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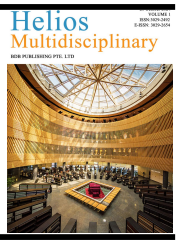

Pathogenesis, Replication, Advance Genetic Variants and Major Organ Effects of COVID-19 Infection. A Literature Review

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ABSTRACT

The COVID-19 (corona virus disease-19) infection has been spread in whole and become a global threat effecting every nation throughout the world. The COVID-19 virus has a complex spike like structure and also exhibits a complex replication process. It can effect different organs of body such as brain, kidneys, lungs, eyes and also induce psychological effects in patients which may lead to serious complications even death. With the passage of time it's genetic makeup is also changing and the new COVID-19 strains are more resistant because of unique flexibility in it's genetic makeup. A number of genetic variants have been identified by researchers to date but no specific treatment has been available against any variant. The aim of our study is to explore the pathogenicity, replication process, major organ effects and different genetic strains of COVID-19 virus that has been identified by researchers currently.

1. Introduction

The virus known as SARS-CoV-2, or severe acute respiratory syndrome coronavirus, first appeared in late December 2019 and is extremely contagious and pathogenic. The acute respiratory illness known as "coronavirus infectious disease-2019 (COVID-19)" is brought on by this SARS-CoV-2 infection. On March 11, 2020, the World Health Organization (WHO) declared this SARS-CoV-2 outbreak to be a major pandemic. SARS-CoV-2 reported around 67 million cases and over 6 million deaths as of January 31, 2023. The World Health Organization (WHO) issued a warning at the end of 2019 on the emergence of infectious diseases (unknown viruses) in Wuhan, Hubei province, central China. These respiratory sickness symptoms, which included fever, dyspnea, and cough, were

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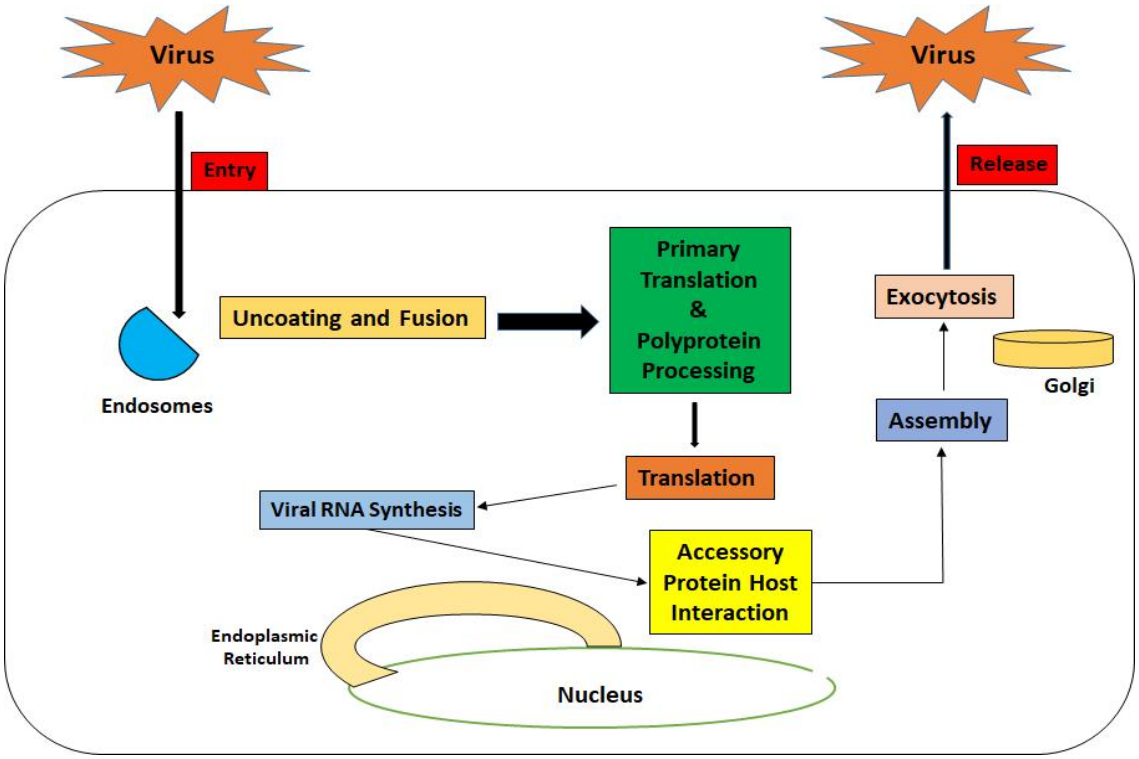
similar to those of viral pneumonia (Saleem et al., 2023). Afterwards, researchers isolated this unidentified virus, carried out high throughput sequencing in December 2019, and discovered a novel strain of the beta type coronavirus (β-COV) (Zhu et al., 2020; Wu et al., 2020). The bat severe acute respiratory syndrome (SARS-SL-CoVZC45 and SL-CoVZXC21 strains with 88% homology), SARS-CoV-1 (79.5% homology), and Middle East respiratory syndrome (MERS) (50% homology) coronaviruses were hereditarily parallel to this new COV strain (Wu et al., 2020; Lu et al., 2020). The WHO and the International Committee on Taxonomy of Viruses (ICTV) officially recognized this unusual β-COV strain as a new strain of SARS-CoV-2 virus due to its genetic similarity to earlier COV strains. Humans' upper (sinus, nose, and throat) and lower (windpipe and lungs) respiratory tracts are directly infected by SARS-CoV-2. Other COV family strains, such as human coronavirus NL63 (hCoV-NL63), hCoV-229E, hCoV-OC43, hCoV-HKU1, and hCoV-NL63, that infect people and cause serious health issues occurred prior to SARS-CoV-2. (Kahn et al., 2005; Hamre et al., 1996; Tyrrell et al., 1966; Lan et al 2020). Most individuals have mild SARS-CoV-2 infections, but certain older adults and those with underlying medical conditions can have serious complication such multi-organ failure and acute respiratory distress syndrome (ARDS). The SARS-CoV-2 disease severity varies between asymptomatic and symptomatic individuals. (Wu et al., 2020; Guan et al., 2020). By January 31, 2023, there were approximately 6.8 million confirmed deaths worldwide from 67 million cases.

2. Structure of SARS-COV-2

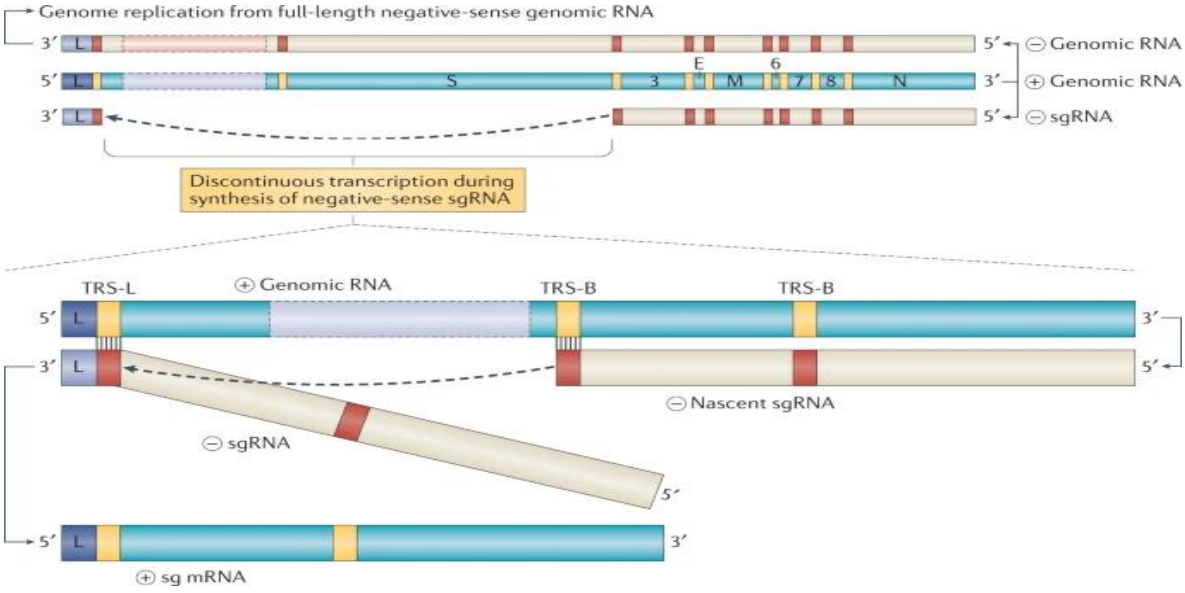
The cause of COVID-19, which spread to become a global pandemic in 2020, is SARS-CoV-2. SARS-CoV-2 is a positive single-stranded RNA (SSRNA) that is spherical, enclosed, non-segmented, and has a genome size of 30 kbp. It is a member of the Corona viridi family. The helical capsid that the nucleo- capsid (N) protein creates and the envelope protein (E) that encloses it protect SARS-CoV-2. (Hofmann et al., 2004; Vennema et al., 1996). Spike (S) protein permits the virus to infect hosts, while membrane (M) and E proteins aid in the assembly of the virus inside the structure of the SARS-CoV-2 protein. The researchers called the novel SARS-CoV-2 strain a coronavirus (the Latin word corona means "crown") because of its "crown-like" spike look (Ren et al., 2006; Wrapp et al., 2020). The replication of covid-19 is in series of stages shown in Figure 1, to release the new virions. (Figure 1)**Figure 1.** Showing the replication cycle of COVID-19 virus (Ren et al., 2006).



Structural proteins, spike (S), envelope (E), membrane (M), nucleocapsid (N), and, for some betacoronaviruses, haemagglutinin-esterase (not shown), make up the coronavirus virion. N encapsidates the positive-sense, single-stranded RNA genome (+ssRNA), while M and E make sure it gets incorporated into the viral particle during assembly. S trimers give cellular entrance receptors selectivity and emerge from the host-derived viral envelope. b | Cell surface serine protease (TMPRSS2) and other host factors, along with specific S interactions with cellular receptors like angiotensin-converting enzyme 2 (ACE2), bind to coronavirus particles and facilitate viral uptake and fusion at the cellular or endosomal membrane. After entry, two big open reading frames, ORF1a and ORF1b, are translated as soon as the incoming genomic RNA is released and uncoated. The polyproteins that result, pp1a and pp1ab, undergo post-translational and co-translational processing to separate into the distinct non-structural proteins (nsps) that comprise the transcription and replication complex of the virus. The biogenesis of viral replication organelles, which include small open double-membrane spherules (DMSs), convoluted membranes (CMs), and characteristic perinuclear double-membrane vesicles (DMVs), is consistent with the expression of non-structural proteins (NSPs). These organelles provide a protective microenvironment for the replication of viral genomic RNA and transcription of subgenomic mRNAs (sg mRNAs), which include the distinctive nested set of coronavirus mRNAs. Structural proteins that have been translated relocate into the membranes of the endoplasmic reticulum (ER) and pass through the ER-to-Golgi intermediate compartment (ERGIC). There, they interact with recently synthesized genomic RNA that has been encapsulated, leading to budding into the lumen of secretory vesicular compartments. Lastly, exocytosis is used to release the virions from the infected cell. Important stages blocked by drugs that are under validation right now and that seem like good antiviral targets are indicated in red. L is the leader sequence; dsRNA is double-stranded RNA; An is the 3′ polyA sequence; cap is the 5′ cap structure; and RdRP is RNA-dependent RNA polymerase.

The creation of coronaviral RNA and discontinuation of replication process is shown in Figure 2, in which both full-length negative-sense copies for genome replication and subgenomic negative-sense RNAs (–sgRNA) to make subgenomic mRNAs (sg mRNA) are produced using full-length positive-sense genomic RNA as a template. One sg mRNA is produced by the negative strand RNA synthesis process, which is demonstrated. It involves a template swap from a body transcription regulatory sequence (TRS-B) to the leader TRS (TRS-L). The distinctive nested set of coronaviral mRNAs will be produced as a result of this process, which can occur at any TRS-B (V' kovski et al., 2021). (Figure 2)

Figure 2. Showing the discontinuation of replication process (Oxley et al., 2020).



3. Pathogenesis of COVID-19

Primarily in China's epidemic zone, the severe symptoms of COVID-19 are linked to an increase in the number and rate of mortality. The China National Health Commission released information on the first 17 deaths on January 22, 2020, and on January 25, 2020, there were 56 deaths total. As of January 25, 2020, the reported 2684 cases with COVID-19 had a mortality rate of roughly 2.84%, with a median age of 75 (with a range of 48–89) years (Wang et al., 2020; Huang et al., 2019). Individuals with COVID-19 infection reported elevated amounts of pro-inflammatory cytokines in their plasma, aberrant respiratory findings, and a greater number of leukocytes. According to one of the COVID-19 case reports, a patient had a body temperature of 39.0 °C, a cough, and coarse breathing sounds coming from both lungs after five days of fever. Real-time polymerase chain reaction findings from the patient's sputum were positive, confirming the COVID-19 infection. Leukocyte counts in the laboratory investigations indicated leucopenia, with 2.91 × 10^9 cells/L, of which 70.0% were neutrophils. Furthermore, blood C-reactive protein was measured and found to be 16.16 mg/L, above the usual range of 0–10 mg/L. D-dimer and erythrocyte sedimentation rate were also found to be elevated (Lei et al., 2020; Huang et al., 2020). As a respiratory system-targeting virus, COVID-19 infection was mostly caused by severe pneumonia, RNAaemia, ground-glass opacities, and acute heart damage. Patients infected with COVID-19 had significantly elevated blood levels of cytokines and chemokines. Elevations of pro-inflammatory cytokines and TNFα (tumor necrosis factor-alpha), have been linked to an increased risk of severe cases admitted to the intensive care unit (Huang et al., 2020; Huang et al., 2020).

4. Effect of COVID-19 virus on different organ

It has quickly reached every continent. The most often afflicted system in individuals who experience a clinical disease as a result of SARS-CoV-2 is the respiratory system. But every organ in the body can be impacted by the virus. In critically ill individuals, organ dysfunction is frequently multifactorial. Angiotensin converting enzyme 2 (ACE2) receptors found in vascular endothelial cells, the brain, kidneys, colon, liver, pharynx, and other tissues are the sites where the virus attaches itself. It may harm these organs directly. Additionally, organ dysfunction results from systemic illnesses brought on by the virus. It is crucial to assess a patient for damage to several organs during care. In the early stages, disturbances in vascular endothelium and coagulation are prevalent but may not cause symptoms. They play a part in harm to several organs. Renal and cardiac problems are prevalent in people who pass away. It's possible for organ damage to show symptoms long after the acute infection has cleared up. At different times, different organs could be impacted. It is possible to sustain a chronic injury. Rehab can be challenging and time-consuming.

5. Effect on endothelial cell

Vasoconstriction results from diffuse lymphocytic endotheliitis, which is caused by SARS-CoV-2 infection of endothelial cells in several organs (Varga et al., 2020). Hypoperfusion from concomitant inflammation, hypercoagulability, and edema results in organ ischemia. COVID-19 does not, however, put patients who already have immune-mediated inflammatory diseases under treatment with anticytokine biologics and other immunomodulatory treatments at higher risk (Haberman et al., 2020).

6. Renal effect

About 15% of patients in Britain who passed away had chronic renal disease. The kidneys have ACE2 receptors (Puelles et al., 2020). The kidney's podocytes, tubular epithelium, and glomerular cells are all home to the virus. Acute kidney injury (AKI) frequently results from systemic abnormalities such as coagulopathy, diabetes, hypertension, hypoxemia, and chronic renal disease. AKI as well as severe hypoperfusion can result from cytokine storms. Rhabdomyolysis brought on by hyperventilation or drugs, such as antivirals like Remdesivir, can also result in acute kidney damage. About 90% of patients in New York who were receiving mechanical ventilation went on to have AKI (Hirsch et al., 2020).

7. Effect on brain

Those with more advanced illnesses are more likely to experience neurological symptoms. They may be caused by changes in carbon dioxide and oxygen levels. These consist of headaches, dizziness, impaired consciousness, delirium, and difficulty rousing oneself. Delirium is a common condition that can cause memory problems and other long-term cognitive impairment. Benzodiazepines are being used for sedation due to a lack of regularly used sedatives such as propofol and dexmedetomidine. They might make delirium worse. Although encephalitis and other virus-related abnormalities are uncommon, hypoxic changes have been observed in the brains of deceased patients (Solomon et al., 2020). Edema and inflammation of the brain can result from cytokine storm. Some patients experience symptoms similar to seizures due to sympathetic storm. A cerebral artery blockage can cause a stroke in young people even if they have never had one before (Oxley et al., 2020).

8. Effect on eye

There are ACE2 receptors and TMPRSS2 proteases in the cornea, inside the eyelids, and in the white of the eye, which are essential for SARS-CoV-2 infection (Zhou et al., 2020).

9. Psychological effects

Financial hardships and social isolation brought on by COVID-19 might lead to a variety of psychiatric issues. There may be a months-long delay. Suicide and drug abuse-related "deaths of despair" are on the rise. Individuals with autism, mental disease, and dementia are more at risk. It is helpful to communicate with friends and support professionals both in person and virtually. A third of patients with dysexecutive syndrome—which includes inattention, disorientation, or clumsy motions in response to commands—have this syndrome when they are discharged from the intensive care unit (Helms et al., 2020).

10. Pulmonary effects

According to autopsy examinations, the individuals had characteristic diffuse alveolar destruction without organization or fibrosis during the acute period (Barton et al., 2020; Xu et al., 2020). Disruption of alveolar and endothelial cells is the cause. Hyaline membrane development and fluid and cellular exudation result from this. There are additional reports of acute fibrinous and organizing pneumonia (Copin et al., 2020). Alveolar fibrin aggregation is what it consists of. There is inflammation of the airways. Alveolar and interstitial edema are brought on by increased capillary permeability. One characteristic that sets COVID-19 apart is vascular angiogenesis (Hariri & Hardin., 2020; Ackermann et al., 2020).

11. SARS-COV-2 variants

The virus's capacity to cause disease can be altered by adaptive mutations in the genome linked to the virus. The ability of the virus to elude the immune system can be seriously disrupted by even a single amino acid mutation, which also makes developing a vaccine against the virus more difficult. Hereditary evolution is a common occurrence for viruses such as SARS-CoV-2, as they adapt to new human hosts by one or more mutations. This leads to the emergence of several distinct variations that differ from the ancestral strains. The WHO and the Centre for Disease Control and Prevention (CDC) have separately established a cataloguing system to separate the new SARS-CoV-2 variations into variants of interest (VOIs) and variants of concern (VOCs) in light of the discovery of many novel variants.

12. COVID-19 variants

Alpha (B.1.1.7)

Comparing the B.1.1.7 variant to the original SARS-CoV-2 strain, there are 23 distinct changes in the viral genome. Of these, eight mutations have been found in the spike (S) protein: N501Y, A570D, P681H, S092A, D1118H, T7161I, Δ69-70 deletion, Δ144 deletion, and S982A. The B.1.1.7 variant's N501Y mutation causes the amino acid at position 501 in the ACE2 receptors of the S protein to change from asparagine to tyrosine, which facilitate the virus's entry into the host cells (Wu et al., 2021; Davies et al 2021; Walensky et al., 2021).

Beta (B.1.351)

Nine distinct mutations (D80A, D215G, R2461, K417 N, E484K, A701V, L18F, D614G, and L18F) are present in the B.1.351 variant of the S protein. Of these, three mutations (K417 N, E484K, and N501Y) are located in the receptor-binding domain (RBD) of the S protein's S1 subunit, which facilitates the virus's entry into host cells (Wu et al., 2021; Wibmer et al., 2021; Mwenda et al., 2020).

Gamma (P.1)

Next up come the P.1 variation, also known as the Gamma variant or GR/501, which was initially discovered in Brazil in December 2020. This P.1 variant carries 17 distinct mutations in the viral genome than the original SARS-CoV-2 strain. Among these, the S mutations consist of 10 variants: T20 N, E484K, K417T, D138Y, N501Y, T10207I, R190S, H655Y, T10207I, and V11176. These contain three alterations that increase the virus's ability to infiltrate host cells: E484K, K417 N, and L184. These mutations are located in the RBD of ACE receptors like beta (B.1.351) (Faria et al., 2021).

Delta variants (B.1.617.2)

In December 2020, the B.1.617.2 variant—also referred to as the Delta variant—was initially identified in India. Because this variety is more than twice as infectious as previous variants, the WHO and CDC designated it as a fourth VOC. In many nations, especially India, this B.1.617.2 variety

is also to blame for the fatal second wave of COVID-19 infections. Ten distinct mutations, including T19R, Δ156-157deletion, L452R, T614G, P781R, R158G, L452R, D950 N, and G142D in the S protein, are present in the B.1.617.2 variation (Zhang et al., 2021).

Omicron variant (B.1.1.529)

There are 18,621 mutations in this Omicron variant. Of these alterations, 558 (3%) are in the extra-genic area while over 17,703 (97%) are in the coding region. As soon as possible, the CDC and WHO designated this Omicron variant as a VOC due to its distinct genome construction from the other variants. Among those, the S proteins contained over 30 mutations (T91, E31del, S33del, R203K, P13L, G204R, Q19E, A63T, Y145del, Y143del, T95I, G142D, H69del, A67V, N501Y, G496S, Y505H, E484A, T478K, S477 N, N440K, K417 N, S371L, S373P, G339D, D796Y, N969K, L981F, Q954H, and S375F) (Gu et al., 2022; Daria et al., 2022). Researchers have recently discovered some concerning mutations, including N501Y, K417 N, D641G, and T478K. These mutations, in addition to the novel ones in the Omicron variant, cause a rise in infections worldwide (Qader et al., 2024).

13. XE, XD, and XF variant

January 2022 saw the UK report the first detection of the XE version. The recombinant BA is the XE version.1 BA.3 mutations are present in the Omicron variant 2: NSP3–C324IT, V1069I, and NSP12–C14599T. This XE version is classified as a VOC by the WHO. The genetic material of the Omicron BA.1 and Delta AY.4 variants is shared by the XD and XF sub variants. Initially discovered in Belgium, Denmark, and France, the XD sub variant in the UK, the XF sub variant was initially discovered in 2022 (Shabbir et al., 2023).

14. Conclusions

The SARS-CoV-2 pandemic has posed a threat to global medical, economic, and public health systems. It can impose very lethal effects on different organs of human body. It is also expected that further unique SARS-CoV-2 mutations would emerge in the future. As a result, work should be done to create comprehensive policies to stop zoonotic eruptions in the future. We think that this post will offer vital and current information regarding SARS-CoV-2.

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Conflict of interest

The authors have no conflict of interest.

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