Journal of Advanced Biomedical Sciences
https://jabs.fums.ac.ir/
Online ISSN: 2783-1523
Journal of Advanced Biomedical Sciences
Fasa University of Medical Sciences

Risk Factors of Coronavirus Disease 2019 Reinfection: Findings of a Hospital-Based Case-Control Study from Southwest of Iran

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Article Info

Article Type:
Case Control Study

Article history:
Received
08 Jul 2025
Received in revised form
23 Sep 2025
Accepted
24 Sep 2025
Published online
10 Oct 2025

Publisher
Fasa University of Medical Sciences

Abstract

Background & Objectives: Following the global pandemic, Coronavirus Disease 2019 (COVID-19) has remained endemic in many regions of the world; therefore, examining the various factors influencing reinfection can help establish a stronger evidence base for effective prevention and control. Accordingly, this study aimed to identify predictors of COVID-19 reinfection and the associated risk factors.

Materials & Methods: A hospital-based case-control study was conducted with 147 patients in southern Iran. Information on the case group was collected, and a control group was selected. Structured interviews were conducted to obtain relevant data, which were documented in a checklist. The data were then analyzed using chi-square tests and logistic regression.

Results: The study included 74 (50.3%) men, with a mean age of 36.45 years. The control group reported a higher frequency of mask use and daily fruit consumption compared to the case group. In the univariate analysis, mask use, underlying diseases, and fruit consumption were significantly associated with reinfection. However, in the multivariate analysis, only the association with underlying diseases remained statistically significant ($p = 0.031$, $OR = 3.445$).

Conclusion: The findings indicate that underlying diseases substantially increase the risk of COVID-19 reinfection and should therefore be prioritized in prevention strategies.

Keywords: Risk factors, Case Control, Uunderlying Diseases, COVID-19 reinfection

Cite this article: Bagheri P, Mousavi SeyedJalali MS, Montasei Z. Risk Factors of Coronavirus Disease 2019 Reinfection: Findings of a Hospital-Based Case-Control Study from Southwest of Iran . J Adv Biomed Sci. 2025; 15(4): 396-403.
DOI: 10.18502/jabs.v15i4.19735

Introduction

On March 11, 2020, the World Health Organization declared Coronavirus disease 2019 (COVID-19) as a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). According to global statistics, as of January 2022, more than 299 million individuals worldwide had been infected with COVID-19, resulting in over 5 million deaths. Iran has also been severely affected, reporting more than 6 million confirmed cases and 131,000 deaths (2).

One of the major challenges associated with COVID-19 is reinfection. After recovery, the acquired immunity may be neither sufficiently strong nor long-lasting (3), thereby increasing the likelihood of reinfection. A study reported that individuals often experienced more severe symptoms during a second infection, typically occurring approximately three months after the

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initial episode, as confirmed by positive real-time polymerase chain reaction (RT-PCR) results along with IgM and IgG antibodies (4). Another study documented a positive RT-PCR test seven months after the first infection (5). Similarly, in Hong Kong, reinfection was observed four and a half months following initial recovery (6). Additional cases of reinfection have been reported in Pakistan (7) and Bangladesh (8).

Reinfection has also been investigated in Iran. One Iranian study reported that healthcare workers, younger individuals, urban residents, and patients with underlying conditions were at higher risk of reinfection. Among those with comorbidities, kidney and lung diseases, as well as malignancies, were particularly influential (9). Another longitudinal study in Iran estimated the risk of reinfection to be 2.5 per 1,000, with the average time to reinfection occurring 135 days after the initial infection. The immune profile of individuals was found to play a decisive role in this phenomenon (10).

Despite the global development and deployment of vaccines, real-world vaccination coverage has been insufficient to fully control recurrent outbreaks, and cases of reinfection continue to be reported. Factors such as age and prior infection have been shown to influence vaccine effectiveness and susceptibility to reinfection (11).

Reinfection has critical clinical and public health implications, as repeated episodes contribute to cumulative morbidity and impose an additional burden on healthcare systems. Understanding the determinants of reinfection is therefore essential for anticipating disease burden, optimizing clinical management, and informing vaccination strategies. By quantifying the impact of reinfection, this study seeks to generate evidence to support both clinical decision-making and public health policy. Consequently, to minimize the risk of reinfection, it is crucial to identify the factors contributing to it, which in turn can help establish a robust consensus of evidence to guide prevention efforts. Hence, this study aims to identify predictors of COVID-19 reinfection in order to prevent recurrence, reduce complications, alleviate the strain on healthcare resources, and promote economic stability.

Materials and Methods

This case-control study was conducted among patients treated at hospitals affiliated with Fasa University of Medical Sciences in southern Iran between 2021 and 2022. The study included both urban and rural residents who sought care at these hospitals. The study population comprised patients who had previously tested positive for COVID-19 and experienced reinfection within the specified timeframe. A case was defined as an individual who contracted COVID-19 for a second time during the study period and tested positive by RT-PCR. The control group comprised individuals with a single prior episode of SARS-CoV-2 infection who had not experienced reinfection at the time of the study.

To verify the absence of reinfection, PCR test results for controls were checked in the COVID-19 data collection center. Additionally, participants for whom contact details were available were telephoned to confirm that they had not experienced symptoms consistent with COVID-19 after their initial infection. Only individuals meeting these criteria were included as controls.

Cases and controls were selected taking into account factors such as proximity to treatment facilities, geographic location within the city, and the local course of the COVID-19 epidemic and related quarantines. Efforts were made to ensure that cases and controls represented the citywide patient population. Additionally, participants were required to be alive during the study period. For each case, a risk-set control, defined as an individual previously infected who had not yet experienced reinfection at the index date, was selected. This selection followed the risk-set technique, which considers the

[DOI: 10.18502/jabs.v15i4.19735]

population at risk of reinfection. Participants were sampled using simple random sampling from a complete registry.

The sample size was calculated based on a previous study by Jeffery-Smith et al. (12). That study reported 23 reinfections among 656 previously infected patients. Assuming a 95% confidence level and a 5% margin of error, a minimum of 52 participants per group (104 total) were required. To ensure adequate statistical power, a total of 147 individuals were ultimately enrolled. The university health department's data center assisted in subject selection, and the investigator conducted telephone interviews to collect study data.

The study examined variables including age, sex, body mass index, individual and household occupation, travel history, mask use and public transportation usage, COVID-19 vaccination (number of doses and vaccine type), interval since the last vaccine dose, presence of underlying conditions (cardiovascular disease, diabetes, cancer, hypertension) and prior hospitalizations, physical activity level, and dietary habits (daily fruit and vegetable intake and types of meat consumed per week). The relevant checklist is available as a supplementary file.

Normally distributed quantitative variables were summarized using mean and standard deviation; non-normally distributed variables were reported as median and interquartile range. Categorical variables were reported as frequencies and percentages. Univariate analysis of categorical variables used the chi-square test. Variables with $P \leq 0.20$ in univariate analyses were entered into a multivariate logistic regression model to assess independent associations. Analyses were performed using SPSS version 22, with statistical significance set at $\alpha = 0.05$.

Results

A total of 147 participants were enrolled: 71 cases and 76 controls. Of the participants, 74 (50.3%) were male and 73 (49.7%) were female (P = 0.807). The most common age group was 25–35 years (P = 0.662). Regarding occupational distribution and family status, the most prevalent occupation in both groups was employment in public-facing workplaces (P = 0.136). Travel history analysis revealed that 83.1% of cases reported travel history, compared with 77.6% of controls (P = 0.405). With respect to mask use, individuals in the control group reported a higher rate of consistent mask wearing (Table 1).

Also, analysis of vehicle usage data revealed no statistically significant difference in the frequency of public transportation use between the two study groups (P>0.05). Furthermore, there were no statistically significant differences in the frequency of prescribed vaccine doses and types of vaccines administered between

Table 1. Distribution of mask usage in case and control groups

Group / Use pattern		Case	Control	Total	P-value
Never	Frequency	12	5	17	0.007
	%	16.9%	6.6%	11.6%	
Sometimes	Frequency	12	3	15	
	%	16.9%	9.3%	10.2%	
Often	Frequency	6	11	17	
	%	8.5%	14.5%	11.6%	
Always	Frequency	41	57	98	
	%	57.7%	75%	66.7%	
Total	Frequency	71	76	147	
	%	100%	100%	100%	

[DOI: 10.18502/jabs.v15i4.19735]

the two groups (P>0.05). The time elapsed since the last vaccine dose also did not show a statistically significant difference between the two study groups (P>0.05). However, there was a significant difference in the presence of underlying diseases, with individuals with underlying conditions exhibiting a 3.12 times higher chance of re-infection (Table 2).

Further analyses of hospital admission during the initial illness, body mass index, physical activity level, fruit and vegetable intake, and weekly consumption of white and red meat indicated that the only significant difference observed between the two groups was in terms of fruit consumption patterns (Figure 1). Specifically, the case group had a significantly higher frequency of not consuming fruit (19.7% versus 7.9%) and consuming only one unit of fruit per day (62% versus 57.9%) compared to the control group (P=0.029). Subsequently, eligible variables were included in the multivariate regression model (Table 3). At this stage, it was found that, except for underlying diseases (P=0.03, OR=3.44), none of the variables had a significant relationship with reinfection.

Discussion

The results of this study suggest a significant independent association between various variables and reinfection with COVID-19. However, only the presence of underlying diseases demonstrated a statistically significant relationship with COVID-19 reinfection.

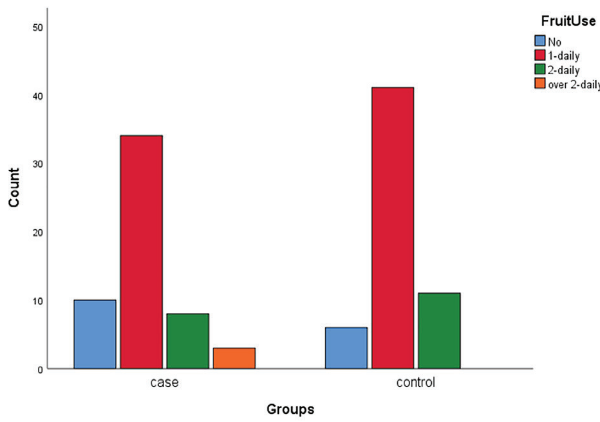

Figure 1. Distribution of fruit use in case and control groups

Table 2. Distribution of underlying diseases in case and control groups

Group / Use pattern		Case	Control	Total	OR (CI95%)	P-value
YES	Frequency	21	9	30	3.12 (1.32-4.7)	0.008
	%	29.6%	11.8%	20.4%		
NO	Frequency	50	67	117		
	%	70.4%	88.2%	79.6%		
Total	Frequency	71	76	147		
	%	100%	100%	100%		

Table 3. Logistic Regression Results for Predictors of COVID-19 Re-infection

Variables	B	S.E.	Wald	df	Sig.	EXP(B)	95% C.I. for EXP(B)	
							Lower	Upper
underlying disease	1.237	.574	4.641	1	0.031	3.445	1.118	10.612
job	-	-	6.193	3	0.103	-	-	-
Freq of mask use	-	-	6.666	3	0.083	-	-	-
Physical activity	-	-	4.384	3	0.223	-	-	-
Fruit consumption	-	-	7.106	3	0.069	-	-	-
Consumption of vegetables	-	-	5.849	3	0.119	-	-	-
Constant	-2.094	1.157	3.278	1	0.070	-	-	-

[DOI: 10.18502/jabs.v15i4.19735]

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Some variables that initially seemed significant in the univariate analysis did not maintain significance in the multivariate analysis, a finding consistent with previous research (13). This may be due to methodological constraints, such as a small sample size, or to differences in the roles these variables play during primary infection compared with reinfection. The immune response and prognosis of COVID-19 patients can vary based on demographic characteristics, lifestyle, and immune profiles. Additionally, there is a lack of research on factors influencing reinfection compared to the extensive focus on initial infection.

Although there are limited studies on reinfection factors, some of their findings align with the results of this study, particularly regarding the relationship between underlying diseases and the absence of a correlation between nutritional habits and reinfection. In our univariate models, higher fruit intake appeared protective against SARS-CoV-2 reinfection, but this association attenuated to non-significance after multivariable adjustment. This pattern is consistent with classical confounding mechanisms and precision issues in observational epidemiology. Individuals who consume more fruit often differ systematically in other reinfection determinants—e.g., age, comorbidity burden, vaccination status/recency, socioeconomic position, occupation/exposure risk, and other health behaviors (physical activity, mask use)—so crude associations can partly reflect these correlated factors rather than a direct effect of fruit intake itself. Adjusting for such variables can appropriately reduce or eliminate the apparent effect if the crude association was confounded (14, 15).

Several other studies also report that higher overall diet quality and greater intake of fruits and vegetables are associated with lower risk of infection or severe COVID-19, although these studies focus on first infections and often use composite diet scores rather than single foods. For example, a comprehensive study observed lower COVID-19 risk and severity with healthier plant-based dietary patterns in UK/US cohorts after multivariable adjustment, and other recent studies have similarly concluded that better diet quality is linked to lower infection risk (16-18).

In terms of the impact of various underlying diseases on COVID-19 reinfection, our results indicate that patients with chronic illnesses are more than three times as likely to experience reinfection with COVID-19. This finding aligns with a study by Krishna et al. (19), which also found an increased risk of reinfection. The higher risk in patients with underlying diseases may be due to frequent interactions with healthcare providers and facilities, as well as factors like immunosuppression and weakened immune responses to SARS-CoV-2 (20).

In the current study, outpatient treatment was primarily provided to patients with milder disease complications to ensure that hospital beds were available for critically ill patients. Although our study reported significant associations between mask usage and underlying diseases with reinfection, other studies have produced divergent results. For example, in one study, mask users reported a higher incidence of infection, likely attributable to confounding factors such as greater exposure or heightened risk perception among mask wearers.

Researchers in this study reported that participants who wore face masks "often or sometimes" had a 33% higher incidence of self-reported COVID-19 (adjusted relative risk, aRR 1.33; 95% CI: 1.03–1.72) compared with those who "never or almost never" wore masks. Those who reported wearing masks "almost always or always" had a 40% higher incidence (aRR 1.40; 95% CI: 1.08–1.82). This finding illustrates the potential for inconsistencies in observational studies of mask effectiveness (21). In another study, an ecological investigation conducted across 24 European countries during 2020–2021 found a positive association between national

[DOI: 10.18502/jabs.v15i4.19735]

mask usage rates and age-adjusted excess mortality. In bivariate analyses, mask use correlated with excess mortality (Spearman's ρ = 0.477, p = 0.018), and this relationship persisted in multivariate models (standardized coefficient = 0.52, p = 0.0012). Notably, no significant correlation was observed between mask use and COVID-19 morbidity as measured by case counts. The authors emphasized that the results highlight how aggregate associations between public health interventions and outcomes may diverge from individual-level findings, thereby underscoring the need for careful methodological consideration when drawing inferences about causality from population-level correlations (22).

Similarly, the DANMASK-19 randomized trial in community settings did not demonstrate a statistically significant reduction in SARS-CoV-2 infection among individuals assigned to mask use compared with controls during a period of modest community masking and limited source control (23).

With respect to underlying diseases, a multicenter retrospective study from Saudi Arabia by Shaheen and colleagues defined reinfection as RT-PCR positivity ≥90 days after clinical recovery from the first COVID-19 episode. They observed that the presence of any underlying disease had an odds ratio of 1.121 (95% CI: 0.726–1.730; p = 0.606), indicating no statistically significant association between underlying diseases and reinfection risk (24). Likewise, the Shanghai cohort of 3,001 individuals reported no significant difference in reinfection rates according to underlying disease status (12.3% vs. 12.7%). This discrepancy may relate to contextual factors such as uniformly high exposure in dense urban settings, immune escape of viral variants, or sampling limitations (25).

However, it is important to note the limitations of the present study. The most significant operational challenge was the process of collecting data from both case and control groups. It is likely that not all data were recorded consistently across groups. Additionally, the study was constrained by a relatively small sample size due to technical challenges and non-participation by some eligible subjects. Therefore, it is recommended that future studies recruit larger sample sizes to achieve greater precision and statistical power, enabling a more comprehensive examination of the determinants of reinfection. To mitigate these issues, multiple sources were pursued to obtain data, and the study objectives were explained to participants in order to maximize cooperation. It is also essential to ensure that patient questionnaires are evaluated rigorously and responses recorded objectively.

Finally, the criterion for diagnosing reinfection in this study was based solely on the RT-PCR test, which may misclassify cases of prolonged viral shedding. This limitation, though unavoidable due to time constraints, could have introduced bias in group classification. Future studies should therefore employ more robust approaches, such as genomic sequencing, to enhance diagnostic accuracy and reliability. Among the key strengths of this study is its pioneering nature as one of the first local investigations in this region, coupled with the comprehensive inclusion of demographic and lifestyle factors.

Conclusion

It appears that the presence of underlying diseases in patients is the most significant factor influencing COVID-19 reinfection compared with other variables such as demographic characteristics, lifestyle, and diet. This finding underscores the importance of careful consideration by patients, policymakers, and healthcare providers in treatment planning and prioritizing patients with comorbidities in booster vaccination and follow-up programs. At the same time, the result highlights the urgent need to incorporate comorbidities into both clinical management and broader public health strategies.

[DOI: 10.18502/jabs.v15i4.19735]

From a policy perspective, prioritizing individuals with chronic conditions for preventive measures such as vaccination, booster campaigns, and targeted health education may help reduce the burden of recurrent infections. In addition, health systems should strengthen surveillance and early intervention protocols for high-risk populations, ensuring timely access to testing, treatment, and follow-up care. At a broader level, these findings emphasize the necessity of integrating chronic disease management into pandemic preparedness and response frameworks. By recognizing underlying diseases as key determinants of vulnerability, health authorities can design more equitable and effective policies that protect the most at-risk groups, mitigate the impact of COVID-19 reinfections, and ultimately improve population health outcomes. Further research is warranted to achieve a more comprehensive consensus in this area.

Acknowledgment

This article is based on the doctoral thesis of a medical student, completed with the support of the Research and Technology Vice-Chancellor of Fasa University of Medical Sciences (code 400250). We would like to express our gratitude to the vice-chancellors of both the Research and Technology and Health departments, as well as to Hazrat-Waliasr Hospital, for providing essential data for this research. We also extend our appreciation to the study participants.

Conflict of Interests

The authors declare that they have no competing interests.

Funding

This study did not receive any financial support.

Code of Ethics

Fasa University of Medical Sciences (Code 400250).

Ethical Considrations

The study protocol was reviewed and approved by the Ethics Committee of Fasa University of Medical Sciences (Approval No. IR.FUMS.REC.1401.155). All methods were carried out in accordance with relevant guidelines and regulations. The selected hospital was a teaching hospital, and at the time of patient selection, informed consent was obtained from all participants. Every effort was made to ensure that patients' personal information was kept confidential and used exclusively for research purposes. Participation was entirely voluntary, and there was no coercion to take part in the study.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to the absence of participant consent for data release but are available from the corresponding author on reasonable request.

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[DOI: 10.18502/jabs.v15i4.19735]