ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

COVID-19 Relapse, Reinfection Frequency, and Clinical Features of Cases

COVID-19 Nüks, Reenfeksiyon Sıklığı ve Vakaların Klinik Özellikleri

Hümeyra ASLANER[1] *Hacı Ahmet ASLANER*[2] *Yasemin SAVRANLAR*[3]

Ali Ramazan BENLİ[4]

ÖZ

Amaç: SARS-CoV-2 ile enfekte kişilerin virüse karşı bağışıklık yanıtının nasıl geliştiği ve ne kadar süreyle etkili olduğu pandemi döneminde en önemli sorulardan biridir. Bu çalışmada nüks ve yeniden enfeksiyon sıklığını, etkileyen faktörleri, vakaların klinik durumlarını ve semptomlarını değerlendirmeyi ve sonraki enfeksiyon şiddetini incelemeyi amaçladık.
Araçlar ve Yöntem: TC Sağlık Bakanlığı Halk Sağlığı Yönetim Sistemi (PHMS) kayıtlarının kullanıldığı tanımlayıcı ve kesitsel tipte bir çalışmadır. Klinik düzelme ile birlikte RT-PCR test sonuçları negatif çıkan ve ilk enfeksiyondan en az 45 gün sonra tekrar RT-PCR test sonucu pozitifleşen vakalar bu çalışmaya dahil edildi. CDC tarafından önerilen şekilde vakalar iki gruba ayrıldı: İlk enfeksiyondan 45-89 gün sonra pozitif olanlar nüks grubu ve 90 gün sonra pozitif olanlar yeniden enfeksiyon grubu olarak belirlendi. Demografik özellikler, sağlık çalışanı olup olmama, eşlik eden kronik hastalık ve tekrar pozitiflik dönemleri değerlendirildi.
Bulgular: Toplam vaka sayısı 103.096 idi. 45 gün sonra tekrar pozitifliği saptanan vaka sayısı 78 oldu. Çalışmada nüks grubundaki (45-89 gün) vaka sayısı 49, reenfeksiyon grubundaki (90 gün üzeri) vaka sayısı 29 ise olarak belirlendi.
Sonuç: İkinci enfeksiyonda çok düşük reenfeksiyon oranı ve daha hafif semptomlar aşı çalışmaları için umut vericidir. COVID-19'un yeniden bulaşmasını anlamak, önümüzdeki aylarda hükümet ve halk sağlığı kararlarına rehberlik etmenin anahtarı olabilir.

Anahtar Kelimeler: epidemiyoloji; pandemi; SARS-CoV-2

ABSTRACT

Purpose: How the immune response of people infected with SARS-CoV-2 develops against the virus and how long its effectiveness is one of the most important questions during the pandemic period. We aimed to examine the frequency of relapse and re-infection, examine the influencing factors, evaluate the cases' clinical conditions and symptoms, and examine the severity of subsequent infection.
Materials and Methods: This is a descriptive and cross-sectional type study using the Public Health Management System (PHMS) records of the Turkish Ministry of Health. Clinical improvement and negative RT-PCR test results, and positive RT-PCR test results at least 45 days after the first infection were included in this study. The cases were divided into two groups: the relapse group, those positive for 45-89 days after the first infection, and the reinfection group after 90 days recommended by the CDC. Demographic characteristics, whether or not to be a health worker, accompanying chronic illness, and re-positivity periods were evaluated.
Results: The total number of cases was 103.096. The number of cases with repeat positivity detected after 45 days was 78. In the study, the number of cases in the relapse group (45-89 days) was 49, while the number of cases in the reinfection group (over 90 days) was 29.
Conclusions: The very low rate of reinfection and milder symptoms in the second infection are promising for vaccination studies. Understanding the COVID-19 reinfection could be the key to guiding government and public health decisions in the coming months.

Keywords: epidemiology; pandemic; SARS-CoV-2

Received: 07.10.2021; Accepted: 30.05.2022

[1] Kayseri City Hospital, Family Medicine, Kayseri, Türkiye.
[2] İncesu County State Hospital, Internal Medicine Clinic, Kayseri, Türkiye.
[3] Nuh Naci Yazgan University, Faculty of Dentistry, Kayseri, Türkiye.
[4] Health Directorate of Kayseri, Kayseri, Türkiye.

Corresponding Author: Hacı Ahmet Aslaner, İncesu County State Hospital, Internal Medicine Clinic, Kayseri, Türkiye. e-mail: draslaner@gmail.com

How to cite: Aslaner H, Aslaner HA, Savranlar Y, Benli AR. COVID-19 relapse and reinfection frequency, clinical features of cases. Ahi Evran Med J. 2022;6(3):319-325. DOI: 10.46332/aemj.1005961

INTRODUCTION

COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused approximately 100 million cases and 2 million deaths in one year. How the immune response of people infected with SARS-CoV-2 develops against the virus and how long it is effective is one of the most important questions during the pandemic period. Long-term sustainable immunity following COVID-19 infection and the potential mechanisms mediating it has not been fully elucidated, and research on this subject is still ongoing.[1-3] For viruses such as measles and hepatitis A, lifetime immunity can be achieved after the first infection. However, immunity is short-lived, and reinfections are observed in many respiratory viruses, such as seasonal influenza, including human coronaviruses.[4,5] It is known that there are asymptomatic/symptomatic RT-PCR positive cases reinfected after negative real-time reverse transcription-polymerase chain reaction (RT-PCR) test results and clinical recovery.[6] The Centers for Disease Control and Prevention (CDC) recommends two time intervals for research in retransmission cases. The first cases are ≥90 days after the first infection/illness for people with/without COVID-19-like symptoms, and the second case are 45-89 days after the first infection/illness for people with COVID-19-like symptoms.[7]

In a second COVID-19 infection, how the patient's course and symptoms are compared to the first infection is another question. In a study conducted in the United Kingdom, it was reported that none of the 11.000 healthcare workers who were proven to be infected during the first wave of the epidemic between March and April 2020 experienced symptomatic re-infection in the second wave.[8] On the other hand, a case report was published stating that the patient who survived mildly in the first infection had a more severe course in the second.[9] Despite all this, it is currently impossible to clearly predict the disease's course when the infection develops for the second time.

Various vaccines are currently being used in many countries. How protective these vaccines will be understood more readily by determining the frequency of reinfection. Because the high antibody titer alone is not sufficient for protection, even if it is, reinfection increases with the decrease in the amount of antibody. However, one study reported that antibodies protect against severe forms of the disease, even if they do not protect against reinfection.[10,11]

In this study, we aimed to examine the frequency of relapse and re-infection, examine the influencing factors, evaluate the cases' clinical conditions and symptoms, and examine the severity of subsequent infection.

MATERIALS and METHODS

Type of Study

Descriptive, cross-sectional type and retrospective.

The Place of the Study and the Selection of the Participants

COVID-19 cases from all age groups with positive RT-PCR test results in Kayseri Province, clinical improvement and negative RT-PCR test results, and positive RT-PCR test results at least 45 days after the first infection were included in this study. The cases between the date of 16.03.2020, the date of the first COVID-19 case in Kayseri, and 07.01.2021, were included in the study. The study was terminated on 07.01.2021 since the vaccination program had started on 10.01.2021. The cases were divided into two groups: The relapse group (n=49); clinical improvement and negative RT-PCR test results, and positive RT-PCR test results at least 45 days after the first infection and the reinfection group (n=29); positive RT-PCR results ≥90 days after the first infection recommended by the CDC.

Data Collection

The case information was obtained by file scanning through the Public Health Management System (PHMS) records of the Turkish Ministry of Health. Following the guideline published by the Ministry of Health of the Republic of Turkey, the RT-PCR sample for SARS CoV-2 is taken when people apply to the health center with COVID-19 compatible symptoms, from those who have high-risk contact with the COVID-19 case, preoperative patients, in such instances as before some specific job applications and going abroad. Cases with positive RT-PCR test results per-

formed in any authorized laboratory in the country are recorded in the web-based national system called Public Health Management System (PHMS), which belongs to the Turkish Ministry of Health. Later, the case's home address is reported to the district health directorate official, where it is registered. The authorized person is contacted with the case, and the general condition, symptom, subdisease, hospitalization need, medications to be used, and contact information are recorded by the health team consisting of a doctor and a nurse at the address. The case is taken into isolation, and quarantine is applied to the contacts. If the case is admitted to the hospital, the procedures applied during the hospitalization are recorded in PHMS in the same way.

While the records were being scanned, there was no duplication since all cases had national identification numbers. Demographic characteristics, whether or not to be a health worker, accompanying chronic illness, and re-positivity periods were evaluated. In the first infection, the total number of cases and the relapse and reinfection rates of the cases were determined by months. Participants in the relapse and reinfection groups were compared in terms of demographic and clinical data. Also, in the first and second infection periods, parameters showing clinical progressions such as general condition, hospitalization, intubation, intensive care admission, pneumonia, and symptoms (fever, cough, sore throat, back pain, weakness, etc.) were examined separately. The post-second infection mortality rate was also evaluated.

Statistical Analysis

The study's statistical evaluation was made using the SPSS version 22.0 (IBM Corp., Armonk, NY, USA) computer package program. Descriptive statistics are given as mean, standard deviation, median, minimum and maximum. Frequencies (n) and percentages (%) were used for categorical data. The distribution of the data was analyzed using the Kolmogorov-Smirnov test. Chi-Square test, Mann-Whitney U test were used for numerical data that did not conform to normal distribution. The relationship between numerical data was evaluated using the Spearman correlation test.

This study was conducted after obtaining approval from the ethics committee of Nuh Naci Yazgan University Non-Interventional Research Ethics Committee (Decision No: 1/714, Decision Date: 22/09/2020) and written consent was obtained from all participants.

RESULTS

The population of Kayseri Province in which this study was conducted was 1.421.455 in 2020. COVID-19 cases between March 16, 2020, and January 07, 2021, were included in the study. Between these dates, 493.521 PCR tests were carried out. The total number of cases was 104.281. The number of cases with repeat positivity detected after 45 days was 78. In the study, the number of cases in the relapse group (45-89 days) was 49, while the number of cases in the reinfection group (over 90 days) was 29.

The cases' median age was 36.5 years (range: 12-95 years), and 51 (65.4%) were male. 25 (32.05%) were healthcare workers, 13 (16.7%) had at least one chronic disease. It consisted of chronic diseases such as hypertension 8 (10.25%), chronic lung disease 8(10.25%), diabetes mellitus 5 (6.41%) 1 (1.28%), cardiovascular disease 1 (1.28%), chronic renal failure 1 (1.28%).

The reinfection rate was 0.05%, and the relapse rate was 0.03% in all cases. The number of cases and the relapse and reinfection rate of the cases by month were also evaluated (Table 1).

Table 1. Number of cases of relapse and reinfection according to months

Date	Number of RT-PCR Test	Number of Cases	Relapse n(%)	Reinfection n(%)
March 2020	1.168	62	0	0
April 2020	11.932	537	0	5(0.93)
May.20	14.318	382	1(0.26)	2(0.52)
June 2020	21.317	673	1(0.15)	2(0.30)
July 2020	22.176	2.518	6(0.24)	1(0.04)
August 2020	66.053	10.518	10(0.10)	8(0.08)
September 2020	104.890	34.891	23(0.07)	9(0.03)
October 2020	71.856	14.887	6(0.04)	2(0.01)
November 2020	93.658	21.919	2(0.01)	0(0)
December 2020	79.402	16.709	0(0)	0(0)
January 2021(1-7 days)	6.751	1.185	0(0)	0
Total	493.521	104.281	49(0.05)	29(0.03)

RT-PCR: Real-Time Polymerase Chain Reaction

The relapse group's median age was higher than that of the reinfection group (p=0.010), but it was similar in gender (p=0.398). The number of healthcare workers were higher in the reinfection group (p=0.018). The number of cases with at least one chronic disease was higher in the relapse group (p=0.016). Initial parameters such as pneumonia, hospitalization, service admission, intensive care admission, and general condition indicating the clinical status and progression of the cases were similar in both groups (p=0.323, p=0.282, p=0.215, p=0.628, p=0.110, respectively). In both groups, no cases were intubated at the first infection. In the relapse group, COVID-19 compatible pneumonia was seen in 8 (80%), and 4 (40%) in the reinfection group at the first infection and were similar (p=0.085). The most common cause of hospitalization in both groups was pneumonia (10 (%90.9), 8 (%27.6), respectively). In the second infection, there were two deaths (4.1%) in the relapse group and 1 (3.4%) in the reinfection group (p=0.690).

There was no difference between the relapse group 43 (87.8%) and the reinfection group 24 (82.8%) in terms of drug use for the treatment of COVID-19 in the first infection (p=0.384). Regarding the drug subgroups, the use of favipiravir 24 (49%) in the relapse group and 7 (24.1%) in the reinfection group was higher, but statistically, there was no difference in terms of drug use (p=0.155) (Table 2).

Table 2. Comparison of demographic and clinical data of the cases in relapse and reinfection groups

Variables	Relapse n,%	Reinfection n,%	p
Male	31(63.3)	20(69)	0.398
Age (Year)	42 (12-75)	30(16-95)	0.010
Repositive day	62(45-86)	115(51-264)	
Children	2(4.1)	2(6.9)	0.477
Healthcare workers	11(22.4)	14(48.3)	0.018
Comorbid disease	12(24.5)	1(3.4)	0.016
Hospitalization	11(22.4)	9(31)	0.282
Intensive care unit	1(2)	0(0)	0.628
Pneumonia	10(20.4)	8(27.6)	0.323
General condition			
Mild	35(71.4)	25(86.2)	0.110
Moderate	14(28.6)	4(13.8)	
Severe	0(0)	0(0)	
Death	2(4.1)	1(3.4)	0.690
Antiviral therapy			
Yes	43(87.8)	24(82.8)	0.384
No	6(12.2)	5(17.2)	
Antiviral drugs			
Favipiravir	24(49)	7(24.1)	
Hydroxychloroquine	18(36.7)	15(51.7)	0.155
Favipiravir + Hydroxychloroquine	1(2)	2(6.9)	

When the groups were evaluated in terms of symptoms in the first infection, the cough was proportionally higher in the relapse group, while fever was higher in the reinfection group (p=0.141), (p=0.446). Other symptoms of both groups during the first infection were similar (Table 3).

Table 3. Comparison of symptoms in relapse and reinfection groups

Symptoms	Relapse n,%	Reinfection n,%	p
Myalgia	33(67.3)	18(62.1)	0.408
Fatigue	28(57.1)	14(48.3)	0.300
Cough	19(38.8)	7(24.1)	0.141
Loss of taste/ smell	19(38.8)	9(31)	0.330
Sore throat	8(16.3)	3(10.3)	0.353
Dyspnea	8(16.3)	4(13.8)	0.518
Backache	8(16.3)	5(17.2)	0.576
Anorexia	7(14.3)	2(6.9)	0.274
Fever	5(10.2)	4(13.8)	0.446
Diarrhea	2(4.1)	1(3.4)	0.690
Headache	2(4.1)	3(10.3)	0.264
Hemoptysis	1(2)	1(3.4)	0.608

In the relapse group, the rates of factors such as hospitalization, presence of pneumonia, service admission, and intensive care admission were similar in the first infection and the second infection (p>0.05). In the reinfection group, hospitalization and service admission were higher in the first infection than in the second infection (p=0.039, p=0.021) (Table 4).

In the relapse group, cough, sore throat, muscle, joint pain, loss of taste, and smell were more common in the first infection than in the second infection (p=0.001, p=0.039, p=0.000, p=0.000, respectively). The cough was more common in the first infection in the reinfection group than in the second infection (p=0.016).

There was a weak, negative correlation between age and the day when RT-PCR was positive again (p=0.003, r=0.331).

Table 4. Comparison of clinical data in the first infection relapse and reinfection period

	Relapse			Reinfection		
Situations	**First Infection**	**Second Infection**	**p**	**First Infection**	**Second Infection**	**p**
Hospitalization	11	7	0.454	9	2	0.039
Intensive Care	1	2	0.999	0	2	0.500
Pneumonia General Condition	10	5	0.267	8	2	0.070
Mild	35	44		25	26	
Moderate	14	3	0.434	4	2	-
Severe	0	2		0	1	

DISCUSSION

Currently, the World is still under the influence of the COVID-19 epidemic. It has created serious health and economic problems. Studies on prevention, treatment, and vaccination are carried out in the fight against the pandemic. The reinfection of the people who have had the disease is important in terms of guiding vaccination studies.

In COVID-19 cases, it has a high level of protection from the first infection, reinfection, and symptomatic disease.[12] Studies reporting the relapse-re-infection rate are few in the literature.

When the COVID-19 reinfection is evaluated in terms of age and gender, especially gender varies by region. In a study conducted in Austria, 62.5% of those who reinfected were female, and the median age was 39.8 (15.4-93.8) years, and in another study conducted in Iran, 64.9% of the reinfected were male, and the mean age was 37.54±15.16 years (range from 24-94 years).[13,14] In this study, 69% of those who reinfected were male, and the median age was 30 (ranging from 16-95 years). Comorbidities of the case, SARS CoV-2 viral load, and immunosuppression during the first infection may predispose the case to relapse.[15] In a meta-analysis with 24 peer-reviewed journals, Liu et al. found that pre-existing chronic diseases were strongly associated with increased disease severity (OR 3.50, 95% CI 1.78 to 6.90).[16] Santos et al. reported that comorbidities such as arterial hypertension, obesity, diabetes, and asthma are not associated with reinfection, but the second infection's clinical presentation is associated with severity.[17] When both groups were analyzed in this study, comorbidity was higher in the relapse group than in the reinfection group, and this may be because comorbid diseases increase the case's susceptibility to relapse and prolong the recovery period of the infection.

Older cases are hospitalized for a long time due to COVID-19 infection and recover later.[18] In this study, the reason for the higher rate of relapse than reinfection in the elderly may be the late recovery in older age, as in the literature.

Being a healthcare worker is one of the risk factors for reinfection.[17] There are a rapid decrease in antibody titers and pro-inflammatory cytokines after the mild COVID-19 infection in healthcare workers. As a result, authors report that antibody-mediated protection against reinfection with SARS-CoV-2 takes a short time. In another study conducted with healthcare workers, it has been reported that the presence of anti-spike or anti-nucleocapsid IgG antibodies in the blood within six months following the first infection significantly reduces the risk of SARS-CoV-2 reinfection.[19,20] In this study, healthcare workers are more reinfected, and this is thought to be because healthcare workers, whose protective antibodies have fallen off, have repeatedly encountered the virus compared to individuals in the community.

A comparison of symptoms in the first infection and the second infection can give an idea about the clinical courses of relapsed-reinfected cases. In the study by Gousef et al., published with 11 cases, the symptoms and the severity of the infection were similar during the first and second infection periods.[6] In another study, the clinical findings and general conditions of the first and second infection of cases were found to be similar.[21] Some authors reported that symptoms (excluding cough) in this study's reinfection group were not different in the first and the second infection. However, symptoms such as cough, sore throat, muscle and joint pain, and loss of taste and smell were less common in the relapse group.

The first infection prevents a severe clinical course in the second infection. Therefore, hospitalizations are less in reinfection, and almost none of those with symptoms related to COVID-19 require hospitalization in the intensive care unit.[12] The cases' general condition were better in the second infection period in both groups, and hospitalization in intensive care was similar in the first and second infection groups, but hospitalization was less in the reinfection group.

In a study within ten months, in which they accepted RT-PCR positive patients to be reinfected at least 90 or more days after the first infection, the mean reinfection day was 131.4±40.4 days (range 90.2 - 269.0 days).[12] In a study the mean elapsed time between two clinical periods were 5.6±2.3 months.[21] In this study, the second infection's median day in the relapse group were 62 days (45-86 days) and 115 days (91-264 days) in reinfection, consistent with the literature.

In a study conducted by Dan et al. on how long the antibodies against the virus remained positive in COVID-19 infection, it was found that there were memory B cells after six months.[22] In a study conducted with 705 patients in the United Kingdom, it was found that the antibody positivity continued in 87.8% of the patients after six months, and the antibodies became negative in only 5 of the participants in the same study.[23] In this study, the cases between March-June 2020 have completed their 6-month period after the first infection in September-December 2020. Reinfection occurred in only 9 out of a total of 1654 cases in the period of March-June 2020. When evaluated together with these data, it is seen that the antibodies formed are protective, and the likelihood of the same individuals being reinfected in at least 6 months is low. Already in this study, 4 cases were RT-PCR positive again after 180 days.

In a study on the efficacy of favipiravir used in the treatment of COVID-19, the significant shortening in clinical recovery time suggested that favipiravir may be beneficial in mild to moderate COVID-19.[24] In the study on hydroxychloroquine, it was found to reduce hospitalization.[25] Studies on favipiravir and hydroxychloroquine were generally on clinical efficacy. In this study, there were cases using favipiravir, hydroxychloroquine, and favipiravir+hydroxychloroquine in the first infection period in both groups, and it was observed that drug use did not affect relapse and re-infection. However, drug use is thought to be effective in the milder clinical symptoms of both the first and the second infections.

Limitations of the Study

The most important limitation of this study is that it is retrospective, and the cases have no antibody results. Nevertheless, examination of 104.281 cases and comparison of clinical findings of relapse and reinfection groups constitute the study's strengths.

In conclusion, in the ten months, 78 (0.071%) of 104.281 cases were re-positive after 45 days. Although it was thought that there were re-positive cases that could not be detected, these people did not need to have an RT-PCR test because they did not cause symptoms or the infection was mild. The very low rate of reinfection and milder symptoms in the second infection are promising for vaccination studies. Understanding the COVID-19 reinfection could be the key to guiding government and public health decisions in the coming months. Nevertheless, we think that more studies are needed to clarify the relapse-reinfection frequency, comorbidity, clinical situation, and findings.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was conducted after obtaining approval from the ethics committee of Nuh Naci Yazgan University Non-Interventional Research Ethics Committee (Decision No: 1/714, Decision Date: 22/09/2020) and written consent was obtained from all participants.

Authors' Contributions

Concept/Design: HA, ARB, HAA. Data Collection and/or Processing: HA, YS. Data analysis and interpretation: ARB, HAA, HA. Literature Search: HA, YS, HAA. Drafting manuscript: HAA, ARB, YS. Critical revision of manuscript: ARB, HAA. Supervision: ARB, HA.

REFERENCES

1. Siracusano G, Pastori C, Lopalco L. Humoral Immune Responses in COVID-19 Patients: A Window on the State of the Art. Front Immunol. 2020;11:1049.
2. García LF. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. Front Immunol. 2020;11:1441.
3. Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424-432.
4. Mo H, Zeng G, Ren X, et al. Longitudinal profile of antibodies against SARS-coronavirus in SARS patients and their clinical significance. Respirology. 2006;11(1):49-53.
5. Payne DC, Iblan I, Rha B, et al. Persistence of antibodies against middle east respiratory syndrome coronavirus. Emerg Infect Dis. 2016;22(10):1824-1826.
6. Gousseff M, Penot P, Gallay L, et al. Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound? J Infect. 2020;81(5):816-846.
7. Investigative criteria for suspected cases of SARS-CoV-2 reinfection (ICR).2020. https://www.cdc.gov/coronavirus/2019-ncov/php/invest-criteria.html Access date April 15, 2021.
8. Jones NK, Rivett L, Sparkes D, Forrest S, et. al. Effective control of SARS-CoV-2 transmission between healthcare workers during a period of diminished community prevalence of COVID-19. eLife. 2020;9:e59391.
9. Tillett RL, Sevinsky JR, Hartley PD, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis. 2021;21(1):52-58.
10. Garcia-Beltran WF, Lam EC, Astudillo MG, et al. COVID-19-neutralizing antibodies predict disease severity and survival. Cell. 2021;184(2):476-488.
11. Bentivegna E, Sentimentale A, Luciani M, Speranza ML, Guerritore L, Martelletti P. New IgM seroconversion and positive RT-PCR test after exposure to the virus in recovered COVID-19 patient. J Med Virol. 2021;93(1):97-98.
12. Sheehan MM, Reddy AJ, Rothberg MB. Reinfection Rates among Patients who Previously Tested Positive for COVID-19: a Retrospective Cohort Study. Clin. Infect. Dis. 2021;73(10):1882-1886.
13. Pilz S, Chakeri A, Ioannidis JPA, et al. SARS-CoV-2 re-infection risk in Austria. Eur J Clin Invest. 2021;51(4):1-7.
14. Salehi M, SeyedAlinaghi S, Alavi Darazam I, et al. COVID-19 Reinfection or Relapse? A Retrospective Multicenter Cohort Study from Iran. Arch Clin Infect Dis. 2021;16(5):e116381.
15. Ye G, Pan Z, Pan Y, et al. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. J Infect. 2020;80(5):14-17.
16. Liu H, Chen S, Liu M, Nie H, Lu H. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: A systematic review and meta-analysis. Aging Dis. 2020;11(3):668-678.
17. Adrielle dos Santos L, Filho PG de G, Silva AMF, et al. Recurrent COVID-19 including evidence of reinfection and enhanced severity in thirty Brazilian healthcare workers. J Infect. 2021;82(3):399-406.
18. Alkundi A, Mahmoud I, Musa A, Naveed S, Alshawwaf M. Clinical characteristics and outcomes of COVID-19 hospitalized patients with diabetes in the United Kingdom: A retrospective single centre study. Diabetes Res Clin Pract. 2020;165:108263.
19. Bruni M, Cecatiello V, Diaz-Basabe A, et al. Persistence of anti-SARS-CoV-2 antibodies in non-hospitalized COVID-19 convalescent health care workers. J. Clin. Med. 2020;9(10):3188.
20. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers. N Engl J Med. 2021;384(6): 533-540.
21. Lechien JR, Chiesa-Estomba CM, Radulesco T, et al. Clinical features of patients who had two COVID-19 episodes: a European multicentre case series. J Intern Med. 2021;290(2):421-429.
22. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science. 2021;371(6529):4063.
23. UK Biobank. UK Biobank SARS-CoV-2 serology study.https://www.ukbiobank.ac.uk/media/x0nd5sul/ukb_serologystudy_report_revised_6months_jan21.pdf. Access date April 23, 2021.
24. Udwadia ZF, Singh P, Barkate H, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis. 2021;103:62-71.
25. Ip A, Ahn J, Zhou Y, et al. Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: A multi-center observational study. medRxiv. BMC Infect. Dis. 2021;21(1):1-12.