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REVIEW ARTICLE

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A systematic review on the recurrence of SARS-CoV-2 virus: frequency, risk factors, and possible explanations

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ABSTRACT

Background: Since late 2019, SARS-CoV-2 which leads to coronavirus disease 2019 (COVID-19), has caused thousands of deaths. There are some pieces of evidence that SARS-CoV-2 genome could be re-detectable in recovered patients.

Methods: We performed a systematic review in the PubMed/Medline database to address the risk of SARS-CoV-2 recurrence. The last update was for 20 November 2020. Among the 1178 initially found articles, 66 met the inclusion criteria and were considered.

Findings: In total, 1128 patients with at least one-time recurrence of SARS-CoV-2 were included. Recurrence rate has been reported between 2.3% and 21.4% in cohort studies, within a mean of 20 (ranged 1–98) days after discharge; younger patients are being affected more. Following the second course of disease, the disease severity decreased or remained unchanged in 97.3% while it increased in 2.6%. Anti-SARS-CoV-2 IgG and IgM were positive in 11–95% and 58.8–100%, respectively. Based on the literature, three possibilities include reactivation of previous disease, reinfection with the same virus, and false negative, which have been discussed in details.

Conclusion: There is a relatively notable risk of disease recurrence in previously recovered patients, even those who are immunised against the virus. More studies are required to clarify the underlying cause of this phenomenon.

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Supplemental data for this article can be accessed here.

Introduction

Since starting pandemic of the coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, by end of November 2020, more than 60 million people have been infected; near 1.5 million of them have died globally, although many of them have been recovered. Routine diagnosis of COVID-19 is based on the detection of SARS-CoV-2 virus genome using real-time reverse-transcription polymerase chain reaction (RT-PCR) test. Today, worldwide concerns about the recurrence of SARS-CoV-2 in recovered people are growing, given reports that up to one of the five discharged patients whose symptoms have resolved and have tested negative for COVID-19 turned positive again [1]. However, currently little is known about whether this phenomenon may be attributable to false-positive or false-negative results, the persistence of virus, or reinfection. It has been reported that up to 21.4% of discharged patients may experience becoming positive for viral genome within the days/weeks after discharge.

It is still unclear whether reinfection or reactivation of the previous infection is the reason for appearance of COVID-19 symptoms in the recovered patients. More precisely, distinguishing between the reactivation and reinfection is impossible with the currently available clinical and paraclinical settings [2–6]. Additionally, some studies have mentioned that the discharge criteria might not be rigorous enough [6,7], while others blame the low sensitivity of the nasopharyngeal swab test kits. Ignoring the important route of oral faecal transmission and the possibility of excretion of the virus from the faeces, and not considering it as a criterion for patient discharge is another case that highlights the importance of more sensitive tests to find the viral genome in the faeces [8–10].

Accepting either the hypothesis of reactivation of previous infection or *de novo* infection can pose many risks in the fight against the pandemic [7,11]. Recently, a meta-analysis has reported 7–23% as the SARS-CoV-2 recurrent RNA positivity rate among the previously recovered COVID-19 patients [12]. However, several other aspects of this phenomenon remained unknown. Considering the important nature of this issue and contradictory results in this regard, we have designed a systematic review to evaluate rate of SARS-CoV-2 recurrence, changes in disease severity, the interval between negative RT-PCR test for SARS-CoV-2 and disease recurrence, disease and patients' characteristics, risk factors for predicting recurrence and outcomes, as well as the prognosis of recurrent patients.

Search strategy

The PubMed/Medline database was searched for any study associated with the recurrence of SARS-CoV-2 in those patients, who had been recovered and showed negative RT-PCR results. The employed keywords are brought in the Supplementary Table 1. The search results were updated on 20 November 2020. Data were extracted by two authors, independently. In the case of any discrepancy, the third independent reviewer was consulted to make the final decision.

Only journal articles published in English, those with the original data, and only human studies related to recurrence of SARS-CoV-2 in previously recovered patients were included. Recurrence was defined as a reappearance of the SARS-CoV-2 genome based on the RT-PCR test. More precisely, all the included patients should previously be diagnosed based on the RT-PCR test, and their tests became negative after disease recovery, and experience positivity of RT-PCR test for SARS-CoV-2 genome again after a while. Additionally, in the cases with positive RT-PCR test for more than 2 weeks, worsening of symptoms was considered as the disease recurrence, if RNA of virus was still detectable. After a primary screening, based on the titles and abstracts, we did the secondary screening, based on the full-text of articles; eligible studies were carefully read to extract any data regarding the rate of recurrence of SARS-CoV-2, characteristics of patients, disease features, risk factors, and outcomes.

Results

Search results

Among the 1178 initially found records, after excluding non-English studies (18 articles), 1160 records had been selected for initial screening, according to the titles and abstracts, in which 1029 of them were irrelevant. Subsequently, among 131 article selected to assessing eligibility for full-text reading, after excluding two non-human studies, and 63 other articles for different reasons including being out of scope or not meeting the inclusion criteria regarding PCR-based diagnosis of patients ($n = 26$), and lack of original data (23 editorial letters/commentary/Correspondence and 14 review articles). Finally, 66 articles have been selected for evaluation. The most important findings of such studies have been categorised into the rate of recurrence, risk factors, and outcomes, which have been discussed in detail. The

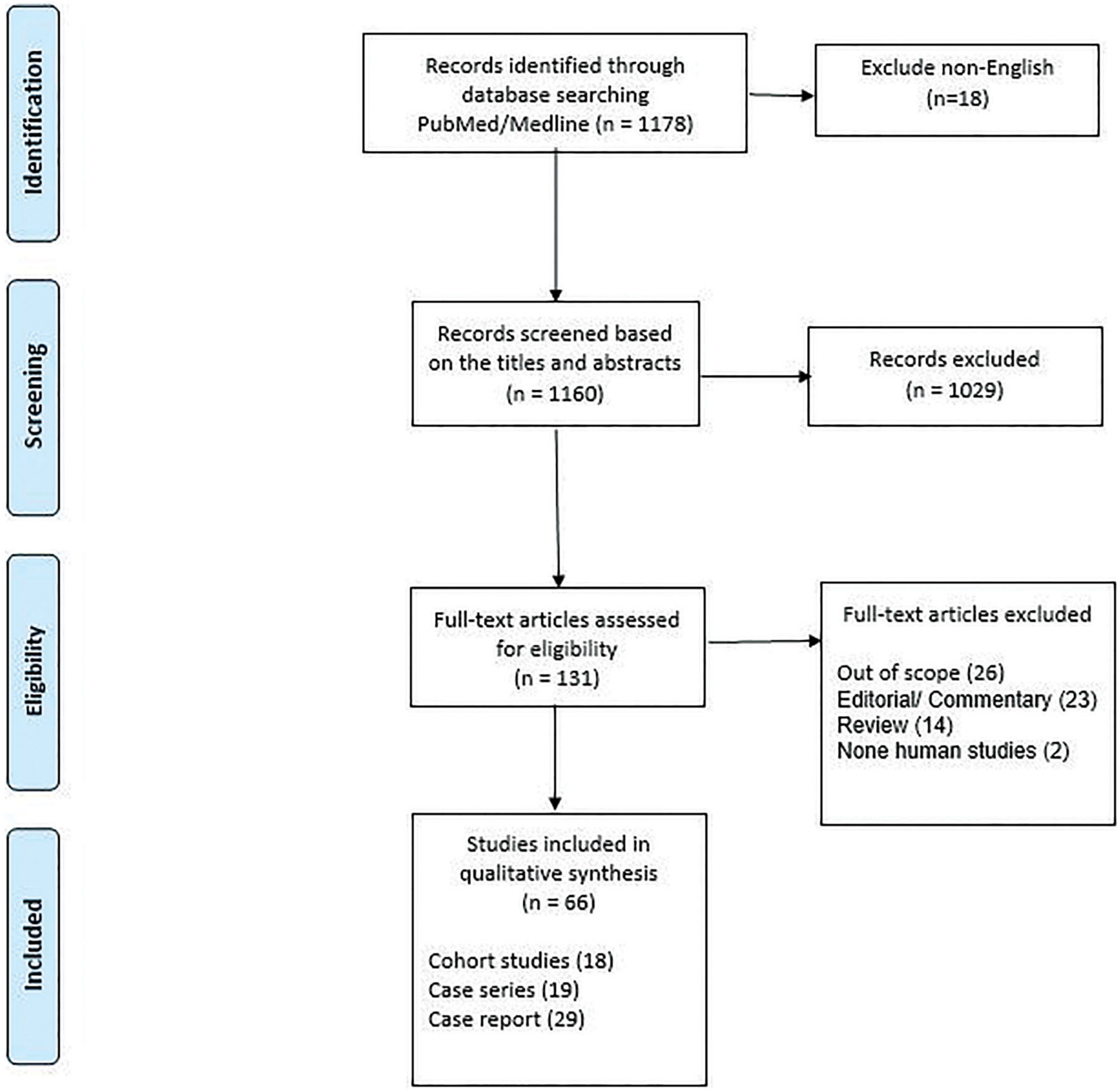

Figure 1. PRISMA 2009 flow diagram.

study selection process and reasons for exclusions are presented in Figure 1.

Patients' characteristics and recurrence rate

Reviewing cohort studies, case series, and case reports led to finding a total number of 1128 patients with the recurrence of SARS-CoV-2; 957 in cohort studies [1,13–28], 142 in case series [3,17,29–45] and 29 in case report studies [46–74]. The recurrence rate, which has been defined as positive SARS-CoV-2 RNA detection by RT-PCR test in patients who were recovered (showed negative RT-PCR test), was reported between 2.3% and 21.4% in cohort studies [1,13–19,21–28,75]. As an exception, a cohort study on paediatrics reported that seven patients out of 14 (50%) experienced recurrence [20]. Regardless of study type, based on 57 studies with available data (1019 patients), the first detection of recurrence of SARS-CoV-2 had been reported within a mean of 20 days, with a range of 1–140 days after meeting criteria for discharge [3,13,15–17,19–23,26–33, 35–39,41–74].

Among the reported patients, eight cases were reported that had experienced recurrence more than once; two times in four patients [20,58,69], three times in two patients [14,50], and four times in two patients [48,62]. In a more detailed review of five cases with positive RT-PCR test for repeated times, most of them were asymptomatic or presented mild symptoms [14,48,50,58,69]. Among them, an eight year-old boy showed the second positive RT-PCR test after 17 days of discharge, and his test remained positive for the next 20 days [14]. In addition, two men, 33 and 35-year old showed the second positive RT-PCR at nearly 2 weeks

Table 1. The details of included cohort studies.

First author	Total number	Number of patients with recurrence	Follow-up duration (days)	Details (if any)
Li Y	–	13	28	–
Wang X	131	8	28	Four re-positive patients were readmitted to hospital.
Zhu H	–	17	14	Disease duration was significantly longer in re-positive group than other group. The level of natural killer cells was higher in re-positive group than in other group.
Zhao W	14	7	14	Two of 7 re-positive patients experienced the second reactivation after being discharged.
Kang YJ	8922	292	21	Positive cases were isolated and the virus was detected again in a PCR test within a very short time.
Zou Y	257	53	1–12	N/A
Yuan B	182	20	21	Twelve cases with negative RT-PCR, 2 cases with positive RT-PCR at the end of follow-up.
Xiao AT	70	15	10–20	N/A
Wu J	60	10	10–20	N/A
Chen JX	1087	81	15–50	Increased serum IL-6, increasing of lymphocytes counts and CT imaging features of lung consolidation during hospitalisation.
Chen LZL	–	44	14	Concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were noticeably increased in re-positive patients.
Chen SLX	1282	189	28	Re-positive patients were considerably younger with a higher proportion of moderate symptoms in the first hospitalisation than in the other group
Du HWC	126	3	60	N/A
He ST	420	24	14	N/A
Lu JP	619	87	14	N/A
Shui TJL	758	59	13	N/A
Zheng JZ	285	27	26–44	N/A
Liu BS	47	8	39	N/A

after discharge. They tested positive for the fourth and third times on days 111 and 49 days of hospital discharge, respectively [48,50].

The most critical data from cohort studies are summarised in Table 1.

Characteristics and clinical manifestations of patients with SARS-CoV-2 recurrence

Based on the 1077 patients in 62 studies, the mean age of patients with disease recurrence was 44.25 years with a minimum and maximum of 3 months and 93 years, respectively. Among the 790 patients with the reported data, there were 377 (47.7%) men and 413 (52.3%) women. Considering 28 studies that have examined comorbidities in detail, the most commonly reported underlying medical conditions in patients with recurrence were hypertension (46.7%), diabetes (21.9%), and coronary heart disease (11.3%). In some patients, lung diseases (8%), hepatopathy (4.8%), cerebrovascular disease (3%), and malignancy (3.6%) have also been reported. Considering the fact that the most common comorbidities were reported as hypertension followed by diabetes mellitus in COVID-19 patients, regardless of disease recurrence, such comorbidities might not be considered as the independent risk factors for the disease recurrence in COVID-19 patients [76].

Within the first admission, considering 1064 patients, the majority of re-positive cases ($n = 987$; 92.7%) were asymptomatic or had mild to moderate symptoms [1,3,13,14,16,17,19, 21–24,26–28,30–33, 36–45,47,48,50–52, 54,56, 58,59,61,62,64–67,69–73,75,77], but some of them had severe or critical disease ($n = 77$, 7.3%) [1,13,18,21, 23,24,27,30,31,35,36,39,42,43,46,49,55,60,63,68,74]. To compare the severity of disease during the first and second courses of illness in re-positive patients, 57 studies including 858 re-positive patients, it was reported that the disease severity decreased or remained unchanged in 835 cases (97.3%) [13,15–20,23,24, 26,28–31,33,36–48,50, 52–54,58–61,65–68,70,71,74,75], and increased in 23 cases (2.6%) [18,19,32,35,36, 39,43,49,51,55–57,62–64,69,72,73]. In a study [55], it was reported that in an 11 month old boy, despite the asymptomatic course of disease in the first phase, the disease was severe in the second phase. Meanwhile, 39 studies reported concerning temporal changes in the manifestations of chest CT scans of 375 re-positive patients. Among them, 290 and 65 cases presented improved [17,18,20,23,26,28–31,36,38,43,47,50,52–54,58–61,67] and unchanged lesions [17,23,30,40,48], respectively. Also, CT worsening was observed in 20 patients [18,19,32,35,39,46,49,51,55,57,62,63,69,72]. Based on the available data, not in all, but in most of the studies, the duration of being positive for the SARS-CoV-2 genome in the second course of the disease was shorter as compared to the first one.

Risk factors

Demographic data and patients' characteristics

In most of the studies, no significant association between the gender and susceptibility of disease recurrence has been found [1,13,14,19,20,34]. Besides, age was not associated with the risk of SARS-CoV-2 recurrence [1,13,14,19,20,34], although in a number of studies, some evidence regarding the increased risk among the younger patients has been shown [1,14]. In a study, it has been suggested that patients in some specific age ranges are at the higher risk of recurrence, in this case, 25% of those with disease recurrence were between 20 and 29 years old [16]. It has also been reported that patients aged under 18 years old had a higher rate of recurrence as compared to patients aged over 18 (4 of 13, 30.8% vs. 16 of 169, 9.5%) [14]. Regarding the disease severity, Wang et al. [18] have reported that the median age of patients with severe disease was significantly higher than non-severe patients. No correlation between body mass index (BMI) and smoking habit with recurrence was reported so far [19]. In addition, some studies evaluated the association between exposure to someone with confirmed COVID-19 and recurrence risk and found no significant association, which suggest the possibility of viral reactivation instead of reinfection [19,20]. It is worthy to note that some evidence represented that the rate of SARS-CoV-2 recurrence did not differ by the comorbidities [13,14,18,19].

Disease's characteristics

There are some associations between the disease severity on first admission and recurrence risk. As an example, in a relatively large cohort study, Yuan et al. reported a statistically significant association between disease severity and recurrence risk. They showed that all of the patients with recurrence were non-severe [14]. This association would raise the assumption of a more likelihood of virus persistence after discharge in non-severe cases due to their faster reach to the discharge criteria, and shorter hospital stays [14,18,20]. In addition, another speculation is the more robust immune response in severely ill patients leading to the more effective elimination of viruses and reducing the risk of recurrence in these patients [14]. However, this evidence is not sufficient to prove a lower risk of recurrence in severely and critically ill patients. In contrast, two cohort studies on 53 and 15 patients with recurrence have found contradictory results, no significant association between the severity of disease and recurrence susceptibility was reported [1,13].

Evidence could not reach any rigorous conclusion regarding the impact of disease duration and hospital stays at first admission on the recurrence rate. Yuan et al. have found a significant correlation between hospital stays and the risk of recurrence. Patients with recurrence stayed for a shorter time in hospitals, suggesting that probably the virus was not eradicated before discharge in such patients [14]. By contrast, Xiao et al. mentioned that patients who experienced a recurrence of SARS-CoV-2 have a longer disease duration [1]. On the other hand, multiple studies have shown no statistically significant correlation between disease duration and hospital stays on first admission and recurrence rate [13,19,20,30].

Three studies revealed no significant correlation between the time interval of onset of symptoms to hospital admission and recurrence risk [13,14,20]. However, the time interval between onset symptoms and final negative RT-PCR test has been reported considerably longer in the patients who had experienced disease recurrence compared to the others [13,19].

Although no significant association between initial symptoms and CT results, on first admission and susceptibility of recurrence was found in different studies [13,19,20], in one study, the possible association between the number of initial symptoms, fatigue, and creatine kinase levels with a re-positive RT-PCR test has been reported [37].

Treatments

Györfi et al. [51] showed that despite the usefulness of specific immunosuppressive drugs in the treatment of COVID-19, non-selective immunosuppressive drugs, such as prednisolone, may cause recurrence, even with first clinical improvement. It has been reported that corticosteroids were used in three of seven patients with disease recurrence [39]. Two of the three patients who did not generate any anti-SARS-CoV-2 antibodies more than 21 days after symptoms received chemotherapy treatments and/or Rituximab. However, no statistically significant difference was found regarding treatment with corticosteroids in their therapeutic schedule between the patients with/without recurrence [13].

Regarding antiviral therapies, no association was found between the risk of recurrence and disease duration, or viral shedding [3,19,20,30,79,80].

Anti-SARS-CoV-2 serological antibodies

In eleven cohort studies and case series, positive rates of serum-specific IgM and IgG against SARS-CoV-2 in patients with recurrence ranged 11–95% and 58.8–100%, respectively [13,14,19,21–23,26,27,31,34,45,75]. Although timing of sampling could affect, some pieces of evidence have cast doubt on the protective role of the specific antibodies, concentrations of antibodies needed for conferring protection, and their protection duration in patients who experienced recurrence. It is worthy to note that Zhu et al. [19] showed no significant differences in the dynamics of specific antibodies that were observed between the re-positive group and non-re-positive group groups [19].

Different studies observed no significant association between the recurrence susceptibility and the presence of these serum-specific antibodies [13,14,34]. Several cases with recurrence have been tested positive for the IgG test [31,34,49]. According to this evidence, it could be speculated that antibody presence does not necessarily prevent disease recurrence. Therefore, physicians need to consider positive antibodies tests as immune certificate and hospital discharge criteria cautiously. On the other hand, some patients with recurrence may produce lower specific antibody titres in comparison to those without recurrence, suggesting that the virus may not confer immunity sufficiently due to limited antibody levels and after that causes recurrence [46,48]. In a case series study, a 33-year old man who experienced recurrence two times did not develop IgM ever during the follow-up period [45].

Conversely, an experimental study on Chinese-origin rhesus macaques could prove the protective role of antibodies. That study demonstrated a gradual increase in the specific antibody levels following primary infection and reinfection with SARS-CoV-2 and a significantly higher level on 28 days after reinfection compared to the primary infection. The study presented that viral replication was not detected upon reinfection, indicating the protective role of the specific antibodies following primary infection [77].

Secondary positive SARS-CoV-2 PCR test: is it a sampling issue, false-negative results, the persistence of virus, or reinfection?

There have been many hypotheses about the explanation and interpretation of secondary positive SARS-CoV-2 PCR tests, but none of them has been conclusively proven. Based on our review, in addition to the sampling issue, three major assumptions for the cause of the secondary positive SARS-CoV-2 PCR test exist, including false-negative results, the persistence of shedding of virus, and reinfection.

The gold standard diagnostic test for SARS-CoV-2 infection is RT-PCR. Failing of appropriate sampling might result in false negative and also missing patients who may still be carriers. Testing a swab from the oropharynx, nose, saliva, or blood is also likely to reduce sensitivity [81–83]. Li et al. [17] found the sputum sample to be more sensitive than the other two sample types. For example, oral swabs have been reported to be 30–50% sensitive. Thus, locations of sampling may play a significant role. Indeed, one study found that the high sensitivity of the nasal test versus the throat test was due to the higher viral load in the nose than in the throat [81]. Also, the sensitivity of diagnostic kits, technical differences in sample collection and preparation, human error, and pre-analytical variables could lead to false-negative results [8]. The other thing is that the RT-PCR may represent false-negative results due to low viral load or sampling errors [30,31,46,49,50]. According to current guidelines for COVID-19 management, one of the main criteria of hospital discharge is two consecutively negative RT-PCR tests. Two studies presented that more than two consecutive RT-PCR tests, which were taken with longer than 24 h intervals, can more accurately identify recurrence potential and reduce the recurrence rate substantially (20.4% versus 5.4% and 0%) [13,30]. Another suggested reason for false-negative tests is the problem with laboratory test kits due to their low cut-off assay [17] or even operator technical error. Aside from the false-negative issue, some studies have even shown that the RNA-based SARS-CoV-2 PCR test can be positive again after one or two consecutive negative tests [3,17,53,84].

It has been speculated that incomplete elimination of the virus after discharge is the main reasons for recurrence; however, definitive data whether the virus is viable infectious or not is lacking [1,3,13–15,29,34,46]. Some studies suggested that positive RT-PCR could be due to shedding of virus residue, which does not result in transmission. Another hypothesis proposed for cause of recurrence has been raised, which mentioned the hypothesis of presence of a latent SARS-CoV-2 infection within immune cells [11]. Others have suggested that SARS-CoV-2 could multiply inside the peripheral blood mononuclear cell (PBMC) through interaction with ACE2 receptor on the surface of human monocytes [36,85,86]. In a way, there may be a hidden infection of SARS inside the cells of the body, and the cause of viral recurrence after a negative test is the presence of these hidden viruses [11] and this could be called a malaria-like action. Also the study by Wang et al. claimed that the entry of the virus into T lymphocytes is not accompanied by proliferation, and the virus somehow settles in the cell. In confirmation of their hypothesis, they showed that the concentration of the viral genome in lymphocytes is higher than its concentration in plasma [87]. This could be another hypothesis for repetitive positive test after consecutive negative test.

It should be mentioned that finding RNA in a sample does not necessarily mean the presence of a complete or active virus in it, so it does not indicate that the virus is alive in the sample [88]. In fact, because the epithelial cell half-life in the respiratory system is 3 months, the virus genome could be detected even after elimination during this time. The mean time when the virus RNA PCR test of first SARS-Cov-2 infection became negative, it was 34 days in faecal specimens compared to 9 days in the respiratory samples, indicating that RNA could persist more in the gastrointestinal tract than respiratory tract [55] and may be mistaken for reinfection. Monitoring the disease symptoms could be helpful in this regard. For example, the unchanged or improvement in CT after recurrence might suggest that a new infection has not occurred.

In the case of disease recurrence, the detection of a positive test might be interpreted as a new infection. Studies mostly have shown no agreement on the third major assumption, which is reinfection. Although the likelihood of reinfection after the first discharge was not completely ruled out, in late of August 2020, following confirmation of the reinfection documented in Hong Kong [89], and also some subsequent cases in Belgium, Netherlands [90], and in the United States [91], it could be speculated that that humans may become infected more than one time by SARS-CoV-2.

In addition to the three mentioned possibilities, one of the possible reasons for reactivation and subsequent positive re-testing is considered to be the antibody dependent enhancement (ADE) phenomenon; a phenomenon that has also been described in coronavirus [92] and probably can lead to more severe disease due to causing an unnecessary immune response [93].

In terms of the impact of immunity on recurrence, there are some controversies. In a study on rhesus monkeys, it has been shown that monkeys conferring sufficient immunity after the first discharge did not show any evidence of reinfection [77]. However, another study proposes that the immunity failure might cause not only the persistence of the virus but also reinfection [34]. Although most the rate of positive IgG antibodies against the SARS-CoV-2 has been reported between 52.8% and 95%, the absence of sufficient immunity in patients with re-positive SARS-CoV-2 test was observed in multiple studies [14,31,34,46]. Robbiani et al. [94] state that plasma obtained from COVID 19-positive individuals did not have high levels of neutralising antibodies but had receptor-binding domain-specific antibodies with strong antiviral activity. This had led to the hypothesis that high affinity versus low avidity could cause the virus to escape the immune system due to low levels of antibodies. However, over the time, the avidity of the antibodies increases, and diagnostic tests detect the viral remnants.

The failure of immunity for protection may lead to the prolonged viral shedding of the non-viable virus, replication of a viable virus, or reinfection. Three studies asserted that non-strong immune response and insufficient immunity led to the persistence of shedding of the virus, but not a replication of a viable virus [14,31,34]. In this regard, a case report study on a patient with four times recurrence within 137 days assumed that the antibody levels are just sufficient for preventing transmission of disease considering negative RT-PCR tests of the patient's parents, not for full clearance of virus [48]. In contrast, in a case series, four patients from one family experienced recurrence [32]. However, Lafaie et al. reported inconsistent evidence with these studies; the reason for the recurrence of COVID-19 in three women who have died was described as the persistence of a viable virus and viral replication [35].

In conclusion, although the underlying cause is not clear, recovered patients, even those with detectable anti-SARS-CoV-2 IgG may show disease recurrence. More studies in this regard and modification of management's protocols for COVID-19 patients might be required.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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