any known immunodeficiency or any classical risk factors for the development of *Pneumocystis* pneumonia, which resulted in a successful treatment with trimethoprim-sulfamethoxazole and an effective extubating on day 7 of hospital stay. In a case reported by Mang and co-workers [42], *Pneumocystis* pneumonia was diagnosed in a German patient after the presence of mild reticular changes visualized by a chest tomography. *Pneumocystis jirovecii* was confirmed in the bronchoalveolar lavage fluid and the patient was treated with intravenous trimethoprim-sulfamethoxazole (20 mg/kg/day of trimethoprim) together with 50 mg of prednisone (a corticoid drug) daily to prevent adverse immune reactions [42].

7. COVID-19 × OTHER CLINICALLY RELEVANT FUNGI

A rare case report in the USA described a 48-year-old Hispanic male presenting both COVID-19 and chronic pulmonary coccidioidomycosis [43]. The authors revealed that the symptoms of both diseases are extraordinarily similar and include fever, dry cough, dyspnea, myalgia and headache. In addition, the authors believed that probably the person contracted pulmonary coccidioidomycosis and subsequently developed COVID-19. In this case, the patient was discharged home without hospitalization.

Zhu and co-workers [4] described a retrospective study in which 94.2% COVID-19 patients were co-infected with one or more different respiratory microbial pathogens. Besides frequent cases of *Aspergillus* and *Candida*, six cases of *Mucor* and one case of *Cryptococcus* were detected in COVID-19 infected patients. In that report, fungal infection occurred in 29.5% of total co-infected cases [4].

8. ANTIFUNGAL THERAPY CHALLENGES IN COVID-19 INFECTED PATIENTS

Beyond the difficulty to treat critically ill patients with one dangerous infection, like COVID-19 (for which in fact no effective drugs are available until now), two potentially deadly infections are even more challenging for the clinicians. In the COVID-19 infection perspective, this scenario is aggravated if the co-infection is caused by fungi, since the antifungal armamentarium is substantially limited, which results in threatening drug interactions, high toxicity and serious and severe side effects, such as kidney or liver injury [44].

Reports of COVID-19 highlight that the viral severe infection alone can cause injury to multiple organs (e.g., liver, kidney and heart). Such safety concerns became even more problematic in the context of multiple infections. Notably, the situation will be more troublesome when combining critical life-threatening COVID-19 patients and fungal infections, especially caused by multidrug-resistant strains. Novel resistance patterns have been documented in several emerging fungal pathogens, rendering the available antifungal drugs unsafe to treat these infections, culminating in a classical therapeutic failure. Antifungal resistance can be developed with prolonged clinical exposure to previously active new triazoles (e.g., posaconazole, voriconazole and isavuconazole) or echinocandins (e.g., caspofungin, anidulafungin and micafungin), resulting in therapy failures. This phenomenon has been described in the literature and it can arise in patients who receive antifungal drugs for long periods [45, 46].

Another point that cannot be overlooked are possible drug-drug interactions during treatment. Many different drugs are currently under investigation or empirically used for COVID-19 therapy. The drugs tocilizumab, an interleukin (IL)-6 receptor blocker, and glucocorticoids, which are commonly used in the suppression of strong and harmful inflammatory processes, stand out in many studies. However, it is known that an over-suppression of the immune system can favor the appearance of potential opportunistic fungal infections. In this context, some studies suggest careful considerations in the administration of tocilizumab in patients with COVID-19, since the disease is sometimes aggravated after its usage, thus resulting in complex pneumonia cases [47] or candidemia episodes [48-50]. Similarly, the use of other immunomodulatory drugs, such as anakinra (recombinant IL-1Ra) and janus kinase (JAK) inhibitors, currently undergoing trials for COVID-19, may also predispose patients to pulmonary aspergillosis [51].

The failure of antifungal therapeutics can be directly linked to an inappropriate sampling of the specimen, the shortage of standard equipment for microbiological examinations, the lack of early detection of fungal elements in infected tissue and the expert professionals to precisely identify the fungal agent (many clinicians disregard fungal infections). Unhappily, this realistic panorama could generate a critical impact on the rise in the number of COVID-19-positive patients that will succumb due to fungal infections.

CONCLUSION

The scientific community has an immediate focus on developing antivirals and vaccines for the treatment and prevention of COVID-19. However, this new emerging serious disease puts many patients at risk for opportunistic microbial infections, including fungal ones. This fact highlights the importance of the continued commitment to developing novel promising effective (and safe) antifungal drugs to combat invasive aspergillosis and other resistant fungal infections. In order to better improve pa-

tient outcomes, experts also point to the important principle of early pathogen identification for the proper management of antifungal treatments [29]. The selection of the best drug regimen, dose, route of administration and therapy duration are not only important to treatment success, but also to overcome the drug resistance in the hospital environment.

There is emerging evidence that patients with COVID-19 are at high risk for fungal co-infection, and these cases highlight the importance of being vigilant about opportunistic fungal pathogens commonly isolated from both hospital and environment. Future recommendations for expanding knowledge as well as the appropriate intervention stewardship of fungal infections in COVID-19-positive patients urgently require the consideration in clinical settings to promote effective reduction of fungal infections as well as robust surveillance at high-risk hosts during the pandemic.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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