IJBPAS, October, 2022, 11(10): 4578-4585

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

SARS COV-2 OMICRON VARIANT (B.1.1.529)- A REVIEW

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Received 17th Nov. 2021; Revised 24th Dec. 2021; Accepted 18th Feb. 2022; Available online 1st Oct. 2022

https://doi.org/10.31032/IJBPAS/2021/11.10.6461

ABSTRACT

Coronavirus disease (COVID-19) is a highly contagious disease that has caused a global health crisis with the death of more than 3 million people worldwide. It is caused by the SARS CoV-2 virus. Ever since the outbreak of the disease, the virus has been mutating constantly giving many variants. The delta variant that originated in Maharashtra, India has caused severe health issues and death. Other variants are alpha, beta, gamma, lambda, and mu. In November 2021, a variant of SARS CoV-2 was discovered in South Africa. The variant is named Omicron and WHO announced it as the Variant of Concern (VOC). This review article highlights the phylogenetics and features of the omicron variant.

Keywords: Omicron, SARS, COV-2, Covid-19

INTRODUCTION

COVID-19 is a viral disease caused by the SARS CoV-2, that is threatening the world for the past 2 years. It originated in Wuhan, China in 2019, where a group of pneumonia cases of unknown origin was reported to the WHO on the 31st December 2019. The WHO identified the cause for the disease to be the novel coronavirus on the 7th of January 2020 and announced it as a global pandemic on the 11th of March 2020. Symptoms of COVID-19 include fever, tiredness, cough, loss of taste and smell and

less common symptoms include sore throat, rashes, aches, diarrhea, headache, and eye irritation. Serious symptoms include difficulty in breathing, shortness of breath, loss of speech, and mobility, and chest pain. The disease severely affects immunocompromised patients and the geriatric population. It spreads through infected droplets that are emitted from an infected person during any action like sneezing, coughing, singing, speaking, or even breathing. Hence strict COVID-19 protocol needs to be followed to prevent the spread of the disease **[1]**.

Ever since the outbreak of COVID-19, India has faced two waves of the disease. Though the primary wave was mild, the second was devastating. The latter caused the approximate demise of 400,000 people in India. The delta variant of the SARS CoV-2 has prompted the second wave of the COVID-19. Other variants of the virus are alpha, beta, gamma, lambda, and mu. Since late 2020, vaccines were made globally that emerged as a ray of hope to fight against the contagious COVID-19 infection. Unfortunately, there is decreased vaccines effectiveness because the antibodies fail to neutralize the alpha, beta, and delta variants due to the mutation acquired by these strains **[2]**.

In early November 2021, a new variant of the SARS CoV-2 was discovered in Botswana, South Africa called the omicron variant. It was reported as a new variant to the WHO on the 24th November 2021 and, the WHO announced it as the variant of concern (VOC) on the 26th November 2021. The mode of spread and severity is unclear. The omicron variant of the SARS CoV-2 is found to have the highest number of mutations of at least 32 mutations in the spike protein alone compared to the previous delta variant with 16 mutations **[3]**. This strain is considered to be milder as suggested by a physician from South Africa. The omicron variant of SARS CoV-2 has been detected in around 60 countries globally **[4]**.

Salient features of the omicron variant of SARS CoV-2

- There is a 10-40 folds reduction of the neutralizing capacity of the antibodies in the omicron variant.
- The Omicron variant is 3 times more infectious and severe than the original Wuhan strain.
- The incubation period is lesser than the delta variant, probably 3 days as per a Norwegian study **[5]**.
- It is causing infections in already vaccinated individuals.
- It is found to have the highest number of mutations of at least 32 mutations in the spike protein alone.
- It exhibits a high risk of reinfection, more rapid doubling time, and

increased transmission rate than the delta variant.

- Possess increased affinity to the ACE2 receptors compared to the delta variant.
- The omicron variant could be from the B.1.1.519 (20B) lineage and this is further divided into 2 subclades- BA.1 and BA.2 according to the phylogenetic analysis.
- Studies by Pfizer Inc. suggested that the booster dose with BNT162b2 can provide protection against omicron.
- Phylogenetic analysis shows a close resemblance of the omicron variant of SARS CoV-2 to the alpha variant.

Phylogenetic analysis of omicron variant

The phylogenetics of the omicron variant revealed a distinct monophyletic clade as per the ultra-metric and the metric clustering method and in contrast to the former method, the omicron variant has a close relationship with the alpha variant according to the NJ method. The genome alignment showed as high as 43 to 63 gaps in the omicron variant.

Method of the genome study includes the collection of the genome from each SARS CoV-2 variant, from the GSAID. Sequencing of the genome and generation of the phylogenetic tree. The number of nucleotide changes was in the order as follows: SARS-CoV-2 USA isolate > Mu variant > Beta variant > Delta variant > Gamma variant > Alpha variant > Omicron variant, with 141, 140, 138, 132, 130, and 109 mutations, respectively. According to the Neighbor-Joining (NJ) method, there is a close resemblance of the omicron variant with the alpha variant. This explains that the omicron variant could have been in circulation for a lengthy period before its discovery **[3]**.

According to the phylogenetic analysis, the omicron variant could be from the B.1.1.519 (20B) lineage. This has 2 subclades- subclade 1(417K, 440N, and 446G) is commonly found in South Africa. It has a low sequence frequency. Subclade 2 (417N, 440K, and 446S) is found globally and has a high sequence frequency. The subclades are found to have either K417N mutation or K440N and S446K mutations. The mutations in the omicron variant are found in the NTD, RBD, RBM, furin cleavage site, and S2 domain. The N-Terminal Domain (NTD) of the S protein (spike protein) has 4 major mutation groups. They are - Group1: A67V, H69del, V70; Group 2: T95I; Group 3: insertion 214-215. These mutations affect the viral binding with the ACE2 receptor and also the antibody binding, which hinders the neutralization. The Omicron variant can be used as a reference

strain for the development of future vaccines since the virus has multiple mutations in the area that bears numerous antigenic epitopes **[6]**.

Symptoms associated with the omicron variant

Common symptoms include cough, runny/stuffy nose, fatigue/lethargy, sore throat, and fever. The incubation period is probably 3 days, which is less than the delta variant and other variants **[5]**.

Details on mutation

The ability of the antibodies to neutralize the virus from previous infection or vaccination is reduced due to many mutations. However, the data generated is restricted to monoclonal antibodies and, that of polyclonal antibodies is unknown. The binding of the antibodies with the receptor-binding domain of the spike protein can be intervened by the mutations such as G446S, Q493R, and G496S, whereas mutations such as E484A and Y505H may restrict antibodies interactions.

A total of 30 mutations were observed in the omicron variant that is considered as significant mutations -A76V, T95I, Y145del, G339D, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F, Y505H, L212I, S371L, S373P, S375F, K417N. 23 mutations among the 30 are definite to the omicron variant. Furthermore, 9 additional mutations were found to be identical in all omicron sequences which are ORF1a: K856R, ORF1a: L2084I, ORF1a: A2710T, ORF1a: P3395H, ORF1a: I3758V, ORF1a: T3255I, ORF1b: P314L, ORF1b: I1566V, and ORF9b: P10S. Among the above, only two mutations (ORF1a: T3255I or nsp4: T492I and ORF1b: P314L or nsp12: P323L) were the same as that of the Delta and Delta Plus variants **[7]**. The mutation in the nucleocapsid R203K and G204R also contributes to its replication **[8]**.

The pseudotyped omicron variant constructed by using VSV vector and the spike proteins of omicron with all 32 mutations were found to cause about 8.4 folds reduction of the neutralizing antibodies titer compared to the reference strain (pseudotyped strains of alpha, beta, gamma, delta, lambda, mu) with only 1.6 folds reduction **[9]**.

The reason behind such a large number of mutations in the omicron variant is unclear. The omicron was first identified in an immunocompromised patient and it is possible that all the mutations could have occurred within the same viral genome in the same patient. A genome sequencing before and after the occurrence of omicron can aid to detect if the omicron strain has occurred in the same patient or emerged through multiple patients **[6]**.

Omicron vs Delta

A computational study revealed that the omicron variant having many mutations has a high level of transmission capacity compared to the delta variant due to the high affinity of the omicron variant to the ACE2 receptors. Omicron has a high docking score compared to the delta variant that explains the increased affinity towards the ACE2 receptors. Half of the mutations in the omicron variant took place in the receptor-binding domain of the spike protein. Such high mutation in the omicron variant compared to the delta variant proposes that the omicron variant may have more immunogenicity towards antibody-mediated protection compared to the delta variant.

The omicron variant has 1270 amino acids which are three amino acids lesser than the wild Wuhan Hu-1 variant and 2 amino acids lesser than the delta variant still, the omicron variant is found to have high molecular weight and theoretical protein's isoelectric point (pI) compared to the Wuhan Hu-1 variant and the delta variant. The omicron variant has a high composition of amino acids like Phenylalanine (P), Isoleucine(I) in the spike compared to the delta variant and low composition of amino acids like Asparagine (N), Glutamine (Q). The receptor-binding protein of the spike protein of the omicron variant has a high level of amino acids like Leucine (L), Phenylalanine (F), and Proline (P).

The omicron variant has an increased alpha helix composition compared to the delta variant. It has a lesser disordered area (8 in omicron and 1 in omicron RBD) compared to the delta variant, and also there is a higher transition of disordered to the ordered area in the omicron **[10]**.

Antibodies effect against omicron variant

There is a 10-40 folds reduction of the neutralizing capacity of the antibodies in the omicron variant. It neutralizes many monoclonal antibodies except LY-CoV555, LY−CoV016, REGN10933, AZD1061. Omicron could get away with most of the existing SARS-CoV-2 antibody drugs targeted spike regions, such as LY233 CoV016/LY-CoV555 cocktail, REGN-10933/REGN-109876, etc. cocktail according to the already existing studies. Prior infection in vaccinated individuals also provides more protection and increased neutralizing antibody titer is evident **[2]**.

The omicron variant, with more than 30 mutations in the spike protein is also found to be resistant and nullify the effects of the antibodies from previous infection or vaccination. The corona vaccines and BNT162b2 vaccines were found to be less effective in neutralizing the omicron variant. Mutations in spike protein 446 and

493 also affect the monoclonal antibodies binding. Studies by Pfizer Inc. suggested that the booster dose with BNT162b2 can provide protection against omicron **[11]**.

Possible diagnostic options

SARS CoV-2 variants are detected using the RT-PCR test that is widely used. Omicron variant is detected through RT-PCR using the 452L marker that was developed by the 1st of December 2021 by the TCDK. People who tested positive in RT-PCR will be subjected to the Whole Genome Sequencing (WGS) **[12]**. Antigen tests can also be used but they are not as accurate as the former. But antigen test can be used as a home kit, and yields result rapidly and easily. According to this study, the antigen test detects the omicron variant of SARS-CoV-2 with the same accuracy as the other variants **[13]**.

Prevention and Treatment

WHO has proposed COVID-19 protocol and that must be strictly followed. Imposing lockdown would greatly impact the control of the disease spread. A homologous or heterologous booster dose can provide more protection and a 25 – 100 folds increase in the antibody titer compared to immunization with just 2 dose vaccines **[2]**.

According to early data, the omicron variant weakens vaccine protection since almost all vaccines aim to act on the spike protein. As far as the small molecular drug is concerned, remdesivir is an intravenous drug approved by the FDA against the COVID-19 infection until its effect was proved controversial.

Paxlovid is a broad-spectrum antibiotic that acts as a protease inhibitor developed by Pfizer Inc. that is believed to be effective against multiple COVID-19 variants including the omicron based on animal studies. It was found to be safe and tolerated and produced no adverse effects when tested at oral dosing of 600 mg/kg/day in monkeys and 1000 mg/kg/day in rats for 14 days. It is also found to have favorable oral bioavailability and pharmacokinetic properties. When phase II/III trial was conducted in humans with SARS CoV-2 infection, paxlovid reduced the risk of hospitalization and death by 89%. Misuse of the drug could lead to clinical resistance **[14]**.

CONCLUSION

Prevention is better than cure, and hence stringent measures have to be taken to control the rapid disease spread. Guidelines should be strictly followed. Omicron is a new variant of the SARS CoV-2 hence only limited data is available. Further studies help to provide an in-depth vision of this new variant. Based on the above pieces of evidence, a booster dose would greatly help to produce antibodies to neutralize the omicron.

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