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Plausibilities of Recurrence of Sars-Cov-2 in Covid-19 recovered patients and efficacy of antibody therapy for Covid-19: A Review

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Abstract: *The world has suffered immensely with outbreak of SARS-CoV-2 in the end of 2019. Amidst this, some cases of recurrence of SARS-CoV-2 in COVID-19 recovered patients have come forward that seeks attention. In desperate times, before the advent of vaccines for this disease, the health care professionals inclined to an underestimated age-old therapy of antibody transfusion for emergency prophylaxis. The authors have explored various research papers and journals leading with relevant words in online database, independently studying to draw inference and finally converge the gathered information into a review paper. Possible reasons for reinfection incline towards falsely negative results mostly. However, people with comorbidities are at a higher risk of reinfection. Viral mutations can also be a cause of reinfection. The underestimated antibody therapy has helped in reducing the symptoms during infection and mitigated the viral replication showing good efficacy. The chances of recurrence are low after recovery. Standardisation of diagnostic tests seeks improvement before discharge from hospital. Post recovery isolation is encouraged. The early transfusion of high titre antibody has been of great help showing effectively low mortality rates.*

Keywords: *COVID-19, recurrence, reinfection, antibody therapy, antibody.*

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Introduction:

The world has suffered severely when the first and second wave of COVID-19 struck us wiping away two years of our lives in lockdowns and still living with precaution amidst the lockdown. Coronavirus disease 2019 (COVID 19) caused by SARS CoV 2 was declared a pandemic by World Health Organization. The SARS-CoV-2 strain is a highly mutating virus. The global reporting of cases as of 4 December 2021 was seen to be 265,314,905 with 5,248,315 death cases (Johns Hopkins University 2021). The majority of the existing

studies on this disease are focused on the epidemiology, diagnosis, vaccines, and clinical aspects of patients with active infections, and little attention is being directed to post-recovery patient follow-up. In terms of a clinical cure for the infection, patients are considered free of the disease 14 days after their last negative diagnostic test. The chances of reinfection in the cured population are still not well established, and this raises the question among researchers and health professionals (Costa, et. al, 2021). Whether reinfection occurs in patients cured of the infection? Recent studies reported that some recovered patients tested positive for virus nucleic acid again. Elderly people with comorbidities are more likely to present with its reinfection. Studies suggested that there are three major mechanisms for reinfection, including short-lived, ineffective, and strain-specific immune responses (Seyed et. al., 2020).

In view of the devastating effects of this disease on human life, there was an urgent need for licensed vaccines or therapeutics for the SARS-CoV-2 infection. However, with the advent of 2021, a huge population has been vaccinated around the globe. The vaccines have shown good efficacy against this contagious disease. But in the first wave of the pandemic in 2020 when no specific treatment could be applied to the sufferers, many health care workers considered the experimental treatment of cocktails of antivirals. Plasma collected from healthy, voluntary donors who have recovered from a recent infection contains pathogen-specific antibodies with neutralizing activity in varied concentrations and plasma with a high titer of these neutralizing antibodies is expected to provide immediate passive short-term immunization (Devarasetti, et. al., 2021). To combat the severity of the disease, many health care professionals considered the administration of antibody therapy. Age-old passive immunization with protective antibodies to neutralize the virus is one of the strategies for emergency prophylaxis and therapy for coronavirus disease 2019 (Sajna and Kamat, 2021).

Methodology:

Search Strategy: We carried out a scientific overview of the opportunities of reinfection of SARS-CoV-2 in recovered patients and the efficacy of antibody therapy for COVID-19. The subsequent databases: MEDLINE, PubMed, Web of Science and Google Scholar were searched. The seek method included: SARS-CoV-2, COVID-19, reinfection, recurrence, reactivation, recovered patients, post-COVID-19 patients, convalescent plasma, antibody therapy, and plasma therapy. Related references have been additionally searched.

Study Selection and Eligibility Criteria: In order to select studies, the following criteria were used: (i) peer-reviewed journal articles, case reports, review articles. (ii) articles on COVID-19 reactivation or reinfection in recovered patients. This study included papers that documented the likelihood of SARS-CoV-2 reactivation or reinfection in individuals with morbidities. Other papers were identified by looking through the references of all qualified research for identification of other potentially eligible studies. Studies must meet certain criteria in order to be considered for inclusion, patients with a verified diagnosis of COVID-19, treatment using convalescent therapy and reported mortality.

Data Extraction: Relevant information had been extracted independently. The generated effects had been compared, and any inconsistency with the information was resolved via way of means of in addition discussions between the authors. The

generated effects were further synthesized. The information analyzed covered the prevalence of SARS-Cov-2 reactivation and reinfection in recovered COVID-19 patients and the efficacy of antibody therapy for COVID-19.

Result and Discussion:

According to the study 11000 healthcare workers got infected in the first wave of the pandemic between March and April 2020 in the UK and in the second wave that was between October and November. None of them had symptomatic re-infection (Stokel-walker, 2021). There are some countries where cases of re-infection were reported like China, Italy and Korea. The first case of COVID- 19 re-infection came from Japan, a woman tested positive for COVID 19 after recovery. One of the largest case series of re-positive COVID 19 was reported by the Korea Centres for Disease Control and Prevention (KCDC), in which they conducted an extensive epidemiological investigation involving 285 re-positive cases and 790 contacts (Osman, et. al., 2020).

Cases of re-infection are comparatively very lower than cases of the first COVID 19 infection. Now the question arises what are the reasons for reinfection?

Plausibilities of Recurrence of SARS-CoV-2 in COVID-19 Recovered Patient

Morbidities of People: It's possible that some cases ended in a false negative at discharge, or that patients didn't match all of the criteria. Although, as some studies have indicated, humoral immunity decreases with time, we should not rule out the possibility of reinfection (Seyed, et. al., 2020). SARS-CoV-2 causes a decrease in T cells in general. The decline in cellular immune response could be linked to the virus's partial clearance, which encourages reinfection. Patients who relapse after being discharged from the hospital are typically elderly, have weakened immune systems, and have other comorbidities. Diabetes and hypertension are the most common underlying illnesses that impair COVID-19 prognosis (Chen et. al., 2020). These variables contribute to longer hospital stays, and patients in these situations are more likely to re-infect themselves (Zhou et. al., 2020).

Despite the fact that some individuals improve the following treatment, factors such as advanced age, weakened immune function, structural lung disease, and pulmonary fibrosis all contribute to poor blood circulation. The partially hidden virus is not completely eradicated in these circumstances, and cells remain infected, but low nucleic acid levels prevent positive diagnostic laboratory results. Low immunity, on the other hand, is a major exacerbating factor, as the virus can restore its infectious capacity and cause the patient to become unwell again (Zhou et. al., 2020).

Diagnostic Testing Error: In a study it shows there might be error in specimen collection and technical errors which are associated with each component of swab testing, method used before discharging recovered patient, it may rise the question on the effectiveness and reliability of commercial testing kit (Roy, 2020). The evidences for reinfection of COVID 19 pandemic poses challenges for public health and vaccination.

Other Plausibilities: It's important to note that the presence of viral RNA does not always imply that the virus is present or that the person is infected. The presence of the entire virus, not only its RNA, is required for viral infectivity. A positive RT-PCR does not guarantee viral viability, even if the genome has been sequenced. Certain aspects must be considered, such as the possibility of a negative RT-PCR following a positive RT-PCR if the

viral load is below the detection threshold. A positive RT-PCR following a negative RT-PCR could also indicate contamination. Shedding could be linked to a lack of nucleic acid removal in some tissues (Alvarez-Moreno et. al., 2020). Thus RT-PCR can't tell the difference between a live virus and RNA.

Another set of researchers detected novel SARS-CoV-2 recurrent mutations and pinpointed their exact position. In Europe, four forms of mutations have been discovered, whereas three have been discovered in England. In European viral genomes appears to be the most common mutation hotspot. As a result, all of these mutations have the potential to impact the primer and probe target, resulting in "false negative" results. They can re-infect people who have recovered from SARS-2-CoV, especially if their infection was milder and lasted shorter time (Krishna et. al., 2020).

Efficacy of Antibody Therapy

To cure infection or reinfection of COVID-19 in patient convalescent plasma therapy has been used. In this study with the help of research paper study the efficacy of convalescent plasma therapy in the treatment of patient was evaluated. Convalescent plasma of SARS patient carries antibodies against corona virus.

Effects of plasma therapy seen in 10 patients by group of researchers are: It improved the clinical symptoms, Reduction of pulmonary lesions on the chest CT examination, Amelioration of routine laboratory criteria and pulmonary function, increase of neutralizing antibody titres and disappearance of SARS-CoV-2 RNA and it had been seen that there is no adverse effect of CP transfusion.

Convalescent plasma (CP) has been applied to improve the survival rate of patients with a variety of viral epidemics, including SARS, MERS, influenza, Ebola virus disease. This therapy also shows improvement as the emergent treatment for serious COVID-19 cases (Zhao and He, 2020).

In a study Shen et. al. (2020) showed that SARS-CoV-2–specific ELISA antibody titres ranged from 1800 to 16,200, with NAb titres ranging from 80 to 480 in COVID-19 convalescent donors. Plasma taken from donors and transfused to receivers on the same day resulted in a reduction in viral load and a time-dependent increase in IgG and IgM titres in the recipients.

Study by the Wang et. al. (2020) presented a meta-analysis of current medical treatment approaches for COVID-19, which found that CP treatment reduced the risk of death in patients with severe COVID-19 (RR = 0.65; 95 percent CI 0.42 to 1.02). The combined results also revealed that individuals receiving CP therapy had a higher viral nucleic acid negative rate (RR = 2.47; 95 percent CI 1.70 to 3.57).

Based on eighteen clinical trials, including five RCTs, thirteen matched-control studies, and twenty case series or case reports including 10,436 COVID-19 patients, Klassen et. al. (2021) conducted a comprehensive review on CP treatment in COVID-19. Patients transfused with CP had a 51 percent lower mortality rate than patients receiving standard treatments (19 percent vs. 29 percent mortality; OR: 0.49, 95 percent CI: 0.37, 0.64, p 0.001, I2 = 53 percent), according to an analysis of mortality data from all clinical trials, including RCTs and matched-control trials. These findings support the use of CP as a treatment intervention in COVID-19 (Klassen et. al., 2021).

Monoclonal antibodies can neutralize the trimeric spike (S) glycoproteins on the SARS-CoV-2 surface that mediate entrance into host cells. The spike proteins of SARS-CoV-2 (SARS2-S; 1273

residues, Wuhan-Hu-1 strain) and SARS-CoV (SARS-S; 1255 residues, Urbani strain) are 77.5 percent identical in primary amino acid sequence, structurally very similar, and usually bind to the human angiotensin-converting enzyme 2 (ACE2) protein as the host receptor (Walls et. al., 2020). SARS-CoV-2 S protein's receptor-binding domain (RBD) binds strongly to human and bat angiotensin-converting enzyme 2 (ACE-2) receptors. According to research, the SARS-CoV-2 RBD has a substantially higher affinity for the ACE-2 receptor than the SARS-CoV RBD. This could prevent SARS-CoV-2 RBD from attaching to ACE2-expressing cells, limiting the virus's ability to infect host cells (Tai et. al., 2020).

This shows that people who have been infected before are at a lower risk of becoming sick again. As a result, the aforementioned research raised the prospect of SARS-CoV-2 reactivation and/or reinfection, which is less likely to result in a severe public health issue. Even though only a small percentage has been reported to have re-positive after discharge, we believe that these RP-SARS-CoV-2 concerns warrant additional examination. This is because, despite multiple research on COVID-19 as part of efforts to contain the virus's transmission, many of its epidemiological characteristics remained unexplained to date (Tang et. al., 2021).

This finding has been attributed to PCR false-negative results after discharge, SARS-CoV-2 long-term shedding, and enhanced virus replication as a result of medication withdrawal after clinical symptoms have improved in some studies (Falahi and Kenarkoohi et. al., 2020). Positive retesting in recovered patients may be linked to dead viruses and viral genomic fragments, according to one study (Kang et. al., 2020).

Convalescent plasma antibodies have been shown in tests to reduce virus reproduction in the acute phase of infection and aid in virus clearance, which is advantageous to the disease's speedy recovery (Cheng et. al., 2005). All of the studies showed positive results following CPT, but they were all assessed to be at risk of bias due to a combination of non-randomized evaluations, confounding, predictor description, and inadequate methodological conduct for participant selection, CPT dosage, and therapy duration (Rajendran et. al., 2020).

Isolating the increased antibodies by SARS-CoV-2 disease recovered patients regionally is critical. SARS-CoV-2 patients should be treated with antibodies that have been generated on a massive scale. While alternative and more time-consuming vaccines and novel medications are being developed, these antibodies could provide an urgent method for emergency prophylaxis and SARS-CoV-2 therapy (Kumar et. al., 2020).

Conclusion:

The chances of recurrence of contracting SARS-CoV-2 after recovery from the first infection is however low but not nil. Our studies gathered that reinfection usually occurs due to diagnostic testing errors, RNA viral shedding and even some mutated strains raise a matter of concern and seeks more attention in this ongoing pandemic. The authors suggest testing standards require improvement and post recovery isolation to prevent any chances of relapse.

The antibody therapy administered in the absence of any vaccine or any specific antiviral drug for COVID-19 in the initial phase of the pandemic has helped in mitigating the viral replication post transfusion and helped in recovery in severe cases. Early transfusion of higher titre of plasma should be preferred.

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