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Understanding and implementing alternative solutions to address the COVID-19 pandemic in the sense of public health emergencies

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Abstract. **The Coronavirus disease (COVID-19) caused by the novel SARS-CoV-2 coronavirus has spread from China and quickly transmitted to most other countries around the world. The World Health Organization announced COVID-19 as a pandemic that is spreading steadily and soon in most states. Coronavirus genomic characterization showed that it most closely resembled another bat-origin beta-coronavirus. Coronavirus has the largest genome of viruses that have RNA. Spike (S) glycoprotein is present in the virus and is responsible for virus entry into the host cell. COVID-19 can spread through the droplet, direct contact, and aerosol transmission in humans. It can remain in the environment and exists on plastic and steel for the longest time, making it a dangerous and contagious disease that can kill other individuals. The virus has an incubation time of 2 to 14 days. Confirmed cases of COVID-19 have evolved exponentially in the world. Possible preventive steps for disease control include more mask use, hand sanitization, and social distancing. There is no antiviral therapy and only symptomatic care. Many inhibitors of HIV protease and other antimalarial drugs have tested. There is currently no vaccine available for COVID-19 prevention, though others are available in clinical trials. Scientists often use spike proteins for vaccine production. Research is needed to develop a new innovative vaccine and targeted medicine, which will meet people's demands.**

Key Words:
COVID-19, Coronavirus, SARS-CoV-2, Pandemic, Vaccine.

Introduction

The first cases of Novel Coronavirus (2019-nCoV)-infected pneumonia (NCIP) in Wuhan, Hubei Province, China, occurred in December 2019. After that, a rising number of cases were found in Wuhan[1-3]. On December 31, 2019, a cluster of unexplained etiology cases of pneumonia reported in Wuhan City, China[2]. As the 2019-Novel Coronavirus (2019-nCoV) causative agent detected on January 9, 2020. The novel genome sequence coronavirus was made available to the World Health Organization (WHO) on January 10, 2020. The World Health Organization initially identified this Coronavirus as the 2019-Novel Coronavirus (2019-nCoV) on January 12, 2020.

WHO formally named the disease as Coronavirus disease 2019 (COVID-19), and viruses are known as SARS-CoV-2, both published on February 11 2020, by the International Committee on Taxonomy of Viruses[4].

Coronavirus is part of the Coronaviridae family and is an enveloped, positive-sense, single-stranded RNA virus. The genome size ranges from 26 to 32 kilobases in length and thus has the most abundant RNA virus genomes[5]. These coronaviruses can affect their host through several clinical manifestations, including problems with respiratory, nervous, enteric, and systemic health. On January 31, 2020, COVID-19 declared a global health emergency[6].

A sample of bronchoalveolar lavage fluid was used from the patient for metagenomic RNA sequencing, resulting in a new strain of RNA virus. The full viral genome contains around 29,903 nucleotides, and the virus had 89.1% similarity of nucleotides to a group of SARS-like coronaviruses of the genus Betacoronavirus and Sarbecovirus subgenus found in Chinese bats. COVID-19 occurred due to the transmission of disease from animal to human, and it has reached a point where the epidemic is difficult to monitor. So, it seems that bats are a potential host for the viral reservoir[7].

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Two hundred eighty-two confirmed 2019-nCoV cases from four countries, including China (278 cases), Thailand (2 cases), Japan (1 case), and the Republic of Korea (1 case) by January 20, 2020, were reported. Before that, in different countries, the people who traveled history to Wuhan were identified as positive. Contaminated cases in China also shipped to the USA. Further claims disseminated to other countries, and there may be a new transmission.

An instance of human-to-human transmission recorded on January 24, 2020, for a person who had no travel history to China. Earlier, the cases of COVID-19 recorded in countries outside China were due to human-to-human transmission. International airports in various countries like India started screening passengers arriving from other countries. All symptomatic people who had returned from China were kept isolated and screened for COVID-19. Cases in many countries continued to increase exponentially[8].

Methodology

Inclusion and Exclusion Criteria

We developed review methods that included: inclusion and exclusion criteria to classify potentially relevant applicable publications, search strategies for papers, abstract review protocols, govt sources, and a detailed rating framework for release on Coronavirus.

Search Strategy

We performed searches for systematic research and reviews written in major available databases, such as Medline (*via* PubMed), EMBASE, Cochrane Library, and Center for Reviews and Dissemination (CRD) and with the possible government sources, data published by the Ministry of Health and Family Welfare, and other government agencies, etc. The search keywords used as "Corona structure", "antiviral treatment for COVID", "alternative treatment for COVID", "Clinical trials for COVID", etc. The hunt was limited to publications in the English language and systematic reviews. We included searches performed in ProQuest Dissertations and Thesis, Conference Proceedings, and Mednar for unpublished systematic studies.

Data Extraction and Synthesis

Information obtained from the different sources are analyzed and detailed. The design and findings extracted from each article/report.

Review

Structure of Virus

Virus structure CoVs are categorized serologically and genotypically into four subfamilies: α, β, γ, and ÿ-CoVs. Beta-coronavirus contains SARS-CoV and MERS-CoV, which are the best known[9,10]. The 29.9 kb genome-sized SARS-CoV-2 virion has a nucleocapsid consisting of the genomic RNA and the phosphorylated nucleocapsid (N) protein. Within phospholipid bilayers is buried the nucleocapside[10]. Some of the subtypes of these corona family are, 229 E α-coronavirus, NL-63 α-coronavirus, OC 43 β-cornonavirus, HKU 1 β-coronavirus. Mostly, 2019 coronavirus is reported for the infection and its related consequences.

One SARS-CoV-19 strain is with 5′-cap and 3′-poly-A tail structure. CoV genome contains 11 open read frame numbers (ORFs). Two-thirds of viral RNA, primarily found in the first ORF (ORF1a/b), translates two polyproteins, pp1a and pp1ab, and codes 16 non-structural proteins (NSP). At the same time, the remaining ORFs encode accessory and structural proteins. The rest of the genome virus encodes four vital structural proteins: spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, as well as many accessory proteins that interfere with the innate immune response of the host. The genome characterization of SARS-CoV-2 is closer to SARS-like bat CoVs2.

Spike glycoprotein is responsible for coronavirus entry into host cells. Spike glycoprotein is composed of units S1 and S2. S1 binds through the receptor-binding domain (RBD) to the receptor cell membrane, and S2 mediates the fusion of the viral cell membrane[9]. A possible target for SARS-CoV-2 is angiotensin-converting enzyme 2. SARS-CoV-2 Binding domain receptor (BDR) has a strong affinity to human angiotensin conversion enzyme 2 (ACE 2)[11].

How it Gets Spread and Become Pandemic

It can be easily transmitted between humans and thus can pose a high risk of becoming pandemic[12,13]. Transmission of SARS-CoV-2 from humans to humans occurs by droplet or direct touch. Droplet is a big particle > 5 micron that moves less than 1 m. Direct interaction is with objects contaminated with droplets and then with eyes, nose, and mouth[12]. Aerosols produced with an infected person's respiratory droplet trigger transmission by inhalation of aerosols in a closed environment[14].

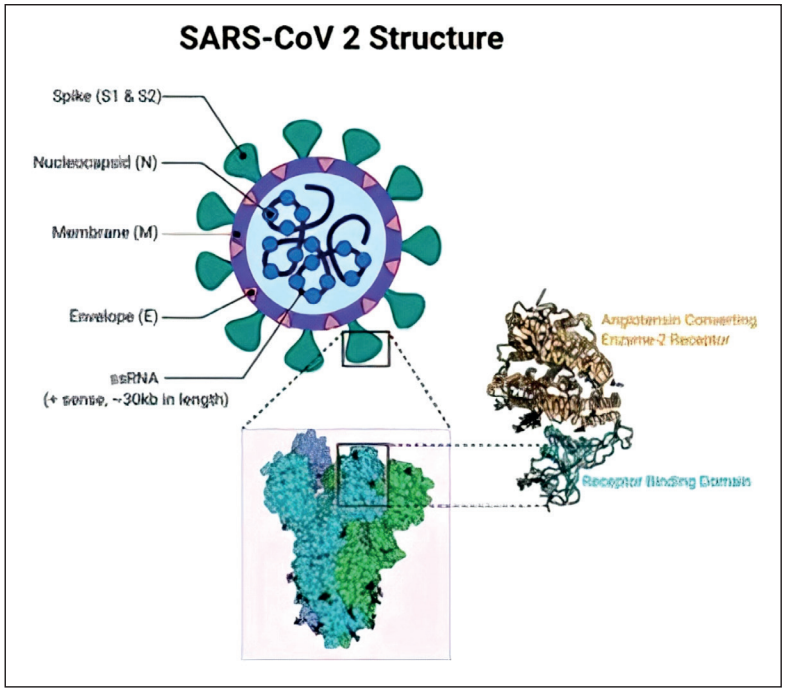

Figure 1. SARS- CoV 2 Structure. Contributed by Rohan Bir Singh, MD; Made with Biorender.com.

At lower temperatures, the transmission increased. It can stay in the air for 3 hours. After application, it can remain on plastics and stainless steel for up to 72 hours[15]. The epidemic of COVID-19 spread very quickly and globally. It spread from Hubei to the rest of the Mainland, China, within 30 days in January. It passed on to health-care staff. Wuhan was put under lockdown on January 23, 2020, with entry and exit restrictions from the region[16]. It currently mainly affected people in Italy, Spain, and the United States of America.

Understanding the Infection (Day-wise Symptoms)

On March 11, 2020, WHO declared Novel Coronavirus Disease (COVID-19) a pandemic, and all countries were ordered to take urgent steps to diagnose, identify, and minimize spread to save people's lives[17]. The most prevalent COVID-19 symptom is fever. The time it takes for a sign to develop after exposure ranges from 2 to 14 days. Approximately 99 percent of patients experienced a high temperature, while more than half had fatigue and dry cough. About one third also felt muscle pain and breathing difficulties. Chinese Center for Disease Control research shows that about 80 percent of cases of coronavirus are moderate. Around 15% of patients have gotten severe cases, and 5% have become critically ill[18].

Here's how symptoms develop in typical patients:

- Day 1: The patient develops fever and also experiences muscle pain, fatigue, and dry cough. Some can experience diarrhea or nausea one to two days earlier.
- Day 5: Patients who are older or who have a previous health condition may have breathing difficulties.
- Day 7: The patient may feel chest pain or lung pressure, shortness of breath. The patient may also have bluish eyes or may turn blue on the forehead.
- Day 8: 15% of patients experience a syndrome of acute respiratory distress (ARDS), a condition that develops when fluid builds up the lungs. In some cases, ARDS is fatal.
- Day 10: Patients are more likely to be admitted to ICU because their symptoms would intensify. Such patients are likely to suffer more abdominal pain and loss of appetite than patients with milder cases. Just a small number of people die, and the official mortality rate is about 2%.
- Day 12: Fever is going down, but other symptoms remain.
- Day 17: After recovery, people released from the hospital after two and a half weeks after recovery.

Recent information on these diseases shows that there might not be any symptoms listed above and is called the asymptomatic stage. These are known as salient carries.

Table I. Situation in numbers total (new cases in the previous 24 hours) as of May 20, 202019.

Sr No.	Region	Confirmed cases (new cases in last 24 h)	Deaths (new cases in last 24 h)
1	Globally	4789205 (57804)	318789 (2621)
2	European region	1928799 (19207)	169033 (1035)
3	Region of the Americans	2105670 (22782)	125843 (1176)
4	Western pacific region	169955 (777)	6780 (15)
5	Eastern Mediterranean region	361902 (5153)	10303 (154)
6	South East-Asia Region	156211 (7450)	4971 (191)
7	African Region	65956 (2435)	1846 (50)

Status of Infected Cases Worldwide and in India

The situation of infected cases worldwide as of 20 May 2020, Data received by WHO from national authorities by 10.00 CET stated that there are 4789205 confirmed cases and 318789 deaths globally[19].

The Situation of Infected Cases in India

On January 30, 2020, India's Ministry of Health & Family Welfare reported the country's first case COVID-19 in a student who arrived from Wuhan in Kerala. India announced the death of its first COVID-19 Coronavirus on March 12. The virus took the life of a 76-year-old man in Karnataka[20]. According to the latest report from the Union Ministry for Health and Family Welfare, as of May 1, 2020, a total of 35043 COVID-19 cases with 1147 deaths and 8888 cured cases were detected. The most significant number of cases, i.e., 10498 cases with 459 deaths is found in Maharashtra. India is now in the second stage of the COVID-19 Coronavirus pandemic. India has announced the 1st phase of the total lockdown of its 1.3 billion citizens for 21 days, 2nd phase for 19 days and 3rd phase by 14 days followed by 4th phase of 14 days.

Possible Preventive Measures

In the present moment, there is no vaccine available for COVID-19. The best protection is to avoid exposure to a virus. For prevention, airborne precautions and other protective measures are taken. Infection prevention and control (IPC) steps can minimize contamination, like covering coughs and sneezes with tissues that are then disposed of. If tissues are not available, use a flexed elbow to cover a cough or sneeze; use face masks; frequent hand washing with soap or disinfection with a hand sanitizer containing at least 60% alcohol (if the soap is available)[14].

The WHO has released comprehensive recommendations on the use of face masks. It is recommended that health care workers must use particulate respirators such as those licensed N95 or FFP2 while performing aerosol-generating procedures and use surgical masks when caring for COVID-19 patients. Similar to this guideline, it is advisable to use medical masks correctly for the infection prevention recommendations for individuals with respiratory symptoms in both healthcare and home care settings. According to this guidance, a person without respiratory symptoms does not need to wear a medical mask in public. It is imperative to properly use and dispose of the masks to avoid any increase in the risk of transmission[20,21].

Droplet contamination can be avoided by wearing a mask in an infected patient. Disposable surgical masks and their technical requirements explicitly developed for the safety of health-care personnel. In procedures, the surgeon successfully used cloth masks until disposable masks were available[22].

Individuals at risk of infection are those who are in direct contact with a patient with COVID-19 or who care for COVID-19. Preventive steps and prevention are essential to avoiding infection[23].

In the absence of vaccination and effective diagnosis, isolation, and quarantine, social distancing is the only viable method for controlling transmittable diseases from person to person. Isolation is the separation of an infected person from the non-infected type, which typically happens in hospital settings, but may also be done at home for a mild infection. Quarantine includes limiting the movement of near associates of infected patients during the incubation phase, preferably coupled with the medical examination during the quarantine period. Social distancing to maintain a healthy distance between people is an essential preventive measure to minimize disease spread[24].

Available Treatment for COVID-19 Patient

COVID-19 has no precise antiviral treatment, and no vaccine is currently available. In patients with a severe infection, oxygen therapy is given and symptomatic care. Mechanical ventilation provided to patients who are unmanageable by oxygen therapy and hemodynamic support is necessary for treating septic shock. Proposed antiviral therapy include hydroxychloroquine (200 mg every 12 hours), lopinavir/ritonavir (400/100 mg every 12 hours), and chloroquine (500 mg every 12 hours). Alpha-interferon (e.g., 5 million units inhaled twice daily by aerosol) is also used[25].

The drug types used for COVID-19 include the following: antiviral drugs used in the treatment of COVID-19, which may function through viral replication inhibition, ion channel inhibition, and serine protease inhibition. Antimalarial medications, such as hydroxychloroquine and chloroquine are currently approved for treatment. Anti-HIV drugs can function by various pathways and used in COVID-19 patient care. Anti-inflammatory drugs are also successful, as COVID-19 shows an enormous inflammatory response. Anti-inflammatory drugs may be effective against the elevated level of cytokines, thus inhibiting viral infection. Monoclonal antibodies are capable of binding, detecting, and neutralizing SARS-CoV-2 viruses[25].

The Following Drugs Can be Used in COVID-19 Patients

- ***Ribavirin*** is a nucleoside analog with a broad-spectrum of antiviral effects. Patients treated with ribavirin and lopinavir/ritonavir in combination show lower risk of acute respiratory distress syndrome (ARDS) and death. Ribavirin should be administered in conjunction with IFN-α or lopinavir/ritonavir by intravenous infusion at a dosage of 500 mg for adults 2 to 3 times/day[25,28].
- ***Sofosbuvir*** is a nucleotide analog that works against NS5B and functions as a polymerase nucleotide inhibitor used to treat hepatitis C. This has been used along with interferon or ribavirin. This medication has previously used to treat Zika virus[25].
- ***Lopinavir/ritonavir*** is a human immunodeficiency virus (HIV) drug used to treat adults and children over 14 days of age diagnosed with HIV-1 in conjunction with other drugs[15,25].
- ***Remdesivir*** is yet another possible COVID-19 therapy drug. Remdesivir is an analog of nucleosides and shows antiviral activity[15,25].
- ***Chloroquine phosphate*** is an antimalarial drug, and it is an active anti-inflammatory agent. Due to antimalarial and anti-inflammatory activities, it was acceptable for the treatment of COVID-19 associated pneumonia. Chloroquine phosphate is given orally in adults at a dosage of 500 mg (300 mg for chloroquine), two times/day for 10 days[15,28].
- ***Favipiravir*** is a dug that is currently undergoing a clinical trial for COVID-19 treatment. Favipiravir is an inhibitor of a new type of RNA-dependent polymerase RNA (RdRp)[25].
- ***Hydroxychloroquine*** found to be appropriate for COVID-19 in combination with azithromycin[28]. Hydroxychloroquine is less toxic and commonly used in COVID-19[15]. Orally 800 mg loading dose followed by 400 mg twice or 3 times weekly can be given.
- ***Interferon-α*** stated as broad-spectrum antiviral inhibiting the *in vitro* replication of SARS-CoV[28].
- ***Arbidol*** is an antiviral, which can be used for influenza diagnosis. Arbidol is given orally to adults in a 200 mg dosage three times a day. Treatment time does not exceed ten days[28].
- ***Darunavir***, which is a second-generation protease inhibitor of HIV-1, has potential effectiveness in treating COVID-19[28].
- ***Camostat mesylate*** is a serine protease inhibitor and partially inhibits the entry of SARS-CoV-2 into pulmonary cells by inhibiting the binding of S protein to host cells and endocytosis[28].
- ***Tocilizumab*** is a humanized monoclonal antibody for the treatment of cytokine release syndrome, currently believed to undergo some degree of cytokine storm in patients with extreme manifestations of COVID-19 that causes acute respiratory disease syndrome which leads to death. Successful treatment with tocilizumab for severe COVID-19 cases is being studied[15].
- ***Nitazoxanide*** is a wide spectrum antiparasitic and antiviral agent used to treat various helminthic, protozoal, and viral infections. At low *in vitro* micromolar concentrations, nitazoxanide was found to inhibit SARS-CoV- 2[15].
- ***Baricitinib*** is widely used in the COVID-19 outbreak when used in conjunction with antivirals (lopinavir or ritonavir, and remdesivir). Baricitinib combinations with these direct-acting antivirals may minimize viral infectivity, viral replication, and the inflammatory response of the aberrant host[25-29].

Alternative Treatment Strategy for Improving Immunity

Boosting the body's immune system will help mitigate the symptoms and accelerate the disease recovery. Body immunity to harmful viruses can be improved by using ayurvedic herbs, such as tulsi, cinnamon, black pepper, shunthi (dry ginger), and raisins. Daily yoga can make the body more resistant to harmful viruses. It also suggested using turmeric, cumin, cilantro, and garlic in cooking, in addition to 10 gm of chyavanprash in the morning. Jaggery and fresh lemon juice may also be useful in combating COVID-19[29,30]. Tulsi is used to relieve pain, diarrhea, cough, and fever, typical in COVID-19 patients. Thustulsi may be helpful in the prevention and management of COVID-19[31]. Some homeopathy medicine, such as "Arsenicum Album 30" may also found profound use for improving immunity.

Tribulations in Treatment

There are several challenges when taking care of the COVID-19 patient, which involves putting on personal protective equipment that includes masks, gowns, respiratory and eye protection, lack of supplies and disposables, and potential oxygen shortages. Most extreme hypoxemic patients receive only high-flow nasal oxygen (HFNO) or non-invasive mechanical ventilation because of a shortage of mechanical ventilators[32,33]. Doctors are concerned with what patients would benefit from using ventilators because it is in short supply. There are not enough ventilators available for COVID-19 patients in the months to come[34].

The creation of the vaccines is underway. But the underlining question is, where phase 3 trials will be performed, and who will be manufacturing vaccines on a scale. Large-scale development requires one or more of the major vaccine manufacturers to take up the challenge and work closely with the biotechnology companies that are creating candidates for the vaccine. This process will take time, and we are probably away from significant vaccine development for at least one year to 18 months[35].

The Future Scenario of the Treatment and Status of COVID-19 after two Months

Currently, no COVID-19 vaccine is available. There is no cure, and medical professionals can handle only the symptoms of the disease. Nevertheless, the production of a vaccine is the long-term strategy to fight COVID-19, which has spread beyond Antarctica to every continent on Earth. It takes time to formulate new vaccines, and they must be tested rigorously and proven safe by clinical trials before using in humans extensively. SARS-CoV-2 has projections similar to crowns on their heads. Such predictions are being studied intensively by scientists in developing a vaccine. The projections cause the virus to invade the human cells, where it can reproduce itself and make copies. They are called spike proteins, or S proteins. The vaccine is at least a year or 18 months away, while clinical trials are under way[36].

First US COVID-19 human vaccine test: on March 16, Moderns Phase I clinical trials in the US. Biotech companies dubbed mRNA-1273, contain spike protein genetic material found in SARS-CoV-2 embedded in a lipid nanoparticle to grow a vaccine mRNA-1273 is a SARS-CoV-2-associated prefusion-stabilized S-protein mRNA vaccine selected by Moderna in collaboration with NIAID Vaccine Research Center researchers[37].

The molecule of proteins S comprises two subunits S1 and S2. The S1subunit has an RBD that interacts with its host cell receptor, ACE 2, while the S2 subunit mediates fusion between the virus and the host cell membranes to release viral RNA for replication into the cytoplasm. Therefore, vaccines based on S-proteins induce antibodies that inhibit the binding of viral receptors and the uncoating virus genome[38]. In countries where the BCG vaccine is used, the frequency of COVID-19 cases is contrasted with countries where it is not used, and it is found that countries, where BCG vaccine is used in neonates, have lower COVID-19 cases[39]. BCG vaccine engages host immune system such that different types of viral infections are considerably reduced[40].

The new vaccine is expected to develop effective against the SARS-CoV-2 virus. ChAdOx1 nCoV-19 is an anti-SARS-CoV-2 vaccine currently under phase I/II study. It has been developed at Oxford University and is a possible vector against human Coronavirus. The vaccine is intramuscularly given[41]. Most countries now face the first wave of outbreak COVID-19. Relaxation of government activities may again lead to transmissibility, i.e., the second wave of infection[42]. China is currently facing the second wave of Coronavirus.

Rintatolimod marketed under the trade name Ampligen which is an immune-modulator, will be

tested against COVID-19 as a therapeutic agent. AdCOVID developed by Altimmune is a single dose and is a clinical trial intranasal vaccine. Clinical trials include HIV protease inhibitors, such as danoprovir plus ritonavir, ASC09 and ritonavir, ASC09 and oseltamivir, ritonavir, and oseltamivir. Treatment for nanobody-based COVID-19 is also under development. BPI-002 is a novel T-cell co-stimulator oral small molecule that can be used to treat COVID-19. Galidesivir is a nucleoside inhibitor of RNA polymerase designed to interrupt the mechanism of viral replication and may be useful among possible strategies to treat and prevent COVID-19[43].

Conclusions

COVID-19 is a disease that is rapidly transmitted from human-to-human transmission *via* respiratory droplets. COVID-19 has affected 213 countries, areas, or territories worldwide. There is no definitive antiviral treatment available for its treatment. However, some drugs like HIV protease inhibitors, hydroxychloroquine can be used for its prophylactic treatments. Implementation of preventive measures like sanitization, social distancing may reduce the speed of this pandemic. Efforts are in progress to develop a new vaccine based on the S protein structure. The discovery of new or existing drugs like danoprovir, ASC 09 is under clinical evaluation. Many researchers and medical professionals are in the race to develop therapeutic strategies and vaccines for COVID-19.

Availability of Data and Material

The raw data containing epidemiological data were obtained from the WHO website (https://www.who.int/zh/emergencies/diseases/novel-coronavirus-2019).

Authors' contributions

RPB & CGB conceived and designed the study. VIS & RPB consulted literature and collected data. RPB wrote the paper. VIS & CGB reviewed and edited the manuscript. All authors read and approved the manuscript.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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