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COVID-19 REINFECTION: DOES IT MATTER?

COVID-19 RE-ENFEKSİYONU: ÖNEMLİ Mİ?

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ABSTRACT

Objective: The aim of this study was to present the descriptive findings of 65 patients evaluated as clinical COVID-19 reinfection.

Materials and Methods: We conducted a retrospective chart review of COVID-19 reinfection cases recorded by the provincial health directorate. The time between infections (days), whether the patient was hospitalized, symptoms at the time of both positive tests, presence of risky contact, occupation, lung imaging results, laboratory findings, and RT-PCR cycle threshold (Ct) values were recorded. Results were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]), and categorical variables were expressed as frequency (percentage).

Results: The mean time between infections was 124.9 (SD 39.7) days and the median was 117 (IQR 96-143.5) days. Reinfection occurred after 45 to 89 days in 10 patients (15.4%) and after 90 days or more in 55 patients. The shortest time to reinfection was 60 days and the longest time was 272 days. The median Ct value was 24.5 (IQR 22-26.5) among patients reinfected after 45 to 89 days and 28 (IQR 25-32) among those reinfected after at least 90 days.

Conclusion: This study demonstrated that the frequency of COVID-19 reinfection is higher than predicted. The complex algorithms recommended by international health institutions make it difficult to detect these cases. However, rapid identification of these patients is essential to prevent new infections and control the pandemic.

Keywords: COVID-19, pandemics, reinfection

ÖZ

Amaç: Bu çalışmada amacımız klinik re-enfeksiyon olarak tanımlanan 65 hastanın tanımlayıcı bulgularını sunmaktır.

Gereç-Yöntem: İl sağlık müdürlüğü tarafından kaydı tutulan re-enfeksiyon vakalarının retrospektif dosya taraması yapılmıştır. İki enfeksiyon arasında geçen süre (gün), hastane yatışı olup olmadığı, vakaların her bir pozitif test sonucu dönemindeki şikayetleri, riskli temas durumları, sağlık çalışanı olup olmadıkları, varsa akciğer görüntülemesi sonuçları, laboratuvar bulguları ve RT-PCR Ct değerleri kaydedilmiştir. Bulgular ortalama±standart sapma, ortanca (çeyrekler arası değer - IQR), kategorik değişkenler frekans (yüzde) olarak sunulmuştur.

Bulgular: İki enfeksiyon arasında geçen ortalama süre 124,9±39,7 gün ve ortanca ise 117 (IQR 96 – 143,5) gündü. 10 (15,4%) kişide 45-89 gün, 55 kişide 90 gün veya daha uzun süre sonra re-enfeksiyon görüldü. Tespit edilen en kısa süre 60 gün ve en uzun süre ise 272 gündü. 45-89 gün arası sürede re-enfekte olanların ortanca Ct değeri 24,5 (22-26,5), ≥90 gün sonra re-enfekte olanların ortanca Ct değeri 28 (25-32) idi.

Sonuç: Bu çalışma ile COVID-19 re-enfeksiyon sıklığının tahmin edildiğinden daha yüksek olduğu gösterilmiştir. Uluslararası sağlık kuruluşları tarafından önerilen kompleks algoritmalar bu vakaların tespiti zorlaştırmaktadır. Ancak pandemi mücadelesi sırasında elzem olan husus vakaları çok hızlı tespit ederek yeni bulaşların olmasını önlemektir.

Anahtar kelimeler: COVID-19, pandemi, re-enfeksiyon

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in China and rapidly spread worldwide, appearing in Turkiye on March 10, 2020 (1, 2). On March 11, 2020, the World Health Organization (WHO) declared it a pandemic, and the first case in Turkiye province was reported on March 15, 2020, in a person who had returned from Umrah (3).

New information about SARS-CoV-2 infection is constantly emerging as scientists all over the world strive to elucidate the disease it causes, coronavirus disease 2019 (COVID-19). However, after the first year of the pandemic, there is still much we do not understand about COVID-19. One of these areas is reinfection.

The American Centers for Disease Control and Prevention (CDC) established research criteria for identifying cases of reinfection and recommended the use and evaluation of genomic testing of paired samples. According to their protocol, genome sequencing should be performed in patients who test positive for SARS-CoV-2 RNA again after a period of longer than 90 days (those with cycle threshold Ct value < 33 or no available Ct value). Patients who retest positive for SARS-CoV-2 RNA within 45 to 89 days must have definitive symptoms that cannot be explained by an etiology other than COVID-19 or have a history of close contact with a COVID-19 patient to be considered reinfection. Again, genomic sequencing of old and new samples (those with Ct < 33 or without a Ct value) is recommended. If genomic testing capacity is limited, the suspicion of reinfection is higher for patients with 90 days or more between two positive tests (4). In contrast, the European Centre for Disease Control and Prevention (ECDC) suggested a more complex assessment, but stated that there is still no consensus and that a case definition must be established (5). Yahav et al. referred to the difficulty of the definitions developed by the CDC and ECDC and emphasized that a simpler definition of reinfection is needed for treatment and infection control measures. In their study, they proposed categorizing reinfection as confirmed, clinical, and epidemiological. They also developed definitions for relapse/reactivation and repositivity (6).

The present study aimed to present the findings of cases of clinical reinfection, which we believe must be defined in order to prevent the disruption of treatment and infection control measures.

MATERIALS and METHODS

Patient selection

This retrospective descriptive study included 65 cases evaluated as clinical reinfection. The first case of reinfection was recorded on August 18, 2020, and the last case within the study period was detected on January 3, 2021.

Our province consists of a total of 20 districts, 3 central and 17 peripheral (the most remote district is 180 km from the center). As part of the pandemic management plan, oronasopharyngeal samples obtained in the 17 peripheral districts are transported to the public health laboratory in the central district at least three times per day using the specimen transport system established. Specimens obtained by contract tracing teams in the central districts are delivered immediately to the public health laboratory. Hospitals designated as pandemic hospitals only process specimens collected on the premises. In the last three months, the mean turnaround time from requesting a specimen to receiving the result was 7.55 hours.

The results of each specimen analyzed in the two laboratories that process SARS-CoV-2 samples were immediately shared with the Provincial Pandemic Operations Center. Based on these results, contact tracing teams were directed (number of teams, etc.). In addition, this data is recorded by the Directorate of Public Health Services, which oversees the Provincial Pandemic Operations Center, and is analyzed daily (e.g., daily new cases, daily test numbers, test positivity rate, case distribution by district/neighborhood/workplace, mortality and case-fatality rates).

As a result, each laboratory test is recorded by the Directorate of Public Health Services, and each patient's previous positive results are also followed. Unfortunately, this monitoring must be performed manually, as there is no application in the contact tracking and reporting systems implemented by the Ministry of Health that presents the previous data of people who have retested positive for SARS-CoV-2.

The Directorate of Public Health Services calls all patients who have a positive test result after an interval of 45 to 89 days to question their symptoms and reason for providing another specimen. Symptomatic patients are referred to a pandemic hospital and examined by an infectious disease specialist. If the physician concludes the patient has clinical reinfection, they arrange treatment. Immunosuppressed patients and those whose symptoms never improved are not considered reinfection.

The following diagnostic criteria for clinical reinfection were used:

i) After 90 days or more:

- Real-time polymerase chain reaction (RT-PCR) positive for SARS-Cov-2 (Ct < 35),

- Recurrence of symptoms consistent with COVID-19 after complete resolution of all symptoms of the first infection,

- High-risk contact or being in a region with an increase in cases,

- Absence of any other etiology to explain the clinical presentation.

ii) Within 45 to 89 days:

- All criteria mentioned above as well as two negative RT-PCR test results between infections (6).

The algorithms of the contact tracing software used were created according to the guidelines of the Ministry of Health. Therefore, the contact tracing process is automatically initiated for patients with another positive test result after more than 90 days but not for those with another positive test result after 45 to 89 days. Creating a new contact tracing process for reinfected patients is performed manually. Then, a contact screening is performed, and isolation and quarantine protocols are implemented.

Data collection

We conducted a retrospective chart review of the list of COVID-19 reinfection cases maintained by the provincial health directorate. The time between infections (days), whether the patient was hospitalized, symptoms experienced at the time of both positive tests, presence of risky contact, occupation, lung imaging results (if available), RT-PCR Ct values, and laboratory findings including C-reactive protein, D-dimer, ferritin, hemoglobin, white blood cell, neutrophil, and lymphocyte counts, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, creatinine, and albumin values were recorded. Because anti-SARS-CoV-2 antibodies are not analyzed in healthcare facilities affiliated with the Ministry of Health, antibody results were not available for these patients. After the study data were collected, the patient list was anonymized, and statistical analyses were performed. During the reinfection dates included in this study, and even at the time of writing, influenza had not yet been detected in the province.

RT-PCR

Bio-Speedy COVID-19 RT-qPCR (Bioeksen, Istanbul) kits were used to detect SARS-CoV-2 RNA in the patients' nasopharyngeal and oropharyngeal specimens. RT-PCR was performed in the C1000 Touch CFX96 (Bio-Rad, USA) device.

Statistical analyses

A statistics software package was used for all analyses. Continuous data were presented as mean (standard deviation SD) or median (interquartile range IQR), and categorical variables as frequency (percentage).

Ethics Committee Approval

This study was approved by the Clinical Research Ethical Committee of the Erzurum Regional Training and Research Hospital (Date:01.03.2021, No:2021/05-85). Due to the retrospective nature, informed consent was not obtained.

RESULTS

A total of 65 reinfection cases were included in the study. The rate of reinfection among all cases followed in our center was 0.12%. The mean (SD) age of the patients was 36.3 (14.8) years, and the median (IQR) age were 31 (24.5-47.0) years. Thirty-four patients (52.3%) were male and 29 (44.6%) were health workers. The health workers included 14 nurses, 5 doctors, and 10 support staff (health technician, security guard, secretary). Twenty-five of the health workers were working in designated

Table 1: Descriptive findings of the patients according to time to reinfection

	Reinfected within 45-89 days (n=10)		Reinfected after ≥ 90 days (n=55)	
	First infection	Reinfection	First infection	Reinfection
Age (years), mean (SD)	38.9 (15.8)	-	35.8 (14.7)	-
Sex (male), n (%)	8 (80.0)	-	26 (47.3)	-
Cycle threshold value, median (IQR)	24.5 (19-27.2)	24.5 (22-26.5)	24 (21-28)	28 (25-32)
Health worker, n (%)	6 (60.0)	-	23 (41.8)	-
Risky contact, n (%)	6 (60.0)	10 (100.0)	34 (61.8)	35 (63.6)
Hospital admission, n (%)	4 (40.0)	1 (10.0)	20 (36.4)	7 (12.7)
Length of hospital stay (days), mean (SD)	9.25 (3.1)	6	9.95 (5.8)	9.1 (3.0)
Negative test between infections, n (%)	10 (100.0)	-	42 (76.4)	-
Comorbidity, n (%)	1 (10.0)	-	17 (30.9)	-
Epilepsy	-	-	1 (1.8)	-
Chronic hepatitis B	-	-	1 (1.8)	
Asthma	-	-	6 (10.9)	-
Diabetes mellitus	1 (10.0)	-	4 (7.3)	-
Hypertension	-	-	8 (14.5)	-
Heart failure	-	-	1 (1.8)	-
Chronic kidney disease	-	-	1 (1.8)	-
History of malignancy	-	-	1 (1.8)	-
COPD	-	-	7 (12.7)	-

COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range, SD: Standart deviation

Table 2: Symptoms according to time to reinfection

	Reinfected within 45-89 days (n=10)		Reinfected after ≥90 days (n=55)	
	First infection	Reinfection	First infection	Reinfection
Symptomatic, n (%)	10 (100.0)	10 (100.0)	41 (74.5)	41 (74.5)
Dyspnea, n (%)	4 (40.0)	2 (20.0)	12 (21.8)	12 (21.8)
Fatigue, n (%)	4 (40.0)	5 (50.0)	23 (41.8)	23 (41.8)
Muscle/joint pain, n (%)	6 (60.0)	7 (70.0)	20 (36.4)	24 (43.6)
Sore throat, n (%)	1 (10.0)	4 (40.0)	8 (14.5)	15 (27.3)
Loss of taste, n (%)	1 (10.0)	1 (10.0)	3 (5.5)	1 (1.8)
Loss of smell, n (%)	1 (10.0)	2 (20.0)	3 (5.5)	2 (3.6)
Hearing loss, n (%)	-	-	1 (1.8)	-
Headache, n (%)	4 (40.0)	4 (40.0)	8 (14.5)	14 (25.5)
Diarrhea, n (%)	2 (20.0)	2 (20.0)	5 (9.1)	1 (1.8)
Cough, n (%)	2 (20.0)	2 (20.0)	11 (20.0)	17 (30.9)

Table 3: Imaging and vital signs according to time to reinfection

	Reinfected within 45-89 days (n=10)		Reinfected after ≥90 days (n=55)	
	First infection	Reinfection	First infection	Reinfection
Radiological findings, n (%)				
CT findings not typical/no findings (%)	2/2 (50.0)	4/2 (66.7)	9/19 (32.1)	9/11 (45.0)
Bilateral lung involvement	2 (50.0)	3 (50.0)	4 (14.3)	5 (25.0)
Ground-glass opacities	2 (50.0)	4 (66.7)	7 (25.0)	9 (45.0)
Greater than 50% involvement	-	-	3 (10.7)	1 (5.0)
Vital findings, n (%)				
Hypoxia (saturation < 93%)	1 (10.0)	2 (20.0)	3 (5.5)	5 (9.1)
Tachycardia (pulse > 100/min)	-	-	5 (9.1)	4 (7.3)

CT: Computerized tomography

Table 4: Laboratory findings according to time to reinfection

Laboratory findings, median (IQR)	Reinfected within 45-89 days (n=10)		Reinfected after ≥90 days (n=55)	
	First infection	Reinfection	First infection	Reinfection
CRP (mg/dL)	7.5 (3.5-14.4)	5.0 (2.8-6.9)	4.3 (3-6.2)	5 (5-13.4)
D-dimer (ng/dL)	245 (190-915)	224 (190-394.5)	305 (155-407.5)	297 (190-502)
Ferritin (mg/dL)	54.6 (3-54.6)	97.1 (21.5-106.9)	34.1 (18.2-93)	33.9 (19.8-95.4)
Hemoglobin (g/dL)	15.5 (13.2-15.9)	16.0 (12.8-16.7)	14.6 (13.6-15.5)	14.3 (13.3-15.6)
White blood cell count ($x10^3$/L)	6680 (5540-7285)	6535 (4675-7902)	7170 (5350-9300)	6640 (5630-8340)
Neutrophil count ($x10^3$/L)	3270 (2705-3670)	2765 (1807-4642)	4440 (3120-5360)	4000 (2990-5365)
Lymphocyte count ($x10^3$/L)	2800 (1305-3420)	2090 (1740-2605)	2290 (1700-3160)	2210 (1505-2655)
PLT ($x10^3$/L)	229 (198.5-319.5)	228 (196.5-292.5)	245 (191-295)	247 (215-289)
LDH (U/L)	186 (166.5-213.5)	195 (187.7-231.7)	190.5 (173.5-227.7)	208 (183.5-262.7)
AST (U/L)	26 (19.5-31)	31 (17-44.7)	18 (16-26.5)	23 (17.5-26)
ALT (U/L)	32 (19-39)	36.5 (17.5-50)	20.5 (14-36.7)	23 (15-27)
Creatinine (g/dL)	0.9 (0.7-1.2)	0.9 (0.7-0.9)	0.8 (0.6-0.9)	0.7 (0.6-0.9)
Albumin (mg/dL)	45 (43-51)	47.1 (43.7-49.5)	45 (42-47)	45.5 (42.2-47)

CRP: C-reactive protein; PLT: Platelet count; LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, AST: Alanine aminotransferase, ALT: Alanine aminotransferase

pandemic hospital that only treated COVID-19 patients. Cases of reinfection were most frequent in August and November, when the province reached peak case numbers.

The mean time between infections was 124.9 (SD 39.7) days and the median was 117 (IQR 96-143.5) days. Reinfection occurred after 45 to 89 days in 10 patients (15.4%) and after 90 days or more in the other 55 patients. The shortest time to reinfection was 60 days and the longest time was 272 days. Fifty-two patients (80.0%) had at least one negative test result between infections.

Eighteen (27.7%) of the patients had at least one comorbidity. These included hypertension (n= 8;12.3%), chronic obstructive pulmonary disease (n=7;10.8%), asthma (n=6; 9.2%), diabetes mellitus (n= 5;7.7%), and one patient each with malignancy, epilepsy, chronic kidney failure, heart failure, and chronic hepatitis.

History of contact with an active COVID-19 patient was present in 40 patients (61.5%) before the first infection and 45 (69.2%) before the second infection, and 29 of these patients were health workers. Twenty-four patients (36.9%) were hospitalized during the first infection, 8 (12.3%) during the second infection, and four patients during both infections. Forty-four (67.7%) of the patients had at least one symptom in both infections. The patients' descriptive information and symptoms according to reinfection time are presented in Tables 1 and 2.

The imaging and laboratory findings of the patients according to reinfection time are presented in Tables 3 and 4. Among those reinfected within 45 to 89 days, pulmonary computed tomography (CT) was evaluated in four patients (40%) during the first infection and six (60%) during the second infection. In two of these patients (20%), lung CT findings were consistent with COVID-19 during both infections. Of those who were reinfected after 90 days or more, pulmonary CT was evaluated in 28 patients (50.9%) during the first infection and 20 patients (36.4%) during the second infection. Four (7.3%) of these patients had lung findings consistent with COVID-19 during both infections. Hypoxia was observed during both infections in only two patients (3.1%).

All patients were alive at the time of writing. One health worker developed pulmonary embolism after reinfection and is currently continuing treatment and follow-up.

DISCUSSION

Studies on SARS-CoV-2 continue at a brisk pace as scientists attempt to better understand it. However, the results vary according to the time and setting of the study. Many different durations of viral shedding have been reported. In a meta-analysis published by Cevik et al. in November 2020, the duration of SARS-CoV-2 RNA shedding was a mean of 17 days (maximum 83 days) from the upper respiratory tract and 14.6 days (maximum 59 days) from the lower respiratory tract (7). In a study published early in the pandemic, shedding occurred for a mean of 20 days after symptom onset and the longest detected shedding lasted 37 days (8). The Korean CDC published a study in which it emphasized that test positivity continued for an average of 44.9 days (range, 8-82 days) after symptom onset and 14.3 days (range, 1-37 days) after discharge (9). For this reason, some have claimed that it is most likely that repeated positive test results within 90 days are due to intermittent viral shedding and that this detected virus does not have reproductive capacity (9). Nevertheless, more and more cases of reinfection occurring within this 90-day time frame are being reported in the literature. For example, genomically confirmed reinfection has been described by Prado-Vivar et al. after 64 days, Larson et al. after 51 days, Lee et al. after 25 days, and Tillett et al. after 45 days (10-13).

In the present study, the minimum interval to retest positivity was 60 days and the maximum was 272 days. There were 10 patients evaluated as reinfected within 90 days. The classification and treatment of these patients were carried out by infectious disease and clinical microbiology specialists. While all of the patients in our study had at least two negative test results between infections, the health workers in particular had a large number of negative results (up to 12) from tests obtained both in order to return to work and during routine screenings. Especially considering the viral shedding times reported in the international literature, genomic analyses of the cases presented here would also likely demonstrate reinfection.

Cases of reinfection have also been reported in the current literature at intervals ranging from 93 to 178 days (14-16). In Turkiye, there have been two cases confirmed by genomic analysis, after 112 and 144 days (17, 18). In fact, more than 80% of these cases had an interval longer than 90 days until reinfection.

Turkiye's national guidelines are based on CDC and WHO criteria, and isolation/quarantine procedures cannot be performed in the Ministry of Health applications for people who retest positive within 90 days of a first positivity, even if they have risky contact or meet the diagnostic criteria for reinfection (19). This results in a gap in isolation/quarantine measures. Although the Korean CDC has stated that these individuals are not contagious, further studies are needed to support this information (9).

At this stage, while we are still trying to control the pandemic by preventing transmission, one of the primary goals should be to decide which cases are reinfections and prevent more risky contact through rapid contact tracing. Therefore, as stated in the Methods section, contact tracing and quarantine/isolation were implemented manually for each case evaluated as reinfection by the infectious diseases' specialist.

Criteria sought in order to be considered reinfection were the presence of characteristic symptoms after complete clinical resolution of the first infection, lack of any etiology other than COVID-19 that could explain these symptoms, and having close contact with a COVID-19 patient (6). All patients reinfected within 45 to 89 days were symptomatic and had high-risk contact. In addition, they all had at least two negative test results between the two infection episodes.

While most reinfections have been reported to be milder, cases reported from the United States and Ecuador were more severe and one reinfected patient died (10, 13, 20). Of the patients we followed, eight people required hospital admission and treatment. A 23-year-old male doctor developed pulmonary embolism and is still undergoing treatment and follow-up.

Most studies have reported seroconversion after infection. However, a few studies also documented patients who never exhibited seroconversion. It has been emphasized that in most cases neutralizing antibodies are formed, although observational studies have shown that all anti-SARS-CoV-2 antibodies decrease over time and that antibodies are even not detected in plasma donors during convalescence. Therefore, there are still gaps in our knowledge regarding the production and protection of antibodies (21-26).

Unfortunately, the main limitation of this study is the lack of genome analysis and antibody detection. However, not every province and laboratory in Turkiye is able to perform genome analysis. In fact, none of the laboratories in the province have this capacity.

Our aim in publishing this study is to report that the frequency of reinfection appears to be higher than predicted. Although international and national centers for disease control and prevention, which have an important say in the scientific community, recommend genome analysis for a definitive decision, epidemiological connections and clinical presentation are more valuable in the fight against the pandemic, especially in countries such as Turkiye that have limited capacity to perform these analyses. Therefore, regardless of confirmed or clinical reinfection, it is essential to identify these cases, organize treatment, and implement quarantine and isolation procedures in order to prevent further transmission. Accordingly, the Ministry of Health should also make its software more flexible and simplify the detection of reinfection cases. There is limited information in the literature on the contagiousness of reinfected patients. This issue should be investigated and included in the decision-making processes of governments and public health workers. Furthermore, at a time when virus variants are a major concern and the immune dynamics after previous infection remain unclear, it is predicted that the incidence of reinfection will increase. Countries should be prepared for this situation.

Ethics Committee Approval: This study was approved by the Clinical Research Ethical Committee of the Erzurum Regional Training and Research Hospital (Date:01.03.2021, No:2021/05-85).

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