When Successive Viral Mutations Prevent Definitive Treatment of COVID-19

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ABSTRACT
NCP (new coronavirus pneumonia) was discovered in Wuhan towards the end of 2019 and quickly spread throughout the city. The infection was identified as a novel coronavirus, and the World Health Organization (WHO) called it coronavirus disease-19 (COVID-19). Most people with this infection can experience mild to severe and even fatal symptoms after a period of disease incubation of 4 to 14 days. In up to 10% of patients, gastrointestinal symptoms such as nausea and diarrhea, as well as associated abdominal discomfort, may occur before respiratory symptoms. Several SARS-CoV-2 variations have been identified during the epidemic, however, only a handful are deemed variants of concern (VOCs) by the WHO due to their worldwide public health effect. In this article, we looked at new mutations in COVID-19 as well as the adverse effects of the virus on the cardiovascular and gastrointestinal tract. The discovery of these novel SARS-CoV-2 variations threatens to undo the substantial success made so far in restricting the spread of this viral disease, despite the extraordinary speed with which vaccines against COVID-19 have been developed and vigorous worldwide mass immunization efforts. Through mechanisms involving the dysregulated ACE 2 receptor and TMPRSS2, the SARS-CoV-2 virus has the potential to induce significant systemic disease in the GI tract, liver, biliary tract, and pancreas. Due to the observation of new and daily mutations of this dangerous virus, the definitive treatment of this disease is becoming more and more difficult and facing major challenges that it requires many clinical trials and researches.

1. Introduction
Disease outbreaks manifest themselves as a rapid increase in sickness in a certain area or population. When an outbreak is not contained, it spreads to a large number of people, impacting a whole region or community, and eventually becoming an epidemic. A pandemic begins with the spread of contaminants to infected and sick people, such as the terrible epidemics of smallpox and plague in history, which caused many casualties in Asian and European lands in the 16th and 19th centuries. The 20th century was not without its epidemics, and the spread of the Spanish flu (H1N1), which researchers believe was the reason for the return of soldiers home in World War I, was the cause of the spread of the disease [1-3].

The NCP initially arose in Wuhan at the end of 2019 and swiftly spread throughout the city. The infection was proven to be a novel coronavirus, and the World Health Organization called it COVID-19 [4, 5]. "The clinical characteristics of COVID-19 include fever, respiratory symptoms, dyspnea, cough and pneumonia" [6-9]. Patients with COVID-
2. Various Types of Mutations in Sars-Cov-2

In comparison to other single-stranded RNA viruses, human CoVs have a moderate to high mutation rate, with an average substitution rate of around 4-10 substitutions per site per year [19]. When two or more related viruses enter the same cell, recombination occurs, resulting in genetic alterations in the subviruses that might impact the host’s function, virulence, immune evasion, and antiviral resistance. While "antigen shift" occurs in segmented viral genomes, such as the influenza virus genome, unsegmented viruses have certain "recombination" processes [20]. SARS-CoV recombinant breakpoints are most commonly found in the gene encoding the S protein, encoding the receptor-binding region, and the gene for the accessory protein [21].

According to earlier studies on the interaction between the SARS-related CoV (SARSr-CoV) S protein and ACE2, certain amino acid modifications are required for the foreign S-protein to connect to the homologous receptor of the current host species [22-24]. Human CoVs are mostly transferred from human to human. However, it has been shown that "Middle East Respiratory Syndrome (MERS) caused by MERS-CoV" sometimes occurs with human-to-human (animal-to-human) transmission. CoVs are spread by direct contact with secretions, fomites, and respiratory droplets in humans [25]. The beta-CoV genus is further
subdivided into five lineages or subgenera [26]. Based on genomic analysis, the most likely gene sources for alpha-Covs and beta-Covs are bats and rodents, while delta-Covs and gamma-Covs appear to be the source of bird species. CoVs are known to be the most common pathogens among the prevalence of emerging respiratory diseases. Camels, cows, cats, and bats are among the cases that can cause respiratory, gastrointestinal, and liver disorders by large members of these viruses. For very complex reasons, this viral family can cross species boundaries and can also infect humans with diseases ranging from the common cold to more severe infections such as MERS and SARS. Seven human CoVs (HCoVs) have so far been discovered as being capable of infecting humans. "Some of the HCoVs were identified in the mid-1960s, while others were only detected in the new millennium. In general, estimates suggest that 2% of the population are healthy carriers of a CoVs and that these viruses are responsible for about 5% to 10% of acute respiratory infections" [27].

2.1 Alpha (B.1.1.7 lineage)

The B.1.1.7 lineage, also known as "Alpha variant or GRY (formerly GR/501Y.V1)", is a new SARS-CoV-2 variant of concern that was discovered in the UK in late December 2020 based on whole-genome sequencing of data from patients who tested positive for SARS-CoV-2 [28, 29]. Aside from genomic sequencing, type B.1.1.7 is frequently employed in a commercial approach that is defined by the PCR sample's lack of the S gene (target failure of the S gene, SGTF). The viral genome of Type B.1.1.7 has 17 mutations. Of these, eight mutations "deletion Δ69, N501Y, A570D, P681H, T716I, S982A, D1118H" is in the spike (S) protein. N501Y shows an increase in spike protein affinity for ACE2 receptors and increases viral binding and subsequent entry into host cells [30-32]. Due to its greater portability, it has spread rapidly around the world and has been reported in 160 countries since June 1, 2021. B.1.1.7 with the E484K mutation was recognized as the new VOC (VOC-202102/02) by Public Health England (PHE) in February 2021 and has subsequently been found in the United States. However, this species has not been found in the UK since March 2021, although according to genetic data, it is spreading outside of the UK [33].

2.2 Beta (B.1.351 lineage)

B.1.351, commonly known as Beta variant or GH501Y, is a SARS-CoV-2 mutation. In October 2020, V2 with numerous spike mutations was first found in South Africa, resulting in the second wave of COVID-19 infections [34]. Type B.1.351 contains nine mutations “L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V” in the spike protein, with three mutations “K417N, E484K, and N501Y” in RBD, and increased affinity for Sars-CoV-2 501Y.V2 (B.1.351 lineage) in the united states was reported at the end of January 2021 [35]. This mutation has been related to a higher risk of transmission, as well as a reduced ability to be neutralized by "monoclonal antibodies", convalescent sera, and post-vaccination sera [36]. Because most people with SARS-CoV-2 produce only low to moderate titers, and larger titers occur primarily in seriously hospitalized patients, there is a dilemma among the unvaccinated community. The loss of recovery plasma neutralizing activity against B.1.351 varies from 11 to 33-fold [35-39], whereas the loss of vaccination serum neutralizing activity varies from 3.4 to 8.5-fold. In addition, type B.1.351 was resistant to neutralization by a variety of NTDs and RBM-specific mAbs [35, 36, 40].

2.3 Gamma (P.1 lineage)

The third worrying type, type P.1, The third worrying type, type P.1, was identified in December 2020 in Brazil and first in January 2021 in the United States and was identified as Gamma or Gr / 501Y.V3 [15]. Type “B.1.1.28 has ten mutations in spike protein (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027V1176, K417T, E484K, and N501Y). Three mutations (L18F, K417N, E484K) are located in RBD, similar to type B.1.351” [15]. It is important to note that this type can reduce neutralization with monoclonal antibody therapies, recovery serums, and post-vaccination sera [36].

2.4 Delta (B.1.617.2 lineage)

B.1.617.2, commonly known as the delta type, was initially discovered in India in
December 2020 and was responsible for the second catastrophic wave of COVID-19 infections in India in April 2021. This species was first discovered in the United States in March 2021. Type "B.1.617.2 has ten mutations (T19R, G142D, 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N)" in the spike. Protein [18].

3. The Impact of SARS-CoV-2 on the Cardiovascular System

Although the exact method through which COVID-19 affects the heart is unclear, it is most likely complicated. SARS-CoV-2 has been reported to cause direct cytotoxicity on the heart, resulting in myocarditis in myocardial cells. IL-6 and other proinflammatory cytokines can cause vascular inflammation, myocarditis, and cardiac arrhythmias [15]. Therefore, cardiac inflammation can lead to a sudden decrease in cardiac contractility, inotropic defects, increased filler pressures, and acute heart failure [41]. Myocarditis caused by SARS-CoV-2 has been defined as a severe acute ventricular illness with extensive myocardial edema [42]. Cases of myocarditis with fulminant development, pericarditis, pericardial effusion, and ultimate cardiac tamponade [42] should also be mentioned. Myocardial involvement can develop even if there are no signs of upper respiratory tract infection [43]. According to examinations performed by physicians in patients affected by SARS-CoV-2 infection, tachycardia, tachypnea, hypotension, and third heart sound have been observed. The ECG may indicate a substantial rise in troponin, BNP/NT-proBNP, and inflammatory activity, as well as widespread ST-segment elevation with a concave shape [43]. Transthoracic echocardiography can indicate diffuse hypokinesia with myocardial thickness and a decrease in left ventricular ejection fraction, whereas cardiac magnetic resonance imaging can reveal substantial interstitial edema [43]. All of these supplemental tests have substantial restrictions due to high SARS-CoV-2’s infectious potential [44], necessitating their logistics. Inotropic support and diuretic medicine have been prescribed for “patients with clinical signs of tissue hypoperfusion and fluid overload” [43].

One of the worst prognostic indicators of COVID-19 is myocardial damage, which is directly linked to greater mortality. Therefore, it is necessary to perform a complete screening through troponin dose, ECG, and bedside echocardiography, due to its association with exacerbation of systemic inflammation, mainly in patients with more severe symptoms and critical infection [43, 45, 46].

One of the known cardiac manifestations of COVID-19 is an acute coronary syndrome (ACS), and studies have suggested that the release of proinflammatory cytokines may exacerbate severe coronary artery disease for several reasons, including increased coagulation in Covid-19. On the other hand, cardiomyopathy and related hemodynamic disorders may occur, which in turn reduce coronary blood flow and oxygen delivery, leading to microvascular instability, coronary plaque thrombosis, or worsening of previous severe coronary artery disease [42, 47-49]. Furthermore, there are few reports in the literature on cardiac arrhythmias in COVID-19 that have no known pathophysiological significance. The potential mechanism of SARS-CoV-2-induced viral myocarditis appears to be [50]. Myocardial inflammation (Figure 1) with severe necrosis can result in re-entry points in the electrical circuit, resulting in ventricular tachycardia and ventricular fibrillation. Because severe myocardial necrosis can cause re-entry points in the electrical circuit, leading to ventricular tachycardia and ventricular arrhythmias [51, 52], fulminant myocarditis associated with cardiogenic shock may be linked to the development of both ventricular and atrial arrhythmias.

3.1 The Destructive Effect of COVID-19 on the Gastrointestinal Tract During Infection

Early reports from China, all based on retrospective data, reported a prevalence of GI symptoms ranging from 11.4 to 50 percent in COVID-19 cases [53, 54]. The prevalence of GI symptoms was 17 percent in a meta-analysis of over 4,000 patients [55]. GI symptoms have been observed in 3 to 10% of adult patients and more frequently in children as an early symptom cluster of COVID-19 infection. Despite the prevalence of upper GI symptoms,
the most common GI symptom in COVID-19 patients is acute diarrhea. As a result of the COVID-19 outbreak, GI symptoms have become a problem in clinical practice. Diarrhea is the most common gastrointestinal symptom associated with COVID-19, and it is usually mild. Before or during the onset of pulmonary symptoms, some individuals experience severe diarrhea with electrolyte abnormalities or bloody, inflammatory diarrhea (Figure 1) [56, 57]. Gastrointestinal bleeding is one of the most prevalent grounds for emergency consultation. GI bleeding requiring the presence of a GI expert can occur in patients with COVID-19, as well as in those who are not infected with the virus, during the SARS-CoV-2 pandemic outbreak. In COVID-19 patients, GI bleeding is less common than other GI symptoms. GI bleeding was reported in two out of 15 studies in a recent review article of 2,023 COVID-19 cases [58], with a frequency of 4% in one study of 52 critically ill patients [59] and 13.7 percent in another study of 73 hospitalized patients [60].

Fig. 1. Description of injury and possible reactions of the body during infection with Covid-19 (especially in the gastrointestinal tract and cardiovascular system).

4. Conclusion

Through processes involving the dysregulated ACE 2 receptor and TMPRSS2, the SARS-CoV-2 virus has the potential to induce major systemic disease in the GI tract, liver, biliary tract, and pancreas [61]. Because endoscopic procedures are rarely used and patients are treated conservatively, GI bleeding in COVID-19 patients is less prevalent than one might think, and the source of the bleeding is typically unknown. There have been reports of herpetic-like lesions in the upper GI tract, as well as ischemic lesions ascribed to a hypercoagulability syndrome and thrombotic events in the colon [61]. In terms of cardiac complications, heart damage is a common complication in hospitalized patients, whether or not they have had a previous CV, and it has a strong link to in-hospital mortality and a poor developmental prognosis [41]. Due to the observation of new and daily mutations of this dangerous virus, the definitive treatment of this disease is becoming more and more difficult and facing major challenges that it requires many clinical trials and research.

Abbreviations

tract; H1N1: influenza A virus subtype; URI: upper respiratory infection; ALT: Alanine transaminase; AST: aspartate aminotransferase; LDH: Lactate dehydrogenase; CK-MB: Creatine kinase-MB; CRP: C-Reactive Protein; ESR: Erythrocyte sedimentation rate; ARDS: Acute respiratory distress syndrome; HCoVs: Human Coronaviruses; RBD: Receptor-Binding Domain; NTDs: neglected tropical disease; ECG: electrocardiogram.

Conflict of Interests
All authors declare no conflict of interest.

Ethics approval and consent to participate
No human or animals were used in the present research.

Consent for publications
All authors read and approved the final manuscript for publication.

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All the data are embedded in the manuscript.

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All authors had an equal role in study design, work, statistical analysis and manuscript writing.

Informed Consent
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