IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 2 | Mar – Apr 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i2.9

SARS-CoV-2 Variants and Clinical Implications: A Review Article

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ABSTRACT

Introduction: Since being declared a global pandemic on March 11 2020 by the World Health Organization (WHO), the SARS-CoV-2 virus has caused more than 6.7 million global deaths as of January 2023. This literature review is to review the clinical implications of the SARS-COV-2 virus variant. ***Discussion:*** According to WHO, there are five SARS-CoV-2 VOCs have been detected since the start of the pandemic: alpha, beta, gamma, delta, and omicron. SARS-CoV-2 is an RNA virus that, like other RNA viruses, is susceptible to genetic evolution when adapting to a human host, resulting in changes over time and the production of numerous variants with distinct characteristics from the initial strain. Viruses originating from the same lineage may contain different subsets of mutations so that they are classified as different variants. Variants are characterized by their degree of transmissibility, severity of disease, and ability to evade the humoral immune system. ***Conclusion:*** SARS-CoV-2 variants are associated with increased transmission and infection capabilities of the virus through a mechanism based on mutations in the viral protein structure.

Keywords: SARS-CoV-2; pandemic; virus

INTRODUCTION

Since being declared a global pandemic on March 11 2020 by the World Health Organization (WHO), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has caused more than 6.7 million global deaths as of January 2023.[1,2] Like other RNA viruses, SARS-CoV-2 is susceptible to genetic evolution as it adapts to a mutating human host over time.[3]

Ever since the beginning of the pandemic, there are several variants of SARS-CoV-2 have been considered variants of concern (VOC) which are associated with increased virulence, reduced neutralization ability by antibodies obtained through natural infection or vaccination, and reduced effectiveness of vaccination or therapy.[4] As of 4 November 2021, the government of the Republic of Indonesia has reported that 4,246,802 people were confirmed positive for COVID-19 with a total of 143,500 deaths related to COVID-19 or a case fatality rate (CFR) of 3.4%. Data also states that as many as 4,091,938 patients have recovered from COVID-19.[6] Based on data by WHO as of 11 December 2021, five SARS-CoV-2 VOCs have been identified since the start of the pandemic, including alpha, beta, gamma, delta, omicron.[5]

Based on this background, this literature review aims are to discuss the implications of SARS-COV-2 virus variants. It is hoped that this study can contribute knowledge in managing the pandemic caused by the SARS-COV-2 virus.

Coronavirus

Over the past 2 decades, Coronavirus (CoV) has been associated with significant disease outbreaks in the Middle East and East Asia. Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) began to appear in 2002 and 2012 respectively.[6]

Coronaviruses are known to contain exonuclease enzymes that increase replication accuracy by about 15-20-fold in vitro, resulting in mutation rates about 10-fold lower than influenza viruses. Despite this, coronaviruses are capable of accumulating mutations and generating further diversity through the process of recombination when variants with different mutations infect the same host. Recombination between coronaviruses related to different SARS cases allowed the emergence of SARS-CoV-2.[5] In addition, host-mediated addition of RNA molecules by APOBEC and ADAR enzymes, as evidenced by the predominance of C to U complex changes in specific dinucleotide contexts also contributes to the diversity of SARS-CoV-2 variants.[4,6]

Variants of Concern and its Clinical Manifestation

The WHO has assigned simple, easy-to-remember labels to SARS-CoV-2, the virus responsible for COVID-19, and they seek to encourage national authorities, media outlets, and other stakeholders to adopt these labels. Those variants that have been designated by WHO as Variants of Interest (VOI) or Variants of Concern (VOC).

Some VOCs are classified as B.1.1.7, B.1.351, P.1, B.1.617.2, B.1.1.529, etc. Due to their difficult pronunciation, unfamiliar scientific names, and high prevalence of misreporting, people often refer to variants by their detection sites, which is stigmatizing and discriminatory. To prevent this and simplify public communications, later on they become Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) [7,8]

SARS-CoV-2 Variants

1. Alpha Variant

In the second quarter of 2021, the world was shocked with the Alpha variant of SARS-CoV-2. This variant accounted for the majority of infections in the United States and many country in Europe.[6] There were epidemiological studies show that the variant has a higher tendency as much as 50% more transmissible than the variant circulating in the UK with a three to eightfold higher risk of upper respiratory tract failure and a 50% increased risk of death.[9]

The RBD mutations N501Y, P681H, and NTD deletion are among these alpha variant mutations.[10] The mutation results in a condition known as S-gene target failure (SGTF), which has been used as a proxy and identifier for this variant. It precludes amplification of one of the three genomic segments in a routinely used diagnostic PCR test. A number of non-spike changes, such as nsp6: Δ106–108 and nucleocapsid alterations D3L, R203K, and G204R, are also present in the Alpha version. These mutations may enhance transmission in the environment by increasing resistance to innate immunity. [6,10]

The Alpha variant is also susceptible to neutralization by most mAbs and plasma samples from someone previously infected. The fact that the rare Alpha variant is associated with reduced susceptibility to convalescent plasma is consistent with a reduced risk of reinfection.[9] The Alpha variant has shown a 3-fold to 10-fold reduction in susceptibility in approximately 15% of plasma samples from authorized mRNA vaccine recipients. In a cohort study from Israel and Qatar, the BNT162b vaccine also maintained efficacy of more than 90% against the Alpha variant. In a post hoc analysis of the NVX-CoV2373 clinical trial, vaccine effectiveness was reported to be 86.3% against the Alpha variant compared with 96.4% against the non-Alpha variant.[11]

2. Beta Variant

In May 2020, the Beta variety was initially reported in South Africa, where it was associated with a rise in hospital admissions and fatalities throughout the nation's second wave. Additionally, it seems that vaccines are less successful in preventing the COVID-19 Beta form. The Pfizer vaccine is 75% effective in preventing infection from the Beta form after two doses. Nonetheless, the vaccination's 97.4% efficacy against the deadly Beta variant illness is extremely high. [2] Clinical trials on Novavax revealed 89% efficacy in the UK and just 60% in South Africa. In South Africa compared to the US, clinical trials of the Johnson & Johnson vaccination revealed reduced levels of protection against mild to severe COVID-19. The immunological response that the vaccination elicits can be evaded by mutations in the Beta variant's spike protein.[12]

The Beta variant may spread faster than other variants. Current data does not show any comparatively severe disease or death due to this variant.[13] The B.1.351 variant has eight mutations in the S gene, three of the eight mutations are K417N, E484K and N501Y. This variant is also often called 501Y.V2. This B.1.351 variant has 20 times stronger affinity for ACE-2 than the SARS-CoV-2 variant that became an outbreak in Wuhan.[15]

Previous research shows that there is no indication that the symptoms of the beta variant are significantly different from other Covid variants. However, recent research also shows that the beta variant is believed to be more contagious than the wild type but is not thought to cause a more severe disease course.[12,13] Furthermore, it has been found that the beta variation is less neutralized by convalescent serum, post-vaccination serum, and monoclonal antibody treatment, and has a higher risk of transmission. Moreover, as many as 14% of beta variant sufferers show no symptoms and 26% require additional oxygen.[15]

3. Gamma Variant

The Gamma variation, which is thought to be 1.7–2.4 times more transmissible than other local variants in the nation, was first identified in Brazil in November 2020. More than 15,000 occurrences of this variation have been documented from Canada. In [16] Because it shares several alterations with the Alpha and Beta variations, the Gamma form can attach itself to human cells more readily. Transmission is slower than with the Alpha or Delta models, though. Compared to other strains, prior SARS-CoV-2 infection seems to offer less defense against reinfection with the Gamma form. Compared to the Beta form, this one is known to be less resistant to antibody reactions from prior infections or immunizations. Unlike the Gamma variation, whose trend is declining, the Alpha version is a common cause in patients.[15]

One study discovered that the gamma variation of COVID-19 causes a more severe risk spectrum for pediatric individuals. The likelihood of dying did not, however, vary between outbreak waves. Compared to children and adolescents treated during the first wave, patients treated during the second wave required more noninvasive ventilatory assistance, had more substantial hypoxemia, and were admitted to the ICU. The first wave's mortality and in-hospital mortality rates were 766 (7.6%) and 896 (7.7%) in the second.[15] Patients infected with this variety present with several symptoms. The most prevalent symptoms are those that resemble the cold. In [15] Dysgeusia and hypo-/anosmia are more common in younger female patients. With rates ranging from 5 to 87% in COVID-19, the elevated incidence of taste and smell problems has been thought to be a helpful signal for clinical triage of respiratory diseases during the pandemic.

In [16] According to other research, these patients had modest symptoms, including myalgia, physical asthenia, mild coryza, and recurring cough. [19]

4. Delta variant

When it comes to the Delta variant, one dose of the vaccine seems to be less effective, but is still very effective after two doses. Two doses of the Pfizer vaccine are known to be 88% effective against symptomatic disease from the Delta variant. Two doses of AstraZeneca are known to be 60% effective against the Delta variant. However, both vaccines are only 33% effective against the Delta variant after one dose.[16]

The Delta variant more often infects young adults. Children and adults under 50 years of age in the UK have twice the risk of being infected with this variant. The Delta variant was associated with increased disease severity, such as oxygen requirement, ICU admission, or death, compared with other non-VOC variants (aOR=4.90 and 95%CI=1.43–30.78). This variant was associated with significantly higher odds of severe infection (OR=3.02 and 95%CI: 1.41–6.32). Patients infected with this variant are more likely to receive remdesivir and/or corticosteroid treatment.[18] The Delta variant is associated with increased transmissibility when compared with the Alpha variant and reduced levels of antiviral IgG in the upper respiratory tract.[19]

5. Epsilon variant

The epsilon variant is a variant of SARS-CoV-2 which has now been included in the VBM since 21 September 2021 after previously undergoing several status changes from VOI on 26 February 2021, then changing to VOC on 19 March 2021 and being re-designated as VOI on 29 June 2021.[13] Based on research conducted in several regions of the United States including California, Alameda, Santa Clara, and San Francisco by sequencing 2,172 viral genomes, it was found that the epsilon variant is known to have a better ability in transmission as seen from the number of viral loads in positive patients, two times higher and increased infectious ability in in vitro studies. The mutation in the L452R gene in this variant causes an increase in the binding stability of the spike protein in the virus to the ACE2 receptor in humans, thereby causing an increase in the ability of the virus to infect.[20]

Based on data compiled by the Washington Department of Health, it was found that the epsilon variant was found in around 2.5% of all hospitalized cases with a mortality of 0.7% of the total deaths due to SARS-CoV-2. In addition, based on the same source, it was found that the epsilon variant tends to be found in the 0-19-year age group at 25%, the 20-34-year age group at 31%, and the 35-49-year age group at 22% of the total COVID-19 cases. which is known to be caused by the epsilon variant. [19,20]

6. Omicron variant

The omicron variant was first discovered based on sequencing results in a COVID-19 case in Botswana on 11 November 2021, then followed by a case in Hong Kong, where the patient was a traveler from South Africa.[10] This finding was based on the failure to identify the S gene during examination using the PCR method. due to a deletion that is almost similar to the deletion found in the Alpha variant.[21]

This variant has 30 modifications to its amino acids, three deletions and one insertion. [21] Based on the genetic changes that occur in this variant, the omicron variant has a higher transmission potential than previous variants. Apart from that, the omicron variant also has the ability to neutralize antibodies that have been formed from infection with previous variants and as a result of vaccination.[10]

The high transmissibility of the Omicron variant can be influenced by numerous factors. More than 30 mutations have been found in the spike protein, which is where the SARS-CoV-2 protein detects host cells, according to genome sequence data from the Omicron variety. Analysis of these mutation data points to the potential for enhanced transmission through immune-evading pathways. The primary cause of increased transmission is the N501Y mutation's increased binding affinity with the ACE2 receptor; this binding affinity is further strengthened when combined with the Q498R mutation. Furthermore, it is evident that individuals who have already contracted the Omicron strain of COVID-19 have a higher risk of reinfection. [20]

7. Omicron subvariant

To date, several studies have shown that there are at least 310 Pango Lineages related to the Omicron variant, but the sub-variants determined to date are BA.1 (B.1.1.529.1) and BA.2 (B.1.1.529.2), BA .3 (B.1.1.529.3), BA.4 (B.1.1.529.4) and BA.5 (B.1.1.529.5). They share many mutations, but also differ significantly. In general, BA.1 and BA.2 share 32 mutations. BA.1 itself is divided into two, the original BA.1 and BA.1.1 (or B.1.1.529.1.1) where the main difference is that the latter has the R346K mutation [23]

BA.1 was initially the most common sub variant detected worldwide, but BA.2 overtook BA.1 as the dominant variant globally. BA.1 and BA.2 share many common mutations, but each also has unique mutations for example BA.2 has an additional 8 unique mutations not found in BA.1 and lacks 13 mutations that BA.1 has. Recently there were two new sub variants, namely BA.4 and BA.5, which were discovered in South Africa, and were subsequently detected in countries such as Belgium, France, China, Botswana, Portugal, Germany and Australia. [23,24]

According to research, BA.2 has a 30% to 60% higher transmission rate than BA.1. BA.2 was first known to be present in samples from November 15, 2021. As of January 17, 2022, BA.2 has been detected in at least 40 countries and on all continents except Antarctica. A study from Strasser et al in the UK in late October 2022 found that BA.2 actually caused less severe disease compared to BA.1 (which was less severe disease compared to the delta variant).[22]

TABLE 1: The variants of Covid and the clinical implications.

	Alpha Variant	Beta Variant	Gamma Variant	Delta Variant	Epsilon Variant	Omicron Variant
Mutation of viral component	Non-spike mutation nsp6: Δ106–108 dan mutasi nukleokapsid D3L, R203K dan G204R	The B.1.351 variant has 8 mutations in the S gene, three of the eight mutations are K417N, E484K and N501Y. This variant is also often called 501Y.V2. This B.1.351 variant has 20 times stronger affinity for ACE-2 than the variant that caused the outbreak in Wuhan	This variant has 10 mutations including N501Y and E484K.	The increased transmissibility of the Delta variant has been linked to mutations in D614G, L452R, P681R, and T478K in the S protein. Increased affinity of the S-protein and ACE2 has been postulated as the main reason for the reduced vaccine efficacy in the Delta variant.	increasing the stability of the spike protein binding in viruses to the ACE2 receptor in humans, causing an increase in the ability of viral infections	There are 30 modifications to the amino acid, three deletions and one insertion, causing the omicron variant to have a higher transmission potential than previous variants
Transmission rate	50% more transmissible than the previously circulating UK variant	More infectious than Alpha but slower than Delta	Transmission is not as fast as the Alpha or Delta variants	It is highly contagious beyond the Alpha variant	better in transmission in terms of the number of viral loads in positive patients which is 2 times higher and increased ability of infection in in vitro studies	has a higher transmission potential than previous variants
Disease severity	With a three to eightfold higher risk of upper airway failure and a 50% increased risk of death	The variant with the highest risk of hospitalization	Increases the risk of hospitalization by 1.52 times compared to the wild type virus	was associated with increased disease severity, such as oxygen requirement, ICU admission, or death, compared with other non-VOC variants	The epsilon variant is associated with a hospitalization rate of 2.6% with a mortality rate of 0.7%.	The omicron variant is associated with a hospitalization rate of 1.4% with a mortality rate of 0.5%.
Ability to evade the humoral immune system	The RBD-2 and RBD-3 antibodies associated with humoral escape from the virus are strongly influenced by the p.K417N/T, p.E484K/A and p.N501Y mutations found in the Alpha variant of concern	Mutations in the spike protein of the Beta variant can evade the immune response elicited by the vaccine	This variant mutation increases receptor affinity and reduces ACE2 neutralization of anti-RBD antibodies	Mutations in the ACE2 receptor binding domain abrogated binding to some monoclonal antibodies but did not increase ACE2 binding, indicating that these delta variant mutations arise to evade immune recognition. Remodeling of the N-terminal domain allows the delta variant to escape recognition by most neutralizing antibodies.	three mutations in the epsilon variant affect the N-terminal domain of the glycoprotein. This resulted in complete neutralization of the 10 antibodies tested specific for the N-terminal domain in the glycoprotein.	Fourteen mutations in Omikron (K417N, G446S (BA.1), E484A, Q493R, G496S (BA.1), Q498R and to a lesser extent, G339D, S371L/F (BA.1/BA.2), S373P, N440K, S477N, T478K, N501Y and Y505H) may affect antibody binding.

	Alpha Variant	Beta Variant	Gamma Variant	Delta Variant	Epsilon Variant	Omicron Variant
General symptoms	Fever, cough and rhinitis. Median Ct value was 24.0 (min 17.0; max 32.7)	There is no indication that the symptoms of the beta variant are significantly different from other Covid variants	Stomach pain, diarrhea, nausea, or vomiting	Cough, fever, vomiting, diarrhea, sore throat, shortness of breath and headache. Other symptoms: loss of taste, myalgia, fatigue, anosmia, and rhinorrhea	headache, muscle aches, fever, anosmia, cough and sore throat, shortness of breath, nausea, vomiting, diarrhea, abdominal pain	sore throat and cough. headache, fever, muscle pain, nausea, vomiting, anosmia and shortness of breath, diarrhea and abdominal pain
Mortality	Death depends on age. age <70 years, case fatality rate 0.84%. Age >70, case fatality rate 31.5%	Causes a 1.5 times higher risk of death than the wild type virus	Causes a 1.22 times higher risk of death than the wild type virus	The Delta variant caused death in at least one person who had been fully vaccinated against COVID-19	found in 2.5% of all cases, mortality was 0.7% of total cases of death due to SARS-CoV-2	The epsilon variant is associated with a hospitalization rate of 1.4% with a mortality rate of 0.5%.

CONCLUSION

Even though the SARS-Cov-19 virus has a more accurate replication ability with a lower mutation rate than the influenza virus, the accumulation of mutations that occur has led to the existence of new variants of this virus. These variants are generally associated with increased transmission and infection capabilities of the virus through a mechanism based on mutations in the viral protein structure. The Delta variant was known to be associated with the highest transmissibility and highest severity of illness compared to other variants.

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