Chapter

SARS-CoV-2 Mutation Mechanism, Features, and Future Perspective

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Abstract

Over two years, the SARS-CoV-2 virus has evolved by producing several variants by RNA polymerase mutation. This mutation created many virus variants that five of them are designated by WHO. These are Alpha, Beta, Gamma, Delta, and Omicron, among them Alpha, Delta, and Omicron spread faster. Coronaviruses (CoVs) are enveloped in positive-sense RNA viruses and contain huge RNA virus genomes. RNA polymerase controls the replication in which the genomic material is copied, and it often makes errors that lead to create a new mutation. Most mutations create a virus that cannot replicate and spread among people. However, some mutations lead to a virus that can replicate and create a variant. This chapter will discuss the mechanism of the mutations during the last two years and the future of these mutations in SARS-CoV-2.

Keywords: SARS-Cov-2 mutation-biochemical mechanisms, RNA polymerase

1. Introduction

To begin, most known human-associated coronaviruses have caused colds, therefore, to date, this family of viruses has not been extensively researched and is still very unknown to humanity, and only a number of severe human diseases have been attributed to this family.

However, in 2003, a virus from this family, which was responsible for severe acute respiratory syndrome (SARS) appeared and spread rapidly among humans and was the starting point for research into coronaviruses [1]. In addition to the 2003 SARS outbreak, coronaviruses (CoVs) have had two other large-scale outbreaks in the last two decades: middle eastern respiratory syndrome (MERS) and now COVID-19. Current coronavirus (COVID-19) originates from a cluster of pneumonia related to the seafood market in Wuhan City, Hubei Province, China [2]. With the occurrence of the MERS and the SARS outbreaks within the past couple of decades combined with the ongoing pandemic, coronaviruses are now considered "emerging pathogens" [1, 3–5]. In (**Figure 1**), you can have a better understanding of the types of diseases and viruses that cause the disease, as well as their relationship and year of spread.

In addition, CoVs disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infectious disease [6]. SARS-CoV-2

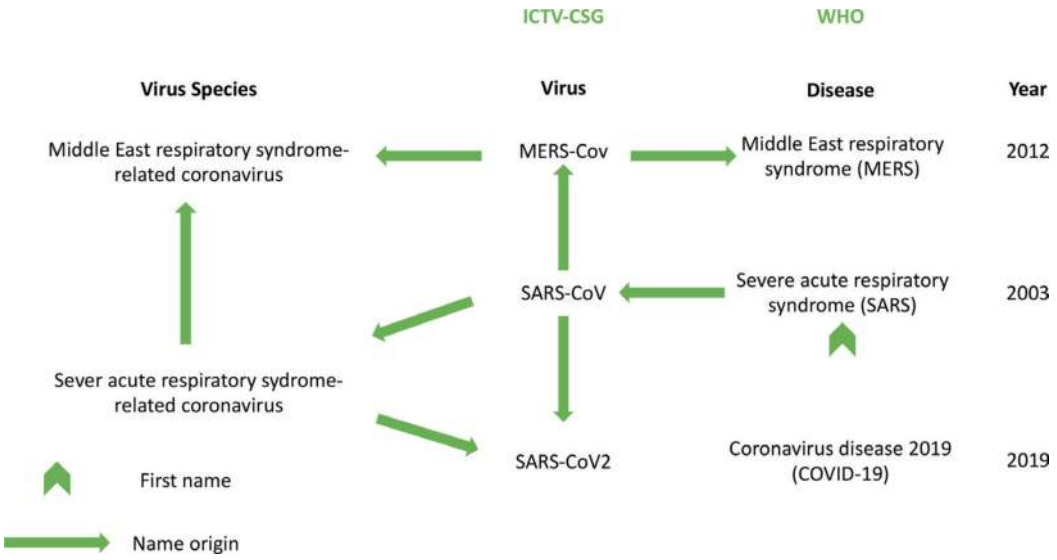

Figure 1.
History of coronavirus naming during the three zoonotic outbreaks in relation to virus taxonomy and diseases caused by these viruses. According to the current international classification of diseases, MERS and SARS are classified as 1D64 and 1D65, respectively.

belongs to the betacoronavirus genus [1]. As mentioned above, the third highly pathogenic coronavirus to enter the human population is SARS-CoV-2, which is more contagious and has a broad tissue tropism that is likely to increase the prevalence [7].

In December 2019, the SARS-CoV-2 first spread to Wuhan, China, and the rapid spread of the virus sounded the alarm around the world and all countries were on alert. The World Health Organization (WHO) declared the outbreak an epidemic, and several countries quickly confirmed several cases. By May 4, 2020, more than 3.3 million cases had been diagnosed with the disease, a staggering number. It was a concern for governments and humanity [8].

The first observations showed that the virus is transmitted from a carrier to a healthy person through close contact, such as shaking hands and kissing, and by small droplets produced during sneezing, coughing, and talking [9].

Most researchers and scientists are now focused on identifying different types of coronaviruses and in particular the regular identification of new types of mammalian coronaviruses. For example, in 2018, the HKU2-associated coronavirus of bat origin was identified as responsible for the deadly acute diarrhea syndrome in pigs **Figure 1** [5].

1.1 SARS-CoV-2 genome and structure

Coronaviruses (CoVs) of the family Coronaviridae are enveloped, positive-sense single-stranded RNA genomes ranging from 26 to 32 kilobases in length, which replicate in the cytoplasm [1, 3–5]. All of the highly pathogenic CoVs, including SARS-CoV-2, belong to the betacoronavirus genus, group 2. The SARS-CoV-2 genome sequence shares ~80% sequence identity with SARS-CoV and ~50% with MERS-CoV [3, 4]. Its genome comprises 14 open reading frames (ORFs), two-thirds of which encode 16 nonstructural proteins (nsp 1–16) that make up the replicase complex, whereas the remaining one-third encodes the structural proteins envelope (E), spike (S), nucleocapsid (N), and membrane (M). [1, 4, 5].

1.2 Entry mechanism of SARS-CoV-2

All external agents that want to enter the host cell have their entry mechanism, and the covids have their mechanism. All covids first bind to the host cell receptor by a surface glycoprotein called spike, which is encoded by themselves, and whose main job is to mediate entry into the host cell. Covids transfer their nucleocapsid to the host cell cytoplasm when their coating fuses with the host cell layer. This occurs in acidic endosomal portions or, in some cases, in the plasma membrane. The route of infection is driven by the spike glycoprotein (S), which is also a major determinant of cellular tropism. This protein is a class I combination protein and plays a key role in binding the virus to the corresponding receptor at the surface of the host cell, also the role of interference between the host membrane and the virus in the cycle is driven by critical structural changes in the spike protein. For beta-coronaviruses, there is a receptor-binding region (RBD) in the spike protein that is involved in binding to the host cell receptor. This occurs when the spike is cleaved by the proximal host protease, then the spike combination peptide is released to facilitate virus entry. ACE2 for SARS-CoV and dipeptidyl peptidase-4 (DPP4) for MERS-CoV have identified receptors. Past investigations have announced that RBDs from the heredity B of beta covids can be arranged into practically distinct clades. Those from clade 1, which incorporates SARS-CoV-2 can enter cells expressing ACE2. This has been tentatively approved by a few investigations exhibiting the crystal construction of the RBD of the spike protein with that of ACE2. ACE2 is enhanced in the ciliated bronchial epithelial cells, which have all the major targets of being significant focuses of SARS-CoV-1 and -2, though DPP4 is advanced in the unciliated epithelial cells, which act as target cells for MERS disease. The two receptors are expressed in the sort II pneumocytes, which are contaminated by both infections. Aside from the ACE2 receptor, neuropilin-1 has been as of late distinguished as an entry factor that functions in concert with ACE2 to facilitate SARS-CoV-2 entry. In any case, expression of ACE2 in the mix with a host transmembrane serine protease has been displayed to confer susceptibility to SARS-CoV-2 [1].

Like other covids, the SARS-CoV-2 section happens by means of a multi-step interaction of cell surface connection, receptor commitment, proteolytic cleavage, and membrane combination that includes a few particular domains on the spike protein [1], which is shown clearly in (**Figure 2**).

As mentioned, the function of the RBD receptor plays the most important role in the virus entering the host cell. Researchers have also recently realized that protease plays a key role in facilitating virus entry, processing covid results, and as a potential barrier to species. Research shows that the entry of the virus SARS-CoV-2 is increased following the external expansion of trypsin. The most colorful role among host proteases is the serine transmembrane protease Tmprss2, although it should be noted that different types of this family, as well as certain cathepsins, are involved. Although the spike protein has been shown to be cleaved by host proteases, there is further evidence that this protease acts on the receptor and activates it [1].

SARS-CoV-2 is different from SARS-CoV-1 and other SARS-related types due to the presence of a furin cleavage (FCS) site containing the PRRAR multi-basic amino acid in the S1/S2 convergence of the viral spike protein (S). Although FCS is present in other relatives of CoVs, such as HKU1-CoV, MERS-CoV, and OC43-CoV. However, SARS-CoV-2 has a growth-enhancing function and it is assumed that other vital factors accompany it and the rate of infection and contagion in these factors is higher [10].

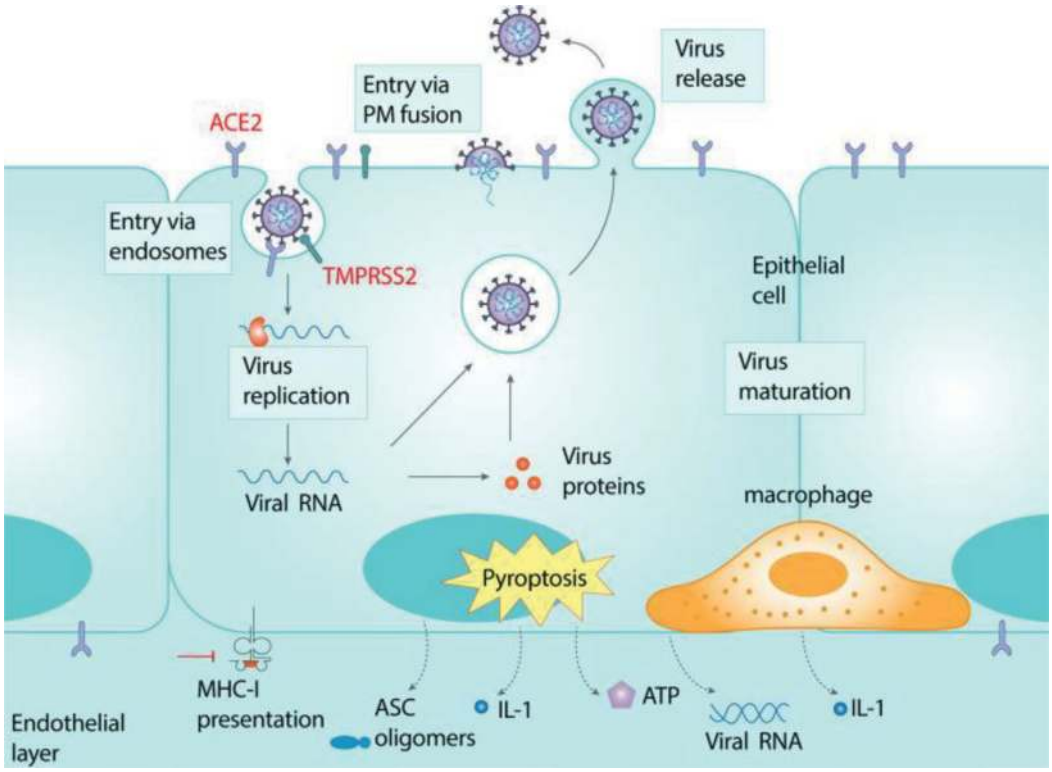

Figure 2.
Schematic of the intracellular lifecycle of SARS-CoV-2 and related immunopathology.

FCS is a known factor in influenza infections and appears to increase destruction and infection. Of course, it should be noted that it has not yet been determined whether this pathogenic function is also present in the SARS-CoV-2 virus [10].

Although various proteases, such as TMPRSS2 and cathepsin-B or -L (CTS-B or -L), cause cleavage at the S1/S2 site of the SARS-CoV-2 virus, the presence of FCS can have benefits for the SARS-CoV-2 virus, although research is needed to prove this. A new report by Johnson et al. shows that a SARS-CoV-2 virus that mutates and lacks FCS in its spike protein reduces the proliferation of Calu3 cells in a human respiratory cell line, thus weakening the disease in the hamster pathogenesis model. Preliminary observations suggest that FCS in the SARS-CoV-2 virus may play an important role in degradation [10].

Observations show that the ACE2 receptor and the TMPRSS2 serine protease are the main factors determining the entry of SARS-CoV-2 into cell tropism. It should be noted that the cells that express these two proteins are always defending against the SARS-CoV-2 virus [1].

Taking into account all the mentioned cases and points, we find that the SARS-CoV-2 virus has higher infectivity and higher transmissibility than previous types of coronavirus, and escapes from the host's immune system and delayed its function, for example, by disabling the system of long-term antibody formation against the virus. They control and direct subatomic pathways in host cells that reduce cell growth and damage in lung epithelial cells. These new discoveries are very large and effective in helping to interpret the basic pathomechanisms in Covid-19 and in particular cause immune disorders **Figure 2** [10].

The cells encoding TMPRSS2 and the angiotensin-converting enzyme 2 (ACE2) are infected by the SARS-CoV-2 virus (severe acute respiratory syndrome

coronavirus 2), which causes it to pass into the host cell through endocyte machinery or fuse into the plasma membrane. The genetic material (genome) of the virus is released into the cytosol of the host cell and transcription, replication, assembly, and translation. Viral progenies are produced and released into the extracellular space through undiscovered mechanisms. Arrival and amplification of the viral lead to cell pyroptosis and arrival of harm-related atomic examples, including ASC oligomers, ATP, and nucleic acids. This is joined by the discharge of supportive pro-inflammatory cytokines and chemokines culminating in a cytokine storm. Then again, MHC-I limited antigen releasing is downregulated in all probability by binding of the viral Orf8 protein, bringing about lessened T-cell activation.

1.3 The origin and evolution of SARS-CoV-2

Researchers have identified and sequenced the complete sequence of the SARA-CoV-2 genome and other beta-coronavirus genomes. The results show that SARS-CoV-2 is 96% similar to covid strain bat Cov RaTG13. And this research clearly shows that SARA-CoV-2 may have originated in bats, and may also have evolved from bat Cov RaTG13 [11].

The genomic RNA of SARS-CoV-2 encodes four driving structural proteins which are known as spike (and which likewise contains the receptor-binding domain [RBD] through which the infection ties to its natural receptor at have cell surface), the envelope (E) protein, the membrane (M) protein, and the nucleocapsid (N) protein. The genome of SARS-CoV-2 likewise contains extra genes, like that encoding for the RNA-dependent RNA polymerase (RdRP). This enzyme is fundamental for replicating viral RNA and for transcription of all RNA virals, both bearing negative and positive-sense RNA. In positive-sense single strand RNA virals, for example, SARS-CoV-2, the enzyme straightforwardly transcribes the positive-sense RNA, which acts precisely like a messenger RNA, yet additionally twofold convert positive-sense RNA into negative-sense RNA and then again in positive-sense RNA, to be gathered in the last viral particle [12].

Researchers demonstrate that an isolate numbered EPI_ISL_403928 shows different hereditary distances of the entire length genome and different phylogenetic trees, the coding sequences of nucleoprotein (N), spike protein (S), and polyprotein (P) from other SARS-CoV-2, with 2, 4, and 22 varieties in N, S, and P at the level of amino acid residues respectively. The outcomes show that at least two SARS-CoV-2 strains are involved in the outbreak [11].

Among the 103 strains, a sum of 149 mutations is distinguished and populace hereditary investigations demonstrate that these strains are predominantly isolated into two kinds. Results recommend that 101 of the 103 SARS-CoV-2 strains show considerable linkage between the two single nucleotide polypeptides (SNPs). The main kinds of SARS-CoV-2 (L sort and S type) are distinguished by two SNPs which situate at the destinations of 8,782 and 28,144. L sort contains 70% of the 103 strains and S type contains 30%, showing that L sort is more prevalent than the S type. Notwithstanding, the S type is the ancestral version of SARS-CoV-2. Until today, 13 mutations in the spike protein have been recognized [11].

1.4 Emergence of SARS-CoV-2 variants and how they mutate

Changes and causes of created virus types are caused by nucleotide changes that usually occur in the virus genome sequence during replication. It should be noted

that these changes are faster in RNA viruses than in DNA viruses. However, the rate of nucleotide changes in CoVs is usually slower than in other RNA viruses, due to the presence of an enzyme that plays a role in correcting defects created during replication. This enzyme is called non-structural protein 14 (nsp14) which has the function exoribonuclease (ExoN) which causes it to play a role in "editing." It is also detrimental to the replication of SARS-CoV-2 and MERS-CoV if this function is inactivated. Nucleotide changes in the genome sequence increase with respect to viral replication, transmission, and escape from the immune system due to natural selection in a population. For example, when a virus is detected by the immune system and its chances of survival are reduced, it is naturally eliminated, so the virus in which the nucleotide change occurred and caused it to escape the immune system and be safe has a better chance of survival. In general, genomic changes that affect viral health can randomly increase or decrease the frequency. Various treatments, such as monoclonal antibodies (mAb), convalescent plasma and vaccines, and even environmental factors, are important factors that have a significant impact on the genomic changes of viruses and cause the continuation of these changes and the emergence of new strains. In the event that variations evidently change the phenotype (transmission and virulence) of a viral, they are alluded to as a strain [13].

Of course, it should be noted that not only the changes that occur during replication and the specified host stresses, not only the formation of different species but also RNA editing or RNA modification can cause the formation of new types of SARA-CoV-2 Be. For example, the replacement of cytosine nucleotides by uracil and adenosine by inosine has been observed in SARS-CoV-2 genome sequence research. These events occur by RNA-editing enzymes, which include apolipoprotein B mRNA editing catalytic polypeptide-like enzyme (APOBEC) and adenosine deaminase RNA specific 1 enzyme (ADAR1) respectively. Host cells have enhanced these editing enzymes as innate viral sensory defense mechanisms; however, viruses can use these mechanisms to evolve. In Covid-19 patients, alterations in the structure of viruses have been observed within the host and are likely to occur by the same RNA-editing enzymes, but how exactly is SARS-CoV-2 altered and manipulated using these enzymes to nucleotide changes is not yet known [13].

Another factor in the development of the new SARS-CoV-2 species is recombination, which occurs in infected cells where the inherited substance of the two types is packaged in a single virion and causes different changes in the sequence of the virus genome. Recently, evidence has shown that a person can be infected with two different types of SARA-CoV-2 at the same time. In this case, the new species resulting from recombination can each have different pathogenic properties and have serious consequences for SARS-CoV-2 interactions, especially when this new species can move away from normal and stimulated antibody resistance. Overall, CoVs have a high recombination rate, and so far, conflicting data on SARS-CoV-2 recombination have been reported and its exact nature is still unclear [13].

An increase in the rate of viral evolution and a decrease in the rate of repulsion of the replicable virus has been observed in immunocompromised individuals with SARS-CoV-2 disease. Several studies during the treatment of this disease with plasma recovery method and mAb treatment have shown that the emergence of various viruses is associated with reduced sensitivity to neutralizing antibodies. However, in patients infected with the human immunodeficiency virus (HIV), an increase in changes in the genomic sequence of the virus has been observed. Single nucleotide polymorphism (SNP) examination distinguished a few varieties, frequently bringing about amino acid changes in the S protein related to immune evasion tracked down

in variations of concern. Beta, for example, was first seen in South Africa and was thought to have evolved through the evolution of a virus within at least one host with delayed viral replication, such as in a person with HIV or immunodeficiency. Intra-host evolution is by all accounts more articulated in immunocompromised populaces, which could act as a drawn-out wellspring of new SARS-CoV-2 variations, but it stays unclear whether basic co-morbidities assume the main part in the development of viral variations [13]. All in all, various factors change the genome and create a new type of virus and disease, as mentioned above, not only the structure and editing enzymes and proteins involved in replication but also the host's immune system and the host body's enzymes and antibodies, which are injected through vaccines, can also be effective in mutation.

1.5 Currently circulating SARS-CoV-2 variants

SARS-CoV-2 variations are classified by the CDC (Center for Disease Control and Prevention) and the WHO into two sorts: variants of concern (VOC) and variants of interest (VOI). A few VOC have emerged from the first wild-type strain detached in Wuhan since the outbreak initially started in December 2019. As indicated by the Center for Disease Control (CDC), a VOC is one that has expanded contagiousness, expanded destructiveness, resistance to the vaccine, or acquired immunity from the previous infection, and can escape symptomatic recognition. The VOCs are classified by the WHO as Beta (B.1.351), Alpha (B.1.1.7), Delta (B.1.617.2), and Gamma (P.1) [13, 14].

2. SARS-CoV-2 variants

2.1 D614G variant

At the beginning of February, a new strain of the disease began to spread in Europe, and the first species to rapidly dominate the world was the D614G strain, which underwent a change in the S protein and caused the disease to become more infectious, but still, It was treatable by neutralizing with recovery serum [13]. This species rapidly replaced the original and weaker species, a mutation that increased replication capacity and sensitivity in both human and animal models. SG614 is more steady than SD641 and less S1 shedding is noticed, so the SARS-CoV-2 with SG614 could transmit more efficiently. One review shows that in different cell lines, the SARS-CoV-2 containing the D614G change is eight times more effective at transducing cells than wild-type spike protein, providing evidence that the D614G mutation in SARS-CoV-2 spike protein could increase the transduction of multiple human cell types. TheD614G in the furin binding is a conspicuous common mutation depicted in nearly all of the new variations. The D614G mutation could decrease neutralization sensitivity to the sera of convalescent COVID-19 patients [11, 13, 14].

2.2 Alpha variant (B.1.1.7 lineage)

In late December 2020, a new strain of the disease was identified that quickly became dominant in the UK, called alpha (B.1.1.7). This species of SARS-CoV-2 is highly contagious. The alpha species (B.1.1.7) is caused by a receptor-restricting space (RBD) in the spike protein. As mentioned earlier, it is important to identify the original

genomic sequence of the SARS-CoV-2 virus to control the epidemic and identify how new species formed, and find a way to treat and prevent further changes or predict the next mutation. The researchers identified seventeen mutations in the viral genome sequence in which eight mutations occurred in the spike (S) protein, such as Δ144 cancellation, Δ69–70 deletion, A570D, N501Y, D1118H, S982A, T716I, and P681H. Another important mutation that increases the incidence of the disease and binds the spike protein to the ACE 2 receptor is the N501Y mutation, which accelerates and improves the viral binding and thus cells entry. This species was seen in Britain and the United States in September and December 2020, respectively. The death rate was seen to be high in B.1.1.7 variant tainted patients and the changed peril proportion was examined as 1.67, 95% CI 1.34–2.09. The B.1.1.7 predominant variation SARS-CoV-2 strain is flowing in different nations worldwide. Research has shown that people who have been vaccinated have each been somewhat resistant to the species. The following results show some data. Those who received the BNT162b2 vaccine had a significant reduction in the neutralization titer against the alpha species (B.1.1.7). Individuals vaccinated with the Janssen vaccine (Ad26.COV2-S) had a moderate effect *in vitro* against alpha species (B.1.1.7) but were less effective than against the reference strain. In the case of individuals who had been vaccinated with Novavax (NVX-CoV2373), the data showed that they were 96% effective against the first strain and 86% effective against the alpha species (B.1.1.7). In Phase III clinical trial in the United Kingdom containing 15,000 members (18 to 84 years old), AZD1222 was 70% effective in alpha (B.1.1.7) infected individuals and 77% effective in non-alpha species was observed. Studies have identified a variety of amino acid changes in the spike protein of the alpha species (B.1.1.7). The reason for these changes is N501Y, P681H, 69/70, ORF8, and E484K mutations. In addition to the above, another F888L mutation in protein (S) has been identified in the Nigerian species alongside E484K. This mutation increases the virus's permeability to the host cell by hydrolysis by TMPRSS2 to alter the biological efficacy of SARS-CoV-2. Every one of the above examinations was completed with their restrictions regarding methodology, sample size, and immune reaction [13, 14].

2.3 Beta (B.1.351 Lineage)

In October 2020, a new species called beta (B.1.351) was identified for the first time and quickly became the dominant strain, causing the second wave of epidemic in South Africa [13]. This species is caused by E484K mutations and has more side effects than other species. New mutant species are more resistant to species originating in Britain and South Africa but are less effective against vaccines. The K417N and E484K mutations give rise to the V2.501 variant seen earlier in South Africa, which is more contagious and has a strong correlation with the parent strain. E484K mutation also assumes a significant part in immune component, host receptor affinity, and infectivity. Starting discoveries have demonstrated that the Oxford-AstraZeneca immunization has shown an extensive decrease in inadequacy against these variations and was checked on by the WHO. Novavax vaccine can protect to a moderate level, while the Pfizer-BioNTech and Johnson and Johnson vaccines immunizations likewise have diminished the viability against the β-variant (B.1.351) [14].

2.4 Lineage B.1.258

In late 2020, the species B.1.258 was first identified in the Czech Republic and Slovakia, it had a greater ability to escape the immune response, as well as a more

acute infection in the host. The N439K mutation in the terminal region of the spike glycoprotein has given rise to this species, although 69–70 deletions in the receptor-binding domain (RBD) have been observed to be modified. Also, due to the change of antigenic peptides in the amino-terminal region, neutralizes this species when exposed to vaccine and serum [14].

2.5 Gamma variants (P.1 or 20 J/501Y.V3)

In January 2021, four Brazilians traveling to Japan brought a new strain of the disease with them to the Brazilian city of Manaus, where it was first found, and named it the gamma species (P.1). The disease has exacerbated the number of cases in Brazil [13].

This new species of gamma (P.1) is caused by 11 mutations in the spike protein. Researchers have been conducting extensive research on SARA-CoV-2 cases since December 2021, and about 42% of cases have infections of the gamma species (P.1). Mutations that cause this species have increased the infectivity rate of the disease to +160% and caused them to better escape from the immune system due to antibody-mediated. Statistics also show that this variant is more lethal and can kill up to 2.2 times more people. Gamma and quasi-gamma variants (P.1 and P.1-like) are more common and contagious among younger people. P.1 or 20 J/501Y.V3 were classified as gamma mutations (K417T, N501Y, and E484K) in the RBD domain. In November 2020 and January 2021, it has been seen that the Gamma variant is 1.4–2.2 times more infectious than the baseline [14].

2.6 Delta (Lineage B.1.617 and B.1.617.2)

Delta (B.1.617.2) was first identified in December 2020, which quickly became the dominant species, causing a second wave of pandemics in India, which was catastrophic and even resumed. The strictures became in the United States [13].

This type of delta (B.1.617 and B.1.617.2) is caused by three mutations of the alternative type, these mutations include P681R, L452R, and E484Q. Of these three mutations, two were seen in the RBD domain and the other near the furin that binds to the host. This species is up to 64% more transmissible than the previous, has also increased the number of hospitalizations by 85%, and even affected natural immunity. However, the risk of re-infection in patients is lower than before. Among the 15 mutations found in Delta species are spike protein mutations E484Q, D111D, P681R, and G142D, which have been shown are caused to escape antibody neutralization [14].

2.7 Lineage B.1.168

In West Bengal, a new variant has been found that was created by the deletions of the two amino acids His146 and Tyr145 and the mutations D618G and E484K, called B.1.168. These changes can escape convalescent plasma and numerous monoclonal antibodies [14].

2.8 Variant Omicron (B.1.1.529)

As of late designated VOC by the WHO, was first identified in November 2021 by world-class genomic surveillance laboratories in South Africa and has been tracked down in numerous nations all over the planet. The rise of these variants is disturbing

since they might affect viral transmissibility, virulence, and rate of reinfection by escaping natural and vaccine-induced immunity [13]. The Omicron SARS-CoV-2 variant shows in excess of 30 mutations prompting amino-acid changes in the spike sequence, 15 of them situated in the receptor-binding domain (RBD), which is key for viral-cell association interceded by ACE2 receptor. Deductions to decide transmission rate have endeavored from the Omicron spike quality arrangement. This information revealed a bunch of mutations at the S1–S2 furin cleavage site, which might upgrade viral infectivity. Additionally, docking studies showed that a blend of mutations in the RBD would yield a high binding proclivity with human ACE2 of this variation [15].

2.9 Other VOIs

Numerous other VOI has been accounted for which are just anticipated to influence transmission, virulence, and acquired or vaccine immunity. The VOI and variants being checked to incorporate; **Epsilon (B.1.427/B.1.429)** was first found in California, and research has shown that it is the result of several mutations in the spike protein and ORF1ab. These include the I4205V, D1183Y, and L452R, S13I, and L452R mutations in which the first two mutations occur in ORF1ab and the next three mutations occur in the spike protein, also known as CAL.20C, CA VUI, 21C or 20C/S: 452R. In November 2020, the CAL.20C variant was differentiated in California and eventually named Epsilon [14].

Zeta (P.2) was identified in Brazil, and has key spike mutations (T20N; L18F; F157L; P26S; D614G; E484K; V1176F; and S929I) [12–24]. **Eta (B.1.525)** is recognized in Nigeria and the UK and Iota (B.1.526.1/B.1.526) is distinguished in New York, both have key spike mutations (B.1.525: Δ69/70, A67V, Δ144, D614G, E484K, F888L, Q677H; B.1.526: T95I, (L5F*), D253G, (E484K*), (S477N*), (A701V*), D614G [12–24]. **Theta (P.3)**, additionally called GR/1092K.V1 distinguished in the Philippines were accounted for on February 18, 2021, with two mutations N501Y and E484K. Theta variants were likewise distinguished in Japan, the United Kingdom, and Malaysia in July 2021. Theta variants vanished by July 2021 [13, 14]. **Kappa (B.1.617)** harbor key transformations (G142D, (T95I), E154K, E484Q, L452R, D614G, Q1071H, and P681R) and same as Delta Plus (B.1.617.2.1) distinguished in India [12–24]. **Lambda** (C.37) is distinguished in Peru and Mu (B.1.621) is recognized in Colombia [13].

Eleven COVID-19 vaccines (mRNA-1273 (Moderna), BNT162b2 (Pfizer/BioNTech), ChAdOx1 (AstraZeneca/Oxford), Ad26.COV2.S (Janssen), NVX-CoV2373 (Novavax), BBV152 (Bharat Biotech), CoronaVac (Sinovac), BBIBP-CorV (Sinopharm), SCB-2019, CVnCoV, and HB02)) [25, 26]. Full vaccination of COVID-19 antibodies is highly compelling against Alpha variant, and moderate viable against Beta, Gamma, and Delta variants. A booster vaccination is more powerful against Delta and Omicron variants. mRNA vaccines appear to have higher vaccine effectiveness (VE) against Alpha, Beta, Gamma, and Delta variants over others [26]. So far, we have described all the variants that mutated and spread, mentioning the cause of the mutation and the first place they discovered it. This is definitely not the end of the story, and like all other microorganisms and diseases, they always mutate and adapt to new enemies which are dangerous to their survival.

3. Implications of variants on transmission and virulence

Again, a brief overview of the important issues mentioned above: Spike protein binds to the ACE2 receptor and accelerates the entry of the virus into the host cell.

Replacement and change in amino acids in spike protein, especially in RBD, directly affect the mechanism of virus entry into the host cell and cause many concerns. The N501Y mutation is very common among a variety of alpha, beta, and gamma species, and is also known to enhance cellular infection in animal models. One of the most important amino acids associated with ACE2 receptor binding is asparagine, which is located at position 501 (N501). Replacing this amino acid with the amino acid tyrosine (Y) increases the affinity for binding to the host receptor. This makes the coronavirus more contagious, found in both alpha and beta species. Research in the UK has shown that the alpha type does not essentially increase the risk of hospitalization. Despite this research, further studies have shown that this species increases the mortality rate by up to 61% and the severity of the disease is higher in this species. In addition to the above, the alpha type has the P681H mutation, which is located in the area near the site of the furin incision, and this mutation plays an important role in increasing infection and transmission. Another factor that increases viral infection *in vitro* is the deletion ΔH69/V70, which binds to specific receptors and manages to detect glycoprotein S [13].

In the beta type, the amino acid substitution in the spike protein is higher than in the alpha type. The RBD-ACE2 interaction complex has been examined fundamentally utilizing in silico strategies to evaluate the effect of the K417T, N501Y, and E484K replacements. The N501 residue is significant for ACE2 collaboration, while E484 and K417 are not anticipated to assume a significant part. The last two residues may as a matter of fact diminish binding fondness, which shows that the expansion in contagiousness found in the Beta variation is because of N501Y or different modifications in the viral. Among people infected with the SARS-CoV-2 virus in South Africa in October 2020, only 11% were infected with the Beta, but in December of that year, the number of people infected with Beta increased to 87%. Also in Cape Town, the second wave of the Covid-19 epidemic with Beta variant took half the time compared to the cases of the wild-type variant in 100,000 cases. Also, the mortality rate in the second wave was significantly higher, although one of the reasons could be amazing health care services at that time. Pearson et al. affirmed these outcomes utilizing an adjusted model which showed that this variation has expanded contagiousness and destructiveness [13].

In late 2020 in Brazil, a new strain of the SARS-CoV-2 virus called gamma caused a new wave of epidemics that disrupted health services. The gamma type has 17 amino acid substitutions, which in three cases are similar to the substitutions in the beta-type spike protein. Reports have shown that this species is 1.4–2.2 times more transmissible to the host than the wild type. Doctors' reports indicate that this species could be more serious, as the infected cases were mostly young people with high levels of infection who became infected with the virus. Comparison of the first and second wave data between adults aged 20–39 years showed that this type has increased the mortality rate by 2.7 times and even increased the rate among all people in any age group by 1.15 times. In addition to the gamma type, another type called delta is responsible for the emergence of the second strong wave in India, this dominant type has spread to other countries with eight changes in the spike protein. It also triggered a third wave in South Africa, rapidly weakening and replacing Beta in about three months. One of the reasons was its higher transferability (46%) than Beta. It even eradicated the alpha type in Britain and delayed community activities in June 2021 as the incidence increased, especially at gatherings of young people and unvaccinated people. In this type of mutation, two amino acid substitution mutations have been discovered, one L452R, which occurs in the RBD region, and the other, P681R, which

occurs at the site of the furin cleavage of the spike protein. It should be noted that in addition to the Delta type, the P681R mutation has also been seen in the Alpha type, which increases the binding to the host cell receptor, which directly causes infection and the prevalence rate. Although the P681R mutation has recently been identified as a fixed mutation that alone is not able to change the rate of transmission and infection, several mutations cause this action. Reports indicate that the Delta type is more contagious than both the wild type and other variants. Even doctors' observations and reports indicate that the Delta type has doubled the risk of hospitalization compared to the Alpha type and that patients with the Delta type have a more acute illness and the mortality rate in the hospital emergency room is significantly higher. In addition to all of the above, researchers are analyzing epidemiological data to estimate the transmissibility and rate of Omicron infection. Preliminary reports predict that this type could trigger a new wave of Covid-19 epidemics, especially in South Africa. November 2021, in South Africa, the Omicron type is found in 76% of people infected with the SARS-CoV-2 virus, just where the Delta type was most prevalent recently. Of course, the important point in this type is data from emergency clinics in South Africa that the Omicron type causes less infection and disease than the Delta type [13]. In total, we have so far gained a vast chunk of the sea of information and mechanisms that cause mutations in the structure of viruses. And we have explained to you the most important and main ones that have been proven so far, although as you know, science is always evolving and full of behaviors that have not yet been discovered.

3.1 Future prediction

Our understanding according to other studies that have been done and are mentioned earlier that RNA viruses, such as HIV, can use more than one host receptor to intervene in cell intrusion. Like other CoVs, for example, SARS-CoV and MERS-CoV, it is thought that SARS-CoV-2 may likewise foster the capacity to infect host cells by means of the S protein binding to receptors other than its primary receptor of passage as the viral keeps on developing wellness improving varieties. *In vitro* examinations have proposed that the transmembrane glycoprotein CD147 could act as an elective receptor for SARS-CoV-2. These glycoprotein capacities as a receptor for cyclophilin A, which assumes a part in the provocative reaction by going about as a chemotactic factor for leukocytes and moreover enacts antiviral reactions. Despite the fact that proof is as yet expected for the job of integrins, which are CD147 interacting proteins, they have additionally been conjectured to be SARS-CoV-2 host passage receptors. Neuropilin-1 (NRP-1) and NRP-2 contain a space succession, which as per sub-atomic demonstrating and *in vitro* examinations, could act as a binding site for the SARS-CoV-2 furin cleavage site in this manner going about as a potential co-receptor for viral entry.

4. Lung cancer

The second most common and malignant cancer among men and women worldwide is lung cancer, the leading and most dangerous cause of lung cancer is smoking. There are two types of lung cancer: small cell lung cancer and non-small cell lung cancer, which make up 15% and 85% of all lung cancer patients, respectively. Histological studies and hereditary characteristics of lung cancer are needed to make the right treatment and prevention methods. The SARS-CoV-2 virus, which causes

the Covid-19 epidemic, has severely affected people with lung cancer and how they are treated. Pressures over care frameworks have prompted demonstrative deferrals, the need to sort out for the administration of foundational therapies, yet in addition to oral therapies, lastly postpones in the administration of medical procedures and radiation therapy. It does not give the idea that lung malignant is a considerable risk factor for vulnerability to Covid-19 or deteriorating of contamination, at least not similarly to other comorbidities, such as cardiovascular illness, diabetes, and constant obstructive pneumonic sickness. Interestingly, apparently, when tainted, patients with lung cancer have a higher gamble of deteriorating [22]. Coronavirus is more serious in patients with lung cancer. Patient-specific features, instead of malignant growth explicit highlights or treatments, are the best determinants of seriousness [21].

Severe Covid-19 can be considered a hyperinflammatory issue described by gigantic resistant cell enactment. Accordingly, this might make sense of more awful results in more established individuals and cancer patients. While it very well may be conjectured that the brought down resistance prompted by malignant growth itself or its treatment could be a defensive component against the significant safe response seen in Covid-19, there is natural reasoning for rejecting this proposal. An increase in inflammation is normal during aging and has been characterized as "inflamm-aging." Constant irritation, including from malignant growth and progress in years, as well as immune checkpoint inhibitors (ICIs) can cause a flood in proinflammatory immune responses, prompting upgraded creation of cytokines from T cells and phagocytes, specifically in lung cancer, there is chronic pulmonary inflammation, both from the tumor microenvironment (TME) and the successive hidden lung pathology. This immune deregulation observed in older, lung cancer, or ICI-treated patients might drive the serious pathogenesis of Covid-19 in these exceptional populaces. Additionally, T cells produce proinflammatory cytokines with multiple functions, for example, selecting monocytes and neutrophils to the site of disease and activating other downstream cytokine and chemokine overflows [18].

As of late researchers considered an over-portrayal of cancer patients in the Covid-19 companion. In that, lung cancer was the most frequent sort (5 of 18 patients). In view of their outcomes, the authors have proposed three significant procedures for patients with malignant growth in this Covid-19 emergency: 1- To delay all adjuvant foundational treatment or elective medical procedures for stable cancer in endemic regions. 2- To increment personal protection provisions for patients with malignant growth and in-danger disease survivors. 3- To strengthen surveillance in disease patients tainted with SARS-CoV-2. Albeit these suggestions came from a little example size with a lot of heterogeneity, there is a rising agreement to change our standard administration during this pandemic. Patients with lung cancer are prone to serious entanglements, for example, admission to the emergency unit for invasive ventilation, or demise, from Covid-19. Smoking has additionally been distinguished as an autonomous risk factor in serious Covid-19 cases [19]. Along this line, it has been noticed a relationship between the severity of Covid-19 and subjects with a high-level period of malignant growth illness and a poor ECOG execution status. Furthermore, aging, heftiness, and metabolic condition are inclining factors for disease and address comorbidities that might impact defenselessness to SARS-CoV-2 infectious and the severity of its confusions. A review examination revealed an expected gamble of disease to SARS-CoV-2 and serious or deadly complexities of around 2.31 times higher in lung cancer patients than overall public or contrasted with patients with different malignancies [16].

A study and report published in the Medical Oncology Department of Wuhan University Zhongnan Hospital on 1524 cancer patients admitted to the same hospital on March 25, 2020, reports the consequences of Covid-19. This report shows that people with cancer are more at risk for infection with the SARS-CoV-2 virus than healthy people. This risk is increased in all people with cancer, even those undergoing anti-cancer treatment. The most likely to develop Covid-19 were patients with non-small cell lung cancer (NSCLC) and above the age of 60 [20].

A major challenge in the Covid-19 pandemic comprises making a fast and right differential finding among SARS-CoV-2 prompted pneumonitis and medication incited lung poisonousness. For sure, this might give side effects frequently not explicit, comprising fundamentally of cough (or get worse), dyspnea, chest agony, and fever, which are basically the same as those saw in the SARS-CoV-2 disease. Along this line, likewise, radiological imaging of medication-related poisonousness might cover that run-of-the-mill of Covid-19-initiated pneumonia, accordingly impeding the separation of these clinical elements. Chest computed tomography (CT) is the imaging methodology of decision, for the assessment of pneumonitis in patients with lung cancer who went through target treatment or immunotherapy, and it is likewise the most touchy strategy for the conclusion of Covid-19 pneumonitis, even in the underlying phases of the disease. Concerning ICI-related lung harmfulness, a wide range of imaging signs has been accounted for, for example, ground glass (GG) regions or potentially combinations that happens in roughly 70–80% of cases, as a rule with no particular dispersion, septal thickening, and foothold bronchiectasis in around 15–20% of patients, or elements of acute interstitial pneumonitis (AIP), including consolidations and volume loss that depend on the severity of toxicity; additionally, sores are for the most part multifocal and include the lower lobes [16].

Another challenge of Covid-19 in patients treated with chemoradiotherapy for a locally progressed cancer is likewise the presence of differential findings with different reasons for radiological irregularities, such as radiation-prompted pneumonic fibrosis, which is a typical complication of thoracic radiotherapy for lung cancer. Radiation-prompted aspiratory fibrosis prompts irreversible obliteration of lung engineering and interruption of gas exchange. Immunotherapy could all the while support cytotoxic T lymphocyte insusceptible response against infection contaminated and neoplastic cells. This immune stimulation might cause exacerbate the disease, however, a new report has shown the contrary that proceeding with proceeded with utilization of PD-1 barricade during the Covid-19 pandemic is protected. It is vital to recognize Covid-19 pneumonia from other lung pathologies for the right treatment and right on time as conceivable [22].

Lobectomies, autopsies, and biopsies have yielded information about the histologic impression of the pathophysiology of Covid-19. An especially fascinating report concerns two patients with lung cancer treated with lobectomy, retrospectively diagnosed to have Covid-19, offering a brief look into the early pathologic show of this illness. As in the first SARS illness, Covid-19 can prompt exudative as well as proliferative lung injury in an intense setting. Today, we realize that the super histological discoveries in Covid-19 lung sores are commonplace indications of alveolar harm, including the triad of injury to type II pneumocyte hyperplasia, alveolar epithelial cells, and hyaline membrane development. The hallmark hyaline membrane arrangement found in SARS and seen in resulting pathologic examines of Covid-19 were lacking with regards to, revealing insight into the order of intense lung injury. For this situation, this constellation was reasonable on the grounds that these patients were operated on at a presymptomatic stage. An outstanding perception was a plentiful

invasion of mononuclear inflammatory cells and alveolar macrophages. Strangely, the authors bring up that while clinically asymptomatic, these patients gave leukocytosis lymphopenia, showing the immune reaction was in progress at this early illness stage. Similarly, radiographic changes can go before side effects and should be deciphered circumspectly during an epidemic [18].

Lung cancer patients have a higher death rate than the overall public. Joined azithromycin and hydroxychloroquine treatment appear to be a decent treatment choice [17].

Today, different suggestions have arisen about fitting disease treatments, including for NSCLC, to the truth of the Covid-19. The foundation of these is to diminish unnecessary exposure, accordingly decreasing the risk of transmission. For lung cancer patients, this likewise implies cautiously gauging the risk to benefit proportion of every treatment. While ICI-prompted pneumonitis might look like Covid-19, the two on a pathophysiological and clinical level, there is no proof recommending patients getting these medicines are at increased risk of severe Covid-19 confusions, contrasted and those on other oncological treatments. Also, no information exists about the possible collaboration between SARS-CoV-2 and tyrosine kinase inhibitors. Once more, regardless of whether drug-prompted pneumonitis is thought, Covid-19 ought to be rejected. For all NSCLC patients, the component to remember; notwithstanding, is to be receptive. While anticipating viral swab affirmation, one ought to hinder cytotoxic treatment ought to natural, radiological, or clinical tests be reminiscent of Covid-19 [18].

A group from Milan created, as per clinical information and restorative modalities, a very intriguing help algorithm. This algorithm laid out from sex, PS, age, sex BMI, comorbidities, treatment or not corticosteroids, and tumor characteristics and treatments, arranges patients into three risk classes:

1. A low-risk category that permits keeping up with cancer on the board as arranged before the pandemic, delaying or decreasing the quantity of visits to the medical clinic, utilizing teleconsultation instruments, or utilizing foundational oral therapies.

2. A halfway risk class where the organizing of the illness is efficiently viewed as postponed.

3. A high-risk class that requires intense therapy, yet additionally closer checking of clinical and biological signs.

In that series, the treatment modalities (history of surgery, history of irradiation, systemic treatment) do not seem to affect the seriousness of Covid-19 contamination. The authors found no biological variable especially fundamentally connected with severity. Current treatment choices include medical procedure chemotherapy, radiotherapy, designated treatment, and immunotherapy [23].

5. Conclusion

As you know, the coronavirus epidemic has been affecting all countries financially and socially for almost two years, and like all other viral diseases, it will certainly not be eradicated soon, but it will threaten humanity in a new way each time. In the last

20 years, three CoVsubspecies transmitted to humans, and established researchers must continue to further develop identification and observation methods to prevent such adverse effects in the future.

Worldwide routine observation of SARS-CoV-2 variations and their consequences for destructiveness and right now utilized therapeutics will permit researchers to evaluate on the off chance that immunizations and different treatments are expected to be refreshed occasionally. New variations might infiltrate group invulnerability and taint unvaccinated people or work with immunization escape, which can incline these people toward extreme illness or passing. Nonetheless, most investigations have proposed that antibodies are as yet viable against the now coursing variations and can safeguard against extreme to direct illness results. Proof supporting the utilization of even a single vaccination dosage in keeping serious sickness from the Delta variation in the UK has featured the requirement for quicker immunization arrangement and rollout in more unfortunate areas like Africa. It is trusted that the in-house assembling of Covid-19 immunizations will help South Africa as well as the remainder of the African mainland to accomplish this objective. Also, more examinations are expected to assess the purpose for leading-edge diseases and the chance of winding down resistance to SARS-CoV-2 as well as the job that booster immunization dosages could play in counteraction. To lessen the risk of new and possibly more malicious variants from arising, health specialists ought in on vaccinating people as quickly as could be expected and ought to keep on underscoring the significance of mask-wearing and social distancing. A multipronged treatment approach ought to keep on being carried out in nations, for example, South Africa has a high predominance of co-morbidities, for example, HIV, which might add to the rise of variations. This would not just save lives, yet additionally, give restricted space for the viral to develop. While it may not be imaginable to foresee what the following VOC will be, we can gain from previous encounters and difficulties to more likely adapt to the situation at hand. SARS-CoV-2 is not supposed to vanish soon, however, will probably turn into a (the) essential medical care issue from now on, and as such will stay a challenge.

Besides, the amount of information on the connections between lung cancer and Covid-19 contamination has become richer, mainly because of studies on several patients in multicenter. It is, in this way, vital to make a protected medical care framework during the Covid-19 pandemic and it is fundamental to support clinical service conveyance to patients with lung cancer. One of the hypotheses about the SARS-CoV-2 virus is that it can change the mechanism of its entry into the host cell, that is, the binding to the host receptor no longer occurs through the spike protein and occurs by another method, and, in that method, new mutations occur that make it harder for researchers to find a treatment for this disease, like many other diseases, will be inexhaustible and will constantly evolving.

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