SYSTEMATIC REVIEW

A systematic review on SARS-CoV-2 remission: an emerging challenge for its management, treatment, immunization strategies, and post-treatment guidelines

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Abstract

The COVID-19 disease caused by severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) has posed as a major health concern for people all across the globe. Along with the increasing confirmed patients being readmitted with complaints for fever, cough, cold, the effective monitoring of 'relapse' of the SARS-CoV-2 virus in the previously discharged patients have become the next area of focus. However, availability of limited data on reactivation of SARS-CoV-2 makes the disease prognosis as well as the effective control of re-infection an immense challenge. Prompted by these challenges, we assessed the possibility of re-infection in discharged patients and the risk of the transmission, proficiency of RT-PCR results and approximate period required for the quarantine, and the real challenges for the development of vaccine. In the present review, the published literature on all the possible cases of re-infection from February to July were reported, thereby selected 142 studies from a hub of overall 669 studies after full text screening. The incomplete virus clearance, poor sensitivity of the present diagnostic testing, emergence of mutant strains, insufficient mucus collection from the throat swab etc., are some of the possible causes of re-infection. The new protocols for management of COVID-19 discharged patients should be revised in the guidelines.

Keywords: COVID-19, mutant strains, re-activation, re-emission, re-infection, relapse
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Introduction

The infection of SARS-CoV-2 has made the whole world feeble. Population of many countries got infected by this virus, which was claimed to be originated from Wuhan, China. All the scientists over the globe are engaged in researching the best treatment options and immunization strategies against the SARS-CoV-2 infection. Although a tremendous understanding of the virus, its types, have been done in the last five months but still many questions related to its immunity, mutations, relapse, and vaccination need to be explored. The fate of infection of this virus is still a mystery for scientists.

On one side various antiviral drugs, steroids, monoclonal antibodies, anti-microbials, convalescent plasma therapy etc., had been tried for its treatment, on the other side numerous vaccines have also been developed to combat this COVID-19 pandemic [1,2]. In spite of all these concepts, the incidence of relapse of COVID-19 patients has produced another challenge for the treating physicians as well as the researcher scientists and policymaker organizations all over the world. The conception of immunity to coronaviruses is not yet clear. However, the immunity to common cold viruses is not long-lasting but immunity to the previous outbreaks of coronaviruses like SARS-CoV in 2012 has been found to be long lasting but SARS-CoV-2 is not comprehensive [3,4]. The reports of re-infection or remission of SARS-CoV-2 infection are rising day by day from the last few months. The relapse cases were very

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few in the month of March 2020 but had been increased suddenly till the second week of July, 2020. The published reports of re-infection cases from all over the globe were collected and summarized to find out the trend of re-infection. Moreover, the time of reoccurrence of the infection has also found to be unpredictable. Although a number of reasons for re-infection were discussed in few reports however, the actual cause of re-infection is not clear. In this review, the different reported cases are critically analyzed to accomplish the exact cause and treatment strategies to control the cases of re-infection. This would help in monitoring the COVID-19 patients for re-infection and to decide the quarantine or isolation period for the infected patients. The risk of spread of further infection from these relapse cases has also been discussed.

Objectives of this systematic review

- To evaluate the possibility of re-infection of COVID-19 in recovered/discharged patients and the risk of transmission of infection from re-infected patients
- To determine the certainty of the number of negative tests done on the COVID-19 patients to declare them safe or discharged proficiency
- To re-evaluate the proficiency of the results of RT-PCR to decide the chances of re-infection or remission of the disease
- To decide the approximate quarantine period required for the COVID-19 patients after its first discharge

Materials and methods

Search strategy and selection criteria

The published literature for the present review was obtained by searching the articles published from Feb to 20 July, 2020. This literature search was conducted on 1st April, 2020, using databases like PubMed, Science Direct, Google Scholar, Google), with the search terms: ['*COVID-19*' OR '*SARS-CoV-2*' OR '*SARS-CoV*' OR 'Coronavirus'] AND ['Reinfection OR 'Reactivation' OR 'Relapse' OR 'Herd immunity']. The list of the selected articles was finalized based on relevance to the topics covered in this review with no limitations on the language barriers.

This systematic review was designed to be effective enough to curtail the lacunae of the sufficient evidence of re-infection of the COVID-19 patients. Thus, we conducted a systematic review of studies on COVID-19 that included information on patients, which were re-infected with the SARS-CoV-2 infection. The present systematic review aimed to evaluate the association between the re-infection of COVID-19 and its outcomes incorporating the disease severity, duration of the latent period of re-infection, and management of the re-infection.

Inclusion criteria: Studies mentioning about the cases of relapse of COVID-19 patients were included. Peer reviewed original articles and review articles related to relapse and re-infection of SARS-CoV-2 were also included.

Exclusion criteria: Articles that have not discussed about the cases and reasons of re-infection or relapse of the SARS-CoV-2 virus were excluded. Moreover, articles in pre-print, which were not peer reviewed were also excluded.

After a rigorous search, we retrieved a total of 669 studies, of which 214 were found to be relevant to the topic after full text screening. A total of 142 studies were included after excluding the repeated studies and 14 studies of re-infection were discussed in detail (Fig. 1).

Maximum studies were from six countries namely, China, South Korea, Japan, Indonesia, Italy, and India. The study population included the patients with COVID-19, and the sample size ranged from a single case report to 447 patients. The study design involved retrospective methodology and the timeframe of the studies comprised the initial six months of the COVID-19 pandemic. The summary of all the included studies has been discussed in Table 1.

Results and discussion

The reasons for relapse of COVID-19 infection can be explained by many theories, that is, re-infection, reactivation of SARS-CoV-2, emergence of mutant strains, varied virus replication period, faults in testing results (false negatives). Some of the experimental studies have proven to be against the theory of re-infection. The monkeys when re-infected with the virus did not show the positive tests for the presence of a virus [5,6]. On the other hand, the results of another researcher from Fudan University, Shanghai, also reported low levels of antibodies in patients after COVID-19 infection. The following possible reasons for the relapse of COVID-19 have also been explained in Fig. 2.

To evaluate the possibility of re-infection of COVID-19 in recovered/discharged patients and the risk of transmission of infection from re-infected patient

The peer review survey regarding the re-infection studies, out of 142 studies only 14 studies had reported the relevant clinical cases of reinfection. Only 2–3 studies have done the long term follow up of the COVID-19 patients. The chances of re-infection in the reported studies varied from 2% to 31% [7–9]. The findings from the investigation and analysis of re-positive cases by the Korea Centre for Disease Control and

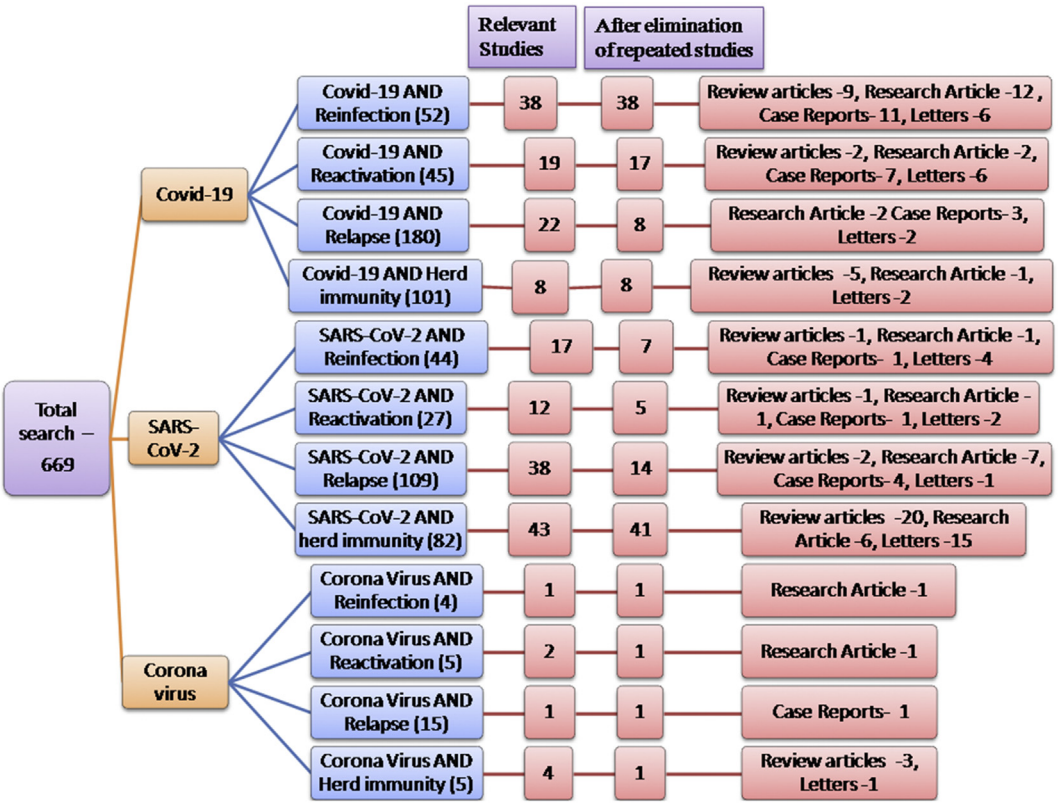

FIG. 1. The possible reasons of relapse of COVID-19.

Prevention (KCDC), 790 contacts of the 285 re-positive cases were evaluated and no case of transmission of the virus from re-positive cases to their direct contacts was reported. Although the sample size of these studies was very less, thus it is difficult to conclude the possibility of relapse of COVID-19 infection [10]. In children, it was reported to be 50% in only one study of 15 patients [11].

Another cause of re-infection may be due to the induction of antibody-dependent enhancement of infection due to the presence of anti-S non-neutralizing or sub-neutralizing antibodies. So, the production of low levels of antibodies in a patient may lead to higher chances of re-infection with exacerbation of the disease.

Emergence of new strain of SARS-CoV-2: Emergence of novel coronavirus variants/strains can also cause re-infection. These variants used to escape the immune system and can cause reinfection in patients already recovered from Covid-19. The incidence of cases of new strain of SARS-CoV-2 originated from UK also leads to another challenge for the management of COVID-19. In the UK, there has been a rapid increase in COVID-19 cases in South East England, leading to enhanced epidemiological and virological investigations. Analysis of viral genome sequence data identified that a large proportion of cases belonged to a new single phylogenetic cluster. This strain is re-infecting the people already infected with SARS-CoV-2 in many countries. This variant strain is upto 70% more transmissible [12]. In India, the incidence of re-infection was reported with the new strain, that is, N440K in health care workers [13]. Thus, the emergence of new mutant strains could be among the various contributing reasons to re-infection.

To re-evaluate the proficiency of the results of RT-PCR to decide the chances of re-infection or remission of the disease

The problem of virus tests giving false negative results also interferes with the discharge criteria. The factors like procedure and time of sampling, transportation, and storage temperature, quality of testing kits result in false-negative tests. The location of virus replication inside the body may be causing hurdles in sampling like lower lungs, intestines, etc. Moreover, the presence of the residuals of viral RNAs can also give positive results. The dead virus or the viral gene fragments without actual viral replication also gave false-negative results [14]. Thus, relapse cases may be due to technical limits of PCR testing.

A large proportion of the discharged patients still carry virus and can act as asymptomatic virus carriers as they may carry

TABLE 1. Details of studies including salient findings and inference of the patients represented with re-infection of COVID-19

Country/study design	Patients (number/age/gender)	Latency period of re-infection	Symptoms on SARS-CoV-2 infection/reinfection	Findings	Inference
Wuhan City, China/case presentation [21]	01 (58-year-old woman)	22 days	Fever, cough, white sticky sputum, chest pain, fatigue, dry mouth/no symptoms	Incomplete virus clearance, poor test sensitivity, insufficient virus collection from throat swabs	To add anal/stool test as diagnostic criteria along with throat swab test To perform IgM and IgG antibody coronavirus test to avoid false negative and false positives
Wenzhou, China/case series [7]	n = 20 (23–57 years)	7 days	Fever and cough/no symptom	RNA positivity is less likely to be due to re-infection	Self-isolation protocols and extended follow up needed for the recovered COVID-19 patients
Korea/report [10]	447 (14.3 years)	14.3 average	44.7% had cough and sore throat	No evidence of infectivity of the re-positive cases	New protocols need to be applied to monitor discharged patients
Japan/newspaper report [22]	01 (40-year-old woman)	2 weeks	Sore throat and chest pain/sore throat and chest pain	Dormant virus with minimal symptoms may exacerbate after entering the lungs	Repeated sampling from different organs should be preferred
Indonesia/newspaper report [23]	01 (25-year-old man)		No symptom/anxiety and stress	Insufficient mucus from the swab tests Presence in dormant virus in discharged patients	Sufficient sampling should be done
India/newspaper report [24]	01	1 week	No symptom/follow up after quarantine	–	Quarantine of the discharged COVID-19 patients for next 14 days Regular monitoring to boost their immunity
China/letter to editor [25]	07 patients	7–11 days	4 = asymptomatic 3 = fever, cough, malaise/no symptoms	The discharge criteria of two repetitive negative RT-PCR tests not reliable	Necessity of adding RT-PCR testing of rectal swab specimens to the criteria for discharged
South Korea/letter to editor [26]	02 (81 and 77 year old women)	2–3 weeks	Cough and fever/dyspnea, fever, and confusion Nonproductive cough	Reactivation of the virus can be assumed in the present scenario	Close monitoring of the vulnerable patient population on the outpatient basis even after they overcome the infection
Wuhan, China/observational study [8]	9% (5 out of 55) (Age- 27–42 years)		Fever and cough/fever, cough, sore throat, and fatigue	Reactivation of the virus	Therapy to be decided based on: **Host factors**: age, sex, type of disease **Virological factors:** baseline SARS-COV2 workload, variable genotype
Yiwu, China/research article [15]	31% (4/13	4 weeks	fever, cough, fatigue, muscle soreness, and sore throat	False negative test, Re-exposure to the virus, fecal-oral route may be another route for the SARS-CoV2	Need to understand relationship of chance of viral transmission with patient viral load, determine whether the viral nucleic acid positivity in the re-positive cases is due to active or residual virus
Italy/Letter to editor [20]	01 (48-year-old man)	1 month	fever, cough, shortness of breath, hyporexia/chest pain	Reactivation of the virus, IgG antibodies are not completely protective	Redefine appropriate quarantine period Risk factors of reactivation vary according to host status and virological features
Ningbo, China/retrospective study [27]	17	4 days	chest pain, stuffiness, nasal congestion, fatigue and diarrhea (other symptoms)/ fever cough	Possibly relapse, recurrent lessons in chest CT scans of the re-positive case, CD3-CD56 + NK cells levels higher in the relapse	CT scan should be considered as a valuable reference for discharge NK cell activation is vital for clearing the infection.
Guangdong, China/letter to editor [28]	07	2–3 weeks	Fever, cough/out of 7, 2 report fever and one itchy throat	Shorter stay time and milder symptoms on re-infection Some patients had positive anal swabs while negative throat swab, false negative results during discharge	Convalescence plasma Fomite transmission and environmental contamination by COVID-19 patients need to be examined Combination of qRT-PCR and imaging examination be used for diagnosis
Shandong, China/case series [29]	07	2 weeks	40% fever, 20 % cough, and 10% head phlegm/6-no symptom and 1-fever, cough, nausea, vomiting, diarrhea	Re-positive patients positive for SARS-COV-2 virus RNA in fecal specimens but negative for respiratory tract specimens	Shedding time of virus longer in respiratory tract than in GIT. Possibility of induction of delayed inflammatory response by the presence of SARS-CoV-2 in the gut

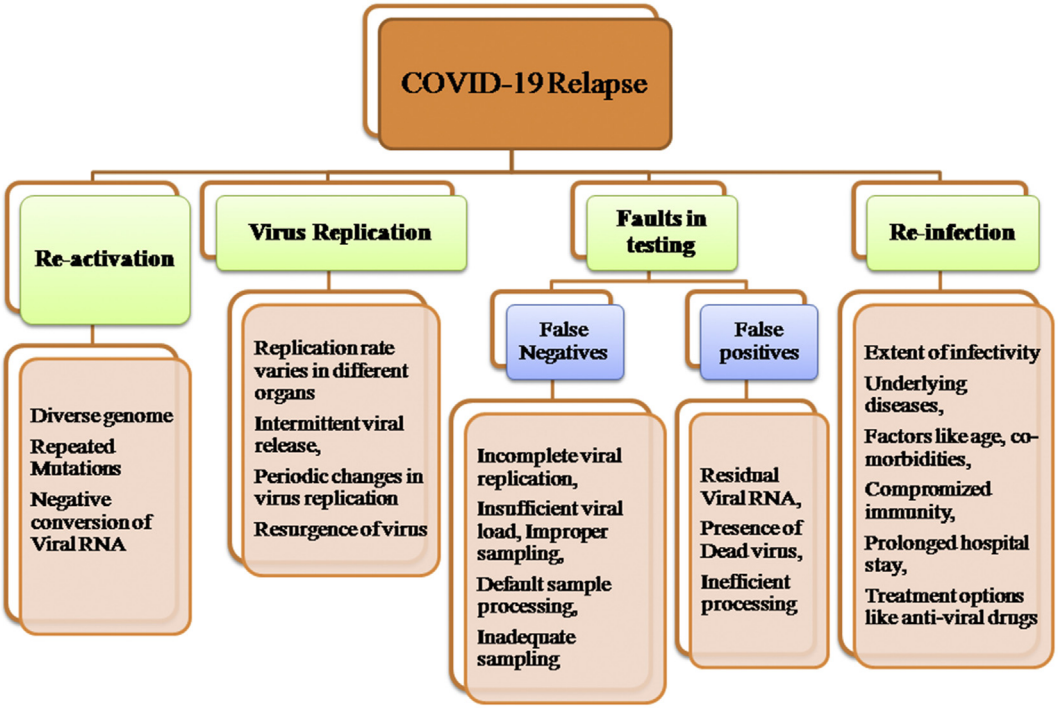

FIG. 2. Summary of database search and article selection.

the low level of virus, which is not detected by the throat swabs. Thus, new suggestions for strengthening the discharge criteria as well as the new testing procedures for testing the COVID-19 patients have been proposed. For example: Li et al. emphasized the inclusion of a negative fecal virus nucleic acid testing in the discharge criteria of the COVID-19 patients. Also, examination of the discharged patients for the changes in the viral nucleic acid should be included [15].

Moreover, FDA has granted emergency use authorization for tests that identify antibodies, that is, IgG and IgM, against SARS-CoV-2 in serum or plasma. It has been found that serologic screening can be an important tool to understand population immunity and distinguish individuals who are at lower risk for re-infection. In some individuals, viral RNA can be detected from the respiratory tract months after the initial infection. Detectable viral RNA, however, does not always indicate the presence of infectious virus, and there appears to be a threshold of viral RNA level below which infectiousness is unlikely [16].

Another cause may be the variation in the clearance of the virus in co-morbid conditions like hypertension, diabetes, etc. Chest congestion in critically ill and elderly patients might also lead to delay in virus clearance [17]. In Shenzhen, 14.5% (38/262) of the patients were again found to be positive after discharge from hospitals without having any history of contact with positive patients. These studies are questioning the importance of herd immunity as well as the individual variations in the immunity against this virus [18].

To decide the approximate quarantine period required for the COVID-19 patients after their first discharge

The coronavirus replication is seething for an unusual long time and can also cause late reactivation. The length of virus detection also varied from person to person. It has been found that some patients showed positive RT-PCR tests after 1–2 weeks of discharge from the hospital after their first COVID-19 infection [19]. These patients may remain as virus carriers for a long time after their discharge. One of the major issues discussed by most of the experts as the possible cause of re-infection may be the insufficient quarantine period for the people before discharge. Thus, the positive tests after discharge do not always interpret the re-infection. As mentioned by Loconsole et al., essential domiciliary quarantine period of 14 days should be made mandatory for all the hospital discharged COVID-19 patients as the average time of the presence of virus in an infected patient fluctuates and the risk of reactivation of virus in previously discharged patients poses a major public threat of transmission. Some other reasons for increasing the quarantine period include the chances of false negative results at the molecular tests, which may be due to the lack of sensitivity of the instrument or the tissue collection errors. Also, after increasing reports of the reoccurrence of the virus, quarantine period also increased to 14 days after recovery [20]. However, according to the reports of the Korea Centre for Disease Control and Prevention, the previous criteria that included a 14 day of self-isolation for the COVID-19 patients after discharge as a step towards

management of the confirmed and re-positive cases was considered to be non-essential from 19 May, 2020 after an extensive epidemiological study on the re-positive cases [10].

Conclusion

Various reports all over the globe came with re-infection after discharge from the hospitals. The latent period of re-infection varied from 7–28 days. It has been found that the symptoms after re-infection in most of the cases were not severe and did not perpetuate to death. In these re-infected patients, although the RT-PCR results were positive but anti-viral therapy was not required. However, the risk of transmission of the virus from these re-infected patients is low but there is no firm evidence that these patients can not transmit the infection further. Thus, the risk of relapse of COVID-19 infection should not be overlooked and larger studies should be conducted to monitor the patients for a long time after their discharge from the hospitals. The guidelines regarding the quarantine period after the discharge of the patients and the frequency of negative RT-PCR results should be updated. There is also an urgent need for the diagnostic tests, which can predict the chances of re-infection with SARS-CoV-2. Further, the advanced strategies about diagnostic criteria, treatment as well as management of this pandemic and its immunity should be made on the evidence-based outcomes.

Transparency declaration

Nothing to declare.

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