

Review Article

Relapse, Recurrence and Re-infection with SARS-Cov-2 after recovery from COVID-19

Running title: Reetika et al: Relapse, Recurrence and Re-infection with COVID-19

ABSTRACT

The whole world is in pain due to increase of number of cases and deaths due to novel corona virus (called COVID-19) which came upon in late 2019 in Wuhan city, in China. This viral entity causes a variety of symptoms that range from mild illness to moderate illness. Breathing difficulties and death occur in very severe cases. The most common earliest manifestation include fever, cough, cold, myalgia, chest pain, ~~diarrhoea~~[diarrhea](#) and headache. This disease is mainly spread through respiratory droplets which are brought about a person who is infected when he or she coughs, sneezes, or exhales.

For SARS-CoV-2, the timing, size, and duration of humoral immunity are unknown. However, understanding this is critical in order to predict the pandemic's expected future dynamics, to guide methods for allowing social distancing measures to be relaxed, and to understand as to how to deploy the vaccine doses for achieving the maximum impact.

So, since this disease is wrecking homes all over the world. There comes a necessity to be able to know about it at the earliest and effectively treating the patients by various drug modalities. Many studies are being done on the same. Tests for detecting coronavirus infection include RT-PCR, Rapid Antigen Testing, Antibodies testing, Chest ~~X-ray~~X-ray and some blood markers like CRP, D-dimer, LFT, KFT, Immunoglobulins etc. And with the upcoming testing options there also has been reports of reinfection or basically repeat RT-PCR test coming out to be positive after the recovery of the previous infection.

According to many studies, it is found that RT-PCR coming out to be positive in patients that have recovered from the ~~disease~~.This disease. This article aims to conduct a review that will summarize the epidemiological as well as clinical characteristics of these patients and also know about the possible explanations for these kind of recurrences, the contagiousness of re-positive SARS-CoV-2 virus, and the management of COVID-19 patients after they are discharged from the hospital.

KEYWORDS

COVID-19; Re-infection; Relapse; Recurrence; RT-PCR; SARS-CoV2;

INTRODUCTION

In December of 2019, a 55-year-old, inhabitant of the Hubei province in China was the first person who was infected with COVID-19, named SARS-CoV-2. (1) From there it has expanded to various countries like America, Europe, UK, Philippines. This virus has grown across the globe and affected people all over the world and caused deaths of more than over 1million people. COVID-19 has dominated the headlines, with stories abounding on rate of transmission and rate of fatality, the value of mask and keeping a social distance, the potency of treatments, quest of vaccinations, and the timing of school ~~reopenings~~reopening and social restrictions. (1)

This outbreak of this coronavirus 2019 disease pandemic, officially recognized by the WHO, has put health care programs at risk and has created a lot of social and economic burden worldwide. (2,3) Coronavirus is reported to spread via droplet infection, especially when the person who is infected coughs, breathes, speaks loudly, sneezes, screams, shouts especially when in confined places. (4).

The most effective methods to limit this contagious content, include nationwide closure and local settlement orders, (5) followed by public distances (at least 6 meters), widespread facial wear (especially when crowded)-, home arrangements, and general hand hygiene. (6,7) Most importantly, effective prevention measures require early and accurate identification of healthy patients and follow-up contact with them. (8,9)

Separating people infected with the virus, regardless of their symptoms, is important in reducing the spread of the virus, as data shows that there are many people with active disease but having no clinical symptoms. (10,11) The genomic data states that the backbone of this new coronavirus genome has a close resemblance to that of a bat coronavirus. Various other incidence of corona virus infection in people include SARS- which is known to arise from cat-like civets; and MERS which arose from camels. (12) SARS-2 is a communicable disease which has led to many deaths in spite -the fact that it has low case fatality rate (CFR).

The severe acute respiratory distress syndrome coronavirus-2(SARS-CoV_2) is a novel coronavirus, which is transmitted by contact transmission and droplets infection. Most of the researches are being done studying the epidemiology, symptoms, genomic structure, transmission, investigations, treatment, developing of vaccines for this virus, but there have been recent reports on the reinfection in patients after successful viral clearance and complete clinical recovery. (13)

These reports suggest the possibility of relapse by this coronavirus. (14)

MATERIALS AND METHODS

A systematic search was done for research articles using keywords COVID-19, RELAPSE, RECURRENCE. The search was made on PubMed. Complete articles were read, studied and analysed properly.

DISCUSSION

Originally the human coronavirus was first identified in 1965, which was known to cause common cold. After almost a decade, a group of similar viruses were discovered, out of which there were seven such coronaviruses that could infect humans. The virus causing SARS came out in 2002 in southern China and got spread to around 28 countries. (11) No further cases were reported for SARS since 2004. Emergence of MERS-CoV occurred in 2012, in a patient in Saudi Arabia. This virus was reported to be less contagious but it was more life threatening. (15)

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In 2019 in month of December, a new virus was identified SARS-Cov2 in Wuhan, China called the novel coronavirus. (13,14,16) this virus is known to cause the disease COVID-19 (coronavirus disease 2019). Due to its widespread infection all over the world, WHO called it as a pandemic infectious disease. (11) By May 16, 2021, 163,897,565 confirmed cases and 3,396,441 deaths have been reported so far all over the world.

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The capability of coronavirus (CoVs) migrating from animals to people is proven since the outbreaks of SARS and MERS in 2002 and 2012 respectively (17,18). The full-length genome sequencing done for five patients revealed that they were almost identical in the early phases of the outbreak, and 2019-nCoV was most comparable to bat coronavirus, at the genome-wide level. (19) The findings demonstrate that the 2019-nCoV ~~genome-genome~~ closely linked to the SARS-CoV virus that is widespread in China, and that it has -genetically recombined with SARSr-CoV, with a total of 82-89 ~~percent-percent~~ genomic similarity (20).

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Yu Wenbin et al. (ChinaXiv) studied 2019-nCoV using population genetics-based analysis methods and discovered that there were two significant population expansions before February 12, 2019, the first of which occurred around December 8, 2019, implying that the 2019-nCoV found in Wuhan was a recent recombinant virus, possibly from natural recombination. It's worth noting that "recombination," ~~is-is~~ defined as the process of destroying and binding nucleic acid molecules in exchange for genetic material, resulting in the deterioration of new genomes, is one of the basic natural processes that can be used to describe the natural recombination of viruses, along with replication and transcription. (21)

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Patient usually present with variety of symptoms including dry cough, fever, fatigue. With the new strain more and more symptoms are getting included in this disease- ~~patients with~~ gastrointestinal involvement show symptoms like diarrhoea, vomiting, anorexia. In fact, it is noted that in many patients with gastrointestinal symptoms, sometimes do not show any respiratory symptoms or fever. Covid -19 also causes ~~hypercoagulable~~ disease that eventually

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increase the risk for ischemia, thrombosis or infarcts, thus increasing the chances of fatal outcomes. Recent researches are also showing evidences of a fungus infection called Mucor mycosis. (22)

Covid 19 is an infectious disease, and so due to high transmission rates, it has posed a threat to the medical system all over the world. (23) Detection of the virus and extent of the disease is being done by various investigations that include RT-PCR, Viral antigen testing, HRCT scan, chest X-ray, Blood tests etc. The outcome for patients majorly depends upon early detection, isolation and early treatment.

This disease was thought to be monophasic, but there have been cases reported suggesting reactivation or recurrence in patients after discharge. (15) according to some researchers the positive retest after recovery is due to persistent presence of this virus in the body of individual which is thought to be for 83 days or there may also be a probability of reinfection occurring in the patient. (12)

The first defence mechanism of our body against the reinfection is humoral immune responses, and the level of response and their persistence also plays an important role. (24)

Antibody response dynamics in these patients are poorly known. The total seroconversion rate was reported to be 96.8% in one research, however the neutralising activity and durability were unknown. (25) Similarly, Zhao et al. (26) found that the total seroconversion rate was 100 percent by 39th day following illness initiation, although no further follow-up was done to assess persistence in this research. In another research, blood samples from 42 corona patients were studied 14 to 60 days following the onset of their symptoms, which was consistent with the previous studies. IgM and IgG antibodies were consistent in everyone, however level of antibodies were significantly lowered 60 days following beginning of symptoms. (24)

However, a research was conducted on the serum of 342 COVID-19 patients. The average time for seroconversion for antibodies against RBD (receptor binding domain) was found to be around 12 days. IgM and IgA antibodies had an average seroconversion duration of roughly 49 and 71 days, respectively. Anti-RBD IgG antibody levels fell modestly over three months, and only a few persons had seroconversion. (27)

Another set of researchers looked at the sera of 59 individuals with varied degrees of sickness; their findings revealed a link between serum neutralising ability and disease severity. Given that the number of neutralising antibodies in patients recovering with COVID-19 predicts the risk of reinfection, it has been suggested that asymptomatic people may acquire reinfection. (12)

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As per a French study group after collecting cases through COCLICO, they defined COVID-19 episode as

* at least one major Covid 19 clinical sign including flu like symptoms, fever or chills, anosmia, dysgeusia, dyspnoea

* RT PCR positive test for SARS-CoV-2 (15)

An ongoing concern since the pandemic started is that, can a person be infected with SARS-cov-2 more than once? There may be multiple explanations for repeat positive status of patient, and one of those is the probability of relapse.

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Now firstly there is a need to define about what relapse actually means.

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Recurrence or recrudescence actually means that there is occurring reappearance of symptoms in corona patients after negative reports and successful clinical recovery.

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On the other hand reinfection defines as chances of attaining a new infection with the virus after recovery. The elimination of virus from body may depend on various factors including age of person, his/her immune status, any underlying lung disease, comorbidities if any, viral load and severity of SARS-CoV-2 infection. And as we know COVID 19 enters through angiotensin converting enzyme-2 receptor which are located mainly on type 2 pneumocytes rather than in the upper respiratory tract, and the samples being taken from oropharyngeal or nasopharyngeal swabs, hence can many a times cause false negative results. (22)

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In a retrospective article, Jing Lu and colleagues found out that 87 out of 619 patients, who initially recovered, were found to be positive by RTPCR test.

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But it was found that these patients had not gotten a new infection with the virus, Aswhen checked, the researchers were unable to isolate the virus by culture, and also they were not

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able to detect full length viral genome sequencing. So the positivity of the test was due to ongoing shedding of viral fragments from the earlier infection. (28)

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An analysis comprised nine observational studies with a total of 283 recurrence and 1,674 nonrecurrence participants. Data was provided for age, gender, length of hospital stay, illness severity, five symptoms, seven comorbidities, nine blood biochemistry indexes, five blood routine indicators, four therapeutic treatments, history of high-risk contact and two antibodies.

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(28)

Secondary infection could be due to inadequacy of the immune system during the first encounter with the body of the viral agent or could be due to decrease in neutralising antibody response over time. (23) According to an article there is a relation between

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reinfection by virus and secondary infection. Particularly, elderly patients, or those with underlying diseases, and the ones who are critically ill are more prone to reinfection.

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Diabetes and hypertension are the two comorbidities that may affect the disease prognosis.

(21) Patients with diabetes are believed to have decreased immune function and so disease progresses early. Also, if they get coinfectd, they get more difficult to manage, thus progressing the disease. Now since these patients are being hospitalised for longer periods, there are more chances of relapse after being discharged.

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It is believed that the using systemic glucocorticoids is controversial in hospitalised patients.

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According to some scholars, the use of systemic glucocorticoids might inhibit the immune function of the body, making it difficult for the body to clear out the virus and thus increasing the chance for reinfection.

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But others also believe that the use of systematic glucocorticoids inhibits inflammatory response in the body and thus decreasing the progression of the lung diseases. (21)

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The current medical observation or containment time for patients infected with coronavirus is 14 days. According to the WHO's clinical care recommendations, a clinically recovered patient can be released from the hospital after two consecutive negative PCR findings at least 24 hours apart. (29)

Managing of the patient after discharge from the hospital is another challenge.

According to the European Centre for Disease Prevention and Control, the discharge criteria for COVID-19 cases include-

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1. There has been no fever for more than three days.
2. Relief of respiratory symptoms
3. Lung scan demonstrating obvious inflammatory absorption
4. There is no requirement for hospitalisation for another pathology.
5. A minimum of two consecutive negative RT-PCR tests in the respiratory system examples (with samples taken at least 24 h apart). Testing should be done at least 7 days following the first positive RTPCR result. The test is indicated for individuals who have shown clinical improvement earlier. (13,30)

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Normally after an infection, body makes specific antibodies against that virus, that helps body fight against the infection for a certain period of time and also protects from any other secondary infection. But in this Covid 19 we still don't know the amount and time period for

antibodies build up in the bodies of patients. And also the patients discharged are yet physically weak, have poor resistance, so they should be protected well.

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Now since the virus is undergoing mutation, so there is a chance that the antibodies formed previously might not be effective against the new mutated virus, and thus causing reinfection. COVID-19 has been a common subject of conversation throughout the world, showing an upsurge in COVID-19 cases, fatalities, and recoveries. The main aspects to coping with COVID-19 are the lessons learnt from previous pandemics, such as keeping ~~a~~ social distance, wearing of masks, and following standard guidelines, as well as keeping your own personal cleanliness. The measures that are given by the medical authorities for the elderly and pregnant women must be rigorously followed. These will assist to minimise COVID-19 instances, easing the burden on hospitals to provide care to individuals in need. (31)

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CONCLUSION

SARS-CoV-2 virus recurrence is prevalent in individuals who have recovered from COVID-19 and have been released from the hospital. The reason for the re-positive test is yet unknown.

Continued surveys for repeat positive people are needed to track their health and determine their degree of infectivity and infection. Tests done on repeat positive people with a high viral load, in particular, should be undertaken to analyse the virus culture and more correctly estimate the contagiousness of these patients. The family members of Corona patients should also be checked for SARS-CoV-2 on a regular basis.

The presence of RNA of the virus in samples collected from air and on the environment's surface implies that environmental transmission plays a significant role. To decrease the creation of viral aerosols, lower the aerosol burden, and avoid cross infection in isolation wards, good ventilation, careful cleaning of surroundings, mainly in hospitals, and stringent hand hygiene should be emphasised. Toilet sanitation should also be prioritised.

In addition, quarantine and other measures should be maintained long after the infection has been treated and the patients have been discharged. To further understand the mechanism of SARS-CoV-2 recurrence in patients with coronavirus, large-scale and multi-center research are suggested. Finally, it's critical to re-evaluate and standardise isolation duration for

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Normally one considers in contagious diseases the R-value (number of people infected by one infected person) as a velocity of spreading. Of course one uses the average R-value. As it is governed by a non linear differential equation, considering average R-values may lead to completely wrong result. (32) This effect is particularly strong in Covid-19 (33) leading to a huge acceleration in spreading. It is enhanced by the fact that many infections are undiscovered though virus is spreading. With the delta variant and probably omicron it is becoming worse. This makes re-infection particularly worse. There is hardly any virus were reinfection or infection of vaccinated people is 100 % impossible. With the very many undiscovered though contagious cases, reinfection may become a much bigger problem than a low reinfection rate suggests. Furthermore one should be careful using ordinary statistics with Covid-19. One is the already mentioned inhomogeneous R-value which may imply effectively no her immunity. Other problems with the reliability of the vaccine can be found in (34).

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discharged patients. As more experience and clinical breakthroughs are gained, norms for discharge from hospital or freeing from isolation should be modified.

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