

ORIGINAL ARTICLE

Re-infection in COVID-19: Do we exaggerate our worries?

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Abstract

Background: Protective long-term immunity following coronavirus disease 2019 (COVID-19) is unclear. The study evaluated the relationship between the vaccination status and risk factors in the re-infection of patients with a diagnosis of COVID-19 who reported to the Public Health Management System in a province in south-eastern Turkey.

Methods: Patients with positive results for the severe acute respiratory syndrome coronavirus 2 by the real-time reverse transcription polymerase chain reaction (RT-PCR) test in respiratory samples were defined as confirmed cases. Reinfection was diagnosed in cases with COVID-19 real-time RT-PCR positivity, with or without COVID-19-like symptoms, in at least 90 days after the first infection/disease.

Results: A total of 58 811 patients with the diagnosis of COVID-19 from March 11, 2020, to August 31, 2021, were included in the study. Re-infection was detected in 421 (0.7%) of all patients. The mean age of the cases was 38.0±16.0 years, and 51% of them were female. Eight (2.0%) of the cases resulted in death due to re-infection. No hospitalization or mortality was observed in fully vaccinated patients. Additionally, none of the mortal cases had completed the vaccination schedule.

Conclusions: We are concerned that the re-infection rates and mortality may increase due to new variant strains. Vaccination is the greatest weapon against progression to critical illness in re-infections, even with existing mutations. Therefore, it is important for those without a full vaccination schedule to be vaccinated, even if they have been previously infected.

KEYWORDS

coronavirus, COVID-19, re-infection, SARS-CoV-2, vaccination

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in December 2019, has infected more than 250 million people and caused more than five

million deaths as of December-2021, with these numbers are increasing day by day.¹ One of the key points in predicting the course of the coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 is how well and for how long the immune response protects the

host from re-infection. It is stated that re-infection may result from inadequate immune response at the first encounter with the virus or from a decrease in neutralizing antibody responses over time.² In addition to variable immune stimulation, the evolution of SARS-CoV-2 may also play a potential role in re-infection. Although it has been stated that the clinical signs and symptoms may be milder in re-infection, there is still no consensus on this issue.³

Protective long-term immunity following COVID-19 is unclear, and the potential mechanisms mediating this condition are not yet fully understood. Understanding the dynamics of re-infection in COVID-19, along with these mechanisms, will play an important role in guiding government and public health policy decisions in the months ahead.⁴ Studies indicate that immunity lasts for at least 5–6 months after infection.^{5,6} The available data suggests that re-infection with SARS-CoV-2 is rare and occurs in less than 1% of people who have previously been diagnosed with SARS-CoV-2.⁷ The literature on re-infection is limited, and this aspect of the pandemic is not scientifically clear. Practically, re-infection can be defined as having recurrent COVID-19-like symptoms with a positive RT-PCR test for at least 90 days following the initial infection, without any hint of another infection.⁸

This study aimed to evaluate the causal determinants of re-infection, associated risk factors, and vaccination status in patients with a diagnosis of COVID-19 who were reported to Public Health Management System throughout the province.

2 | MATERIALS AND METHODS

2.1 | Study design and the population

The study was designed retrospectively. It was carried out in one province (Batman) located in the Southeast Anatolian Region, one of the most under-developed areas of Turkey. The Public Health Management System, in which all patients diagnosed with COVID-19 in Turkey have to be notified, is a web-based application controlled by the Ministry of Health. All the patients with a diagnosis of COVID-19 in Batman recorded electronically by the healthcare workers between 1 March 2020 and 21 August 2021 was included in the study. In the first stage of the study, after evaluating the Public Health Management System data throughout the province, including towns and villages, general data in the province center were obtained. In the second stage, re-infection was detected from all SARS-CoV-2 reverse transcription-polymerase chain

reaction (RT-PCR) positive cases. Reporting of the study conforms to broad EQUATOR guidelines.⁹

2.2 | Case definition

There is still no widely accepted definition of SARS-CoV-2 re-infection. The use of a variety of tests and diagnostic methods around the world also makes the definition difficult. Centers for Disease Control and Prevention (CDC) examined appropriate time periods following initial SARS-CoV-2 infection or illness to investigate re-infection.¹⁰ In this study, the patients positive for the SARS-CoV-2 by the real-time RT-PCR test in respiratory samples were defined as confirmed cases. Reinfection was diagnosed in cases with COVID-19 real-time RT-PCR positivity, with or without COVID-19-like symptoms, at least 90 days after the first infection/disease.

2.3 | Data collection

The demographic features (age, gender, job and presence of comorbidities), vaccination status, clinical and laboratory data were recorded on a standardized case form. The diagnosis was confirmed by the detection of SARS-CoV-2 ribonucleic acid (RNA) with RT-PCR test from nasal or nasopharyngeal swabs. Chest computed tomography (CT) findings were assessed from images retrieved from the Radiology Information System and Picture Archive and Communication System databases. Monthly cumulative rates of cases with re-infection were calculated. In this calculation, the number of re-infected cases at the end of the month was multiplied by 100 000 after dividing by the total number of cases.

2.4 | Statistical data

The data were analysed by using SPSS 26.0 version. Descriptive analysis was conducted using frequencies and proportions for categorical variables and means and standard deviations for continuous variables. The relevance of the variables to the normal distribution was verified by the Kolmogorov-Smirnov tests. The continuous variables were tested by Student's t-test or one-way ANOVA test. The categorical variables were tested by Chi-Square and the McNemar test. The cumulative probability of the mortality and hospitalization in re-infection for each independent variable was analysed with the method of Kaplan and Meier. To calculate the relative risks of hospitalization, hazard ratios (HRs) were obtained using Cox

proportional hazard models. Statistical significance was determined using two-tailed tests, and $p < .05$ was considered statistically significant.

2.5 | Ethics committee approval

Ethics committee approval of the study was granted by the Ethics Committee of Batman Training and Research Hospital with decision number 268, on 23 March 2021. Also, necessary approvals were received from the Turkish Health Ministry and Provincial Health Department in Batman.

3 | RESULTS

3.1 | Descriptive analysis

A total of 58 811 patients with the diagnosis of COVID-19 from 11 March 2020 to 31 August 2021 were included in the study. The mean age among the cases was 42.5 years, and 52.0% ($n = 30,596$) of them were female. The 20.3% ($n = 11,964$, mean age: 54.3 years) of all cases were hospitalized, and 2.7% ($n = 1618$, mean age: 64.8 years) were followed at the intensive care unit. The mortality rate was found to be 1.4% ($n = 855$, mean age: 73.2 years). The demographic and clinical characteristics of all cases are shown in Table 1 and distribution of cases by months are shown in Figure 1.

Re-infection was detected in 421 (0.7%) of all patients. At the end of all investigations, we excluded 13 cases since we could not reach sufficient information, and continued with 408 cases. The median interval between the initial and second infection times was 290.5 ± 105.3 days (min-max: 90–498 days). The rate of re-infection in the COVID-19 patient group was 0.69% (95% CI: 0.0063–0.0076). The mean age of the cases was 38.0 ± 16.0 years, and 51% of them were female. Among all re-infected cases, 72 (17.6%) were healthcare workers (20 nurse, 5 doctor, 47 other). Chronic diseases were detected in 127 (31.1%) cases. Hypertension, diabetes mellitus and coronary artery disease were the most common comorbidities with a rate of 9.1% ($n = 37$), 7.6% ($n = 31$), and 6.9% ($n = 28$), respectively. While the hospitalization rate was 15.9% during the first infection, it was 9.1% for re-infection. The intensive care unit admission rate was higher in re-infection (2.9%, $n = 12$) than the first infection (0.5%, $n = 2$). The clinical and demographic data of the cases and the information of the chronic diseases are presented in Tables 1 and 2, respectively.

Among re-infected cases, 272 (66.7%) were unvaccinated. Of 136 (33.3%) vaccinated cases, 23 (5.6%) were fully vaccinated (vaccinated with three doses of

TABLE 1 Demographic and clinical characteristics of cases

All cases	<i>n</i> (%)	The mean age (year)
<i>Sex</i>		
Women	30596 (52.0)	40.6
Men	28215 (48.0)	42.0
Total	58811 (100.0)	42.5
<i>Hospitalization</i>		
Woman	5897 (49.3)	54.7
Men	6067 (50.7)	53.8
Total	11964 (100)	54.3
<i>Intensive care unit</i>		
Women	728 (45.0)	64.6
Men	890 (55.0)	63.3
Total	1618 (100.0)	63.8
<i>Mortality</i>		
Yes	376 (44.0)	73.5
No	479 (56.0)	71.7
Total	855 (100.0)	73.2
<i>Re-infected cases</i>		
<i>Sex</i>		
Women	208 (51.0)	38.28
Men	200 (49.0)	37.73
<i>Age group</i>		
0–34	210 (51.5)	26.32
35–49	114 (27.9)	40.15
50–64	50 (12.3)	56.34
≥65	34 (8.3)	76.09
<i>Occupation</i>		
Healthcare worker	72 (17.6)	31.72
Others	336 (82.4)	39.37
¹ Presence of chronic disease	127 (31.1)	50.57
<i>Hospitalization</i>		
First infection	65 (15.9)	46.09
Re-infection	37 (9.1)	55.92
<i>Intensive care unit</i>		
First infection	1 (0.2)	65.00
Re-infection	11 (2.7)	68.64
Needed in both episodes	1 (0.2)	86.00
<i>Severity</i>		
First infection	193 (47.3)	38.22
Re-infection	165 (40.4)	38.94
No difference	50 (12.3)	34.12
<i>Frequency of symptoms</i>		
Higher for first infection	25 (6.1)	36.08

(Continues)

TABLE 1 (Continued)

All cases	n (%)	The mean age (year)
Higher for re-infection	38 (9.3)	36.92
No difference	337 (82.6)	38.46
Asymptomatic	8 (2.0)	31.33
Mortality	8 (2.0)	71.00
Total	408 (100)	38.01

¹Details are presented in Table 2.

Sinovac-CoronaVac or two doses of Pfizer/BioNTech or two doses of Sinovac-CoronaVac plus one dose of Pfizer/BioNTech and who were having a minimum period of 14 days following the last vaccination date). No hospitalization or mortality was observed in fully vaccinated patients. Chest CT was performed in 10 patients who were fully vaccinated, and there was no radiological sign in any case. The COVID-19 vaccination status of re-infected cases is presented in Table 3.

Eight cases were fatal (2.0%) although two cases that resulted in death were excluded. These two cases were excluded because they died two and three months after re-infection and the cause of death was not related to re-infection. The mean age of fatal 8 cases was 71.0 years, and 4 (50%) of them were women. There were at least two chronic diseases in each of these eight cases. In addition, none of them had a completed vaccination schedule by

the date of re-infection. Five of them died in August 2021, when the delta variant spread intensively in our country. The data of mortal cases are shown in Table 4.

In the present study, the rate of re-infection was 0.1% ($n = 36$) until 31 January 2021 which can be considered the first period of the pandemic. At the end of the study, the total number of cases doubled, re-infected cases showed an increase 11-fold with 421 cases, and the re-infection rate reached 0.7%. Most of the re-infections coincided with the period when we were under the influence of the delta variant. The increase in our cumulative re-infection rate over time is seen in Figure 1.

3.2 | Analysis of measurement variable

In this study, the statistical comparison between the periods (time between two infections) and variables of gender, age, chronic disease status, CT findings, attack severity, symptom frequency, vaccination status, hospitalization, mortality were evaluated. The scores from the Kolmogorov-Smirnov Test and Skewness & Kurtosis values were measured. Skewness & Kurtosis values for each variable were between -1.5 and $+1.5$; that is, the distribution was normal.¹¹ Therefore, the statistical comparisons between the continuous (time between two infections) and independent variables were evaluated using the student t and one-way ANOVA tests. The time interval

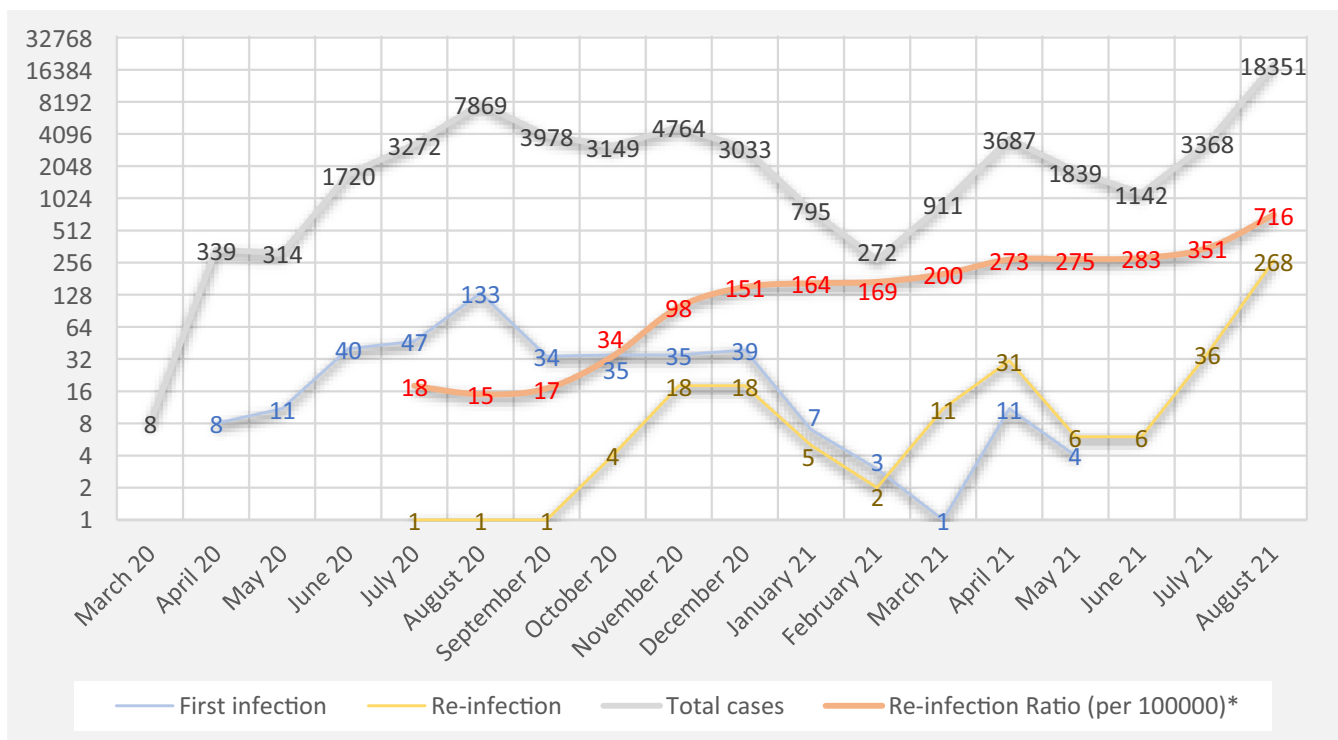


FIGURE 1 Distribution of cases by months. *Monthly cumulative rates of cases with re-infection were calculated. In this calculation, the number of re-infected cases at the end of the month was multiplied by 100,000 after dividing by the total number of cases

TABLE 2 Chronic disease information of the cases

Variable	n (%)
No chronic disease	281 (68.9)
Presence of chronic disease	127 (31.1)
Hypertension	37 (9.1)
Diabetes mellitus	31 (7.6)
Coronary artery disease	28 (6.9)
Asthma and allergic disease	24 (5.9)
Renal disease	9 (2.2)
Hepatic disease	8 (2.0)
Rheumatological disease	8 (2.0)
Neurological disease	7 (1.7)
Malignity	7 (1.7)
Thyroid disease	6 (1.5)
Chronic obstructive pulmonary disease	6 (1.5)
Haematological disease	1 (0.2)

between two infection periods was significantly longer in the patients hospitalized than in those who were not hospitalized in the first infection period. The time interval between two infection periods was significantly lower in the unvaccinated patients and in those who had been vaccinated with a single dose when compared to the other vaccinated patients. Also, it was significantly higher in the fully vaccinated group than the others. The analysis of independent variables is presented in Table 5. The relationship between the time intervals between the two infection periods and the time passed from the last vaccination until re-infection in vaccinated patients ($n = 136$) was evaluated by the Spearman correlation test. A significant correlation was found between the two variables ($p = .024$).

3.3 | Analysis of outcomes

In this study, the hospitalization in re-infection was taken as an outcome. The difference between hospitalizations in the first infection, and re-infection periods was evaluated by the McNemar test. The number of hospitalized patients in the first infection period ($n = 65$) was statistically higher than that in re-infection ($n = 37$) ($p = .002$).

The relationship between the independent variables (gender, age, chronic disease status, CT findings, attack severity, symptom frequency, vaccination status) and outcomes were primarily evaluated with Kaplan Meier survival analysis. The multivariable Cox regression model consisted of four variables with a p -value $< .1$.

In the re-infection period, hospitalization was significantly higher in patients aged 50 years and over ($\chi^2:54.7, p = .001$) and those who had a second attack more severe than

the first attack ($\chi^2:41.5, p = .001$). Patients with one or more chronic diseases were more likely to be hospitalized than those without any chronic disease in the re-infection period ($\chi^2:27.8, p = .001$). Hospitalization rates were found significantly higher in the patients with diabetes mellitus ($\chi^2:8.8, p = .003$), hypertension ($\chi^2:43.5, p = .001$), coronary artery disease ($\chi^2:25.0, p = .001$), renal disease ($\chi^2:14.3, p = .001$), neurological disease ($\chi^2:5.2, p = .022$), malignancy ($\chi^2:4.6, p = .033$) than those without. In the multivariable Cox regression model, hospitalization was more likely 5.4 times (HR: 5.4; 95% CI: 2.2–13.8) in those aged 50 and over, 3.5 times (HR: 3.5; 95% CI: 1.2–10.6) in those having more severe infection in the re-infection period than in the first infection period, and 11.1 times (HR: 11.1; 95% CI: 4.6–26.8) in those with positive CT findings in the re-infection period. The Cox regression analysis is presented in Table 6.

4 | DISCUSSION

In this study, the risk factors associated with the development of re-infection in COVID-19 and the effect of vaccination status on re-infection were investigated.

From the beginning of the pandemic to 31 August 2021 in a province with a population of more than 620,000, the re-infection rate was found to be 0.7%. The re-infection rates are reported quite differently in the literature. In one of the prospective studies¹² in which small groups were followed, re-infection was found at a rate of 0.33% and, in the other,¹³ 3.6%. In one of the observational studies that included a larger number of patients,¹⁴ the rate was 0.08% and in the other,¹⁵ 0.27%. The interval between two attacks was accepted as at least 90 days in both studies similar to the present study. In a meta-analysis, the prevalence of re-infection was found to be 0.3%.¹⁶ The difference in re-infection rates among studies might be explained by many reasons. One of these reasons is that the definition of re-infection has not yet reached a consensus. The re-infection rates may vary among countries according to the vaccination rates, herd immunity rates of the population, and different variants being studied at different times.¹⁶

A study reported from Marseille showed that those infected in the first wave of COVID-19 were less protected from re-infection than those infected in the second wave.¹⁷ In another study, it was suggested that the risk of re-infection increased over time, and the emergence of new variants with the increase in the number of tests and social contagion might be a reason for this.¹⁸ It has been claimed that the risk of re-infection is further increased with Omicron, the most active variant of recent times.¹⁹ In the present study, we found that the cumulative re-infection risk increased over time. While our re-infection rate was 0.1% in the first half of the study, this rate reached

Variable	n (%)
<i>Covid-19 vaccine scheme</i>	
Unvaccinated	272(66.7)
One dose of Sinovac	13 (3.2)
Two doses of Sinovac	39 (9.6)
Two doses of Sinovac, one dose of Pfizer/BioNTech	12 (2.9)
One dose of Pfizer/BioNTech	46 (11.3)
Two doses of Pfizer/BioNTech	20 (4.9)
<i>Covid-19 vaccine doses</i>	
Unvaccinated	272 (66.7)
One dose (<14 days)	20 (4.9)
One dose (≥14 days)	50 (12.2)
Two doses (≥14 days)	57 (14.0)
Three doses (≥14 days)	9 (2.2)
Total	400 (100)

TABLE 3 COVID-19 vaccination status of re-infected cases

Case no	Sex	Age	Time (days) ^a	Chronic disease	Vaccination status
Case-1	M	72	91	CAD, AML	None
Case-2	M	77	136	DM, CAD, HT	Single dose SCV
Case-3	F	97	387	CAD, HT, COPD	Single dose SCV
Case-4	F	71	210	DM, HT, CRF	None
Case-5	M	71	352	CVA, DM, HT, CAD	Two doses SCV
Case-6	M	50	350	CVA, lymphoma	Single dose BNT
Case-7	F	64	126	CAD, HT	None
Case-8	F	66	423	DM, HT, CAD	Two doses SCV

TABLE 4 The clinical characteristics and vaccination status mortal cases

Abbreviations: AML, acute myeloid leukaemia; BNT, Pfizer/BioNTech; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CVA, cerebrovascular accident; DM, diabetes mellitus; F, female; HT, hypertension; M, male; SCV, Sinovac-CoronaVac vaccine.

^aDuration between first infection and re-infection.

0.7% at the end of the study. Although we could not perform variant analysis, the majority of our re-infected cases (310/421) coincided with the period (June to August 2021, Turkey) when we were under the influence of the delta variant. The decreased immune response over time and the ability of new variants to evade the immune response seem to be the main reasons for this increase.

In the current study, it was observed that re-infection developed after 290.5 ± 105.3 (min-max: 90–498) days, while in other studies this interval was reported to be between 172–277 days.^{15,20,21} In a meta-analysis that did not specify a time criteria between two attacks, this interval was found to be approximately 64 days.²² In the present study, we found that the interval for re-infection was longer in those who were vaccinated and those who were hospitalized in the first infection period. In addition, the interval was longer in those who stated that their first infection was more severe. According to the findings of the

present study, we believe that antibodies that developed in the patients who had a severe infection in the first attack and whose vaccination schedule was complete protected the patients from re-infection for a longer period of time. In our literature search, we could not find any studies focusing on the interval between initial infection and re-infection.

It has been suggested that the presence of a higher viral load or being infected with a more virulent variant may be important risk factors for a more severe clinical course of re-infections.²³ Despite these theories, it has also been claimed that the immune response that develops after primary infection paves the way for milder re-infections.^{21,24} In a study dealing with re-infected patients in a large population, there was no mortality due to COVID-19 re-infection.²¹ Similar results have been shown in other studies as well.^{12,14,15} On the other hand, in another study pointing to the opposite of this situation, declared that

TABLE 5 The average time between two infections in accordance with the demographic and clinical characteristics of the cases

Independent variables		<i>n</i>	Time period (Mean ± SD)	<i>p</i>
Sex	Men	200	284.7 ± 109.7	.272*
	Women	208	296.2 ± 100.8	
Age	<50 years	324	292.0 ± 104.5	.589*
	50 years and over	84	285.0 ± 108.9	
Chronic disease	No	281	290.2 ± 104.9	.928*
	Yes	127	291.2 ± 106.6	
CT results	No need/no sign	264	290.5 ± 98.2	.134**
	First infection	81	301.1 ± 118.0	
	Re-infection	46	261.4 ± 108.9	
	Both episode	17	318.9 ± 129.1	
Severity	First infection	193	299.7 ± 107.7	.052**
	Re-infection	165	275.3 ± 104.3	
	No difference	50	305.3 ± 93.5	
Frequency of symptoms	Higher for first infection	25	252.7 ± 118.7	.075**
	Higher for re-infection	38	268.5 ± 112.9	
	No difference	337	296.7 ± 102.6	
	Asymptomatic	8	256.0 ± 105.3	
Hospitalization	The first infection (+)	65	332.4 ± 123.1	.001*
	The first infection (−)	343	282.6 ± 99.9	
	Re-infection (+)	37	277.1 ± 124.5	
	Re-infection (−)	371	291.9 ± 103.3	
Mortality	No	400	291.2 ± 104.8	.526*
	Yes	8	259.6 ± 133.2	
Vaccination ¹	Vaccinated	116	331.8 ± 82.9	.001*
	Unvaccinated + vaccinated in 14 days	292	274.2 ± 108.9	
Vaccination ²	Fully vaccinated	23	356.2 ± 74.2	.002*
	Unvaccinated/partially vaccinated	385	286.6 ± 105.7	

Abbreviation: CT, Computed tomography.

¹Vaccinated: At least one dose of BioNTech or sinovac, >14 days.

²Fully vaccinated: Three doses Sinovac-CoronaVac or two doses Pfizer/BioNTech or two doses Sinovac-CoronaVac plus one dose Pfizer/BioNTech, >14 days.

*Student *t*-test.; **One-Way ANOVA test.

re-infections have more severe clinical courses and cause mortality.²⁰ In the present study, the number of patients who died during re-infection were considerably higher than that in the literature.^{12,14,15,21,22} As far as we investigated, the mortality rates of the present study were quite consistent with the results of a meta-analysis focusing on re-infections.²² While a total of 10 (1.8%) deaths were reported in this meta-analysis, we found 8 (2%) deaths in the present study. It was remarkable that none of our patients with a mortal course did not have a completed vaccination schedule and all of them were aged and had at least two chronic diseases. Similarly, in one study, the severity of COVID-19 re-infection was significantly associated with patients' age, comorbidity, and COVID-19 vaccine status.²⁵ In the meta-analysis²² mentioned above,

all patients who died had comorbidities and were elderly, but the vaccination information was not defined. It has been shown that the substantial comorbidities that determine the prognosis in COVID-19 are diabetes mellitus and hypertension.²⁶ The presence of at least one of these two diseases in 87.5% of the cases that resulted in mortality in the present study indicates that diabetes mellitus and hypertension are the most important chronic diseases for mortality in re-infections.

It is a definite fact that healthcare workers are the highest risky group for re-infections. In our literature search, we noticed that the studies addressing this issue are quite limited. In one study,²⁵ it was shown that 37.1% of re-infected cases were healthcare workers. In the present study, we found that 17.6% (72 cases) of re-infected

Variables		Hazard ratio (95% Confidence Interval)	<i>p</i> *
<i>Hospitalization</i> ¹			
<i>Age</i>			
<i>Reference:</i>	a. 50 years and over	5.6 (2.2–13.8)	.001
	b. <50 years		
<i>CT findings</i>			
Reference:	a. Re-infection	11.1 (4.6–26.8)	.001
	b. Others		
<i>Severity</i>			
Reference:	a. More severe re-infection	3.5 (1.2–10.6)	.024
	b. More severe first infection and same in both attack		

TABLE 6 Multivariate Cox regression model showing variables associated with hospitalization

Abbreviation: CT, Computed tomography.

¹Variables included in the multivariate Cox regression analysis: age, attack severity, chronic disease status, CT findings.

*Significant at $p < .05$.

ones were healthcare workers. There was no serious disease in healthcare workers. We attributed this situation to the higher vaccination rate (at least 1 dose: 50% vs 33%; full vaccinated: 16.7% vs 5.6%), younger average age (31.7 years vs 38.8 years) and lower comorbidity rate (20.9% vs 31.1%) of healthcare workers when compared to the general population.

Vaccination has been shown to be beneficial for people who have been previously infected.^{25,27} In one study, it was shown that full vaccination provides additional protection against re-infection in people infected with SARS-CoV-2. In the present study, it was found that the risk of re-infection was 2.34 times higher in the previously infected people who were not vaccinated than those who were fully vaccinated.²⁷ While full vaccination does not completely prevent re-infection, it is beneficial to keep the pandemic under the control by reducing symptomatic, critical, and mortal cases. In the present study, only 5.6% of the cases had been fully vaccinated. None of these cases required hospitalization, no mortality developed, and no radiological findings were detected. Additionally, the mean interval between the first infection and re-infection periods was longer in those who were vaccinated. With this respect, our study supports the limited studies available in the literature so far.

5 | CONCLUSION

There are many unknowns in COVID-19. Among these unknowns, re-infections will remain one of the most mysterious focal points. Although almost two years have passed, the studies focusing on re-infections are limited,

with conflicting results due to the labour-intensive workforce. So much so that many studies at first claimed that re-infections were not possible. Some studies suggested that this positivity was due to prolonged scattering and re-infection would therefore be excluded.^{28,29} Successive new cases and limited series are reported after the Hong Kong case that refuted these studies.³⁰ Although there is a general view that the number of re-infections and mortality rates are low in these limited studies in the literature, we have a concern that re-infection rates and mortality may increase due to the new variant strains and the decreased immune response over time. The cumulative risk of re-infection and the most of mortal cases coincided with the last period in our study confirms this concern. When we evaluate the results of our study, another important claim is that vaccination is the greatest weapon against progression to critical illness in re-infections, even for new variants. Therefore, it is important to vaccinate the individuals without a full vaccination schedule, even if they are infected.

5.1 | Limitations

Since our study included an observational retrospective population, genetic and variant analysis, threshold value, negative RT-PCR test between attacks, and the level of neutralized antibodies were not evaluated in any of our cases. Re-infection is defined by the CDC in case of any positivity after 90 days following the first infection, as validation by genotypic testing consumes time and resources.¹⁰ Although a positive repeated test may be an indicator of a long-term viral shedding in some cases,²⁹ re-infection is the most likely situation in our cases,

considering the minimum 90-day interval between the attacks in our study. Additionally, the repeated tests in our cases were taken due to a new symptom and sign or a close contact history, which strengthens the possibility of re-infection. We believe that our study will contribute to the literature due to a large number of included population and re-infected cases. However, further studies will be vital to understand re-infection dynamics.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest. No external funding was received for this study.

AUTHOR CONTRIBUTIONS

YA, FA and ST designed the study and directed the study design. YA, FA, BS, and ZSV reviewed the literature and evaluated appropriate datasets. YA, ST, BS, and ZSV performed the statistical analysis. YA, ZSV, BS, and ST wrote the draft of the article. All authors contributed to the discussion of results, interpretation, and writing of the article and jointly approved the final article.

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