A Systemic Review on Omicron Variant of SARS-CoV-2

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As the new strains spread around the world, scientists have been trying to learn more about the different strains, especially Omicron, and how SARS-CoV2 acts in general. Studying historical trends of virus spread and the structure of the virus and its strains, as well as all the mechanisms it needs to survive, can help identify the symptoms and diagnose and treat the disease. The research has shown that the new strains, including Omicron, have a higher rate of mutation and transmissibility. Additionally, due to the rapid spread of the virus, there has not been a significant amount of time to understand the severity of the infection. To better understand the novel variants, a detailed analysis of the basic pathophysiology of the virus is needed. This includes transcriptome analysis for the recombination index to identify variation in the strand. This aided in the diagnostic process, and therapeutics for mutants of the virus could be treated. The Omicron strain is particularly threatening due to its rapid transmission rate and its property of immune evasion, which can make it less vulnerable to vaccination.

Keywords: Entry mechanism; Omicron; SARS-CoV-2 Variant.

While in the past, coronaviruses have only been responsible for very mild respiratory infections, with the arrival of COVID-19 in 2019, the whole world was taken by surprise, culminating in a pandemic. The scientific research community and the medical community actively collaborated to develop a vaccine and a method to prevent the spread of the disease. This has resulted in several skills being developed to help deal with similar outbreaks. Having already gone through two to three major waves worldwide, researchers were certainly more prepared when the new strain, Omicron, came to light. There was rapid progress in the field in learning more about the patterns and behaviours of the coronavirus with the new strain. To better understand the variant, it is essential to compare it to the original strain. This would involve studying the morphology and genomic structure of the virus, along with major processes like replication, transcription, recombination, and translation. Understanding how to deal with the new strain would involve studying the infection cycle and the process of diagnosis and treatment for the new strain. Meanwhile, a comparison with the other strains of the virus would also be essential to understanding the patterns of infection based on the mutations in the genome. Alongside this, taking a look at the biomarkers can help identify the disease based on the virus and all its strains to distinguish them and decide the course of treatment for the disease.
Background of coronavirus

Rapid spread of communicable airborne viruses is not an uncommon occurrence. However, coronavirus is among the few outbreaks that have progressed to pandemic levels. The virus has a characteristic crown-like morphology, hence its common and familial names. The first human coronavirus in records is human coronavirus strain B814 (HCoV-B814 and Coronavirus-OC43 (CoV-OC43). These were detected in the respiratory tracts of patients demonstrating symptoms of the common cold. The overlapping features of the pathogenesis are predominant pneumonia, asthma, and chronic bronchitis. The spread is more prevalent in humid and cold climatic conditions. The novel virus was first spread in China between the end of 2002 and the beginning of 2003, then spread worldwide. After isolation, it was planted on a cell line and studied more extensively than strains like 229E and OC43 in particular. It spread in 2002 and stayed an epidemic until 2004. The different strains of coronavirus spread zoonotically through bats while also remaining prevalent in human forms. The second outbreak was MERS-CoV (Middle Eastern respiratory syndrome), for which there was an outbreak in Saudi Arabia in 2012. While most of the coronavirus alpha and beta species proliferated through bats, humans acted as vectors. Human COVID infection rates were low till it emerged in Wuhan, China, resulting in a major outbreak leading to the pandemic. There are a lot of different viral strains under COVID 19. In the 2019 pandemic, there are different strains due to mutations after infections, which will be discussed in detail later. There are several variants of COVID-19 in the world, with Omicron being one of the more recent and possibly more dangerous variants of the disease.

Background of Omicron

Omicron is more easily transmissible in comparison to the delta-variant, or “variant of concern”. There are three hypotheses about the evolutionary history of the O-micron variant of coronavirus. These include poor surveillance, antigenic drift, or zoonosis. Antigenic drift due to host sensitivity and high mutability is the most probable explanation. The mutations could have occurred due to ROS (reactive oxygen species) or the translocation of cytidine deaminases. However, according to RNA assays conducted, the Omicron variant had 31 mutations uncharacteristic of the human-human transition. This introduces the possibility of host shift from transitional vectors like mice. The variant demonstrated rapid transmission, which made it a public threat.

There were several dangerous strains of the family Coronaviridae, which is part of the order Nidovirales. There are four genera under the family Coronaviridae, including alpha, beta, gamma, and delta. Seven strains of Co-Vs were detected in the respiratory tract. Viruses in general are classified on the basis of variants of interest, being monitored, of concern, and variants of consequence and interest. According to this system of classification, Omicron currently is a strain of concern, with a sharp increase in the number of cases across the world.

Morphology of coronavirus strand

They are spherical, positive single-stranded RNA viruses enveloped in a lipid bilayer, containing a structural club-shaped glycoprotein, which is known as a spike protein. It is a triple-enveloped structure containing a membrane, a spike, and an envelope. The virion size varies between 70 and 90 nm. After entry through nasal pathways, the virus can be immobilised and inoculated with 2% paraformaldehyde and 2.5% glutaraldehyde. The virus attaches to the target cells with the help of the spike protein through interaction with the receptor. The virion is either spherical or polymorphic, vested with coronal fibrils on the envelope. The spike protein constructs a homotrimer emerging from the viral surface. The spike is composed of two functional subunits, S1 for binding to the host cell receptor and S2 for fusion of the viral cell membrane with the host cell membrane. The RBD (receptor binding domain) for the spike protein does not possess glycan shielding, resulting in immunodominance of the domain. ACE2 (Angiotensin-converting enzyme-2) was identified as the highest-functioning receptor that enables infection. The binding affinity of ACE2 often determines the severity of the infection. This is dependent on glycans and integrins present in host. The virus genome encodes 9680 amino acids.

Genomic organization

Being an RNA-based single-stranded genome; it can be transcribed and replicated within the capsid transcription to form messenger RNA. The genome contains 16 non-structural and 4 structural proteins. The genome is about 26–32
kb with 6–11 ORFs (open reading frames). The common features among all six known strands include:

- The large gene, separated by ORFs 1a and 1b, covers over two-thirds of the genome. It contains the proteins needed for viral genome replication and sub genomic mRNA synthesis.
- Expressed gene analysis includes RNA coding for spike glycoprotein, small envelope, membrane glycoprotein, and nucleocapsid proteins present in the genome.
- A third of the genome starting from the 3’ end forms a nested set of sub genomic mRNAs (sg mRNA). These sets with high degree of variability are responsible for infliction of host responses, determinant properties of viral pathogenicity.
- The ORF (Open reading frame) of Omicron is highly mutated which defines the mechanism of action, allowing entry of the variant into the membrane through ACE2.
- NSP 4, NSP 5, and NSP10 possess cis acting elements, and the mutation cannot be neutralized by the trans-acting elements of another virus. The action of the mutants can be determined by temperature shift protocols. These cis acting elements act as regulators of the rate of transcription. The positive strand of the RNA is also responsible for the folding and formation of domains.

**Translation**

Coronaviruses bind to cellular proteins through the receptor (i.e., ACE2) and host factor (serine protease TMPRSS2), promoting viral uptake and fusion with the host cell membrane, which is a characteristic move of the virus. After the entry of the virus, the first step is the translation of ORF1a and ORF1b, forming the polyproteins PPLA and PPIAB. The two proteins are precursors for the viral transcription and replication complexes. Meanwhile, a safe microenvironment for replication and transcription is maintained with the help of double-membrane vesicles, convoluted membranes, and small linear vesicles. Further cleavage of PP1A and PP1AB forms NSP1, NSP2, NSP3, and NSP4. Proteolysis releases NSPs 15–16 and NSP4. After proteolytic analysis of viral components, MPRO can be blocked by lead components without affecting the host microenvironment. RTC is also a target for antivirals, having been important for the process of viral replication.

The presence of a 5’-terminal methylated cap on genomic and sub-genomic mRNAs is indicative of a host-ribosome-mediated entry. Based on the pattern analysis of UTR regions, there is a scanning mechanism for the interaction of ribosomes with ORF1. Capping is essential for translation to occur. A leader is responsible for the regulation of translation rate. Promoter with bulged stem-loop conformation acts as a molecular switch for cis-regulation; an alternative but uncommon pathway involves cyclic phosphates, which act on NendoU of NSP15.

**Replication and transcription**

Target recognition site (TRS) is present next to a leader sequence; 70 nucleotides upstream, sub-genomic mRNAs are produced in infected cells. NSP3, NSPNSP4, and NSP6 act as replication organelles. Replication units include NSP3, NSP5, and NSP8. The viral infection cycle progresses through organelles like the endoplasmic reticulum (ER) to form a primitive secretory complex. This is followed by the replicated virions leaving the cell in the form of vesicles. The subgeneric microRNA follows discontinuous transcription. The transcription is the leader-primed transcription, which is then transformed into minus-stranded sub-genomic RNA. Upstream of the leader peptide, transcriptional regulatory sequences are present.

Omicron variants have a higher affinity for infection of the bronchus in comparison to other strains that infect the lungs. The replication process is also less dependent on TMPRSS2 receptor. It is however more dependent on endocytosis. Replication is less efficient in comparison to delta variant. Plus and minus strands are both regulated by cis-acting elements. Enzymatic activity in the viral proteins is required for bioenergetics and duplicating the virus.
- Papain-like proteases formed in NSP3 is
responsible for the deubiquitinating group with finger pal, thumb, and Fingertips containing z spin binding domain.

- ADP(adenosine dinucleotide phosphate) ribose phosphatase with ADRP or X domain in NSP3 responsible for folding, with three layers, is common in other plus strand RNA viruses.
- 3C’ like cysteine proteins in NSP5 with proteinase activity with twelve antiparallel beta-strand alpha helix with Carboxyl terminal domain III
- RNA dependent RNA polymerase with RdRp domain from NSP12 with finger palm thumb-like structure.
- 5’ to 3’ helicases with HEL in NSP12 modelled to E.coli rep helicase, adjacent to zinc-binding domain.
- 3’ to 5’exonucleases with ExoN domain in NSP14, structure like hex helical bundle but not capable of cleaving ribose 2-O methylated RNA substrates.
- Uridylate-specific endonuclease with NendoU domain within NSP15 with a butterfly fold.
- S- adenosylmethionine dependent methyl transferase from NSP16 with a methyl transferase fold.

**Recombination in coronavirus**

Homologous recombination, more prominent in positive-strand RNA viruses, occurs at a rapid rate. It has been discovered in several RNA viruses, which, through natural selection, give them a high genetic advantage to survive. This property also increases the difficulty for virologists to find vaccines for different strains of the virus. Normally, recombination is possible at any point in the viral genome. However, it is known that there are some preferred crossover sites where genetic recombination is far more prominent. Genetic drift refers to a dramatic change in the frequency of an existing allele. This phenomenon occurs significantly with spike protein-coding gene. The genomic instability of coronaviruses can however be used to our advantage through vaccination to cause RNA interference and silence specific genes in the viral genome. Additionally, because of pleiotropy in the modification of spike proteins, selective recombinants can hence be targeted to fight specific strains of the virus. Recombination occurs through reverse genetics with the involvement of NSP-mediated synthesis of RNA. Deletion is also done with the help of virus growth and RNA synthesis. Meanwhile, the N protein is responsible for the rescue of recombinant coronaviruses.

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### Table: Characteristics of Coronavirus Variants

<table>
<thead>
<tr>
<th>No.</th>
<th>Strain</th>
<th>Type of variant</th>
<th>Country of first seen</th>
<th>Date of first case</th>
<th>Characteristic feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alpha</td>
<td>Variant of concern</td>
<td>United Kingdom</td>
<td>September 2020</td>
<td>High severity and rapid circulation</td>
</tr>
<tr>
<td>2</td>
<td>Beta</td>
<td>Variant of concern</td>
<td>South Africa</td>
<td>May 2020</td>
<td>Spike protein mutation, increased transmissibility</td>
</tr>
<tr>
<td>3</td>
<td>Omicron</td>
<td>Variant of concern</td>
<td>Multiple countries</td>
<td>November 2021</td>
<td>Rapid replication rate, immune evasion</td>
</tr>
<tr>
<td>4</td>
<td>Delta</td>
<td>Variant of concern</td>
<td>India</td>
<td>October 2020</td>
<td>High infection rate, 3 mutations in spike proteins</td>
</tr>
<tr>
<td>5</td>
<td>Gamma</td>
<td>Variant of concern</td>
<td>India</td>
<td>November 2020</td>
<td>Completely evades vaccines’ immunization, 3 mutations</td>
</tr>
<tr>
<td>6</td>
<td>Mu</td>
<td>Variant of interest</td>
<td>Peru</td>
<td>December 2020</td>
<td>High mortality rate and high transmissibility</td>
</tr>
<tr>
<td>7</td>
<td>Lambda</td>
<td>Variant of interest</td>
<td>Colombia</td>
<td>Jan 2021</td>
<td>High mortality rate and high transmissibility</td>
</tr>
</tbody>
</table>
because of pleiotropy in the modification of spike proteins, selective recombinants can hence be targeted to fight specific strains of the virus. Recombination occurs through reverse genetics with the involvement of NSP-mediated synthesis of RNA. Deletion is also done with the help of virus growth and RNA synthesis. Meanwhile, the N protein is responsible for the rescue of recombinant coronaviruses 17.

**Immune response to coronavirus**

The body has its own mechanism of natural immunity through the lymphatic system. In order to keep track of microbes entering the body, there is a vesicular exchange between the lymphatic system and the blood. The most important part of the immune system is the WBCs (white blood cells)18. As the lymph moves to a lymph node, there are compartments where known viral antigens can be encountered. If an antigen is recognised, vessels filled with immune cells and antibodies flow through the body19, 20. In the case of SARS-CoV 2, pathogen recognition receptors present in the immune cells, for instance, toll-like receptors 3, 7, and 8, lead to interferon production21, 22. The humoral response meanwhile involves the production of IgG and IgM, which are responsible for the neutralisation of the immune system23. This is also accompanied by B cells targeting N proteins, as well as some targeting S proteins. Meanwhile, when it comes to the active response, there is a cytokine storm due to the hyperactive immune response, resulting in excessive inflammation.

**Biomarkers of COVID-19**

Biomarkers are essential for the diagnosis and prognostic treatment of the disease. An improved immune system and biochemicals injected to treat the disease can target it with the aid of biomarkers. Studying virus propagation techniques can help find biomarkers. Biomarkers can be haematological, biochemical, as well as inflammatory and coagulation biomarkers.

**Haematological**

These markers include the changes derived in blood content following infection with the virus. This includes eosinophil count, platelet count, neutrophil count, lymphocyte count, lymphocyte/neutrophil ratio count, as well as haemoglobin content24. Lymphopenia, which is a drastic decrease in the number of lymphocytes, is associated with a large number of SARS-CoV-2-positive patients. There is a higher leukocyte and neutrophil count, and in severe cases, a lower count of monocytes, eosinophils, and basophils25. The same applies to platelet count, which only drops

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Fig.1. External morphology of mew variant COVID-19
in cases of severe infection. Both T cell and helper T cell counts drop significantly on infection by the virus.

**Biochemical**

The biochemical biomarkers were identified between fatal COVID cases and survivors. In non-survivors, there was a notable surge in bilirubin and creatine kinase (CK), along with an increase in iron concentration in the serum, WBCs, and IL-6. In cases of cardiac injury, this was also accompanied by a surge in cardiac troponin, which can progress into myocarditis and result in multiple organ failure. Multiple organ failure is brought about by the rise in liver enzymes, including aspartate aminotransferase and alanine aminotransferase. Problems with liver function are a definite indicator of infection, as SARS-CoV2 binds to ACE2-positive cholangiocytes in the liver. Inadequate functioning of the liver related to cholangiocytes is associated with COVID-19 infection.

**Inflammatory**

Inflammation of blood vessels is associated with a certain stage of the infection. This is accompanied by an increase in CRP (C-reactive protein), which is a characteristic early feature of COVID-19. Procalcitonin is released by the C cells in the thyroid. This is upregulated by endotoxin cytokines like IL-6, while it is reduced by the secretion of other cytokines (CT) like TNF-. The CT curve is more prominent in comparison to the curve for WBC. Release of IL-6 is associated with a phenomenon known as a cytokine storm, which is responsible for ARDS and acute lung injury. This, along with biochemical markers, is associated with more severe infections among patients.

Coagulation factors are associated with an increase in D-dimer and fibrin degradation products (FDP). The concentration of these products and the rate of coagulation peak when the patient is close to death. With freely circulating thrombin and no anti-coagulants to stop it, fibrinolysis occurs with the help of platelets. This can lead to thrombocytopenia, which is a potentially fatal disseminated intravascular coagulation.

**Diagnosis**

COVID tests are done after the detection of some basic symptoms, including those of the flu, including sore throat, cough, fatigue, and fever. This, however, is not applicable to all patients, as some people are asymptomatic. Nevertheless, the tests used for the diagnosis of SARS-CoV2 are the same, including RT-PCR (reverse transcription polymerase chain reaction), qRT-PCR (real-time

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Fig. 2. Entry, replication mechanism and infection cycle of COVID-19 virus
quantitative reverse transcription PCR), and RT-LAMP (reverse transcription loop-mediated isothermal amplification)\textsuperscript{32}. The incubation time for COVID-19 is approximately 5.2 days. qRT-PCR, which detects ORF1b and N. The RT-PCR test displayed the results after several days (2–8). Meanwhile, the COVID-19 infection can be diagnosed with certainty with positive CT scans\textsuperscript{33}. CT scans have a higher accuracy in comparison to RT-PCR tests. After diagnosis, severe cases are admitted to follow the prognosis, while all other patients are responsible for practising isolation at home. The O-micron variant is also detected with the help of RT-PCR. The process conducts PCR,

<table>
<thead>
<tr>
<th>Name of vaccine</th>
<th>Type of vaccine</th>
<th>Age group</th>
<th>Interval between doses</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/ BioNTech Comirnaty</td>
<td>mRNA</td>
<td>65+ first priority Not for people below 12</td>
<td>21-28 days</td>
<td>95.3%</td>
</tr>
<tr>
<td>AstraZeneca/ Covishield</td>
<td>Chimpanzee adenovirus vector</td>
<td>Health workers and 56+ priority</td>
<td>12-16 weeks interval</td>
<td>78%</td>
</tr>
<tr>
<td>Janssen</td>
<td>Vector virus</td>
<td>Health workers and 56+ priority 18+</td>
<td>14 days</td>
<td>86%</td>
</tr>
<tr>
<td>Moderna</td>
<td>mRNA vaccine</td>
<td>Health workers and 56+ priority 18+</td>
<td>28 days</td>
<td>95%</td>
</tr>
<tr>
<td>Sinopharm</td>
<td>Inactivated vaccine with adjuvant</td>
<td>Health workers and 56+ priority 18+</td>
<td>3-4 weeks</td>
<td>79%</td>
</tr>
<tr>
<td>Sinovac- CoronaVac</td>
<td>Inactivated vaccine with adjuvant</td>
<td>Health workers and 56+ priority 18+</td>
<td>2-4 week</td>
<td>71%</td>
</tr>
<tr>
<td>Bharat biotech COVEXIN</td>
<td>Inactivated vaccine, indigenous</td>
<td>Health workers and 56+ priority 15+</td>
<td>28 weeks</td>
<td>78%</td>
</tr>
</tbody>
</table>

![Fig. 3. Transmission of COVID-19 into various organs](image-url)
followed by looking for the genes responsible for the formation of the parts of the virus, including the spike (S), nucleocapsid (N), or inner area, and envelope (E). If the S gene is not detected, it is possible for the strain to be Omicron 52. This may be followed by genomic sequencing. The symptoms of omicron include aches and pains without taste or smell 34.

**Treatment**

Antivirals can prove to be a successful treatment for flu-like infections in the future. These are prescribed medicines capable of targeting and diminishing a virus. While none of the antivirals have been approved for SARS-CoV2, they can prove to be an efficient remedy for flu-like viruses. Some of the antivirals designed for the coronavirus include lopinavir, which blocks the protease activity of the coronavirus 35. Ribavirin works for a variety of different viruses, targeting SARS-CoV-2 5s RNA dependent RNA polymerase. Meanwhile, Remdesivir and IFN-beta have a high antiviral capability, which reduces the damage caused to the lung cells by COVID 19 36. Meanwhile, chloroquine and hydroxychloroquine are broad-spectrum antivirals as well as immune boosters which can inhibit the virus through a change in endosomal pH resulting in merging of the virion membrane 37, 38. Another class of drugs capable of reducing the extent of COVID-19 infections is corticosteroids, which are capable of reducing swelling in the lungs 39. Monoclonal antibodies are an important part of the COVID-19 treatments and are generally targeted towards the spike protein, which is capable of inducing the response host. SARS-CoV-2, however, has a human-specific monoclonal antibody that can help neutralise the infection 40. This, however, is more challenging to design for new infections, given that it has to be very specific to the antigen 41. Another way to introduce antibodies to the patient is through plasma transfusion, provided that the donor has recovered from COVID and has premade antibodies in the serum. This, however, introduces the probability of graft host rejection 42.

Meanwhile, vaccines are a well-known preventative measure against COVID. The list of vaccines approved by the WHO for COVID has been listed above. Unauthorised vaccines are only to be taken in case of a domestic emergency 43. The functions of the vaccine involve the introduction of a part of a virus, which can alert the immune system and probe lymphocytes to produce antibodies against the virus. When it comes to the treatment of the O-micro strain and others, it is not too different from that of the original strains 44. The severity of the infection has not been confirmed yet, as the long-term reaction has not been monitored. Currently, symptoms of O-micro are managed with the help of corticosteroids by blocking the IL-6 receptor. It has also been confirmed that the strain can be neutralised with the help of monoclonal antibodies 45-52.

**CONCLUSION**

The O-micro strain certainly caused concern for wave. Flipping the pages on the basic features of SARS-CoV-2 can certainly help us compare and contrast to create a clear picture for the diagnosis and treatment of the new strain. This includes studying the genome’s organisation, morphology, replication, transcription, and translation, along with the host’s response, the infection cycle, and general methods of diagnosis and treatment. While the coronavirus has had a negative impact on our lives, it is a point that will be beneficial for progress in the field of virology. With the unique recombination patterns and high transition rates observed in emerging viruses, it is crucial for the field to progress.

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