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Review

A review on the COVID-19: Facts and current situation

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ABSTRACT

COVID-19 has affected our life drastically. National lockdown, Social distancing, and working from home are the new normal. Many developed countries with their advanced medical facilities find it challenging to tackle the pandemic situation. The second wave of covid-19 is associated with unexpectedly higher rates of mortality relative to the first wave. The breakout of mutant strains that make the virus highly transmissible across the country has led to new challenges for scientists and researchers alike in developing vaccines and finding a cure for the disease. While several Biopharma companies and Research Centre like Pfizer-BioNTech, Moderna, AstraZeneca, Bharat Biotech, and Sinoppharm, and Gamaleya Research Institute of Epidemiology and Microbiology have come up with different vaccines, their efficacies on the mutant strains of the virus are still being documented and researched. This article deals with the current scenario, the nature of the virus, and the treatment against the viruses.

Introduction

After the first COVID wave, the situation was decreased for some time from September 2020 to starting January 2021, but with the advent of the second wave of the pandemic, the number of cases and the transmission of the disease increased higher fatalities. India is the new center of the second wave due to the spread of variants of the virus. Transmission during the second wave was higher as compared to the first due to its high mutation rate. Evidence shows that the virus has a unique ability to change in genetic sequences according to the host and the environment, making it more virulent than any other microbes present on earth. On 6 April 2021, India witnessed 4,522 deaths in 24 hrs which is higher than the record number of deaths of 4,468 patients in the US on 12 January 2021 in a single day. The number of deaths in India on 6 April 2021 is the highest death record for any country in a single day. It is assumed that multiple variants are responsible for this enormous breakout in India. B.1.617 variant is the dominant variant of the virus in several parts of India. On 31 May 2021, WHO classified B.1.167 as a Global variant of concern. Earlier it was identified as a variant under investigation by authorities in the UK. Figures 1 and 2 showing the current scenario of India, from January to May 2021. Figures 3 and 4 showing the current scenario of the world, from January to May 2021.

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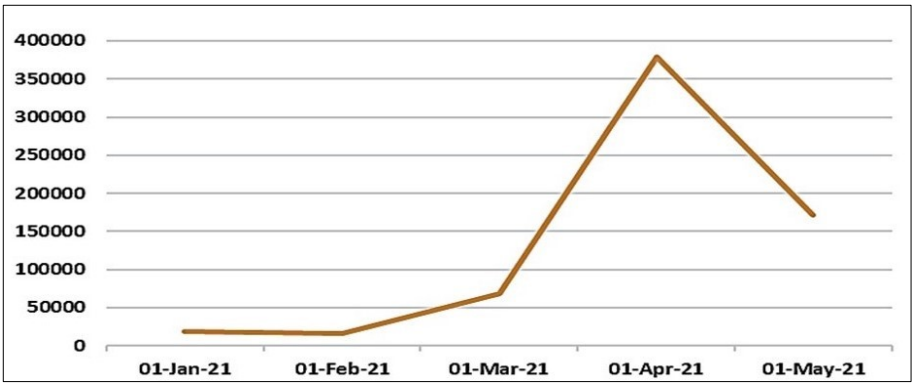

Figure 1: Daily New Cases: showing the rapid increase in cases of new variant in India by Worldometer from January to May 2021 (https://www.worldometers.info/)

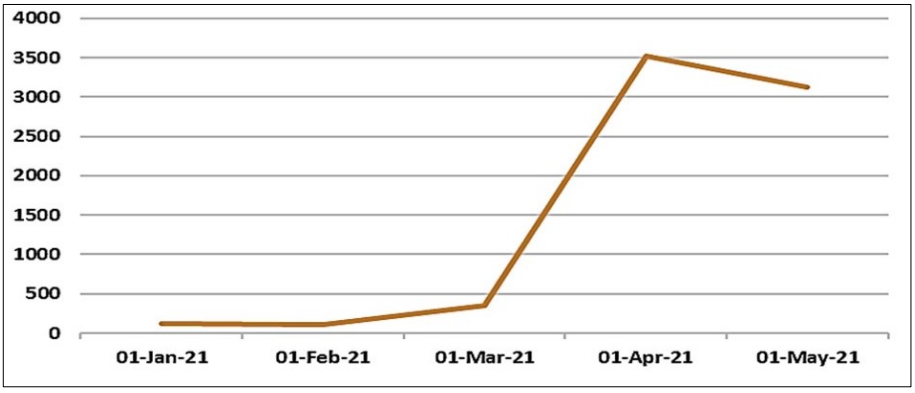

Figure 2: Daily Death: showing the rapid increase in India by Worldometer from January to May 2021 (https://www.worldometers.info/)

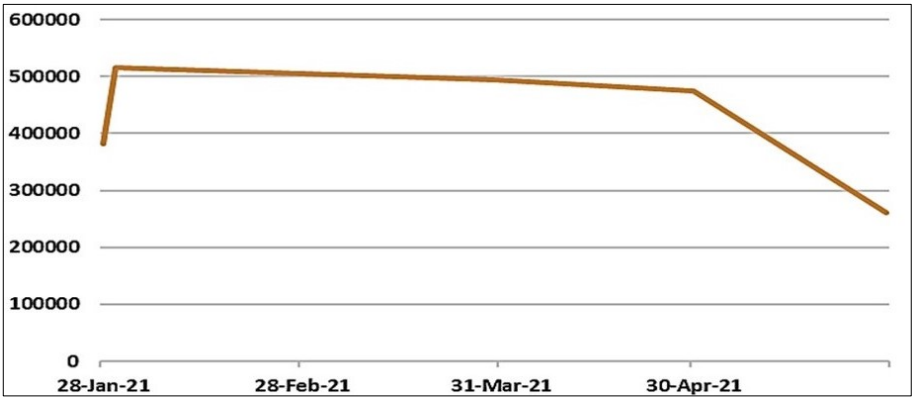

Figure 3: Global Daily New Cases: Showing the current situation of new cases by Worldometer from January to May 2021 (https://www.worldometers.info/)

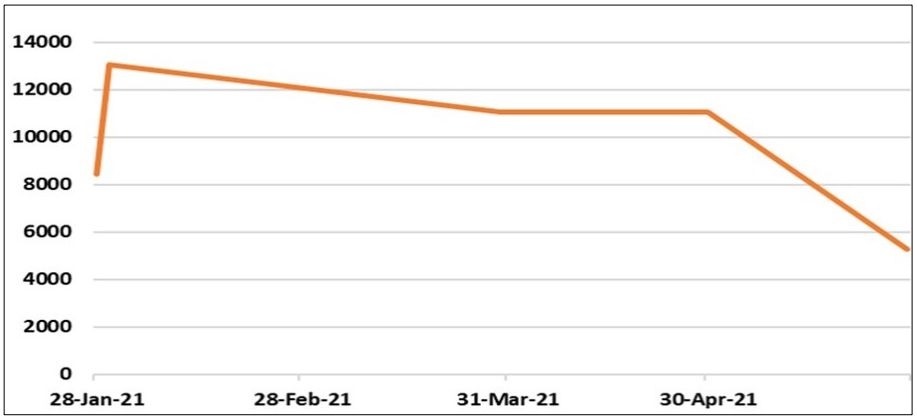

Figure 4: Global Daily Deaths: Showing the current situation of Deaths by Worldometer from January to May 2021 ((https://www.worldometers.info/)

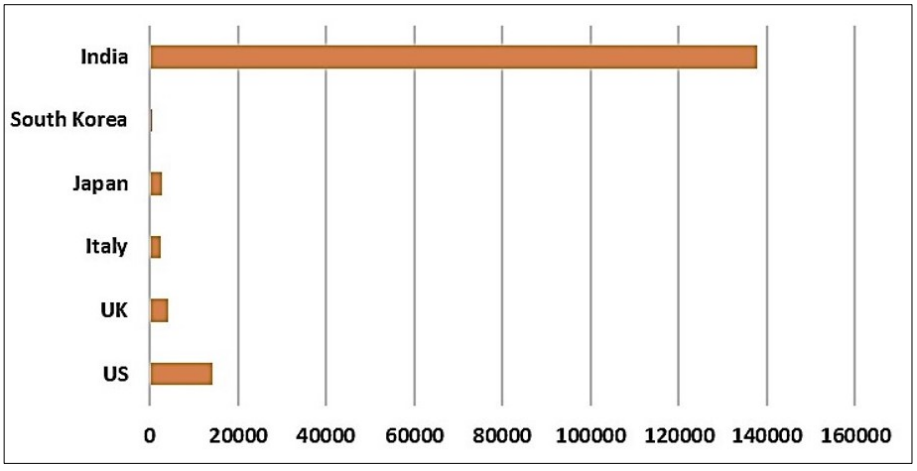

Figure 5: Daily confirmed cases: a comparative study of confirmed new cases in mentioned countries based on their testing till 4 June 2021 (https://www.worldometers.info/)

SARS-CoV-2

Coronaviruses (CoV) are a group of single-stranded RNA viruses. It contains spike-like glycoproteins on its outer surface, due to which it appears like a crown.[1] The name coronavirus gave to it based on its crown-like appearance. The family Coronaviridae has divided into two sub-family Letovirinae and Orthocoronavirinae. The latter classified into four genera: α, β, γ, and δ coronaviruses. α and β coronavirus are responsible for infection in mammals while γ and δ coronavirus infects birds. Human coronaviruses were identified first in the mid-1960. There are four common types of human coronaviruses i) 229E (α-coronavirus), NL63 (α-coronavirus), OC43 (β-coronavirus), HKU1 (β-coronavirus) causes mild respiratory infections, ii) Middle east respiratory syndrome (MERS-CoV), and Severe acute respiratory syndrome (SARS-CoV) which causes serious respiratory tract infections.[2] Both MERS and SARS are β-coronaviruses.[3,4] SARS-CoV-2 is the new addition in Human coronavirus, which causes COVID-19 Disease.

Structure of SARS-CoV-2

The isolated SARS-CoV-2 is 29.9 kb in size, similar to MERS-CoV and SARS-CoV, 27.9kb and 30.1kb, respectively.[5] Coronavirus contains 6-11 open reading frames (ORF).[6] Its genome consists of a 5' methylated cap and a 3' polyadenylated tail. Two-thirds of viral RNA is present in the first open ORF, which translates into two polyproteins and encodes 16 non-structural proteins. The remaining ORFs are responsible for accessory and structural proteins. Structural proteins contain four proteins: Spikes (S)glycoproteins, Envelope (E) proteins, membrane (M) protein, and Nucleoprotein (N).[7] Nucleoproteins are attached with a positive-sense, single-stranded RNA genome, the largest genome among RNA viruses. Accessory proteins deal with the host's innate immune response.

Process of development

A human cell has an angiotensin-converting enzyme-2 receptor which is specific to SARS-CoV-2. It is present in the lower respiratory tract of humans.[8] The S protein helps in the attachment of the virus with the ACE2 receptor of the human cell.[9] S glycoprotein consists of S1 and S2 subunits.[10] S1 subunit has a receptor-binding domain that helps in the binding of the virus with the human receptor ACE2, while the function of the S2 subunit is the fusion of virus and human cell membrane fusion with the help of two domain heptads repeats 1(HR1), and heptads repeat 2(HR2).[11] After the membrane fusion, RNA is released in the host cell's cytoplasm, and now it translates to produce two polyproteins pp1a and pp1ab, which form non-structural proteins and Replication transcription Complex(RTC).[12,13] The RTC continuously replicates and forms subgenomic RNAs that are responsible for viral structural proteins and accessory proteins. At last, the viral vesicles release from the host.[11]

What kills the host?

Currently, it is very tough to determine the whole process of viral infection in the human body, but some facts may help explain it. SAR-CoV leads to acute lung injury clinical syndromes, which causes respiratory tract failure, sepsis, and cytokine storms.[14,15] Similar process may also involve the SARS-CoV-2. According to research done by the team of Zunyi Medical University on COVID-19 patients, SARS-CoV infection results from an excessive immune response.[16] Spike protein of virus attacks the alveolar epithelial cells, which results in overexpression of immune responses in the host's body. This overexpression of immune response and acute inflammation causes excessive Cytokine release; it usually defends the host body from pathogen infection. However, the uncontrolled immune response in a single place causes multi-organ failure called multi-organ failure dysfunction syndrome.[17] Acute inflammation in cytokine storms causes redness, heat, swelling, pain, and loss of function.[15] The number of infectious and non-infectious diseases are linked with Cytokine, and SARS-CoV is one of them.[18,19] Like other β-coronavirus, Covid-19 also induces cytokine storm.[16] Cytokine storm produces acute mononuclear/neutrophilic inflammatory response, chronic fibro proliferation, collagen deposition in the lung, disturbance in epithelial and endothelial barriers, loss of alveolar-capillary membrane, excessive transepithelial neutrophil migration. All of them cause acute lung injury in the host, which fails the respiratory tract, and the end patient with Covid-19 dies. Acute lung injury is the expected outcome of the cytokine storm.[20,21] Overall, symptoms of a cytokine storm are similar to the other two β-coronaviruses: SARS and MERS.[22]

Transmission of SARS-COV-19

Human coronavirus, including SARS-Co V and MERS-CoV, is found in wild animals because they are zoonotic pathogens.[23] SARS-CoV-2 genomic structure shows more than 95% similarity with the bat coronavirus isolated from *Rhinolophus affinis* bats and more than 70% similarity with SARS-CoV.[24,25] Bats

are not immediate hosts for the virus that is directly transmitted into the human body, and it may require an intermediate host for the transmission of the virus from animal to human, which is still unknown to us.[26,27] It is also a fact that before SARS-CoV-19 came to light, generally, coronaviruses were responsible for the infections of respiratory tracts, gastroenteritis, and hepatitis in mammals and birds.[28,29] After SARS-CoV-19, it was discovered that bats are the intermediary host for many novel viruses because of their multiple origins and co-evolutionary properties.[30] HCoV genome was isolated from a group of a patient infected with pneumonia. This patient was examined after they returned from Wuhan city, China. The isolated HCoV from this patient showed 89% nucleotide similarity with batSARS-like-CoVZXC21 and 82% similarity with human SARS-CoV. Because of its similarity, the International Committee on Taxonomy of Viruses named it SARS-CoV-19. The genome of SARS-CoV-19 contains 29891 nucleotides which encode 9860 amino acids.[31] It is a bitter truth that human greed is the cause of human plight. Humans exploit mainly all kinds of natural resources for their desires and comfort. Due to these activities, humans are now closer to those wild animals, who are the natural gene sources of these viruses. It is believed that about 70% of pathogenic infections in humans are due to animals. This positive-stranded RNA contains high mutation rate capabilities, which may be due to its genetic recombination and reassortment with other genomes.[28] The common symptoms of COVID-19 disease are Fever, cough, sore throat, headache, fatigue, myalgia, and breathlessness.[32] The disease spreads through the respiratory tract by droplets, respiratory secretions, and direct contact.[24-34] According to the research done by The Fifth Affiliated Hospital, Sun Yat-Sen University, Guangdong, China, and Zang with his team on his article Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes, oral-fecal is also a source of transmission of coronaviruses.[35] The incubation period of COVID-19 disease is 14 days.[36] People with medical conditions like immune disorders, heart infections, asthma, hypertension, and diabetes are get infected easily. The incubation period depends on the patient's age, in children and patients above 70 yrs. The virus may enter and replicate less than its actual life incubation period because of its body response. Patients with hypertension and severe respiratory issues continuously produce ACE2 receptors that allow the SARS-CoV-2 to enter the host's body and replicate the virus.[37] The cytokine storm produces disturbances in the immune response of Type 1 and Type 2 T helper cells, respiratory dysfunction, and hypoxemia, which in turn damages the myocardial cells.[32-38] Apart from these, loss of weight, loss of smell and taste (metallic taste), extensive weakness, deranged feeling are also observed in some patients. It is also seen that the due to continuous mutation in genome sequences also changes the transmission process of the virus into the host. The current scenario shows that the virus may also be transmitted from the air. Different things like plastic, steel, paper, wood, and other materials may carry the virus and transmit transmission.[39] We cannot precisely identify how the virus may enter the body and to what extent it will harm us.

Variants of SARS-COV-2

SARS-CoV-2 can change itself according to the host cells and their surrounding environmental conditions. Their new mutative forms are more virulent and deadliest in the world. Several variants have been identified during this time of the pandemic, but only a few are the topic of concern. These types of variants are called variants of concern (VOCs). The first VOCs were identified in the United Kingdom (UK) named the B.1.1.7 lineage or VOC 202012. The second was B.1.351 lineage or 501Y.V2, reported in South Africa. The third was identified in Brazil, named B.1.1.248/B1.1.28 or 501Y.V3, and the most recent one was found in California, named B.1.427/B.1.429 lineage. According to WHO, the most recent variant present in India is named B.1.617, which has three lineages. The WHO also informed that the B.1.617 variant is present with one additional deletion in the spike protein.

Diagnostic criteria

On 12 January 2020, China shared the genomic sequence of COVID-19 with the world. Diagnosis criteria are set based on different symptoms and severity of the disease. China uses its classical Koch's postulates and examines the morphology by electron microscopy.[40] The following standard diagnosis methods are the nasal and throat swab sampling, Bronchoalveolar lavage, tracheal aspirate, pleural fluid, lung biopsy, respiratory tract samplings by real-time PCR, Chest-X-ray, CT scans, Lung imaging tests.[41-44]

Treatments

Approx. 33.3% of persons are asymptomatic. Actual medicinal treatment is still the topic of research, and the whole world is waiting for that. However, the current treatment is based on the specific symptoms of the disease. For mild states, just like fever, coughing, throat infection, normal antibiotics drugs are used. Remedesiver, lopinavir, ritonavir, interferon-α nebulization, ribavirin, chloroquine, umifenovir are used as anti-viral drugs, but still, there are certain conditions for it.[32-49] These may leave side effects and may not be acceptable to the host body. For developing neutralizing antibodies, convalescent plasma therapy[50-52], regn-cov2[53,54], bamlanivimab, and etesevimab[55-57] are used. In Rajasthan, India, patients were treated with the anti-HIV drug, an anti-malarial drug, and anti-swine flu drug, published in the Economic Times newspaper on 16 March 2020. On 23 March 2020, the Indian Council of Medical Research suggested using hydroxychloroquine, an anti-malarial drug and used for severe cases of the covid-19 disease.[58] It can modify the immune responses of the body. Hence it is used in treatment, but it also shows some adverse effects.[59] In April, a 49-year-old patient became the first Indian to recover from covid-19 by plasma therapy. It is also supplied to other nations because of its positive responses to treatment. For immunomodulation and those struggling with severe inflammation lung injury, corticosteroids, interferon-β-1a, interleukin (IL)-1 antagonists anti-il-6 receptor monoclonal antibodies, tocilizumab, sarilumab, and rituximab are being used.[60-68] Viruses infect the lower respiratory tract and may damage the alveoli. Alveoli in the air-filled sacs that exchange oxygen and carbon dioxide in the bloodstream. So, if we think the last option to save the life, then the only answer is respiratory support. In covid-19 cases, the alveoli are starting filling with fluid instead of air and results in the lack of oxygen supply in all body parts. Conventional oxygen therapy is given to the patients.[69,70] High-flow nasal cannula (HFNC), non-invasive positive pressure ventilation (NIPPV), endotracheal intubation, and invasive mechanical ventilation (IVM) or extracorporeal membrane oxygenation (ECMO) are used for that patient who is dealing with acute hypoxemic respiratory failure.[71-74] Conservative fluid strategies are used for fluid replacement in infected patients. For hyperdynamic circulation, hemodynamic disorder, and improving oxygen supply and prevention from multiorgan failure, circulatory support like aggressive hemodynamic and metabolic marker monitoring saves the patient. The virus changes its form and becomes more virulent day by day. Therefore, its variations are a big challenge to our medical infrastructures. France, the USA, and now India has almost seen the horrible form of viruses. The second wave in India shown the deadliest and horrifying images of infections. According to the WHO, the US, UK, and Italy confirmed 41008, 814, and 126 new cases, respectively (WHO), which are more than South Korea at that time. Figure 5 shows the comparative study of confirmed new cases in mentioned countries based on their testing till 4 June 2021.

Current COVID-19 vaccine

Researchers are trying their best to find an effective vaccine against SARS-CoV-2. Effortless researches develop novel vaccines against the virus. More than 100 vaccine candidates are still in various trial phases. The Vaccine Centre at the London School of Hygiene and; Tropical Medicine listed ten candidates in

different clinical trial stages. These help to develop antibodies against the virus. There is also a new challenge for these vaccines because of the variants of SARS-CoV-2.[75-81] Some vaccines are as follows:

mRNA-1273: ModernaTX Inc, manufactures it. It is a novel lipid nanoparticle (LNP)-an encapsulated mRNA-based vaccine that encodes for a full-length, perfusion stabilized spike (S) protein of SARS-CoV-2.[82] Moderna announced it on May 18, 2020. Currently in phase-3, randomly given to volunteers. It claimed that the efficacy of vaccines is 94.1% against covid-19 mild to severe cases.[83] Its efficacy against variants is still unknown.

Ad5-nCoV: It is a first novel the first novel recombinant coronavirus vaccine for COVID-19. It is a single-dose vaccine introduced to the world by CanSino Biologicals, China.[84,85] February 25, 2021, the company announces the results of phase-III clinical trials, which shows that the vaccine is 65.25% effective at symptomatic diseases 28 days after single-dose vaccination while it shows 68.83% efficacy at symptomatic disease 14 days after single-dose vaccination. According to the company, Vaccine efficacy is 90.07% against severe disease 28 days after single-dose vaccination and 95.47% against severe disease 14 days after single-dose vaccination.

ChAdOx1 nCoV-19**:** It is from the university of oxford, which is based on an adenovirus vector that encodes for spike protein of SARS-Co V -2. According to The Lancet- the first interim safety and efficacy data of this vaccine are examined in four trials across three continents, and the results showed that it is 70.4% effective after two doses and 64.1% effective after a single dose against the symptomatic disease with no safety concerns.[86,87] It is showed 70.4% efficacy against B.1.1.7 variant and 81.5% efficacy against the non- B.1.1.7 variant.

BNT162b2: vaccine-ongoing multinational, randomized, placebo-controlled, observer-blinded, pivotal efficacy trial showed 95% efficacy against the disease. It is a lipid nanoparticle-formulated, nucleoside modified RNA vaccine that encodes perfusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein.[88]

LV-SMENP-DC and Pathogen-specific aAPC: Both are from the Shenzen Geno-Immune Medical Institute. These are lentiviral vectors. LV-SMENP-DC, a vector expressing the minigene based on the domain of structural protein of the SAR-CoV-2. It is currently in phase 1/ 2 and examines over 100 patients. It claims to be complete in July 2023. On the other hand, the pathogen-specific APC vector is used to express viral proteins and immune responses to modulate the expression of artificial antigen-presenting cells (APC) and T-cell activation. It is also expected to complete by July 31, 2023.[89,90]

India also launched its first indigenous vaccine against COVID-19. The Indian Pharmaceuticals company: Bharat Biotech India, in collaboration with the Indian Council of Medical Research and its part National institute of virology, developed India's first vaccine named 'Covaxin' by using Whole-Virion Inactivated Vero Cell-derived platform technology. The Central Drugs Standard Control Organisation has approved this project. In April, Bharat Biotech, along with FluGen and the University of Wisconsin- Medison, has developed and evaluated the Covid-19 vaccine called ChloroFlu. The main of this vaccine is to produce immune responses, but in May, Bharat Biotech joined the Thomas Jefferson University (Philadelphia) US to develop a COVID-19 vaccine candidate. However, its approval from WHO is still pending. Bharat Biotech claimed that the vaccine shows 78% efficacy against mild to severe conditions of disease.

Conclusion

Despite all of the trials and treatments, no one can predict the situation of the future. Some researchers also claim that the virus changes its nature according to the environment and changes its form from mild to severe because its ability to recombine and reassortment makes it more prone to mutation. Social distancing, sanitization, and lockdown are looking like not enough to protect us from the virus. It also the

fact that despite all of these, the recovery rate is also more significant than any other virus outbreak in the world. USA, India, Russia, and Italy are highly affected by this. The actual death toll from COVID-19 is still not in the frame because of limited testing. Due to the limiting testing, there is a significant difference between reported deaths and total deaths. Vaccines also face challenges to make the efficient immunization against the virus, but it takes time to come on the floor. Variants are the central area of concern and most significant challenge to the developed vaccines. Vaccines make our body resistant against any virus, but how the world tackles the infected patient is still challenging for us. The fight with coronavirus is still On, and the doctors and researchers are standing at the forefront.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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