Review article

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Review article -Reinfection scenario of patients who recovered from COVID-19 and relation with viral genetic diversity

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Abstract

Severe acute respiratory syndrome associated with SARS-CoV-2 emerged in 2019 and has rapid prevalence around the world, causing over 146 million recorded cases of coronavirus disease (COVID-19) and more than 31 million deaths by the April of 2021. Recently, many studies have shown that re-positive tests for SARS-CoV-2 by RT-PCR in recovered COVID-19 patients are very common. The aim to conduct this review is to summarize the recent findings and reports of COVID-19 reinfection in patients formerly recovered from the disease, evaluate the potential of reinfection. Research in NCBI-PubMed and the bioRxiv and medRxiv preprint servers for publications using the terms (SARS-CoV-2 OR COVID-19) and reinfection for preprint articles. One thousand one hundred and two articles were identified using a methodical search strategy. After a review of these articles and filtering by human studies and removing duplication, 1027 were excluded, only 75 articles met the inclusion criteria and were included in the final review. Inside the literature percentage of reinfection in discharged COVID-19 patients is varied based on the age of patients and population size. Other studies described false positive or negative RT-PCR tests, reactivation, recurrence, re-positive tests, persistence, and reinfection for SARS-CoV-2 in recovered COVID-19 patients.

Keywords: COVID-19; reinfection; genetic of variants; immunity.

Introduction

Coronaviruses were first recorded in the 1960s. At the end of November 2019, an epidemic of acute respiratory infections rapidly spread in Wuhan, China. It was due to a new coronavirus, lastly named SARS-CoV-2 or COVID-19. SARS-CoV-2 is highly infective, with the ability to spread directly through human transmission by the airways, and the epidemic spread quickly worldwide [1, 2]. SARS-CoV-2 enter host cells through associated with angiotensin-converting enzyme 2 (ACE2) receptor and causes respiratory illness [3]. Clinical manifestations that result from disease progression typically include dry cough, fever, anosmia, ageusia, mild to severe pneumonia, coagulopathy, and dyspnea [4, 5]. Seasonal coronaviruses include OC43, HKU1, 229E, and NL63, which are endemic to humans, orderly infecting and reinfecting humans while typically causing asymptomatic to mild respiratory infections. Those viruses are adaptive in zones of the viral spike protein that are exposed to human humoral immunity [6]. Newly, studies have reported eight OC43 genotypes and, in East Asian populations, certain genotypes were shown to temporally replace other genotypes [4, 6, 7]. The antigenic variation between these groups contributes to this epidemic switching [8]. The presence of more than 80 genotypical distinct variants of this virus, the prospect of reinfection, and the short period of seropositivity for neutralizing antibodies raise the concern that vaccination may not result in an effective and long-term immunity against SARS-CoV2 [9]. The presence or absence of defensive immunity after infection with, or with vaccination against, SARS-CoV-2 will affect the severity of illness and transmission of the virus [2]. Several studies have shown a re-positive test for the virus using RT-PCR in recovered patients [10-60]. The importance of this review will interpret the role of immune responses in the recovery process of COVID-19 disease and reinfected cases based on the acquired immunity and new variants that are antigenically distinct from the early circulating strains. These suggestions will help to ameliorate the health policies for the screening of patients, suspected cases and improve diagnostic evaluations. More importantly, this review helps to understand how herd immunity may alleviate future outbreaks of SARS-CoV-2.

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Study selection

We searched NCBI-PubMed and the bioRxiv and medRxiv preprint servers for publications using the terms (SARS-CoV-2 OR COVID-19) and reinfection and immunity. We found 1102 articles, 233 were published on the bioRxiv, 731 on the medRxiv server, and 138 on PubMed. After filtering by human studies and excluding duplicates we identified 75 articles.

Genetic diversity of SARS-CoV-2

SARS-CoV-2 belongs to family coronaviridae, genus β-coronavirus. An enveloped virus with a diameter of 60 to 140 nm, round or oval-shaped with some polymorphism and possess a long positive-sense single-stranded RNA genome with size ranging from 29825 to 29903 nucleotides (**Figure 1**).

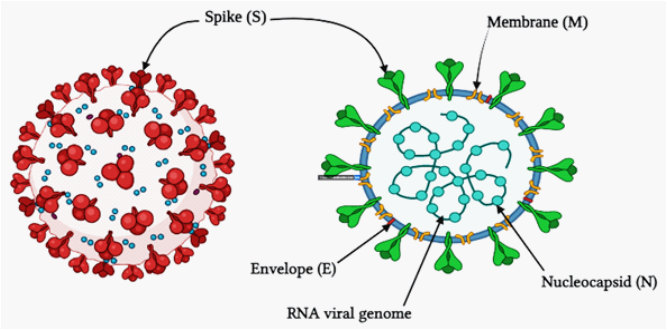

Figure 1: *Structure of SARS-CoV-2 virus.*

The biggest RNA genome gives flexible power in host adaptation and genome amendment. Genetic analysis of the SARS-CoV-2 genome exhibits arrangement of the coding genes are, 5`-replicase ORF1a, ORF1b, spike (S), envelope (E), nucleocapsid (N), membrane (M), and other small ORFs (ORF9, ORF13, ORF14, ORF10) 3`inserted between two short untranslated regions (UTR) (**Figure 2A** and **2B**).

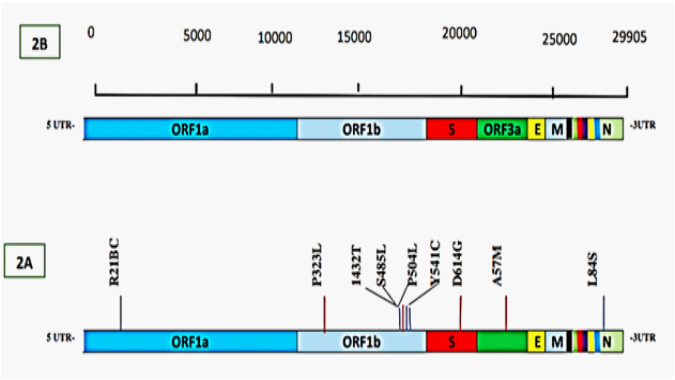

Figure 2: *(A) Genes arrangement in the genome of SARS-CoV-2, (B) Some mutation occurs in genes SARS-CoV-2.*

However, variable numbers of additional ORFs are present in between nucleocapsid and spike genes in different strains of coronaviruses. The transcription regulatory motif (TRS) is sitting at the 3`end of the genome, which plays a vital role in RNA replication and recombination. The ORF1a and ORF1a genes are the largest genes segment of the SARS-CoV-2 [61]. Despite, coronaviruses have genetic proofreading mechanisms. The rate of genome SARS-CoV-2 substitutions is estimated at ~ 1.1x 10-3 per site per year. Over 12,000 mutations have been detected in the SARS-CoV-2 genome sequence comparable with the reference sequence recorded at the beginning outbreak in Wuhan, according to different databases and bioinformatics platforms [62]. Koyama and his colleagues recorded 5775 distinct genome variants, involving 2969 missense mutations, 1965 synonymous mutations, 142 non-coding deletions, 100 in-frame deletions, 484 mutations in the non-coding regions, 66 non-coding insertions, 36 stop-gained variants, 11 frameshift deletions, and two in-frame insertions [10]. Recently, Wang and coworkers characterized 13 variation sites in SARS-CoV-2 ORF1ab, S, ORF3a, ORF8, and N regions, among which positions 28144 in ORF8 and 8782 in ORF1a showed a mutation rate of 30.53% and 29.47%, respectively [63]. Percentage of mutation gene occur in the SARS-CoV-2 genome according to the GISAID database https://bioinfo.lau.edu.lb/gkhazen/covid19/genomics. html were found E, M, N, ORF10, ORF1a, ORF3a, ORF7a, ORF1b, ORF7b, ORF6 ORF8 and other 1.82, 5.99, 15.95, 16.92, 3.4, 7.3, 2.98, 3.39, 3.77, 2.62, 10.36, 19. 17, respectively (**Figure 3**).

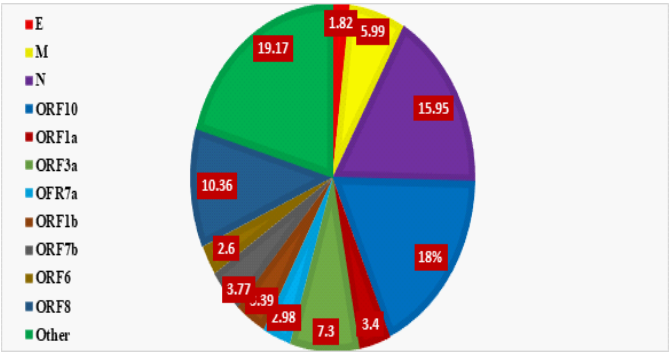

Figure 3: *Average distribution of mutation in SARS-CoV-2 per 1Kb/gene until 2-1-2021.*

The mutations in the genome of SARS-CoV-2 led to genomic variation and effects on, viral transmission, replication, severity, induced immune responses, and immune escape. The emergence of variants SARS-CoV-2 was noted in different parts of the world (**Figure 4** and **5**).

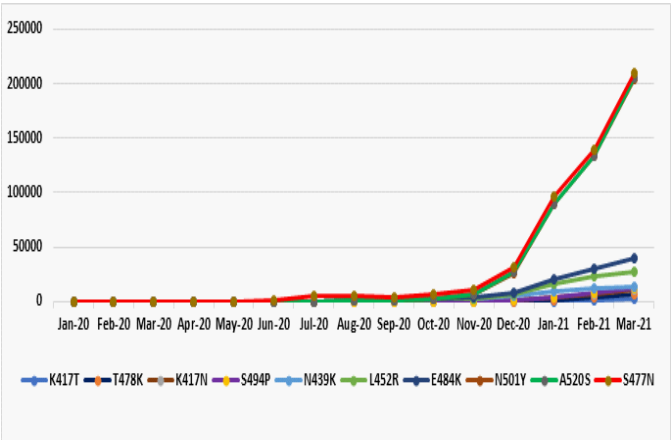

Figure 4: *Top 10 RBD region mutations timeline from Gisaid.*

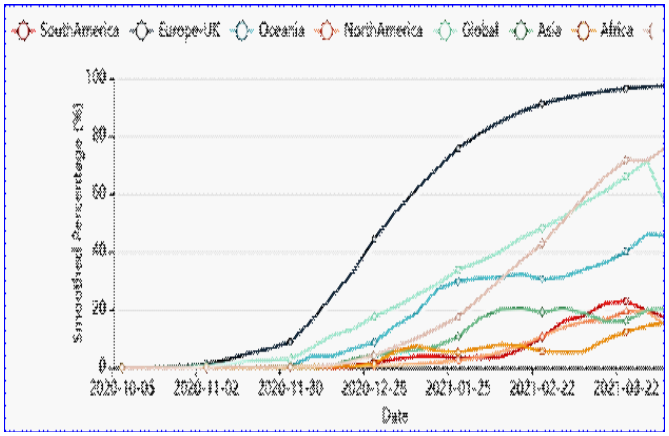

Figure 5: *Relative Variant Genome Frequency per Region (exponentially smoothed alpha=0.3) from GISAID.org*

Variants of SARS-CoV-2 with a mutation in spike protein

Over 3561 mutations in the viral spike protein were identified. Lately, emergence SARS-CoV-2 variants with mutations that occur in the spike protein gene (S) are prevalent rapidly in the UK (variant B.1.1.7), South Africa (variant B.1.351 and B.1.1.529), Brazil (variant B.1.1.248), and California (variant B.1.429) [64]. The highly pathogenicity and transmission include on:-

D614G

From early February 2020, the SARS-CoV-2 D614G strain, characterized by substitution in the viral spike protein, gradually replaced other subtypes and rapidly spread, becoming the major circulating strain of the COVID-19 pandemic [65]. The D614G mutation is characterized by high replication and transmission in primary human cells but does not affect virus virulence [66-68]. Ozono et al., and Zhou et al., were found that the D614G substitution of the viral spike protein enhances the affinity with host receptor ACE2 [66, 67]. Further studies showed that D614G mutation changes the conformation of the SARS-CoV-2 spike and enhances protease cleavage at the S1/S2 junction [69].

N501Y

In August 2020, a new SARS-CoV-2 variant, named N501Y, was recorded in the United Kingdom. The first reported strain N501Y (Variant1) has six mutations, namely S944L, T14I, N501Y, H2357Y, M6723I, and P3395L, [70]. Then, a second N501Y (Variant 2) mutant (named 20B/501Y or lineage B.1.1.7) was discovered in England at end of September 2020 and became the dominant lineage in December 2020 [70]. The N501Y contains 17 mutations, involving H69-V70 deletion (Δ69/Δ70), Y144 deletion (Δ144), N501Y, A570D, P681H, T716I, S982A, D1118H, T1001I, A1708D, I2230T, S3675-G3676-F3677 deletion, Q27stop, R52I, Y73C, D3L, and S325F. The N501Y strain has more transmission ability, which is 40-70% higher than the original strain [70]. Moreover, the infection rate of children has increased significantly and viral escape from neutralizing antibodies [71].

501Y-V2

In November 2020, a new strain of SARS-CoV-2 variant similar to the N501Y mutant was detected in South Africa, which was named 501Y·V2 strain (or B.1.351 lineage). Up to now, there are three most popular variants of 501Y·V2 lineage, including 501Y·V2–1, 501Y·V2–2, and 501Y·V2–3 [72]. The 501Y·V2–1 was the dominant variant in the early stage of the second wave of epidemic in South Africa, which enhances ACE2 affinity through many mutations in spike protein, E484K, D614G, D215G, D80A, R246I, A701V, and N501Y. Subsequently, two other mutations K417N and L18F were identified in 501Y·V2–1, resulting in strain 501Y·V2–2. Following this, deletion (Δ242–244) of spike protein was deleted in the 501Y·V2–2 strain, leading to appear the third variant 501Y·V2–3 [72, 73]. The new strain 501Y·V2–3 contains eight mutations: three mutations in viral RBD (N501Y, E484K, and K417N) four mutations in NTD (D80A, L18F, Δ242–244 and D215G), and one mutation in the S2 region (A701V) compared with the spike protein of SARS-CoV-2 Wuhan-1 strain [72, 74]. These mutations on the RBD of 501Y·V2–3 may lead to higher viral load and transmission ability than that of the Wuhan-1 strain. Mutations K417N and E484K may also reduce the susceptibility of the virus to neutralizing antibodies by more than 10 times from the original strain. These mutants, which can escape the immune system and re-infect discharge patients, have the strong advantage of becoming an epidemic strain. [72, 74, 75].

Omicron (B.1.1.529) Variant

In November 2021, South Africa reported a new SARS-CoV-2 variant, B.1.1.529, in December the first case attributed to B.1.1.529 was reported in the United States. The Omicron variant has also been detected in travel-related cases in several European countries, as well as Australia, Brazil, Canada, Egypt, Nigeria, Hong Kong, Israel, Japan, Norway, Sweden, and the United Kingdom. WHO and European Center for Disease Prevention and Control also classified this variant as a VOC due to concerns "regarding immune escape, potentially increased transmissibility compared to the Delta variant." and able spread from person to person. The omicron variant is characterized by at least 30 amino acid substitutions, three small deletions, and one small insertion [76, 77].

View on SARS-CoV-2 progression and immunity

The clinical manifestations are accompanied with SARS-CoV-2 infection progress in several stages involved on (I) asymptomatic incubation duration (median 4-5 days, sometimes more), (II) moderately symptomatic duration (10-11.5 days), with various levels and severity of clinical symptoms, (III) severe respiratory symptomatic phase progressing during 8-9 days after symptom appearance and reaches the highest level of viral load [78, 97]. Over then, 80% of infected patients with COVID-19 had no clinical manifestations of mild to moderate symptoms, around 15% progressed to severe respiratory disease, and 5% transform into acute respiratory distress syndrome (ARDS), lung failure, septic shock, or multi-organ failure [4, 80, 81]. Patients' recovery from COVID-19 after lowering and disappearing of symptoms, besides viral clearance estimated by two negative RT-PCR test results taken at least 24h aloof. According to WHO reports, the average from symptomatic onset to clinical recovery for mild cases is approximately fourteen days and for patients with severe or critical cases is 21 to 42 days [82]. Various mechanisms may participate in virus clearance during the aforesaid stages (I, II, and III) of COVID-19 progression, and nonspecific response play a role as a primary responder at early phases, which induced specific immune re-

sponse [83]. The seroconversion in major COVID-19 patients includes a total antibody, IgM, and IgG, present after 14 days from disease onset, with belated seroconversion time for IgG, and was not a consequence of the quick decline in viral load [84, 85]. The antibody response particularly anti-spike IgG synchronizes with stage III and ARDS progression due to antibody-dependent enhancement (ADE) response. The majority of patients recovered from COVID-19, virus-neutralizing antibodies reached a peak several days after the severity phase [86]. The immune response leads to significantly neutralized viruses prevents their binding to the receptors and lowers viral replication [87]. Studies by Seow et al. showed that antibody neutralizing titers reached a peak at approximately three weeks after the onset of symptoms and then declined; persons with more severe disease had higher levels of peak neutralizing titers and still had detectable levels of these antibodies 60 to 90 days after the onset of symptoms, while those who were asymptomatic or had mild symptoms had lower levels of peak antibody titers and some fell below the level of detection at 60 days after infection [88]. T cells also have a vital role in the conservation of long-term immunity to viruses. Recently study showed that both CD4 and CD8 SARS-CoV-2-specific T cells persist for >120 days after infection [89]. T cells that know spike, membrane proteins, and nucleocapsid of the virus were more widespread than T cells that responded to SARS-CoV-2 appendix proteins. T cells present in mucosal tissues, particularly tissue-resident memory T cells, are particularly important to keeping long-term immunity for viral infections that get in mucosal surfaces [90]. The passive immunity experiments in which antibody from SARS-CoV-2 convalescent macaques was given to naive animals before virus infection, the antibody was protective from virus infection, but CD8+ T cells were not fully protective [91]. In the majority of patients infected with SARS-CoV-2, neutralizing antibodies titer increases during days to weeks of symptom onset. These antibodies produce immunity to reinfection in primates re-challenged with SARS-CoV-2 to four weeks after the infection. [9].

Reinfection scenario

Numerous studies reported that a re-positive test for SARS-CoV-2 using RT-PCR in recovered patients was confirmed (Table 1). Despite the uninterrupted efforts of scientists around the world, there is still a big gap of knowledge regarding the infection process, clinical symptoms, immunopathogenesis, recovery, and reinfection. But some experts speculated that the potential scenario about reinfection is concerned with virus genetic diversity and weak immune profiling of infected persons. In the context of the virus genetic diversity, although the viral replication process is fidelity, many variables affect viral genetics [92]. One of these variables is the total population size of infected individuals. Many millions of persons have been infected by SARS-CoV-2 [93]. Follows these SARS-CoV-2 genomes encoding every potential single amino acid substitution are present in the global population, and perhaps in a significant fraction of individual COVID-19 patients. Thus, the frequency with which particular variants occur in the global SARS-CoV-2 population is strongly affected by the frequency with which negative and positive selection pressures that favor their propagation are encountered, as well as founder effects at the individual patient and population levels [94]. Some studies have been published on the phylogenetic analysis and confirmation of reinfection with different variants that are antigenically distinct from the early circulating strains [21, 27, 28, 47, 48, 52, 55, 95, 96]. The emergence of neutralizing antibody escape mutations will also be strongly influenced by the frequency with which SARS-CoV-2 encounters neutralizing antibodies [93]. Some mutations have little or no consequence on virus fitness, and other mutations affect receptor binding, reduce antibody neutralization, increase transmission and clinical disease severity [95]. SARS-CoV-2 variants that resist commonly elicited neutralizing antibodies are now present at low frequencies in circulating SARS-CoV-2 populations [97]. Wibmer et al. reported that a novel lineage of coronavirus causing COVID-19, SARS-CoV-2 501Y.V2 (B.1.351), contains substitutions in two immunodominant domains of the spike protein and completely escapes three classes of therapeutically relevant antibodies [98]. Also, Prado-Vivar et al. described different SARS-CoV-2 variants that were identified in each infection event, first infection belonging to the 20A clade according to NextClade, and to the B1.p9 lineage in GISAID, while the second infection variant belongs to the 19B clade according to NextClade, and the A.1.1 lineage in GISAID [48]. Among coronaviruses, point mutations have been demonstrated to confer resistance to neutralizing antibodies in MERS-CoV and SARS-CoV-1 [75]. Lee et al. confirmed that viral RNA from the re-positive test clustered in clade G as defined by the S D614G substitution, while the viral RNA from the first infection was found to be clade V, as defined by the ORF3a G251V substitution. Clade V and clade G represent various geographic distributions and temporal evolutions of the SARS-CoV-2 genome [21]. Studies by Tillett et al. revealed that first and second infections from the identical clade (clade 20C), but genomic sequence analysis of the first infection SARS-CoV-2 identified five mutations (single nucleotide variants) while the reinfection with six mutations (single nucleotide variants) [46]. The full-length genome sequencing with ONT MinION shows that the initial infection was caused by a lineage B.1.1 SARS-CoV-2 virus and the relapsing infection by a lineage A [27]. Pucci, et al., predict variants of the SARS-CoV-fitness and more specifically, on viral transmissibility, infectivity, and ability to escape from the host's immune system. Some situations are anticipated to increase the frequency of encounters between SARS-CoV-2 and antibodies that could impact the emergence of antibody resistance [99]. Reinfection with a genetically distinct SARS-CoV-2 strain may occur in an immunocompetent patient shortly after recovery from mild COVID-19. SARS-CoV-2 infection may not confer immunity against a different SARS-CoV-2 strain [21]. The protection may not affect with severity only of the original illness but influenced by viral escape mutations and/or viral inoculum at the time of re-exposure. Asim et al., conclude that SARS-CoV-2 may adapt itself to causing reinfection within the recovered population in the future to sustain its presence in the environment [61].

Future of present vaccine with new variants SARS-CoV-2 emergence

It was demonstrated that the human sera from parsons immunized with Pfizer BTN162b2 vaccine can neutralize some SARS-CoV-2 variants with spike mutations, such as N501Y, 69/70-deletion+N501Y + D614G, and N501Y + E484K + D614G [100]. But, in some vaccines, it is not clear if these vaccines are still active against SARS-CoV-2 mutants uninterrupted generated in the population because increasing evidence shows that SARS-CoV-2 variants B.1.351 and B.1.1.7 does not neu-

tralize antibodies in convalescent plasma and vaccinee sera [101, 102]. Several studies suggest SARS-CoV-2 may escape human immune response through continuous genomic evolution by substitution or deletion and insertion in the viral RBD, especially in the immunocompromised host [103-105]. Studies by Peng et al., [106] found that the pseudorabies virus can escape the inhibition mediated by CRISPR-Cas9 targeting a single site by substitution. Therefore, it is necessary to estimate the effectiveness of current vaccines against SARS-CoV-2 variants, and update vaccines and therapeutic antibodies in time according to virus mutations. In this regard, Novavax is working on the development combination bivalent vaccine in rebuttal to the B.1.351 variant in South Africa [107]. Moderna looking to modification her vaccine to incorporate sequences coding for the new variants of the spike protein [108]. Also, BioNTech study releases a new version of the Pfizer-BioNTech vaccine that would be more effective against variant in South Africa' [109]. According to Lipsitch and Kahn, the vaccines against SARS-CoV-2 need continuously to assess the ability to reduce transmission of different viral lineages [110]. The main problem, when to decide to modification the vaccine composition, as the dispersal is not uniform globally. Vaccines against SARS-CoV-2 would need to be frequently medication to match the circulating variant.

Conclusions

Based on the findings on literature, the reinfection may be due to adapted variants that are antigenically distinct from the early circulating strains or failure of the immune system to eliminate virus particles and prevent reinfection with SARS-CoV-2. This study highlights that recovered individuals must be kept under the monitor to find if any reinfection leads to the persistence mutant strain due to the selection pressure. The current vaccines against SARS-CoV-2 would need to be frequently reformulated to match the circulating strains, as is done for seasonal influenza vaccines.

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