Evaluation of Reinfection in COVID-19 Patients in the World: A Narrative Review

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Abstract

Background: The evaluation of reinfection and the genetic structure of all human and virus genomes could help to develop programs and protocols for providing services and ultimately to prevent the disease by producing more effective vaccines. Therefore, the aim of this study was to investigate the presence and occurrence of COVID-19 reinfection through a narrative review study.

Methods: We searched the Medline (PubMed), Embase, Scopus, Web of Science, Cochrane library, Ovid, and CINHAL databases. Inclusion criteria included all studies whose main purpose was to provide information about the occurrence or presence of reinfection in patients with COVID-19. An independent samples t test was used to compare the continuous outcomes between the 2 groups.

Results: The mean duration of the first episode in the group with mild or moderate COVID-19 was 24.42±1.67 days, and it was 21.80±3.79 days in the group with severe COVID-19. The mean duration of the second episode (reinfection) in patients with mild or moderate form was 15.38 ± 5.57 days, and it was 19.20±2.98 days in patients with severe form. In both episodes, the duration of the disease did not significantly differ between the 2 groups (p=0.484 in the first episode; p=0.675 in the second episode), but the interval to the occurrence of reinfection in patients with the mild or moderate form was significantly longer than those with the severe form (p<0.001). In this instance, the time interval in patients with the mild or moderate form was 36.63±5.71 days while in those with the severe form of the disease it was 29.70±5.65 days. Besides, the genomes of the viruses isolated from the first and second episode were different.

Conclusion: According to the results, all patients should be very careful about the severity of the second episode because of the more need for medical interventions for saving the patients. The interval between the first end and the second episode as well as the duration of each episode is highly important for better management of the disease.

Keywords: Reinfection, COVID-19, Narrative Review

Introduction

The spread of COVID-19 was unique because of its high transmission rate, causing an emergency in global health in less than a few months around the world (1).

When the number of cases and deaths increased, the number of requests and referrals to health care services would increase and the service provision to different

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↑*What is "already known" in this topic:*
The evaluation of reinfection and the genetic structure of all human and virus genomes could help to develop programs and protocols for providing services and ultimately to prevent the disease by producing more effective vaccines.

→*What this article adds:*
All patients should be very careful about the severity of the second episode because of the more need for medical interventions for saving the patients.

groups of society became difficult (2, 3).

Therefore, in addition to the major problems and obstacles in manufacturing and accessing vaccines, acquired immunity due to natural infection was also very controversial. Many studies in the world on the safety of the disease reached a final summation, but the first case of reinfection in a 33-year-old Hong Kong man created the suspicion that immunity from the disease may not be too long, and the recovered people who were discharged from medical centers would be reinfected (4-6). The evaluation of reinfection and the genetic structure of all human and virus genomes could help to develop programs and protocols for providing services and ultimately to prevent the disease by producing more effective vaccines. Therefore, the aim of this study was to investigate the presence and occurrence of COVID-19 reinfection through a rapid review approach.

Methods

This study was designed as a narrative review and was conducted in 4 basic steps, including information sources and literature search, screening and selecting articles, data extraction, and qualitative and quantitative analysis of the results (7-9). The review was not registered in PROSPERO and corresponding authors were not contacted due to time constraints.

Information Sources and Literature Search

In this study, first, keywords related to the subject, such as COVID-19 and reinfection, were identified, and then the synonyms of these keywords were extracted from MeSH and Emtree databases and related articles. In the next step, these keywords were placed next to each other, and in accordance with each search database, the search strategy and syntax were developed. The desired databases included PubMed, Scopus, Medline, Embase, and Web of Science. To perform gray literature, related sites such as those of the World Health Organization (https://www.who.int/emergencies/diseases/novel-coronavirus-2019), Centers for Disease Control and Prevention (https://www.who.int/emergencies/diseases/novel-coronavirus-2019), European Centre for Disease Prevention and Control (https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases), and medRxiv.org, and the preprint server for Health Sciences were searched. The mentioned databases were explored up to November 20, 2020. The search strategy was independently conducted by 2 authors and disputes were referred to a third author. Inclusion criteria contained all studies whose main purpose was to provide information on the occurrence or presence of reinfection in patients with COVID-19.

Screening Process

After searching, the results were entered into version 8 of the endnote software. Then, the papers were screened based on titles, abstracts, and full-texts. The screening was independently conducted by the 2 authors and the disputes were referred to the third author.

Data Items and Data Abstraction Process

Data extraction in this study was performed through a checklist designed according to the recommendations of study experts and specialists. The checklist included questions such as authors' names, year of publication, country, type of study, main findings, and comments on the study. In addition, the clinical signs and symptoms in each study were extracted and analyzed separately.

Synthesis

To combine the results of the studies, a review through the qualitative strategy was applied. The method of analysis was performed by the 2 authors as a content analysis. For quantitative analysis, patients were divided into mild or moderate group and severe group based on the severity of the second episode of the disease. An independent t test was used to compare the continuous outcomes between the 2 groups. The outcomes, including the duration of disease in each episode and the time interval between the 2 episodes were presented as mean ± SE. The significant level was set as $p<0.05$. All statistical analyses were executed in STATA Version 16 (StataCorp).

Results

After screening, 3248 articles were retrieved from different international databases. A total of 3002 articles were excluded based on their titles and abstracts. Thus, 227 articles were evaluated based on their full-texts and, finally, 20 articles were entered into the final qualitative and quantitative analysis (Fig. 1). Of all the articles included in the present study, 14 were case reports (5, 10-22), 2 case series (23, 24), 3 original studies (25, 26), and 1 was a letter to the editor (27). Six studies had been conducted in European countries (the Netherlands, Italy, Belgium, and France), 6 in China, 5 in the United States, 1 in Hong Kong, 1 in Brazil, and 1 in India (Table 1).

The findings of this rapid review showed that people with COVID-19, after a period of treatment and recovery, could be reinfected. According to previous studies, the virus could not reappear in vitro (21, 27). This result led to the hypothesis that it could not reappear in the human body too, but the results of several case studies indicating the presence of reinfection in recovered patients were entered into this review. Immunoglobulin M (IgM) levels were very high in the first 2 weeks of the disease, indicating an acute infection, and after 1 week, IgG levels increased, representing the presence of antibodies and a history of infection. High IgG levels in the body could be demonstrative of high immunity in people. By reducing its levels over time, it could be concluded that the person became susceptible to reinfection (21, 27) (Table 1).

Epidemiological, clinical, serological, and genomic analyses in many case studies included in this review confirmed that the patient would be infected again, instead of the continuous reduction and loss of virus load from the first infection (28, 29). SARS-CoV-2 may be reactivated and circulated between humans despite the acquired immunity due to infection, which made the disease appear after a while (22, 30).

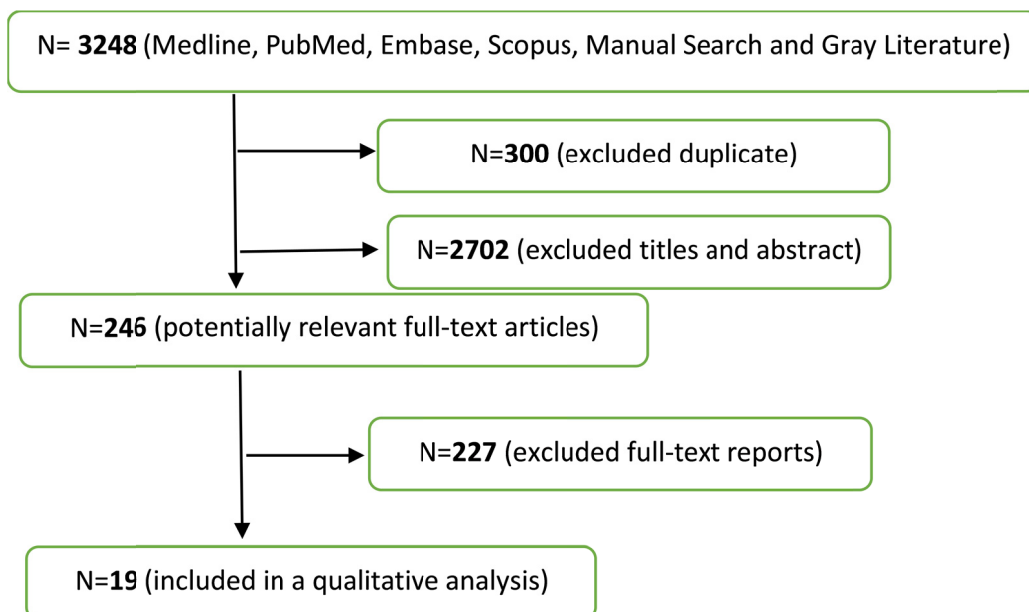Confirming these results required further studies and

Fig. 1. Study Flow Diagram

genome analyses of COVID-19 affecting people in order to develop more detailed plans for vaccine preparation and immunity of the medical staff. On the other hand, another reason for the need for the evaluation of the genome of the virus and people with COVID-19 was that the polymerase chain reaction (PCR) could stay positive for up to 104 days, and after this period, it was possible to be infected again, but it could not be diagnosed by the available tests. Also, many tests did not have an appropriate diagnostic performance and could not recognize it even if there was a virus in the body (10, 31) (Table 1).

The results showed that asymptomatic and mild cases usually had more RNA loss than severe cases. Therefore, it could be concluded that mild and asymptomatic cases were more susceptible to be reinfected with more severe symptoms (13, 14). Several studies were conducted among medical staff, indicating reinfection in these patients. These people were more likely to be reinfected because of dealing with different groups of society and different types of patients with COVID-19. On the other hand, the elderly compared with the other age groups were very sensitive to the reinfection. These people had more severe symptoms and even death because of taking different medications and chronic diseases. The results of some case studies expressed that in the case of reinfection, the severity and frequency of symptoms would be much higher than those of the first episode (6, 12, 14, 17, 18, 22, 30, 32, 33). In most case studies on the occurrence of reinfection, the evaluated cases were mostly women, which made the hypothesis that women were more likely to develop reinfection than men (6, 12, 14, 17, 18, 22, 30, 32, 33) (Table 1).

A case study conducted on a patient with lupus who had COVID-19 showed that after treatment, a complete recovery was observed following various symptoms and tests; however, after a while, the patient was diagnosed with COVID-19 again. The results of this case study indicated

that because of taking different types of drugs for treating the underlying disease, the immune system had been weakened, which caused the increased risk of reinfection in these populations (34) (Table 1).

Reinfection was identified in many studies based on SARS-CoV-2-RNA findings, which could be controversial (4, 28, 29, 35, 36). It was recommended that further studies with larger sample sizes and more accurate analyses of patients with reinfection be done to provide better information and documentation of protective cognitive immunity and the vaccine design. Conducting a high-volume sample cohort study was highly important to determine the occurrence of reinfection and to evaluate the signs and symptoms in vitro and molecular forms. Through detecting this evidence, the vaccination program and the method of dealing with it would become much more noticeable for health policymakers, health practitioners, and health care staff. A vaccine should be produced with a very high safety duration to prevent reinfection in patients and people. Also, to produce such a vaccine, the relationship between disease severity and infectivity of the virus should be considered (Table 1).

Moreover, in this review study, clinical and laboratory features were extracted in each episode of COVID-19 based on whether people in the second episode had a mild or moderate form of the disease or a severe form. Thus, the patients in our study were divided into 2 groups according to the second episode: "mild or moderate" and "severe." The results are reported in Tables 2 and 3.

Figure 2 shows the mean duration of first and second episodes as well as the mean interval between the 2 episodes in each group. As summarized in Table 4, the mean durations of the first episode of COVID-19 in the mild or moderate group and the severe group were 24.42±1.67 days and 21.80±3.79 days, respectively. In this instance, there was no significant difference in the first episode duration between the 2 groups (p=0.484).

Table 1. The characteristics of included studies

Author and year of publication	Country and type of study	Main findings of the study	The comments of the study
Gidari A et al. (2020) (45)	Italy, Case report	Averagely, 34.5 days after the initial attack from COVID-19, re-infection occurs in people. 5.6% of them had fever again and 27.6% showed other symptoms. 96.7% of those who have been re-infected had good general health, while 2.1% died. ICU admission=1 Comorbidity=3 Leukopenia=2 Normal WBC=6 High CRP=0 IgG+= All patients PCR in second episode= All Negative One patient had a significant immune response despite myelodysplastic syndrome and Lymphopenia.	The findings of this study are based on the results of preliminary studies that have identified people with re-infection based on the findings of SARS-CoV-2 RNA, which can be controversial. The results of previous studies have shown that the virus cannot reappear in vitro; so, it cannot reappear in the human body. IgM levels are very high in the first two weeks of the disease, indicating acute infection, and after one week, IgG levels increase, indicating the existence of antibodies and a history of infection.
Kim AY et al. (2020) (27)	USA, Letter to editor	Re-infection is possible; so, the necessary training should be given to people and health care providers to give the patients the necessary advice. In patients with re-infection, an appropriate and detailed history should be prepared in order to perform appropriate studies. Most patients had mild symptoms in the first period and mild or asymptomatic symptoms in the second period of the disease. It is recommended that the concept of re-infection be properly defined. The important point in this study is that selection bias is mentioned that high-risk cases are tested either in clinical or more exposure.	Re-infection with coronavirus is very important because the vaccination program and how to deal with it will become much more significant for health policymakers. A vaccine should be produced with a very high safety duration to prevent re-infection in patients and people. In order to produce such a vaccine, the relationship between disease severity and infectivity of the virus should be considered.
To KK et al. (2020) (22)	China, Case report	Immunity is gradually lost after COVID-19 in people, but it remains unclear whether re-infection occurs in these people. In this study, genome sequencing analysis of respiratory samples of patients with COVID-19 was performed. PCR, IgG, and IgM results were also performed. The results showed that the second episode of the disease occurred 142 days after the first infection. The signs were increased levels of IgG and C-reactive protein. Genetic results showed that the genome affecting the first and second episodes belonged to different genomic groups and lineages, indicating that the genome varied in different episodes. Comparison of viral genomes showed that the first episode of the virus genome was phylogenetically closely associated with strains collected in March/April 2020 while the second episode virus genome was closely associated with strains collected in July/August 2020. The patient's CRP was 8.8 in the second episode without symptoms. The low titer of neutralizing antibodies in the patient's body can be justified by mild symptoms of the patient and insufficient stimulation of the immune system.	Epidemiological, clinical, serological, and genomic analyses confirmed that instead of continuously reducing the virus load after the first episode, the patients are at the risk of re-infection. SARS-CoV-2 may continue to spread between humans despite herd immunity obtained during vaccination or natural infection. Further studies with higher sample sizes and more accurate analysis are necessary for protective cognitive immunity and vaccine design.
Larson D et al (2020) (10)	USA, Case report	51 days after treating a patient with COVID-19, he returned with COVID-19 symptoms (fever, cough, chills, headache, excessive fatigue, chest pain). He was re-infected. Unlike other studies, re-infection was much more severe than the initial infection, possibly due to strengthening the immune system, obtaining a more pathogenic strain, or perhaps a further inoculation of the infection due to a person's re-exposure to risk factors. The genomes of two viruses were different.	Conducting a high sample-volume cohort study is very important to determine the occurrence of re-infections and to investigate the symptoms in vitro and molecular form.

*Table 1.*Ctd

Author and year of publication	Country and type of study	Main findings of the study	The comments of the study
Gupta V et al. (2020) (31)	India, Case report	The results of several studies in the world by examining genome sequencing have shown that re-infection is possible in patients with severe or serious symptoms. Meanwhile, this study showed that re-infection also occurs in asymptomatic patients with COVID-19. The genomes of the virus between two episodes were different and the genetic variant in re-infection was resistant to neutralizing antibodies. Also, the viral load during re-infection was more than that in the first episode. Both cases in this study were hospital staff and had re-exposure.	In order to confirm these results, further studies and genome analysis for vaccine preparation and immunity of medical staff are needed.
Van Elslande J et al. (2020) (12)	Belgium, Case report	A 51-year-old woman was infected with COVID-19 in March. After three months (93 days), this person had the symptoms of fever, cough, fatigue, and headache, and COVID-19 re-infection was confirmed by SARS-CoV-2 PCR. Laboratory and molecular assays also showed that the genes of both infections were different. Complete genome sequencing showed that the initial infection was caused by lineage B.1.1 SARS-CoV-2 and recurrent infection by lineage A SARS-CoV-2. There were eleven mutations between the genome of the two strains.	Despite all these studies and genome sequencing analyses, it is not possible to say with 100% accuracy and reliability that there is a recurring infection. More reviews are needed in this area. But it can be claimed that vaccine production should be difficult considering these gene mutations.
Goldman JD et al. (2020) (13)	USA, Case report	The recovery of COVID-19 is associated with the production of anti-SARS-CoV-2 antibodies, but whether or not this increase in antibodies causes immunity, is still under discussion in the world. Viral RNA decrease rate was checked over time. Out of 818 samples that had positive tests for the first time, 43 were tested positive within 12 to 75 days later. This could have different reasons. First, there might be problems with the kits, second, the diagnosis may have been done with a CT scan, which is not accurate, and third, the antibody level has been lowered in re-infected patients. 2 different strains with 10 genetic mutations with an interval of 100 days were isolated from the patient. The neutralizing antibody titer was low despite the high overall IgG titer and has failed to produce immunity. 11622 patients were tested and 643 had at least one positive test (5.5%) and 176 patients had at least 2 positive tests. Median (interquartile range) shedding duration was 12.1 (6.4, 24.7) days, with a positively skewed distribution (kurtosis = 10.7)	Currently, the issue in the world is the re-infection of COVID-19, but it has not yet been definitely determined. The important point is that all health policymakers, practitioners, and researchers in the field of vaccine production should go hand in hand to further investigate these cases of re-infection. Because some people may be susceptible to re-infection and others may not. The virus may be seasonal so that a seasonal vaccine should be produced. Re-infection may challenge all vaccines under production.
Mulder M et al. (2020) (46)	Netherland, Case report	An 89-year-old female patient was referred in the first episode with symptoms of fever, severe cough, and high lymphocyte count, and its tests were positive. 59 days after this episode, she was referred again with symptoms of advanced fever, severe cough, dyspnea, and positive tests. The results of genome sequencing analysis showed that genetic change and mutation had also occurred in the second episode. Two different strains with 10 genetic mutations were isolated. Immunoglobulin was not formed in her body.	Although negative PCR samples have not been reported in this patient between the two episodes, it can be claimed that the second episode is a re-infection rather than a reduction in viral RNA levels.
He F et al. (2020) (34)	China, Case report	A woman with COVID-19 who had lupus disease 15 years ago was referred. The symptoms of the first episode of COVID-19 were the same as normal patients with COVID-19. After several weeks' post-recovery, COVID-19 relapsed and the person with more severe symptoms was referred to the hospital. Genetic sequencing has not been performed to compare the virus genome on two occasions of the disease. So, contrary to the author's claims, there is still the possibility of re-infection. The level of IgG has not been investigated which could have clarified the cause of mildness of the second episode.	The patient showed a complete treatment, but this recovery may have been due to the patient's young age. Such patients take different types of medications causing their immune systems to become weakened, which increases the risk of re-infection. Therefore, in the future, it is necessary to conduct a better and more accurate study with higher sample size.

Table 1.Ctd

Author and year of publication	Country and type of study	Main findings of the study	The comments of the study
Chen D et al. (2020) (16)	China, Case report	A 46-year-old woman was diagnosed 17 days after complete recovering from COVID-19 using the SARS-CoV-2 RNA test of the pharynx. The symptoms of this patient in the second episode were much more severe and different than the first episode.	Pharyngeal samples should be applied to reduce more false-positive cases in sampling. It is better for people to be followed up for a certain period after discharge and recovery and to be tested again to further investigate the virus activity process.
Bonifácio LP et al. (2020) (17)	Brazil, Case report	A 24-year-old woman who was overweight without any underlying disease was referred to the hospital with severe headaches, malaise, weakness, and muscle pain. On the second day, PCR was negative. Because this person had contact with his colleague whose test was positive, so the patient was advised to repeat the tests. On the 7th day, PCR was positive. After 14 days of treatment and quarantine period, the patient recovered and returned to work. After two weeks of recovery, she was referred to the hospital again with more severe symptoms such as very high fever, malaise, severe weakness, muscle pain, and joints. The PCR was positive. Besides, IgG and IgM were negative on the first days of the second episode, but they were positive on days 19 and 33.	It can be concluded that this instability of symptoms and a positive test after recovery can be explained in three ways: First, the hypothesis of relapsing the symptom due to a single persistent infection may be theoretically possible, but since this person had contact with the affected family and close people who have been infected, it makes it hard to accept this hypothesis. Second, the patient might have contact with another respiratory virus, which is similar to the symptoms of COVID-19, and the test might have been a false positive. Third, it is possible to be a re-infection, which can be almost a strong claim according to the results of other studies. One of the main limitations of this study was the lack of investigation of the virus genome in the first and second episodes. Better and more accurate studies with a higher sample size are recommended.
Malkov E (2020) (25)	USA, Modelling	This study used a mathematical model to estimate cases of re-infection. The results showed that it is not possible to detect the occurrence of re-infection when the patient is at the peak of infection and disease. On the other hand, controlling and preventive measures can delay the occurrence of re-infection. It is a model based on susceptible, exposed, infected, resistant patients that predict up to 10% of the population can be re-infected. If the safety duration after the disease is 60 days and if it remains longer, this number will be lower. The basis of this model with current re-infection observations is different because the cases of re-infection before the formation of active and effective immunity (neutralizing antibodies) are re-infected. So, this model is used for post-immune conditions.	So far, it has not been determined how long the immunity of the disease takes after recovery. So, modeling and estimating the cases of re-infection can be very important. This study showed that it is possible to be re-infected according to the simulation results. Control practices can somewhat prevent or delay its occurrence.
Duggan NM et al. (2020) (47)	USA, Case report	An 82-year-old male patient with Parkinson's disease, diabetes, hypertension, and kidney disorders was referred to the hospital. The first primary symptoms were fever and dyspnea. After positive test results and 28 days of hospitalization in ICU. After one week of complete recovery and discharge, the patient with more severe symptoms and high fever, severe shortness of breath, muscle pain was referred to the hospital and CT results indicated the existence of COVID-19. He was treated again in 15 days. Hospitalization of the patient with Hospital-Acquired Pneumonia is difficult by Corynebacterium. The duration of readmission is lower than the first time and the response to oxygen therapy is better in the second episode. The positive PCR test is not necessarily a sign of its pathogenesis in the positive individual.	There is a possibility of re-infection but other infectious diseases such as bacterial pneumonia with symptoms similar to COVID-19 should also be considered. The patient in this study was discharged from the hospital after a period of appropriate treatment with a negative test, but after one week again he was referred with more severe symptoms and it is likely because of other diseases such as bacterial pneumonia. The diagnostic value of the tests should also be compared in order to be used as the best and most appropriate test.

*Table 1.*Ctd

Author and year of publication	Country and type of study	Main findings of the study	The comments of the study
Lafaie L et al. (2020) (23)	France, Case series	Three elderly women with COVID-19 and underlying diseases were studied (hypertension, diabetes, heart disease, and chronic respiratory diseases). In the first episode, the symptoms were milder and the results of CT scan were positive for two of these elderly and negative for one of them, while for a person with a negative CT scan, PCR test was positive. All three patients had complete treatment. Two months later, all three of them were referred to the hospital with more severe clinical symptoms. PCR and CT scan tests were repeated and all were positive. Clinical symptoms were much more severe than the first episode. Although they received the treatment, none of them survived.	It can be said that there is a possibility of recurring infection. So, in the first step, more attention should be paid to the presence of underlying diseases and their role in the occurrence of this infection. In addition, it can be concluded that the disease in the second episode will be much more dangerous and fatal.
Cao H et al. (2020) (26)	China, Case series	108 COVID-19 confirmed patients were reviewed, of which 8 (7.5%) patients had re-infection. In the second admission of these patients, there were no severe symptoms and CT test results were negative for these patients. WBC=Normal Lymphocyte=Normal PCR=Positive Two patients were discharged, but 6 patients were still hospitalized till the time of writing the article.	Re-infected patients should be the main concern about transmission and the main cause of the outbreak in the community. If the possibility of re-infection is true, the necessary measures should be taken as soon as possible for these people.
Dou C et al. (2020) (19)	China, Case report	A 34-year-old man with COVID-19 and a history of diabetes was discharged from the hospital after two negative PCR tests. After several weeks, his PCR test was positive again. In the second episode, the patient had no symptoms and CT showed the improved bilateral lesions from the first episode. The patient was followed up, and when three PCR tests were negative for him and his bilateral lesions in chest CT were completely absorbed, final discharge was performed.	The results of this study show the importance of follow-up of patients after hospital discharge. These follow-ups can help to better understand the virus and its function in the body or after the treatment.
Gousseff M et al. (2020) (24)	France, Case series	In this study, 4 of 11 patients were medical staff with a median age of 32.5 (19-43) years, and the remaining 7 patients had a median age of 73 (54-91) years. In the first episode, they had all symptoms such as fever and malaise with weakness; besides, in older people, these symptoms were more severe. All medical staff did not receive any special treatment, but the elderly had received medications. Averagely, 20 to 30 days after treatment and withdrawal of symptoms of the first episode, the second episode occurred in these patients.	Re-infection is possible after a certain period of discharge or negative test, which can be caused by decreased power of the immune system or the use of other medications for the treatment of other diseases. The main point about this issue is the health practitioners to be alert, which can help to manage the crisis at the individual and group level. Further studies by evaluating the virus genome can be much more effective.
Parry J (2020) (5)	Hong Kong, Case report	A 33-year-old man was infected with COVID-19 and referred to the hospital. He was completely treated for 3 weeks. After 4.5 months (135 days), the patient was referred to the hospital again with signs and symptoms of COVID-19 as well as a positive test. The important point was the high load of virus in his body in the second episode. Genetic findings also showed that viruses in the first and second episodes differed in 24 nucleotides that this difference resulted in amino acid alteration in 9 proteins.	It can be said that acquired immunity following the first episode of infection only lasted for a short time. When re-infection happens, it can be claimed that the virus has developed genetic mutations over time.
Bongiovanni M (2020) (20)	Italy, Case report	A 48-year-old female nurse was referred to the hospital with fever, headache, malaise, and cough as well as respiratory symptoms with a positive PCR test in the first episode of the disease. After the treatment period and two negative tests, she was discharged from the hospital and returned to work. After 5 months of discharge and routine work in the hospital, this person was referred to another hospital with symptoms and positive test again.	This person has changed her place of work because of her job and has been re-infected due to contact with a companion of a patient with COVID-19. Considering these results, it can be said that there is a possibility of re-infection.

Table 2. The Clinical, demographic, and laboratory characteristics in patients with mild or moderate symptoms of COVID- 19 during the second episode

ID	Patient No.	Age	Sex	Health Condition	First Episode Severity	Second Episode Severity	Lymphopenia (1st / 2nd episode)	1st episode CRP	IgG during 2nd episode	1st episode duration	Gap between episode^	2nd episode duration
Gidari A et al. (2020)	1	50	M	HBV	Severe	Mild	1st	-	+	14	20 P	15
	2	51	M	HTN Dyslipidemia Smoker	Mild	Moderate	-	NA	+	26	11 P	8
	3	45	F	Hypothyroidism	Moderate	Mild	-	NA	+	17	24 P	6
	4	74	M	Healthy	Mild	asymptomatic	-	NA	-/+	26	15 P	9
	5	42	F	Healthy	Moderate	Moderate	NA	NA	+	29	27 P	5
	6	77	F	Chronic Respiratory disease Cardiomyopathy	Mild	Asymptomatic	-	NA	+	22	42 P	2
	7	26	M	Healthy	Moderate	Asymptomatic	2nd	NA	-	16	63 P	4
	8	50	M	DM2	Severe	Mild	-	-	-/+	38	60 P	2
	9	77	M	Cardiomyopathy AF DM2 Alcoholic Cirrhosis Myelodysplastic Syndrome Hepatic neoplasm	Mild	Mild	1st	NA	+	25	30 P	3
To KK et al. (2020)	1	33	M	Healthy	Mild	Asymptomatic	-	NA	-	19	123 P	5
Larson D et al. (2020)	1	42	M	Healthy	Mild	Moderate	NA	NA	+*	10	51 C	14
Gupta V et al. (2020)	1	25	M	NA	Asymptomatic	Asymptomatic	NA	NA	NA	8	106 P	14
	2	28	F	NA	Asymptomatic	Asymptomatic	NA	NA	NA	10	107 P	6
Van Elslande J et al. (2020)	1	51	F	Asthma	Moderate	Mild	-	NA	+	35	90 C	10
Goldman JD et al. (2020)	1	60-69	NA	Severe Emphysema HTN	Moderate	Moderate	NA	2nd	+	41	100 P	>19
He F et al. (2020)	1			SLE Immunosuppressive drugs	Severe	Mild	-	1st	NA	9	12 P	4
Bonifácio LP et al. (2020)	1	24	F	Overweight	Mild	Mild	-	-	-	14	33 C	12
Chen D et al. (2020)	1	46	F	NA	Moderate	Asymptomatic	NA	NA	NA	14	5 P	3
Gousseff M et al. (2020)	1	19	F	None	Moderate	Moderate	NA	NA	+	18	26 C	Ongoing
	2	32	F	None	Mild	Mild	NA	NA	NA	29	36 C	10
	3	33	F	First-trimester pregnancy	Mild	Mild	-	NA	+	13	27 C	8
	4	43	M	None	Mild	Mild	-	+	+	14	24 C	29
	7	91	F	CHD HTN CVD Atherosclerosis Arrhythmia DM	Severe	Moderate	1st	+	+	13	25 C	9
	8	55	M	CLD Cirrhosis Child	Mild	Moderate	1st & 2nd	+	+	21	27 C	20

Table 2. Ctd

ID	Patient No.	Age	Sex	Health Condition	First Episode Severity	Second Episode Severity	Lymphopenia (1st / 2nd episode)	1st episode CRP	IgG during 2nd episode	1st episode duration	Gap between episode^	2nd episode duration
Bongiovanni M (2020)	1	48	NA	-	Mild	Asymptomatic	NA	NA	NA	22	NA	NA
Parry J (2020)	1	33	M	NA	Mild	Asymptomatic	NA	NA	NA	21	NA	145
Cao H et al. (2020)	1	54	F	-	Severe	Asymptomatic	-	NA	+	36	13 P	NA
	2	72	F	-	Moderate	Asymptomatic	-	NA	+	18	13 P	NA
	3	60	F	-	Moderate	Asymptomatic	-	NA	+	30	10 P	NA
	4	65	F	Hypothyroidism	Moderate	Asymptomatic	-	NA	+	36	13 P	NA
	5	58	M	Tuberculosis	Moderate	Asymptomatic	-	NA	+	31	17 P	NA
	6	64	M	-	Severe	Asymptomatic	-	NA	+	6	27 P	NA
	7	36	F	-	Moderate	Asymptomatic	-	NA	+	30	7 P	NA
	8	26	M	-	Moderate	Asymptomatic	-	NA	+	19	7 P	NA
Dou C et al. (2020)	1	34	M	DM2	Severe	Asymptomatic	-	+		22	18 P	22

^: Either reported according as Clinical relief to 2nd positive PCR shown by "C" / negative PCR to 2nd positive PCR shown by "P"

*: Patient was tested 14 days after symptoms onset of the second episode

AF: Atrial Fibrillation, ATC: Anti Coagulation Therapy, CHD: Congenital Heart Disease, CKD: Chronic Kidney Disease, CLD: Chronic Lung Disease, COPD: Chronic Obstructive Pulmonary Disease, CRD: Chronic Renal Disease, CVD: Cerebrovascular Disease, DLBCL: Diffuse Large B-Cell Lymphoma, DM2: Type 2 Diabetes Mellitus, DM: Diabetes Mellitus, HBV: Hepatitis B Virus, HTN: Hypertension, MAG: myelin-associated glycoprotein, SLE: Systemic Lupus Erythematous, NA: Not Available, M: Male, F: Female.

Table 3. The Clinical, demographic, and laboratory characteristics in patients with severe symptoms of COVID- 19 during the second episode

ID	Patient No.	Age	Sex	Health Condition	First Episode Severity	Second Episode Severity	Lymphopenia (1st / 2nd episode)	1st episode CRP	IgG during 2nd episode	1st episode duration	Gap between episode^	2nd episode duration
Mulder M et al. (2020)	1	89	F	Waldenstrom macroglobulinemi (B-cell immunocompromised)	Mild	Severe Expired		1st	-	5	54 C	22 Expired
Duggan NM et al. (2020)	1	82	M	HTN DM CKD Parkinson's Disease	Severe	Severe	NA	NA	NA	39	10 C	12
Gousseff M et al. (2020)	5	85	M	Bronchiectasis CHD Pacemaker Arrhythmia	Severe	Severe	1st & 2nd	+	NA	17	44 C	6
	6	54	M	HTN	Severe	Severe Expired	1st & 2nd	+	+	41	45 C	34 Expired
	9	72	M	Anti MAG neuropathy (rituximab, bendamustine)	Severe	Severe Expired	1st & 2nd	+	-	21	27 C	29 Expired
	10	73	M	DLBCL (chemotherapy d-22)	Mild	Severe	1st & 2nd	+	-	13	24 C	17
	11	84	F	CLD / O2T Mild CRD CHD Arrhythmia/ATC Valvulopathy Atherosclerosis DM	Severe	Severe	1st & 2nd	+	-	23	49	30
Lafaie L et al. (2020)	1	84	F	HTN Heart disease Cancer COPD	Severe	Severe Expired	1st & 2nd	+	-	15	More than one month C	14 Expired
	2	90	F	HTN DM2 Heart disease	Severe	Severe Expired	2nd	+	NA	32	4 C	9 Expired
	3	84	F	HTN Heart disease Immunosuppression	Severe	Severe Expired	1st & 2nd	+	+	12	10	19 Expired

^: Either reported according as Clinical relief to 2nd positive PCR shown by "C" / negative PCR to 2nd positive PCR shown by "P"

*: Patient was tested 14 days after symptoms onset of the second episode

AF: Atrial Fibrillation, ATC: Anti Coagulation Therapy, CHD: Congenital Heart Disease, CKD: Chronic Kidney Disease, CLD: Chronic Lung Disease, COPD: Chronic Obstructive Pulmonary Disease, CRD: Chronic Renal Disease, CVD: Cerebrovascular Disease, DLBCL: Diffuse Large B-Cell Lymphoma, DM2: Type 2 Diabetes Mellitus, DM: Diabetes Mellitus, HBV: Hepatitis B Virus, HTN: Hypertension, MAG: myelin-associated glycoprotein, NA: Not Available, SLE: Systemic Lupus Erythematous
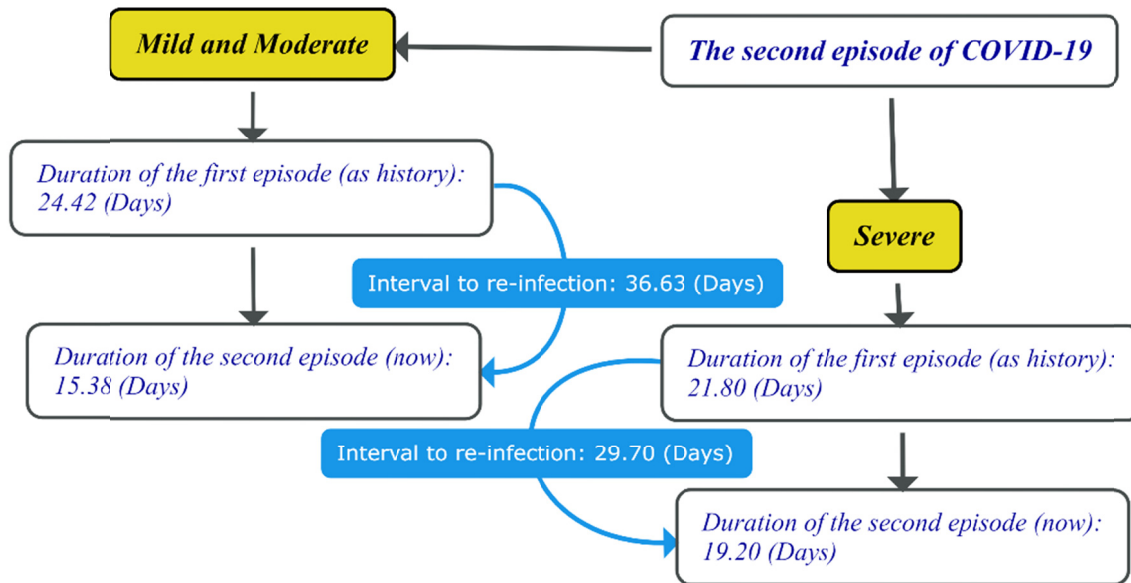
Fig. 2. A schematic diagram of the main finding of our study

Besides, the mean durations of reinfection in the mild or moderate group and the severe group were 15.38±5.57 days and 19.20 ± 2.98 days, respectively; however, these durations did not significantly differ between the 2 groups (p=0.675). The interval duration between the 2 episodes in the mild or moderate group was 36.63±5.71 days, which was significantly longer than this interval in the severe group (29.70±5.65 days) (p<0.001) (Table 4).

Following the assessment of the cases above, this theory could be suggested that, in general, reinfected patients were divided into 2 categories:

1. Healthy people with the mild or moderate disease in the first episode

2. High-risk people with the severe form of the disease in the first episode

In the first category, reinfection occurred because of the lack of effective specific immunity (neutralizing antibody) at a longer interval with the primary infection and possibly as a result of contact with a new strain. There was a possibility of an immune cross-reactivity resulted from other coronaviruses, which made B-cells naive not to be reactivated specifically for COVID-19. Therefore, people who had experienced the disease mildly without any immune response, despite the high level of IgG, did not have neutralization of function to clean the virus and were reinfected with new strains.

In the second category, the second episode was more severe because of the inability to provide an immune response at a shorter interval, being in a high-risk situation (because of long hospitalization in care centers and the need for more services and consequently more contacts), and having lower cardiorespiratory capacity. Inflammation caused the disease not to be diagnosed in patients with underlying diseases, which made the hospitalization process more difficult, leading to increased mortality. As a result, in these patients, if reinfection occurred in a short time and immunity was not formed, the body would not tolerate second stress and mortality would increase. Therefore, the follow-up of cured patients who were critically ill by COVID-19 through PCR is of high importance, and this population should be prioritized for vaccination.

Discussion

The number of confirmed COVID-19 cases and its correlated mortality and morbidity has been increasing so fast since its first report in December 2019. As we all know, COVID-19 is caused by Coronavirus 2 (SARS-CoV-2) (37, 38). It was believed that COVID-19 was an infectious disease whose incidence in the elderly as well as in patients with chronic diseases, such as cardiovascular disease, respiratory disease, renal disease, et cetera, was higher than that in healthy individuals (39, 40). Immunocompromised individuals were at higher risk of pulmonary

Table 4. The comparison of mean episode duration between mild or moderate and sever COVID-19

Episodes	COVID-19 Groups	Mean and SE	Mean Difference	P Value (% 95 CI)
First Episode	Mild or Moderate	24.42 ± 1.67	2.62	0.484 (-4.88 to
	Severe	21.80 ± 3.79		10.14)
Second Episode	Mild or Moderate	15.38 ± 5.57	-3.84	0.675 (-22.31 to
	Severe	19.20 ± 2.98		24.69)
	COVID-19 Groups	Mean and SE	Mean Difference	P Value (% 95 CI)
Gap between two episodes	Mild or Moderate	36.63 ± 5.71	6.93	0.0001
	Severe	29.70 ± 5.65		

or extrapulmonary complications during respiratory infections (41). However, recently, one of the major concerns about COVID-19 was an increasing rate of reinfection in all age groups, which in some cases could be presented with more severe symptoms, rapidly leading to death.

Many cases of SARS-CoV-2 infection in recurrent periods had been described in case reports, and there was not any vast evaluation, such as cohort studies, in this field. The present systematic review was aimed to describe the current scientific evidence on COVID-19 in reinfected patients as well as the mortality and morbidity risk of recurrence in these individuals.

The results were investigative of an infection recurrence episode in different time intervals from 4 to 123 days. They reported that most of the patients were treated after reinfection and the exact rate of mortality and morbidity was still unknown (21, 22, 30, 42). Regardless of mortality and morbidity of reinfection (of course if we considered it low), it was very important for the vaccination plan. Consequently, the coronavirus vaccine should have a longer immune duration. In order to produce such a vaccine, it was necessary to consider the relation of disease severity as well as its pathogenesis (43). The immunity after the first infection disappeared after a short time. One of the major signs of reinfection was IgG and C-reactive protein (CRP) rise (43). IgM levels sharply raised in the first 2 weeks of illness, indicating an acute infection, and after 1 week, IgG levels raised, indicating the presence of antibodies and a history of infection. Then, IgG levels decreased slowly (21). Therefore, it could be concluded that IgG level measurement might be an appropriate guide for diagnosing reinfection.

To KK et al reported that the phylogenic strains of the virus in the first and second episodes were very similar to the collected strains in March/April 2020 and August 2020, respectively (22). Some scientists believed that the second episode of infection could be more severe than the first. It could be more likely due to the strengthening of the immune system, the acquisition of more pathogenic strains, or perhaps an inoculation of the infection because of exposure of a patient to the risk factors (6, 10, 16). In some cases, the patients could be asymptomatic (31). In symptomatic patients, the symptoms were similar to those of the first episode (fever, cough, headache, malaise, chest pain, etc.) (10). The mild and asymptomatic cases had usually more ribonucleic acid (RNA) loss than severe cases. For confirming the reinfection, PCR could not be a good method because it could be positive for almost 100 days. Thus, in these cases, complete genome sequencing or viral culture was needed (12). The results of genetic tests and study of the whole genome showed that in the first episode, mutations occurred in 5 types of genes, and in the second episode, mutations occurred with more numbers in more genes. The SNYs were the same in both samples, but the loci were different and more numerous in the type of re-infection (6). The other important finding was the genetic mutation which could have occurred in the second episode of infection (14).

Another study used mathematical modeling for estimating the reinfection cases. The results demonstrated that it was not possible to diagnose reinfection when the patient was at the peak of infection and disease. On the other hand, control and preventive attempts could delay the occurrence of reinfection (25). There was the likelihood of being another simultaneous infectious disease with COVID-19, such as bacterial pneumonia, which had similar signs and symptoms of COVID-19 (16). Chronic diseases could be important factors of mortality and morbidity in reinfection. In patients with chronic disease, reinfection appeared with more severe signs and symptoms, which may lead to death easier (16, 18).

Reinfection and recurrence in the body after a certain period from discharge or negative tests in individuals were possible, which could be because of the decreased power of the immune system or use of other drugs to treat further diseases. The key was the vigilance of health professionals and health policymakers on this issue, which could help to manage the epidemic at the individual and group levels. Performing more studies and assessing the virus genome could be much more effective (44). One of the important points about reinfection was that the virus load was much higher in the second episode. Genetic findings also showed that the number of nucleotides involved in the first and second episodes may differ so much in terms of protein amino acid cleavage (25).

Study Limitation

Given that in most cases, in the second episode of the disease, the person had severe symptoms, leading to death, we cannot claim with certainty about the duration of the second episode of the disease, and the say that the length of the second episode in severe cases are shorter than in mild or moderate cases may be slightly different from reality.

Conclusion

All practitioners and health providers should be very careful about the severity of the second episode because of the more need for medical interventions for saving the patients. The interval between the first end and the second episode as well as the duration of each episode is very important to have better management. Moreover, it is important to conduct a high sample size cohort study to determine the incidence of reinfections and evaluate the signs and symptoms in terms of laboratory and molecular assessments because if there is such evidence, the vaccination schedule and the way of dealing with it for health policymakers, health professionals, and health care staff will become more significant. The vaccine should have very long immunogenicity to prevent reinfection in patients and members of the community. To produce such a vaccine, the relationship between disease severity and virus pathogenicity must be considered.

Conflict of Interests

The authors declare that they have no competing interests.

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