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Importance of Balanced Attention Toward Coronavirus Disease 2019 and Neglected Tropical Diseases

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Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has been spreading since 2019, causing a worldwide pandemic. Amid the COVID-19 pandemic, tuberculosis, AIDS, and malaria have adversely affected the quality of life of patients and killed millions of people. In addition, COVID-19 continues to impede the delivery of health services, including those for the control of neglected tropical diseases (NTDs). Furthermore, NTDs have been reported as possible co-pathogens among patients infected with COVID-19. However, studies regarding parasitic co-infection among these patients have been limited. This review aimed to explore and describe the cases and reports of parasitic infections in the backdrop of COVID-19 to provide comprehensive knowledge regarding this aspect. We reviewed seven cases of patients who had parasitic co-infection and tested positive for COVID-19, and summarized the literature on the importance of controlling parasitic diseases. In addition, we identified recommendations for the control of parasitic diseases under possible difficulties, such as declining funding for parasitic diseases in 2020. This review highlights the growing burden of NTDs under COVID-19 that may be caused by the deficiency of healthcare infrastructure and human resources as the main reasons. Clinicians should remain vigilant for possible co-infections with parasites in COVID-19 patients, while policymakers are urged to reinforce a balanced and long-term health strategy that addresses both NTDs and COVID-19.

Key Words: Neglected diseases, COVID-19, parasites, diagnostic errors

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has been spreading since 2019, causing a worldwide pandemic.[1,2] Its main clinical manifestations are respiratory symptoms, including cough, dyspnea, sore throat, and fever.[3] Severe COVID-19 may cause extrapulmonary organ dysfunction, pneumonia, hypoxic respiratory failure, and death.[4] It can be transmitted by breathing, coughing, sneezing, and simple conversations via respiratory droplets.

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Many existing endemic diseases, such as tuberculosis, AIDS, and parasitic diseases, still pose a global health burden and remain prevalent, especially in tropical and temperate countries. According to the World Health Organization (WHO), the three most important infectious diseases prior to COVID-19 are tuberculosis, AIDS, and malaria.[5] They adversely affect the quality of life of patients, and continue to kill millions of people even during the COVID-19 pandemic.[6-8] Furthermore, neglected tropical diseases (NTDs), such as soil-transmitted helminthiasis, filariasis, protozoiasis, leishmaniasis, trypanosomiasis, schistosomiasis, trachoma, and dengue fever, have been reported as possible co-pathogens among patients infected with COVID-19.[9-11]

Among possible COVID-19 co-infectious diseases, parasitic infections must be carefully monitored, not only because they are difficult to detect and diagnose when COVID-19 co-infection occurs but also because they could decrease the efficacy of COVID-19 vaccines by activating immunomodulatory activities that hamper the efficacy of several vaccines.[12] This can induce treatment confusion and increase disease severity and morbidity.[13-15]

NTDs are predominantly found in low- and middle-income countries; in Africa alone, NTDs cause approximately 200000 deaths per year due to the lack of proper treatment.[16,17] The COVID-19 pandemic has threatened the control of malaria and NTDs with daily life mass disruptions, including economic recessions, lockdowns, and civil unrest.[18-20] Consequently, poor people who typically experience difficulty in accessing the healthcare system are at an increased risk of being further neglected as healthcare systems have been overburdened, and resources in health systems frequently have to be diverted to deal with the escalating outbreak.[21] Public health systems with limited resources face challenges in managing COVID-19 cases.[22] With the burden of funding COVID-19 control and using managerial resources for eradicating the pandemic, healthcare systems have become compromised by overloading control measures.[23]

As an example of overloading control measures, a recent survey conducted by the WHO showed that COVID-19 continues to impede the delivery of health services, including those for the management of NTDs in 44% of the 135 countries that responded to the survey request.[23] According to the survey results, large-scale preventive chemotherapy campaign for NTD disruptions appeared in 60% of the countries. Among other activities, such as support for self-care, rehabilitation, and psychosocial services for patients with chronic NTDs, 52% of the countries reported a disruption by the pandemic. Furthermore, another 52% reported a retardation in community-based interventions, such as community awareness and health education campaigns for NTDs. At least three-fourths of the countries surveyed had repurposed NTD-associated staff to COVID-19 activities. Of this percentage, 10% of countries confirmed that all NTD-associated staff were redirected to support work pertaining to the pandemic. Due to such interferences, access to primary care for routine case management and the possibility of hospitalization among patients with severe malaria and NTDs have been drastically reduced.[24] Moreover, supply chains providing commodities, such as medicines, bed nets, rapid diagnostic kits, and pesticides, to be distributed for the control of malaria for other parasitic infectious diseases have been at risk of movement restrictions since the outbreak of COVID-19.[25]

Since the pandemic, public spending on health has decreased, which is mostly driven by the economic growth and expansion of overall public spending, which have been hampered considerably due to the pandemic.[26] In a recent study, a national-level respondent in Nigeria noted the concern that the economic damage of the pandemic could exacerbate domestic budget constraints and the donors' eagerness for funding non-urgent global health needs.[21] The UK declared cuts to official development assistance, and as a part of this decision, withdrew support to NTD programs.[27] According to another national-level survey conducted by 291 key public, private, and philanthropic R&D organizations worldwide, R&D funding for NTDs dropped by 4% in 2020 compared to that in 2019, and clinical development funding for NTDs decreased by US $124 million in 2020, representing a drop of 10% from that in 2019.[28] This was primarily due to the difficulties in conducting trials during lockdowns and travel restrictions.

As the healthcare system becomes overloaded, more loopholes appear in patient management. Furthermore, the clinical presentations of malaria and some NTDs strongly overlap with that of COVID-19, which poses an additional challenge for differential diagnosis and treatment. These facts raise concerns pertaining to the case studies that represent the features of patients who experienced the co-occurrence of malaria and NTDs with COVID-19.

However, studies on the association of COVID-19 and parasitic co-infection are limited. Hence, we summarized cases and reports on "parasitic infection" and "COVID-19" to provide more comprehensive knowledge regarding their relationship.

NTDs and malaria represent a crucial issue regarding global health priorities. Disruption and delays are affecting the delivery of services to populations requiring treatment and care for NTDs and malaria as nations continue to combat the COVID-19 pandemic.[6,9,11] The longer the disruptions, the higher the possibilities of NTDs spreading in high-transmission areas, with a risk of undoing decades of progress earned via the rigorous scale-up of programs that aim to prevent, control, and eliminate NTDs.[16,21] In this context, we also reviewed reports of healthcare systems and policy environments related to NTDs and malaria in Africa by focusing on the changes caused by COVID-19.

CLINICAL CASES OF COVID-19 WITH PARASITIC CO-INFECTIONS

In terms of clinical outcomes, the impact of COVID-19 on NTDs is overwhelming as the prognosis of COVID-19 can be more severe in people experiencing chronic NTD manifestations.[9,12,14] Furthermore, the situation similarly applies to malaria-infected patients.[25,26,29] Abdoli reported that simultaneous parasitic infections can increase the morbidity and mortality of COVID-19 patients by inhibiting efficient immune responses to SARS-CoV-2 in the early stages of infection.[14] These infections can also inhibit immune responses and reduce vaccine efficacy by triggering type 2 responses of host immunity; they can also suppress pro-inflammatory activities.[30] Helminths induce regulatory T-cell development and IL-10 secretion, which inhibit pro-inflammatory cytokine release.[31] Furthermore, systemic effects on the modulation of host immune responses remain even after helminths are eradicated due to the modified host microbiome.[32]

According to other reports on protozoan co-infection cases, latent pathogen infections, such as *Toxoplasma gondii*, increase the mortality and morbidity of patients with COVID-19 by causing immune dysfunctions, such as CD8 T-cell exhaustion.[33,34]

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The common clinical symptoms of COVID-19 are rigors, chills, cough, fever, diarrhea, fatigue, and abdominal pain. Its common laboratory features are increased liver enzymes and lymphopenia. However, these features are not distinguishable from some NTDs, malaria, and other infectious diseases. Hence, confusion may occur during diagnosis and treatments. Consequently, delayed treatment due to misdiagnosis can lead to serious outcomes if patients do not receive appropriate follow-up.

THREE CASES OF MISDIAGNOSIS

In Portugal, a 47-year-old male was admitted to the emergency department due to his 5-day history of diarrhea, infrequent dry cough, diaphoresis, and high fever (Table 1). His blood test showed that he had mild thrombocytopenia and anemia but no other signs of kidney or liver dysfunction. Polymerase chain reaction (PCR) test revealed that the patient was COVID-19 positive. Consequently, he was admitted to a COVID-19 ward. However, the patient remained febrile, and his overall condition was still poor. Therefore, he was further examined with various diagnostic tests based on the patient's epidemiologic data and symptoms. His rapid diagnostic test also indicated that he was positive for malaria parasite; furthermore, *Plasmodium falciparum* trophozoites were identified in his blood smear. After diagnosis, he received a combination treatment of antimalarial drugs, and each symptom was completely resolved.[35]

In Venezuela, a 69-year-old male had symptoms of diarrhea, high fever, cough, and loss of taste and smell. PCR test showed that the patient tested positive for SARS-CoV-2, and his chest X-ray revealed a diffuse interstitial alveolar pattern, which is commonly detected in patients with COVID-19. Therefore, the patient received COVID-19 treatment for 10 days. However, his condition worsened, manifesting profuse sweating and chills followed by fever. His blood smear examination and enzyme-linked immunosorbent assay revealed that he had *P. falciparum*. The patient was then treated for malaria, and his condition improved considerably; he was completely cured after several days of the new treatment.[36]

In Iran, a 29-month-old boy with a 2-month history of fever was admitted to a hospital. His PCR test indicated positive results for COVID-19. The patient also had pleural effusion in the lower left lung. He was moved to another healthcare center and promptly received treatments for COVID-19. However, laboratory tests indicated that he had liver dysfunction, hypertriglyceridemia, and pancytopenia, and other tests were performed to rule out differential diagnosis after 6 days of hospitalization. Subsequently, *Leishmania donovani* was found in his bone marrow aspirates, and his antiglobulin test was positive. Following this, the patient was subjected to a secondary diagnosis for visceral leishmaniasis and a new treatment program.[37]

In these cases, the patients could have recovered from their illnesses by undergoing further rapid tests based on epidemiological information. They could still be at risk if they did not undergo proper follow-up for unresolved symptoms.

TWO CASES OF POOR OUTCOMES OF MISDIAGNOSIS

In Ethiopia, an 18-year-old male had a 2-week history of fever with chills, rigors, abdominal pain, and frequent loose stool. His rt-PCR test showed a positive result for SARS-CoV-2. The patient was then transferred to a COVID-19 treatment center. During examination following admission, no hemoparasite was detected in the blood smear. Consequently, the patient received treatment for severe COVID-19; however, his condition deteriorated, and he experienced bleeding and progres-

Table 1. Clinical Cases of Parasitic Infections among Patients with COVID-19

Patient information	Co-infected parasites	Description	Reference
In Portugal, a 47-year-old male	*Plasmodium falciparum*	5-day history of diarrhea (>5 episodes daily), worsening malaise, high fever, diaphoresis, and occasional dry cough	35
In Venezuela, a 69-year-old male	*P. falciparum*	High fever, cough, loss of taste and smell, diarrhea, and diffuse interstitial alveolar pattern predominantly in the lower lobes of both lung fields and the middle right lobe	36
In Iran, a 29-month-old boy	*Leishmania donovani*	2-month history of fever and pleural effusion plus positive findings in the lower left lobe of the lung on a computed tomography scan	37
In Ethiopia, an 18-year-old male	*L. donovani*	2-week history of recurrent high-grade fever with chills and rigors associated with extreme fatigue, loss of appetite, and significant weight loss	38
In India, a 32-year-old female	*Plasmodium vivax*	Abdominal pain, headache and blurring of vision for 10 days, breathing difficulty for 7 days, and fever with chills for 3 days	39
In America, a 68-year-old male	*Strongyloides stercoralis*	8-day history of chills, myalgia, headache, cough, nausea, and worsening dyspnea	41
In Italy, a 59-year-old female	*S. stercoralis*	Malaise, nausea, vomiting, and fever lasting about a week, and bilateral basal interstitial pneumonia appearing on chest X-ray	42

sive liver disorder. After presenting with a worsening condition, he underwent a leishmanial serologic rapid diagnostic test and tested positive for visceral leishmaniasis. However, at the time of diagnosis, equipment and treatment choice for visceral leishmaniasis were insufficient for the patient who was already severely deteriorating. Eventually, after 10 days of hospitalization, the patient died of septic complications and hemorrhage.[38]

In another study, a pregnant Indian female was initially diagnosed with COVID-19 and had symptoms of abdominal pain, headache, blurring of vision, and fever with chills. The patient remained hospitalized for 13 days and was treated for her malaria and COVID-19; however, her fetus died as a consequence of the late diagnosis of malaria.[39] In these cases, the patient could have survived, and abortion would not have occurred if they had been diagnosed with the exact disease earlier and treated timely rather than undergoing a time-consuming treatment for COVID-19.

TWO CASES OF STRONGYLOIDIASIS AFTER IMMUNOSUPPRESSANT TREATMENT

Immunosuppressive therapy, a well-known option for patients with severe COVID-19, can increase the risk of parasitic infections, such as *T. gondii* and *Strongyloides stercoralis*.[40] Therefore, patients with COVID-19 who are at a high risk of parasitic co-infection must be screened and treated rapidly and accurately.

In America, a 68-year-old male presenting with headache, cough, nausea, chills, and worsening dyspnea was referred to a medical institute. SARS-CoV-2 was detected via a nasopharyngeal swab by using the Cepheid Xpert Xpress SARS-CoV-2 assay. Five days after being transferred to the medicine unit, his symptoms deteriorated, and hypoxemic respiratory failure occurred. Thereafter, tocilizumab, which is an anti-IL-6 antibody, and a series of corticosteroids were administered to hamper the possibility of COVID-19-associated cytokine syndrome. However, on hospital day 18, the patient had fever again (38.8°C), and his condition worsened. While other measures were taken to monitor the patient's unstable condition, larvae with the same features as Strongyloides species were found on the sputum culture. Ivermectin treatment was immediately provided, and adjunctive combinational therapy was given. In the ensuing days, the patient developed confusion with high fever and an increased immune cell count; however, fever and hypotension eventually resolved with a normal immune cell count after 5 weeks of treatment courses.[41]

In Italy, a 59-year-old female experienced vomiting, malaise, nausea, and fever for approximately 7 days. Since the patient tested positive for COVID-19 as revealed by her PCR test, she was treated with a corticoid to prevent the possible outcome of overheated inflammation. However, she reported severe hypoxia and developed respiratory performance failure. Soon, she received another immunosuppressive medicine (tocilizumab). On day 25 of hospitalization, the patient reported abdominal pain and itching, and her eosinophil level was abnormally high. Due to these manifestations, stool examination was conducted, and the rhabditiform larvae of *S. stercoralis* were found. Consequently, she received a 4-day treatment with ivermectin, which is the most commonly used drug for *Strongyloides* species infection, and her status substantially improved.[42]

If *S. stercoralis* activities were dysregulated, numerous invasive larvae can penetrate the gut, cycle through the lungs, and re-enter the intestine, leading to *Strongyloides* hyperinfection syndrome (SHS).[43] Untreated SHS is associated with a high fatality rate, and this syndrome in COVID-19-related death cases may be misdiagnosed particularly because these diseases often share similar manifestations and complications.[44] In a review, >80% of more than 133 patients with this syndrome received corticosteroids.[44] In cases of immunosuppression, strongyloidiasis spread accelerates the fatality rates by up to 70%–100%.[45] Given these high fatality rates, screening should be performed while doctors administer immune suppression therapies to patients who may be at a risk of exposure to *Strongyloides*; if a diagnostic test is unavailable, treatment with ivermectin should be considered a preventive action against endemic strongyloidiasis.[46,47]

We observed cases of co-infection between NTDs that have highlighted the dangers of misdiagnosis during the COVID-19 pandemic. To investigate the reasons behind misdiagnosis and determine the potential impact of COVID-19, we conducted country-level searches for articles related to COVID-19 and NTDs. According to related studies,[48-54] COVID-19 has significantly impacted healthcare human resources and infrastructure in many countries, including Portugal, Venezuela, Iran, Ethiopia, India, America, and Italy. These impacts may have led to shortages of medical human resources for the accurate diagnosis and care of patients with COVID-19.[55,56] Additionally, the excessive demand for critical care capacity could lead to a deficiency of core hospital facilities, which is linked to a decrease in proper healthcare services for timely treatment.[57] Based on these studies, we can assume that cases of co-infection were strongly affected by the impacts of COVID-19 in each of their respective countries, and even in other countries where co-infection could occur.

WORLD EFFORTS AND CHALLENGES TO CONTROL NTDS

With serious cases that caused confusion due to the co-occurrence of NTDs with COVID-19, concerns have been raised regarding new strategies and methods to manage the situation.

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To confirm the increasing burden of NTDs resulting from the COVID-19 pandemic, we conducted a trend analysis using the Global Health Observatory (GHO) database.[58] Among the various categories in the database, we identified the most relevant variables: the reported number of people requiring interventions against NTDs and the estimated number of malaria cases, which might reflect the impact of COVID-19 on NTDs in Africa, where NTDs and malaria are most prevalent. Fig. 1 illustrates the trends of the number of NTDs and malaria cases in the latest 4 years around outbreak of COVID-19. Malaria increased by 15.5 million cases (7.28%) in 2020 compared to 2019 (Fig. 1A), and there was an increase of 5.8 million cases (1.01%) of NTDs in 2021 compared to 2020 (Fig. 1B). From the figure, it can be inferred that that COVID-19 has resulted in a higher burden on the control of NTDs and malaria. Consistent with this result, Hogan, et al.[59] reported that malaria cases will increase by up to 36% in low- and middle-income countries over the next 5 years compared with those in the absence of COVID-19.

This growing burden of global parasitic diseases in the COVID-19 pandemic demands new techniques, such as rapid diagnosis, vaccines, surveillance programs, and new treatments. In a study on NTD programs, monitoring tools were necessary to conduct NTD activities during the COVID-19 pandemic.[20] The study suggested a supervision checklist for COVID-19 and NTDs, personal protective equipment tracker, and in-process activity monitoring and reporting as key tools. The checklist includes questions on field preparation, crowd control monitoring, logistics, face mask availability and use, appropriate training space availability, and compliance with COVID-19 mitigation measures in affected countries. This essential method could help prevent systematic confusion caused by the simultaneous onset of multiple diseases, thereby decreasing misdiagnosis and shortening treatment time. Diagnostic equipment should also be developed to respond to various simultaneous infections rapidly.

However, new developments and studies on NTDs are fewer than those on other diseases, such as HIV/AIDS and tuberculosis.[60] The spread of COVID-19 has interrupted financial buoyancy to control NTDs.[61] Approximately 0.6% of global healthcare funding is distributed for the control of NTDs.[62] This scarcity of investment is one of the major hindrances in treatments against NTDs. Furthermore, clinical development funding for NTDs decreased by US $124 million in 2020, which corresponded to a drop of 10% from that in 2019.[28] Such dips in funding have occurred primarily because of the difficulties in conducting trials during lockdowns and travel restrictions.[25] The financial resources for NTD plummeted in 2020 (6% decrease from 2019) because of the adverse impact of COVID-19 worldwide, and most of these diseases are neglected by global funding agencies.[63] Funds for malaria have also been diminishing since 2020, when the coronavirus began to spread.[64] In addition to malaria, other parasitic infectious diseases mostly occur in poor communities and do not give sufficient returns to the pharmaceutical industry.[63] Therefore, multiple non-profit organizations, including philanthropic foundations, multilateral organizations, and governments, should collaborate to raise funds for improving treatments and implementing disease eradication measures.[26]

The WHO's new road map for NTDs 2021–2030 is a turning point in the fight against NTDs. It provides us with a clear route forward and the opportunities to effectively control and eliminate these debilitating diseases.[65] How NTDs perpetuate long-term cycles of suffering and poverty should be noted. Treating the top five NTDs costs less than $0.50 per person per year and can produce a huge return on investments.[66] A study estimated that every dollar invested in NTD control and elimination can be produced between $27 and $42 in economic benefits.[67]; another study estimated that tackling NTDs could restore approximately $600 billion in lost economic productivity by

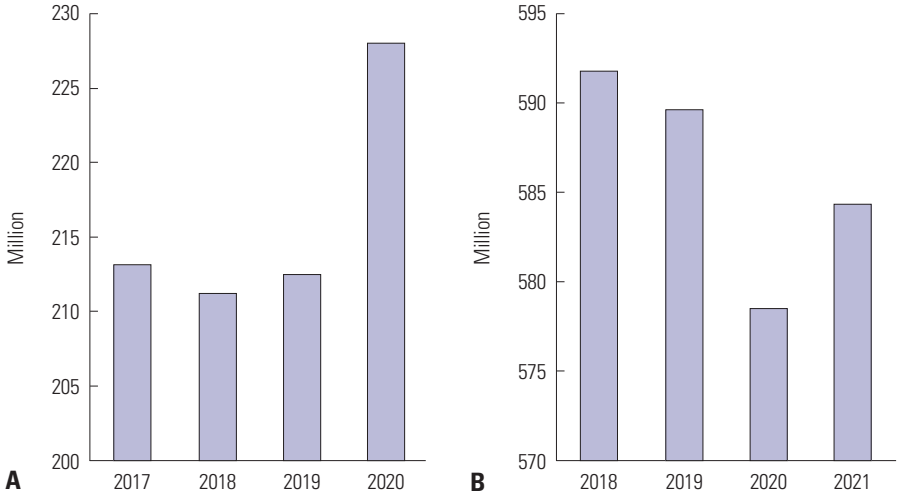

Fig. 1. Cases of (A) malaria and (B) neglected tropical diseases in Africa during the COVID-19 pandemic. Data was obtained from the Global Health Observatory (https://www.who.int/data/gho/data) and the variables were the "estimated number of malaria cases" and the "reported number of people requiring interventions against neglected tropical diseases."

2030.[68] The road map is designed to integrate approaches and actions toward multiple diseases within the national health systems. It also provides chances to assess, evaluate, and adjust programmatic actions as needed over the next decade by setting clear targets and milestones. Its four overarching global targets for 2030 are to reduce the number of people requiring treatment for NTDs by 90%, eliminate at least one NTD in at least 100 countries, eradicate two diseases (dracunculiasis and yaws), and reduce the disability-adjusted life years related to NTDs by 75%.[65]

CONCLUSION

This review highlighted the importance of simultaneously identifying other infections that co-occur with COVID-19 but may otherwise be neglected as the focus has shifted to the COVID-19 pandemic.

We summarized several cases of parasitic co-infections with COVID-19. The reviewed cases were possibly misdiagnosed during the initial examination due to their symptoms, which are similar to those of COVID-19. The diagnosis of some patients was delayed considerably, and they were in critical condition with poor outcomes, while others survived due to continuous examination and treatment efforts. These cases illustrate the importance of devoting more efforts to the diagnosis, management, and treatment of COVID-19 and co-occurring parasitic infections.

In addition, we found that healthcare infrastructure and human resource deficiencies could be the common features for the impact of COVID-19 on the growing burden of NTD control. The growing burden caused by increased cases of NTDs was also found in the GHO database. To address these challenges, efforts are required not only for the controlling program of the diseases but also for fundamental changes in healthcare infrastructure and human resource systems. This transformation might require a long period of cooperation between each government and global health aid organizations.

The new NTD road map proposed by the WHO will help ensure that the global health community is engaged in a mission to eliminate NTDs and raise the funding required to control diseases. Investment in NTDs is not only essential for those directly affected by such diseases but also for others as one of the most cost-effective investments in public health treatment.

Policy makers must know and recognize the importance of controlling not only COVID-19 but also the endemic infectious diseases prevalent in many countries. They should develop and support programs that can improve the capabilities of diagnostic equipment, preventive measures, treatment technologies, and epidemiological investigations beyond short-term achievements.

While efforts devoted to ending the COVID-19 pandemic remain the top priority at this point, support and attention should be modified to establish and reinforce systems for simultaneously controlling malaria, NTDs, and COVID-19.

AUTHOR CONTRIBUTIONS

Conceptualization: Tai-Soon Yong. Data curation: Ju Yeong Kim. Formal analysis: Singeun Oh. Funding acquisition: Tai-Soon Yong. Investigation: Ju Yeong Kim. Methodology: Ju Yeong Kim. Project administration: Tai-Soon Yong. Resources: Tai-Soon Yong. Software: Singeun Oh. Supervision: Tai-Soon Yong. Validation: Moonsoo Yoon. Visualization: Singeun Oh. Writing—original draft: Ju Yeong Kim. Writing—review & editing: Tai-Soon Yong. Approval of final manuscript: all authors.

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