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A Comprehensive Review on Biomolecular Modifications Associated with Coronaviruses

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Abstract: Coronaviruses are enveloped RNA viruses having wide range of applications in pharmaceuticals, medical and biomedical fields. The finding of a recently discovered coronavirus as the root of severe acute respiratory syndrome has increased attentiveness in this viral family during the previous years (SARS). From 2019 to 2022, world has suffered with a serious issue and every stage of people has been affected. In March 2020, WHO announced corona virus as a disease also called COVID-19. At the molecular level, coronaviruses employ a variety of novel methods to carry out a sophisticated system of expression of genes. Coronavirus replication depends on ribosomal frameshifting during genomic translating steps, the synthesis of multiple subgenomic RNA species, and the assembly of virus replication by a method exclusive to encapsulated RNA viruses. According to experimental research, SARS-CoV-2 has a genomic sequence that is 96.2% identical to a bat CoV RaTG13 and 79.5% identical to SARS-CoV. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has undergone various mutations during its Global Circulation. This comprehensive review contains the summary of detailed biomolecular modification related to its different variants. SARS-CoV-2 variants are differentiated into 3 class based on their risk analysis: VOI (Variants of interest), Variants of high consequences and VOC (Variants of public health importance or concern). Such variants with different genetic modifications have been directly related to mortality, morbidity rate and severity as well.

Keywords: Biomolecular modifications, Coronavirus, Disease, SARS-CoV, Variants.

I. Introduction

World Health Organization has announced corona virus case as a disease in March 2020 which is also known as COVID-19. In December 2019, the first case of Corona Virus was reported in China. It is a deadly virus which affect the respiratory tract. It was rapidly spread across the countries around the world. Some of the major symptoms of the virus are fever, cough, tiredness, and difficulty in breathing. At the early stages, because of the mild symptoms people treated it as a mild flu. This virus can be spread by inhaling the droplets in surrounding or it can also be spread by touching the infected in person or infected surface. This virus severely impacted the social lives of people as many of the schools, colleges, and universities and other gathering areas etc. were closed. Festivals, many social and religious ceremonies were suddenly postponed and cancelled [1].

On January 30, the first known case was reported in India. By March 15, a total of 107 laboratory - confirmed patients had been recorded. India experienced around 1071 positive and identified cases with more than 30 fatalities on March 30. According to ICMR, India's case rate would drop to 62% if quarantine and social isolation were successfully implemented. The number of COVID-19 cases peaked on May 18 at 1, 01 and 139. India witnessed total of 1, 90, 648 positively identified cases based on laboratory tests with more than 5400 deaths from this disease at the end of all lockdown phases, up from a low number of positive cases during lockdown due to limited transmission and social distance [2].

For the restriction of community spread of virus various measures where implemented globally which includes promoting isolation quarantine tracking contacts of positive cases during quarantine, sealing of boarders. On 21 January, India began thermal screening of passengers arriving from China. India government stopped issuing new visas on 3rd March and all citizens of India who were travelling through Covid-affected nations were placed in quarantine for 14 days.

On 22 March, Indian Government announced a Curfew (Janata Curfew) wherein people were instructed to remain at home for benefit of people. After this a lockdown was imposed in all districts where positive cases were reported. On 24th March a 21-days national lockdown was announced i.e., from 24th March to 14th April. This lockdown was further extended until May 3rd. On 1st May a third lockdown extending until 17th May was announced which as followed by a fourth lockdown till 31st May 2020 followed by a fifth lockdown which was for infected areas [3].

After the spreading or communication of CoV or corona viruses, ministerial departments of India have divided into different zones like green zone, red zone, and orange zone according to the number of coronavirus cases living in different zones.

Red zone were the areas with highest number of positive cases areas like metro cities such as Delhi, Mumbai, Kolkata. These areas were also called as coronavirus hotspots. Areas which were having limited number of cases and no instant surge in positive cases were categorized under orange zone. Areas with least number of positive cases were categorized under green zone. For the safety of country`s citizens government of India also launched a COVID-19 tracking application. "AAROGYA SETU" on 2nd April 2020. The aim of the application was too involved people proactively in best relevant practices and to make them follow all the advisories to cope well with virus outbreak [4].

After the implementation of all the guidelines, precautions and lockdown still the virus outbreak was not under control because of one prime reason that is the continuous imolecular modification of the virus. Genome structure of the virus rapidly adopting new forms and each time it was different from the existing one. This is also one of the main reasons that delayed the vaccine production.

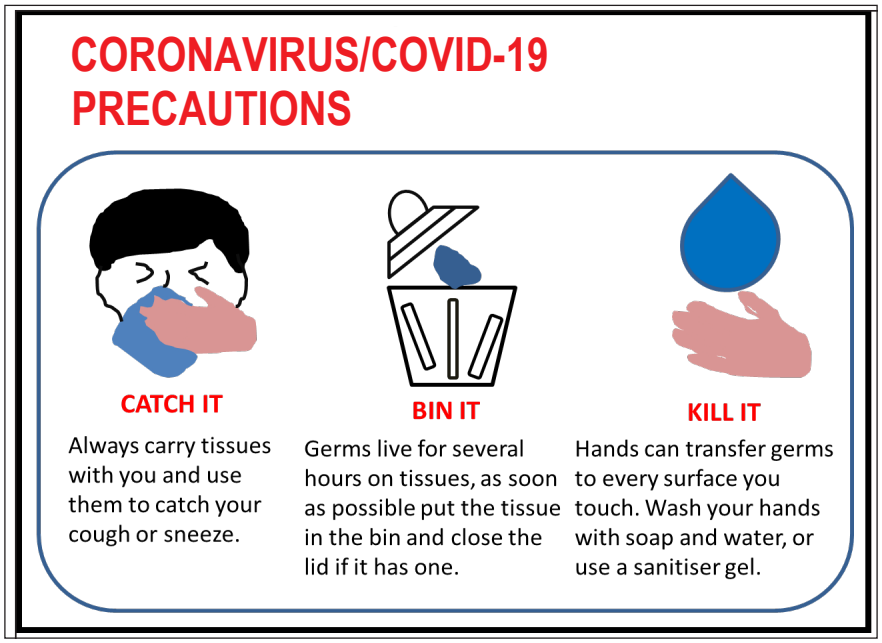

Fig. 1: Precautions against Coronavirus

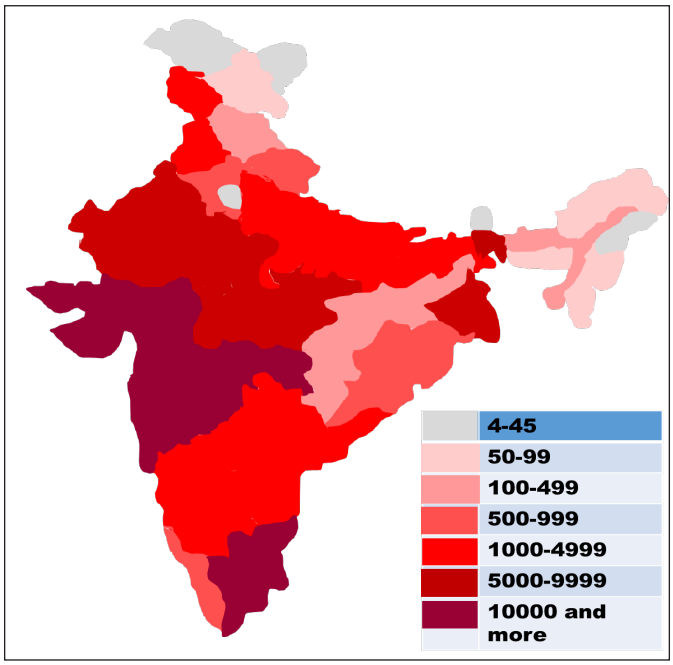

Fig. 2: Geographical Representation of World-Wide Distribution of COVID-19 in India (Per Day)

Coronavirus is considered as a Zoonotic virus having family Coronaviridae of the order Nidovirales. They were first isolated in 1937 and are generally responsible for causing respiratory infections. Their clinical spectrum is quite wide which can range from a simple fever to severe pneumonia [5]. Coronavirus is enveloped positive sense single strand RNA virus having diameter 60-140 nm and genome size 36-42 kb [6].

Coronavirus have spike like projections on their surface which gives them crown like appearance under electron microscope due to this unique morphology they are designated as Coronavirus [7].

II. Classification

Coronavirus belongs to Coronaviridae family of the order Nidovirales. Coronaviridae is further consist of 2 subfamilies which are:

1. Coronavirinae
2. Torovirinae

Members of Coronavirinae are further subdivided into 4 General:

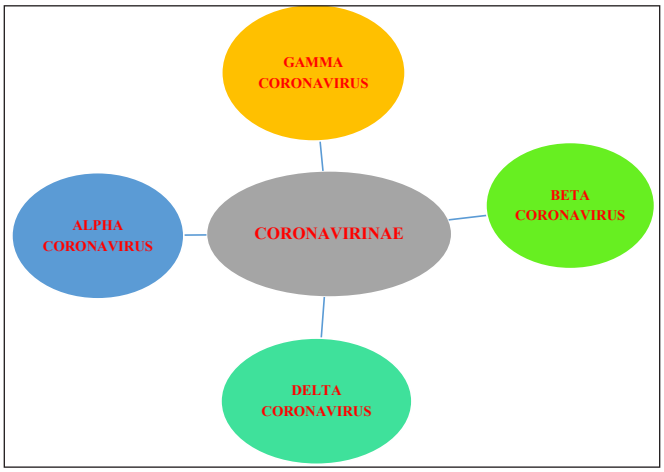

Fig. 3: Members of Coronaviriane

1. Alpha Coronavirus - Having human coronavirus
   a) HCoV-229E
   b) HCoV-NL63
2. Beta Coronavirus
   a) HCoV-OC43
   b) HCoV-HKU1
   c) SARS-CoV- (severe acute respiratory syndrome coronavirus)
   d) MERS-CoV- (Middle East respiratory syndrome coronavirus)
   e) SARS-CoV-2- (which causes coronavirus disease 2019 also called COVID-19)
3. Gamma Coronavirus - Having viruses of Whales and Birds.
4. Delta Coronavirus - Having viruses which are isolated from Pigs and Birds.

Alpha and Beta coronavirus can infect Mammals and the other two Gamma and Delta infect Birds. From Alpha and Beta genera human susceptible virus are identified.

Alpha CoVs like HCov-229E and HCoV-NL63 and Beta CoVs like HCoV-HKU1 and HCoV-OC43 have low pathogenicity and are responsible for causing mild respiratory symptoms like common cold but on the contrary other Beta CoVs like SARS-CoV, SARS-CoV-2 and MERS-CoV are responsible for causing severe and fatal respiratory tract infection.

III. History

1st case of coronavirus in human body was found by Tyrrell and Bynoe in year 1965. They observed it is human embryonic tracheal organ culture which was obtained from respiratory tract of a person having symptoms like common cold [8]. Information about human coronavirus was very limited until the outbreak of (SARS-CoV) severe acute respiratory syndrome coronavirus in 2002 [9].

Again in 2012 a novel coronavirus was isolated in Saudi Arabian patient having severe acute respiratory syndrome. It was named Middle East respiratory syndrome coronavirus (MERS-CoV). MERS-CoV became a major public concern because 1386 cases out of which 587 deaths were reported by Saudi authorities up to 2016. Coronavirus became a topic of interest after MARS-CoV Outbreak [10]. After 2012 similar kind of epidemic broke out in 2019 in Wuhan, China, it was named as SARS-CoV-2 because of its similarity to SARS-CoV after genome sequencing of COVID-19 it was analyzed and it showed 96.2% similarity to Bat CoV RaTG13 genome [11].

IV. Origin

A. MERS-CoV

MERS-CoV is a type of beta coronavirus and its genotype is very similar with Bat coronavirus. From the same lineage like BtCoV - HKU5 and BtCoV - HKU4 that`s why it was consider that MERS-CoV like other coronaviruses was emerged from bats.

Large screening study was conducted between 2009 and 2011 for beta coronaviruses on 5030 bats` fecal specimens. 4758 bats of 10 different species were included from Ghana and 272 Pipistrellus bats were included from 4 European countries. Coronavirus RNA was detected by (RT-PCR) Reverse Transcription Polymerase Chain Reaction.

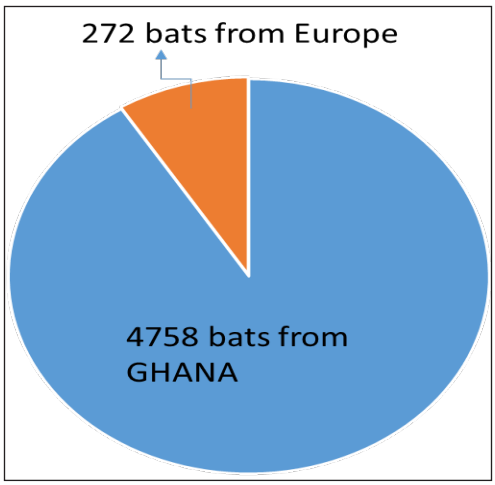

Fig. 4: Beta Coronaviruses on 5030 Bats Fecal Specimens

From that study, it was observed that only Nycterisgambiensis carries 2c Beta-coronavirus in Ghana and around one fourth of 185 Nycteris tested positive and it was 1% of whole tested bat`s population from Ghana. 40 out of 272 that is (14.7%) Pipistrellus bats species in Europe were positive and had 2c beta-coronavirus.

Both 2c beta-coronavirus isolated were very genetically similar to MERS-CoV. Because of this study it was concluded that MERS-CoV was likely to be originated from bats.

Again, in October 2012 in Saudi Arabia studies were conducted and this time a fecal pellet of Taphozous perforates bat revealed 100% nucleotide similarity to MERS-CoV which was isolated from patient from same area.

To find out whether the bats were potential reservoir of MERS-CoV again studies were performed on Jamaican fruit bats. 10 bats were inoculated through intraperitoneal and intranasal routes. There was the evidence of infection in all the bats as they shed virus from there respiratory and intestinal tract but clinical signs of disease were not there. This indicates that MERS-CoV has the potential to replicate in bats without having any signs of disease so bats can act as a potential reservoir [12].

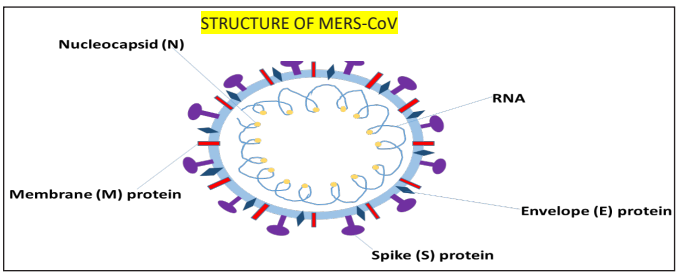

Fig. 5: Structure of MERS-CoV

B. SARS-CoV-2

SARS-CoV-2 is a B-Coronavirus, enveloped and non-segmented positive sense RNA virus [13]. After experimental studies it was observed that SARS-CoV-2 has sequencing of genome which is 96.2% similarity to a bat CoV RaTG13 and on the other hand it has 79.5% similarity to SARS-CoV. After certain evolutionary analysis it was suspected that bats could be the natural host of virus origin and virus can infect human which is transmitted from bats via unknown intermediate. SARS-CoV-2 utilizes same receptor that is ACE 2 as SARS-CoV to infect humans [14].

SARS-CoV-2 also shows similarities to 4 endemic viruses and these human coronaviruses have zoonotic origin: human coronavirus NL63 (HCoV-NL63), human coronavirus-OC43 (HCoV-OC43), human coronavirus-229E (HCoV-229E) and human coronavirus-HKU1 (HCoV-HKU1) [15]. To investigate the possible intermediate animal host of the SARS-CoV-2, experimental studies were conducted in China between the period of 24 December 2019 and 3 February 2020.

In this study, virome data from SARS-related coronavirus isolated from Bats and Pangolins was analyzed with special importance given to the spike glycoprotein gene. This experiment revealed that SARS-CoV-2 was more similar to Beta CoV/bat/Yunnan/RaTG13/2013 virus than to the coronavirus which was acquired from 2 samples (SRR10168377 AND SRR10168378) of Pangolin.

This study also revealed that SARS-CoV-2 contains a special peptide (PRRA) which could impact its host range a transmissibility because of its involvement in the proteolytic cleavage of the spike protein by cellular protease on the other hand coronavirus obtained from Pangolins does not contain RRAR motif thus indicating that human SARS-CoV-2 virus responsible for COVID-19 outbreak did not directly come from Pangolins [16].

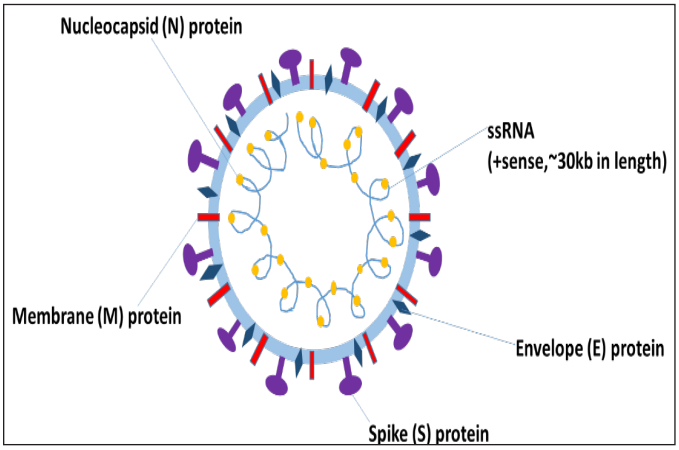

Fig. 6: Structure of SARS-CoV-2

C. Structural difference between SARS-CoV and SARS-CoV-2

Although SARS-CoV-2 is very similar to SARS-CoV in structure but there is a slight difference in the Spike protein

(S) of these viruses. In SARS-CoV-2 furin-like cleavage site is present which helps the S protein priming and increases the efficiency of spread of SARS-CoV-2 as compared to other beta coronaviruses [17]. Both these viruses enter into the host cell through ACE-2 receptor but after doing experimental studies it was found that there are certain configurational dissimilarity in RBD of spike glycoprotein in SARS-CoV and CoV-2.

It showed the differences in RBD of spikes with slight difference in amino acid residue. It revealed the conformational changes appeared in the amino acid residue at the ACE-2 binding site. Due to these conformational changes in ACE-2 binding site in SARS-CoV-2, it showed large number of contacts between receptor binding domain and active binding site in the SARS-CoV-2 when compared to the SARS-CoV and this is also the prime reason which explains the differences in the effectiveness of drugs against both the viruses [18].

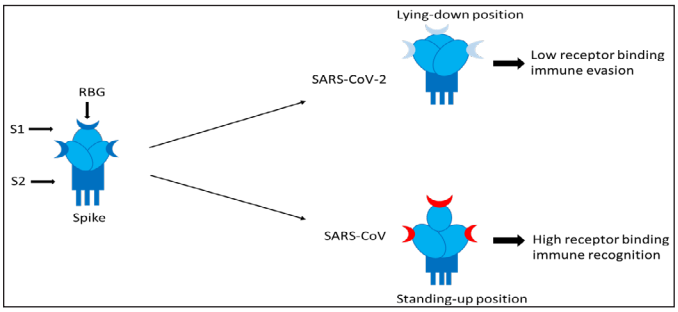

Fig. 7: Difference between SARS-CoV and SARS-CoV-2

As we know that receptor recognition is very important factor for human coronavirus pathogenesis and infection. ACE-2 act as entry gateway for SARS-CoV and SARS-CoV-2 to enter in human cell. The major difference between these two viruses is that SARS-CoV-2 receptor binding protein has higher affinity towards ACE-2 binding on the contrary affinity binding of the entire SARS-CoV-2 S protein towards ACE-2 is lower than the entire S protein of SARS-CoV.

There are conflicting reports about the ACE-2 affinity binding of the CoVs spike proteins this is probably due to the reason that RBD constantly changes its position between "lying down" and "standing up". SARS-CoV-2 RBD mostly remains in "lying down" position which provides ineffective receptor binding on the other hand SARS-CoV RBD generally remains in "standing up" state which is associated with high receptor binding. Studies also shows that "lying down" state is associated with less effective receptor binding as well as it favours the immune evasion on the other hand "standing up" state is associated with high effective receptor binding as well as immune recognition [19].

V. Biomolecular Modification Associated with COVID

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has undergone various mutations during its Global Circulation [20]. When SARS-CoV-2 virus began to spread outside China, in other countries sequencing of the viral genome was done from diseased patients with the reference. Interestingly, genomic sequence of SARS-CoV-2 obtained from 2 COVID-19 patients who were tested in Italy in January and February in 2020 revealed mutation compare to reference which was diagnosed in China. Variation in the genomic sequence was also seen from the patients from other North American and European nations [21].

High rate of mutations which results in different variants in small period. The main grounds for as we know SARS-CoV-2 is an RNA virus in nature that's why it is more susceptible to variation in SARS-CoV-2 is its strand shiftingability and error from action of RdRp. Also, the variations in spike protein such as substitution and deletion and variation in RBD results in highly lethal variants and highly transmissible variants [22]. In first 7 months of 2020, about 1200 genomes of SARS-CoV-2 virus were tested. It includes 12 sets of about 100 genomes collected between January and September. During an experimental study which included approx. 1000 genomes identified over 35 different variants which were regular to approx all genome group. Over time mutations were also occurring according to different environmental factors, population and climate [23].

VI. Different Variants Across Different Countries

There are some variants which attracted most attention in certain countries like B.1.351 in South Africa, B.1.1.7 in United Kingdom, P.1 in Brazil, B.1.617 in India and B.1.427 & B.1429 in California.

A. Indian Variant (B.1.617)

This variant was observed in October 2020 in India. It was also called "Double Mutant" because it had two variants (E484Q and L452R) in the sequence of s-protein. But after sometimes other 11 mutation of this variant was also reported. One of its mutations i.e., P6S1R have higher pathogenic potential because it acts on ACE-2 receptor affection. It also has higher potential to elude the immune system. Three sub-lineages have been also reported that are B.1.617.1, B.1.617.2, and B.1.617.3. They also have some other mutation. This variant had major pathogenic effects and wide transmission capacity in India.

B. South Africa Variant (B.1.351)

In December 2020, South Africa identified a new variant which is called as 501Y.V2 (B.1.351). It was dominant in South Africa and other countries and with continues rise in Europe. This variant showed more affinity towards human cells because of three variations that occur in the receptor RBD in s-protein glycol-protein. Experimental showed that this variant lacked greater infectivity but possess immunologic escape. According

to clinical trials it was found that vaccines like Novartis, Janssen and AstraZeneca were showing decreased protective efficacy towards this variant. ECDC reports that this variation has a significant risk of ICU admission (3.3 times higher) as well as higher risk of hospitalisation (3.6 times more).

C. United Kingdom or British Variant (B.1.1.7)

UK reported a new variant in December 2020. It was from B.1.1.7 lineage there was deletion, at 69-70 positions and Y144 and 7 amino acids substations. Such changes to the spike protein's structure, which is situated in a contact residue of the s-protein also with ACE-2 virus receptors, improved the virus' ability to spread. An English multicenter hospital investigation found no connection between this virus and increased hospitalisation risk or fatalities. According to preliminary analysis of the ECDC this variant had 70% increased transmissibility which made it dominant in USA, England, Europe and other countries. This variant showed no risk of reinfection as it does not escape the antibodies of a person. According to the SIREN study conducted on more than 23,324 healthcare professionals aged from 18 years to 25 years or older than this. Healthcare professionals were selected from UK public hospitals which were vaccinated with Pfizer showed effectiveness in both asymptomatic and symptomatic infection and also contributed to less transmission of this variant.

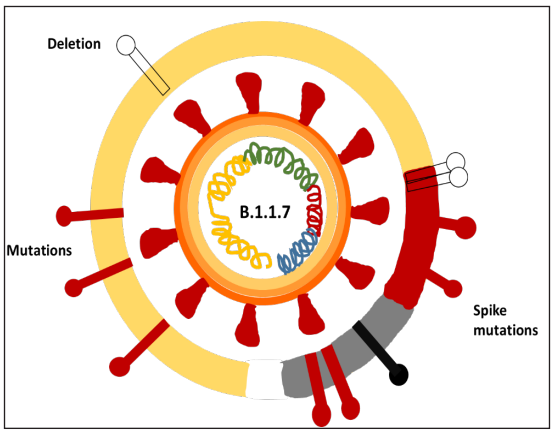

Fig. 8: Structure of B.1.1.7 (British Variant)

D. Brazilian Variant (P.1 or B.1.1.28.1)

It belongs to the B.1.1.28.1 lineage and it also has 17 different mutations. It was considered as virus of concern or virus of interest depending upon the countries. This variant has mutations in the S protein like South African and UK strains. This variant was first discovered in January 2021 in travellers from Japan who were coming from Brazil. This variant is also associated with cases of reinfection. It showed its presence in nearly 21 countries. A study which was conducted in Manaus (Brazil) showed that transmissibility of this virus is between 1.4 and 2.2 times higher than the previous variant and this variant also has high mortality rate. It also estimated that it has moderate effect on the efficacy of antibodies and 25-61% cases of this variant might have evaded the immune system. Another study conducted by ECDS confirms that this variant is associated with high risk of ICU admission (2.2 times higher) and high risk of hospitalization (2.6 times higher).

E. Californian Variant (B.1.427 y B.1.429)

These Californian variants were first observed in February 2021. They were further classified as variant of interest and CDC in March 2021 but in Spain they were called as variant of interest. This variant has approx. 20% increased transmissibility with significant impact on neutralization by certain treatments stated by FDA as EUA (Emergency authorization use). It showed moderate reduction in neutralization when people used convalescent and post-vaccination sera [24].

VII. Understanding of VOI, VOC and Variants of Public Health Significance

SARS-CoV-2 variants are classified into 3 categories based on their risk analysis.

1) VOI (Variants of interest)
2) VOC (Variants of public health importance or concern)
3) Variants of high consequences

Variants of Interest (VOI) – Most of the variants of interest are associated with mutations in binding receptor. These variants are often detected occasionally Mutations in these viruses suggest that they may escape immunity grant by natural infection or vaccination and they may be more contagious. These include variants B.1.526 (associated with continues and rapid spread in New York), B.1.525 (described in Nigeria and UK), P.2 (observed in Brazil). These variants have certain genetic markers which may be responsible to affect virus transmission, increase disease severity, neutralization capacity of antibodies and reduce therapeutics efficiency. These variants include Epsilon, Kapp, Zeta, Lambda Eta and Iota.

Variants of Public Health Importance or Concern (VOC) – These variants are more virulent and more contagious than variants of interests. They have higher mortality rate and causes more serious illness and more hospital stays. They can overcome the effect of antibodies gained with natural infection with vaccination or with previous variants they may also lower the efficacy of treatments. Generally, cases of reinfections are reported with these variants like B.1.351 (South African).

Variants of High Consequence – These are the variants which can cause more severe clinical manifestations. These variants are recognized by CDC and this category includes variants which decreases the efficacy of vaccines and monoclonal antibody therapy. This category also includes variants that are anti-viral-resistant variants [25].

A. Variants of Interest (VOI)

ETA - This variant was first identified in UK and Nigeria in December 2020 and it was included in VOI in March 2021. The second wave epidemic in Nigeria started by the end of 2020 due to the emergency of Eta variants [26]. It is also called as (G/484 K.V3; B.1.525). Different types of substitutions were found in the spike glycoprotein like at A67V, E484K, D614G, Q677H and F888L with three deletions at 144del, 70Vdel and 69Hdel. The major mutation is E484K in the RBD which is also common in other variants like Alpha, Beta and Gamma. Apart from UL and Nigeria, cases were also reported in other countries like Italy, India, Spain, Denmark etc. This also showed reduce neutralization by etesevimab, bamlanivimab monoclonal antibodies and convalescent sera. This variant has notable group of missense mutations which are of particular importance like Q677H, N439K which increases its virulence and reduce effectiveness of vaccines [27].

EPSILON – This is also called GH/452R.V1 it was first discovered in California in 2021 [28]. The major substitution is L452R and D614G in the spike protein due to which it showed 20% increase in transmission. It has 2 different lineages that are B.1.429 which has four mutations (S131, W152C, D614G and L452R) and B.1.427 having 2 spike mutations (L452R and D614G). The most concerning mutation is L452R in RBD which is common in both the lineages and it causes changes in the structure which stabilize the interaction between ACE-2 receptor and spike protein. Immune evasion is also seen in this cause of the mutation by the NTD antigenic supersite's shifting signal peptide cleavage site which forms a new disulfide bond which cause total loss of neutralization by ten NTD-specific antibodies. Epsilon variant was reported from 34 nations which include Canada, Aruba, Denmark, and UK etc. This variant is more virulent than ancestral B.1 (614G) variant according to study conducted on animals which is measured by loss in body weight in Hamsters [29].

IOTA – It was first discovered in New York in November 2020 by the method of phylogeographic analysis, cartographic visualization and space statistics also known as GH/253G. V1; B.1.526 [30]. Major spike protein substitutions of this variant are L5F, T951, D253G, E484K, A701V and D614G. These substitutions reduced the susceptibility to monoclonal antibodies treatment and also their neutralization capacity by post vaccination sera. This variant was found in more than 60 countries like Spain, Columbia, Germany, Mexico and Aruba. mRNA Vaccines like Moderna and Pfizer are effective against this variant. Iota variant which is found in USA have several important mutations like D80G, Y144, LSF, T951, S4779, F157S, D253G, Q957R etc [31].

KAPPA – In Maharashtra, India, this variation was discovered in December 2020 and is also known as G/452R.V3; B.1.61.1 later it was identified in 52 other countries like UK, Canada, Australia, Singapore, and Netherlands but with dominance in India. The SARS-CoV-2 which is found in India is consist of 3 main lineages also called double mutant variants which are kappa variant, delta variant and B.1.618 [32]. It had substitutions in spike protein as well as in RBD like G142D, E154K, P681R, Q1071H, T951 in spike protein and E484Q, L452R in RBD. These substitutions gave the variant decreased resistance to post-vaccination sera's neutralising effects. Covishield (AstraZeneca and serum institute of India) was found to be effective against this variant. Mutation observed in this variant were generally seen in spike ORF3a, ORF1ab and N genes comprising 88.52% of all mutations. This variant outnumbered the alpha variant in terms of mutation [33].

LAMBDA – This variant was first discovered in Peru in August 2020 known as GR/452QV1. This variant has a seven-amino acid deletion in the S-gene, which maybe a regression causes this mutation is present in previous coronavirus that infect other animal host [34]. This unique mutation (RSYLTPGD246-253N) is responsible for evasion from neutralizing antibodies [35]. It has seven major mutations like G75V, del247/253, T761, D614G, L452Q, T859N and L452Q in spike protein and F490S and L452Q mutation in RBD. Mutations in RBD helps this variant to increase its viral infectivity and to neutralize response of monoclonal antibodies. D614G mutation increases its viral load, transmissibility and infectivity making it more dangerous. This variant was also spread in other countries like Mexico, Germany, Israel, Colombia, and Argentina. This variant showed increase infectivity than Alpha and Gamma variant. In Asia, it was mainly reported in Israel. This variant can bypass the vaccine induced immunity that's why it was more concerning and could become reason for next wave.

THETA – This variant was discovered in February 2021 in Japan and Philippines. It is known as P3.B1.1.28.3 and important mutations in this variant are D614G, P681H, E1092K, V1176F and H1101Y and E484K AND N501 in RBDA region. More than 95% of theta variants consists of spike protein mutation at V1176F, D6144, H1101Y and E1092K [36]. It was also found in several other countries like Belgium, Australia, UK, China, USA.

ZETA – This variant also called P.2 was first discovered in Brazil in April 2020 [37]. Major mutations in this variant are E484K, F5651, V1176F and D614G in the region of spike protein.

B. Variants of Concern (VOC)

ALPHA – This B.1.1.7;201/501Y.V1 variant was identified in in UK from 58 years old patient in November 2020 [38]. This variant has 23 mutations from which 14 are nonsynonymous and 6 are synonymous and 3 are deletions like H69del, K1191N, D1118H, S982A, T7161, P681H, D614G, A570D, N501Y, S494P, Y145del, V70del. These mutations increase the tight binding of spike protein with ACE-2 receptor, they provide conformational changes in spike protein, enhance transmissibility. This variant was discovered during second wave of pandemic in India in Punjab and Maharashtra. This variant was further discovered in 160 countries like UK,

Germany, Netherland, Japan, Switzerland, Sweden, France causing community transmission and hospitalization. Patient infected with alpha variant has high risk of death and high risk of transfer to ICU almost 4-times higher as compared to patients infected with old strain [39].

BETA – This variant is also known as B.1351; GH/501Y.V2. It was discovered in Cape Province of South Africa in October 2020 [40]. This variant has 17 major mutations which causes 50% increases in transmission. It has 3 deletions 241del, 242del, and 243del in N5 loop. it has seven substitutions in spike protein that are D80A, A701V, D614G, N501Y, E484K, K417N, D215G and the 3 mutations in RBD that are of great concern are K417N, E484K and N501Y [41]. This can make the monoclonal antibodies ineffective that's why it has better chances of survival. K417N and E484K mutations changes the shape of spike protein which make antibodies ineffective and N501Y mutation causes 4.62 times more binding affinity for ACE-2 receptor than the original SARS-CoV-2 VIRUS. This variant was also discovered from 113 other countries like South Africa, Sweden, France, Canada, Colombia, Belgium, and USA.

GAMMA – This variant was identified in Manus, Brazil in November 2020. This is also known as P.1; GR/501Y.V3 and on January 11, 2021 it was considered as VOC [42]. This variant has 11 major mutations in the spike protein having 5 mutations within NTD that are R190S, D138Y, P26S, T20N and L18F and 3 mutations in RBD that are K417T, N501Y, E484K and 2 in the furin cleavage site in S1(D614G, H655Y) and 1 in the S2 site (T10271). This variant can latch onto cells easily and have twofold transmissibility and higher viral load [43]. This variant was responsible for re-infection in Sao Paulo state and it was also responsible for causing second wave in Brazil. This variant was found in 74 other countries like Belgium, Netherlands, Germany, Brazil, Canada, Mexico, and Spain.

DELTA – This variant is also known as G/478 K.V1; B.1.617.2. It was identified in Maharashtra in India in October 2020. This variant was found to be the dominant lineage detected in more than 100 nations and on May 11, 2021 it was declared as VOC by WHO.

This variant was responsible for second wave in India. In this wave approx 4-lakh cases were declared per day. This mutant was also accountable for third wave in UK, it was 60% more transmissible than alpha. 13 major variations are present in spike protein of this mutant which are K417N, A222V, T951, P871R, D950R, P681R, 614G, T478K, L452R, R158G, 157del, 156del, G142D and T19R. The T478K variation was more adapted and it also influenced the viral affection of virus and increased viral infectivity [44].

Due to certain changes in the position of amino acids like deletions at 156/157 changes the 158th amino acid from arginine to glycine, which cuts direct connection point for the antibody binding on the variant and P681R variation causes change in amino acid at a spot beside furin cleavage site, these changes provide the variant immunity against monoclonal antibodies and also influence the survival of Delta variant. L452R mutation in RBD causes increase transmission efficiency into the cells. This mutation causes 18-24% increase transmissibility and resistant to neutralization by specific antibodies. People who got just one dose of the COVID-19 vaccination had slightly lower protection against this variation. Oxford-AstraZeneca and Pfizer-BioNTech were determined to be 88% and 60% effective, respectively against this variant, 2 weeks after the second dose, but they were only 33% effective after 3 weeks of the first dose.

DELTA PLUS – **(**Possible reason for the third wave) This is also called AY.1 (B.1.617.2.1) and AY.2 (B.1.617.2.2), Indian government declared this as VOC. In addition to mutations which were present in delta like E484Q, P614R and L452R, these sub lineages have other additional mutations like K417N in the spike protein that increases its attachment to infected cells and also have immune evasion properties like beta variant. India discovered Delta plus variants (AY.1) in Punjab, Telangana, Karnataka, Gujrat, Rajasthan and (AY.2) in Andhra Pradesh, Karnataka, and Maharashtra. This variant has higher transmissibility, stronger binding to lung cell receptor and they can also reduce the response of monoclonal antibodies. P871R mutation in furin binding site enhances its efficiency to get into the cell by furin cleavage site itself. It produces syncytia, so that with the help of cell-to-cell transfer mechanism it can infect multiple cells cause of these monoclonal antibodies are less effective and lose their effectiveness in this variant. But as most of the population got vaccinated during second wave, so this variant may not produce fatal illness in population. By July 2021, this variant was discovered in Germany, Italy, Spain, and Canada [45].

VIII. Conclusion

The world has already witnessed enough number of tragedies and related fatalities due to covid diseases after implementing curfews, imposing lockdowns, imposing various strict guidelines still a large number of populations got affected because variations have been added with several critical mutations which make them more spreadable, infective, transmissible and lethal. In India the variants which were seen during second wave cause of the mutation of parent structure were more dangerous and imposed serious threats on the health of individuals. These variants are also called variants of concern which includes Alpha, beta, gamma, delta. Delta variant was the most dangerous amongst them all. In this variant because of its higher transmissibility 4 lakh cases were reported on daily basis, it was 60% more transmissible than alpha variant. Major common substitution which produces the lethal variants occurred at spike protein and RBD. These mutations increase the tight binding of spike protein with the ACE-2 receptor and make the monoclonal antibodies ineffective. These mutations also increased viral transmissibility and these variants also have immune evasion properties. Fight against coronaviruses

was not going to be so typical for the renowned scientists, but continuous typical mutations in the structure of RNA viruses at molecular level made it this fight typical. Our scientists could have discovered anti CoV drugs/supplements/vaccines if it had not started for mutations. Protection plays an important role in viral infections such as SARS-CoV-2. Each and every individual should obey the rules imposed by health authorities and precautions must be taken at a personal level which includes the use of masks, maintaining social distancing and regular handwashing etc. Protective measures that huge public has followed on regular basis was the key factor for its control. In these types of cases people should support the government's regulation and large public gatherings, public transport and crowded places should be avoided. Vaccination is also a major step in the prevention of infection. Various vaccines of high efficiency are available to treat the infection and these should be taken at right time for the prevention of infection.

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References

[1] M. Ciotti, M. Ciccozzi, A. Terrinoni, W. C. Jiang, C. B. Wang, and S. Bernardini, "The COVID-19 pandemic," *Critical Reviews in Clinical Laboratory Sciences*, vol. 57, no. 6, pp. 365-388, 2020.

[2] D. Kohli, "COVID-19 pandemic-impact on Indian people," *Habit Habitat for Pandemic Problems and Disaster Damages*, pp. 101-109.

[3] M. A. Arunachalam, and A. Halwai, "An analysis of the ethics of lockdown in India," *Asian Bioethics Review*, vol. 12, no. 4, pp. 481-489, 2020.

[4] S. Basu, A. Karmakar, V. Bidhan, H. Kumar, K. Brar, M. Pandit, and N. Latha, "Impact of lockdown due to COVID-19 outbreak: Lifestyle changes and public health concerns in India," *Int J Indian Psychol*, vol. 8, no. 2, pp. 1385-1411, 2020.

[5] C. M. A. D. O. Lima, "Information about the new coronavirus disease (COVID-19)," *Radiologiabrasileira*, vol. 53, pp. 5-6, 2020.

[6] P. Mitra, S. Misra, and P. Sharma, "COVID-19 pandemic in India: What lies ahead," *Indian Journal of Clinical Biochemistry*, vol. 35, no. 3, pp. 257-259, 2020.

[7] N. Kaur, A. Sethi, H. Patil, S. Singh, H. Kaur, and U. K. Mishra, "Origin and evaluation of pathogenic coronavirus: A literature review," 2020.

[8] N. K. Chaudhary, "Outbreak of coronavirus disease (COVID-19)," *Journal of Chitwan Medical College*, vol. 10, no. 1, pp. 1-2, 2020.

[9] D. K. Bonilla-Aldana, K. Quintero-Rada, J. P. Montoya-Posada, S. Ramírez-Ocampo, A. Paniz-Mondolfi, A. A. Rabaan, R. Sah, and A. J. Rodríguez-Morales, "SARS-CoV, MERS-CoV and now the 2019-novel CoV: Have we investigated enough about coronaviruses?–A bibliometric analysis," *Travel Medicine and Infectious Disease*, vol. 33, p. 101566, 2020.

[10] H. A. Mohd, J. A. Al-Tawfiq, and Z. A. Memish, "Middle East respiratory syndrome coronavirus (MERS-CoV) origin and animal reservoir," *Virology Journal*, vol. 13, no. 1, pp. 1-7, 2016.

[11] T. Zhang, Q. Wu, and Z. Zhang, "Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak," *Current Biology*, vol. 30, no. 7, pp. 1346-1351, 2020.

[12] H. A. Mohd, J. A. Al-Tawfiq, and Z. A. Memish, "Middle East respiratory syndrome coronavirus (MERS-CoV) origin and animal reservoir," *Virology Journal*, vol. 13, no. 1, pp. 1-7, 2016.

[13] H. K. Saboowala, *Exploring Transmission, Pathogenicity Related Mechanisms, Biomolecular Study and Worldwide Societal Impact of COVID-19*. 2021.

[14] Y. R. Guo, Q. D. Cao, Z. S. Hong, Y. Y. Tan, S. D. Chen, H. J. Jin, K. S. Tan, D. Y. Wang, and Y. Yan, "The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - An update on the status," *Military Medical Research*, vol. 7, no. 1, pp. 1-10, 2020.

[15] E. C. Holmes, S. A. Goldstein, A. L. Rasmussen, D. L. Robertson, A. Crits-Christoph, J. O. Wertheim, S. J. Anthony, W. S. Barclay, M. F. Boni, P. C. Doherty, and J. Farrar, "The origins of SARS-CoV-2: A critical review," *Cell*, vol. 184, no. 19, pp. 4848-4856, 2021.

[16] A. Grifoni, D. Weiskopf, S. Ramirez, D. Oran, E. Topol, A. Grifoni, J. Sidney, Y. Zhang, R. H. Scheuermann, and B. Peters, "The proximal origin of SARS-CoV-2," *Nature Medicine*, vol. 26, no. 4, pp. 450-452, 2020.

[17] A. A. Rabaan, S. H. Al-Ahmed, S. Haque, R. Sah, R. Tiwari, Y. S. Malik, K. Dhama, M. I. Yatoo, D. K. Bonilla-Aldana, and A. J. Rodriguez-Morales, "SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview," *Infez Med*, vol. 28, no. 2, pp. 174-184, 2020.

[18] S. Raparla, X. Li, J. S. Srava, S. Jasti, and B. R. Jasti, "Can structural differences between SARS-CoV and SARS-CoV-2 explain differences in drug efficacy? *Current*

Trends in Biotechnology and Pharmacy, vol. 15, no. 3, pp. 233-240, 2021.

[19] G. A. Rossi, O. Sacco, E. Mancino, L. Cristiani, and F. Midulla, "Differences and similarities between SARS-CoV and SARS-CoV-2: Spike receptor-binding domain recognition and host cell infection with support of cellular serine proteases," *Infection*, vol. 48, no. 5, pp. 665-669, 2020.

[20] J. Singh, J. Samal, V. Kumar, J. Sharma, U. Agrawal, N. Z. Ehtesham, D. Sundar, S. A. Rahman, S. Hira, and S. E. Hasnain, "Structure-function analyses of new SARS-CoV-2 variants B.1.1.7, B.1.351 and B.1.1.28.1: Clinical, diagnostic, therapeutic and public health implications," *Viruses*, vol. 13, no. 3, p. 439, 2021.

[21] S. K. Biswas, and S. R. Mudi, "Genetic variation in SARS-CoV-2 may explain variable severity of COVID-19," *Medical Hypotheses*, vol. 143, p. 109877, 2020.

[22] V. Thakur, S. Bhola, P. Thakur, S. K. S. Patel, S. Kulshrestha, R. K. Ratho, and P. Kumar, "Waves and variants of SARS-CoV-2: Understanding the causes and effect of the COVID-19 catastrophe," *Infection*, pp. 1-16, 2021.

[23] Z. Almubaid, and H. Al-Mubaid, "Analysis and comparison of genetic variants and mutations of the novel coronavirus SARS-CoV-2," *Gene Reports*, vol. 23, p. 101064, 2021.

[24] R. Cantón, P. D. L. Ramos, A. García-Botella, A. García-Lledó, J. Gómez-Pavón, J. G. del Castillo, T. Hernández-Sampelayo, M. C. Martín-Delgado, F. J. M. Sánchez, M. Martínez-Sellés, and J. M. M. García, "New variants of SARS-CoV-2," *Revista Española de Quimioterapia*, vol. 34, no. 5, p. 419, 2021.

[25] V. Thakur, S. Bhola, P. Thakur, S. K. S. Patel, S. Kulshrestha, R. K. Ratho, and P. Kumar, "Waves and variants of SARS-CoV-2: Understanding the causes and effect of the COVID-19 catastrophe," *Infection*, pp. 1-16, 2021.

[26] S. Zhao, S. S. Musa, M. K. Chong, J. Ran, M. Javanbakht, L. Han, K. Wang, N. Hussaini, A. G. Habib, M. H. Wang, and D. He, "The co-circulating transmission dynamics of SARS-CoV-2 Alpha and Eta variants in Nigeria: A retrospective modeling study of COVID-19," *Journal of Global Health*, vol. 11, 2021.

[27] D. Zella, M. Giovanetti, F. Benedetti, F. Unali, S. Spoto, M. Guarino, S. Angeletti, and M. Ciccozzi, "The variants question: What is the problem? *Journal of Medical Virology*, vol. 93, no. 12, pp. 6479-6485, 2021.

[28] V. Tchesnokova, H. Kulasekara, L. Larson, V. Bowers, E. Rechkina, D. Kisiela, Y. Sledneva, D. Choudhury, I. Maslova, K. Deng, and K. Kutumbaka, "Acquisition of the L452R mutation in the ACE2-binding interface of spike protein triggers recent massive expansion of SARS-CoV-2 variants," *Journal of Clinical Microbiology*, vol. 59, no. 11, pp. e00921-21, 2021.

[29] T. Carroll, D. Fox, N. van Doremalen, E. Ball, M. K. Morris, A. Sotomayor-Gonzalez, V. Servellita, A. Rustagi, C. K. Yinda, L. Fritts, and J. R. Port, "The B.1.427/1.429 (epsilon) SARS-CoV-2 variants are more virulent than ancestral B.1 (614G) in Syrian hamsters," *PLoS Pathogens*, vol. 18, no. 2, p. e1009914, 2022.

[30] A. Russell, C. O'Connor, E. Lasek-Nesselquist, J. Plitnick, J. P. Kelly, D. M. Lamson, and K. S. George, "Spatiotemporal analyses of 2 co-circulating SARS-CoV-2 variants, New York state, USA," *Emerging Infectious Diseases*, vol. 28, no. 3, p. 650, 2022.

[31] N. Ghosh, S. Nandi, and I. Saha, "A review on evolution of emerging SARS-CoV-2 variants based on spike glycoprotein," *International Immunopharmacology*, p. 108565, 2022.

[32] V. P. Chavda, and V. Apostolopoulos, "Global impact of delta plus variant and vaccination," *Expert Review of Vaccines*, vol. 21, no. 5, pp. 597-600, 2022.

[33] J. Singh, A. G. Malhotra, D. Biswas, P. Shankar, L. Lokhande, A. K. Yadav, A. Raghuvanshi, D. Kale, S. Nema, S. Saigal, and S. Singh, "Relative consolidation of the Kappa Variant pre-dates the massive second wave of COVID-19 in India," *Genes*, vol. 12, no. 11, p. 1803, 2021.

[34] C. Padilla-Rojas, V. Jimenez-Vasquez, V. Hurtado, O. Mestanza, I. S. Molina, L. Barcena, S. Morales-Ruiz, S. Acedo, W. Lizarraga, H. Bailon, and O. Cáceres, "Genomic analysis reveals a rapid spread and predominance of lambda (C. 37) SARS-COV-2 lineage in Peru despite circulation of variants of concern," *Journal of Medical Virology*, vol. 93, no. 12, pp. 6845-6849, 2021.

[35] C. Padilla-Rojas, V. Jimenez-Vasquez, V. Hurtado, O. Mestanza, I. S. Molina, L. Barcena, S. Morales-Ruiz, S. Acedo, W. Lizarraga, H. Bailon, and O. Cáceres, "Genomic analysis reveals a rapid spread and predominance of lambda (C. 37) SARS-COV-2 lineage in Peru despite circulation of variants of concern," *Journal of Medical Virology*, vol. 93, no. 12, pp. 6845-6849, 2021

[36] R. Rose, D. J. Nolan, T. M. LaFleur, and S. L. Lamers, "Outbreak of P.3 (Theta) SARS-CoV-2 emerging variant of concern among service workers in Louisiana," *Journal of Infection and Public Health*, vol. 15, no. 1, pp. 7-9, 2022.

[37] C. Chakraborty, M. Bhattacharya, and A. R. Sharma, "Present variants of concern and variants of interest of severe acute respiratory syndrome coronavirus 2: Their significant mutations in S-glycoprotein, infectivity, re-infectivity, immune escape and vaccines activity," *Reviews in Medical Virology*, vol. 32, no. 2, p. e2270, 2022.

[38] D. J. Grint, K. Wing, C. Houlihan, H. P. Gibbs, S. J. Evans, E. Williamson, H. I. McDonald, K. Bhaskaran, D. Evans, A. J. Walker, and G. Hickman, "Severity of severe acute respiratory system coronavirus 2 (SARS-CoV-2) alpha variant (B.1.1.7) in England," *Clinical Infectious Diseases*, vol. 75, no. 1, pp. e1120-e1127, 2022.

[39] M. Vassallo, S. Manni, C. Klotz, R. Fabre, P. Pini, E. Blanchouin, A. Sindt, L. Lotte, J. M. Dubertrand, S. Liguori, and N. Berkane, "Patients admitted for variant alpha COVID-19 have poorer outcomes than those infected with the old strain," *Journal of Clinical Medicine*, vol. 10, no. 16, p. 3550, 2021.

[40] M. Cascella, M. Rajnik, A. Aleem, S. C. Dulebohn, and R. di Napoli, "Features, evaluation, and treatment of coronavirus (COVID-19)," *Statpearls [Internet]*. 2022.

[41] H. Tegally, E. Wilkinson, M. Giovanetti, A. Iranzadeh, V. Fonseca, J. Giandhari, D. Doolabh, S. Pillay, E. J. San, N. Msomi, and K. Mlisana, "Detection of a SARS-CoV-2 variant of concern in South Africa," *Nature*, vol. *592*, no. 7854, pp. 438-443, 2021.

[42] E. Torbati, K. L. Krause, and J. E. Ussher, "The immune response to SARS-CoV-2 and variants of concern," *Viruses*, vol. 13, no. 10, p. 1911, 2021.

[43] N. Ghosh, S. Nandi, and I. Saha, "A review on evolution of emerging SARS-CoV-2 variants based on spike glycoprotein," *International Immunopharmacology*, p. 108565, 2022.

[44] D. Gupta, P. Sharma, M. Singh, M. Kumar, A. S. Ethayathulla, and P. Kaur, "Structural and functional insights into the spike protein mutations of emerging SARS-CoV-2 variants," *Cellular and Molecular Life Sciences*, vol. 78, no. 24, pp. 7967-7989, 2021.

[45] V. Thakur, S. Bhola, P. Thakur, S. K. S. Patel, S. Kulshrestha, R. K. Ratho, and P. Kumar, "Waves and variants of SARS-CoV-2: Understanding the causes and effect of the COVID-19 catastrophe," *Infection*, pp. 1-16, 2021.