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Reply to Letter to the Editor: "COVID-19 Infection, Vaccination, and Severe Coronary Artery Disease: Comment"

LETTER TO THE EDITOR
REPLY

The authors[1] are thanked for their interest in the article.[2] As stated, the data in this study were collected retrospectively by examining the records of individuals who presented to the hospital, and therefore, the study has certain limitations. As is well known, behavioral factors such as body mass index, smoking status, physical activity, and nutrition, as well as medical conditions like hyperlipidemia and diabetes mellitus, play a role in the development of coronary artery disease (CAD).[3] However, due to the retrospective nature of this study, behavioral factors were not documented in the records of all patients and due to access restrictions to the health records of patients with limitations on their e-Nabız data, it was not possible to obtain information on comorbid chronic conditions. The absence of these data would have resulted in the exclusion of a large number of patients from the study. Therefore, behavioral factors, comorbidities, and family history could not be included as independent variables in the analysis. Consequently, advanced analyses involving these potential influencing factors on CAD development could not be provided in the article.

A logistic regression analysis evaluating age, sex, history of COVID-19 infection, and vaccination status based on the time elapsed since vaccination is presented in Table 1 of this response letter. This table supports the findings of the main article. Although the *P*-value regarding the relationship between COVID-19 vaccination and the development of CAD was not statistically significant, the odds ratios increased with the time elapsed since vaccination. As mentioned in the letter to the editor, the limited follow-up period in the study may have been insufficient to fully demonstrate this relationship. Moreover, due to the researchers leaving their affiliated institutions, the study could not be planned for a longer period.

The study investigated the status of having had COVID-19 and being vaccinated for COVID-19 in individuals with and without CAD, diagnosed via angiography. Due to its design, the study is not generalizable to the population at large. The authors acknowledge this as a limitation and avoid making overly definitive statements when interpreting the results. In hospital-based studies, not all segments of the population access hospital care, leading to common biases such as hospital access bias and Berkson's bias. Thus, observed relationships in the study may be over- or underestimated.[4] It should also be considered that there may be cases who had clinical COVID-19 disease but either did not undergo PCR testing or tested negative. In such cases, even if CAD developed, the absence or inaccuracy of test results may underrepresent the relationship between COVID-19 and CAD.

To mitigate biases inherent in this hospital-based retrospective study, cohort-type research designs would be more appropriate. However, limitations such as a small number of researchers and lack of funding prevented the use of a cohort design in this study. For future research, cohort studies, which provide higher evidence levels, are recommended.

Although the authors reported the time elapsed since vaccination in their findings, limitations such as the inability to access vaccination records of deceased

Esma Çetinkaya[1]
Ayşe Taş[2]

[1]*Department of Cardiology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy*
[2]*Department of Public Health, Faculty of Medicine, Adıyaman University, Adıyaman, Türkiye*

Corresponding author:
Esma Çetinkaya
✉ es_ma_arslan@hotmail.com

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Table 1. Logistic Regression Analysis

	0-3 Months		0-12 Months		0-36 Months	
	OR	*P*	OR	*P*	OR	*P*
Sex	1.12 (076-1.64)	.571	1.26 (0.91-1.76)	.168	1.17 (0.89-1.53)	.261
Age	0.98 (0.96-0.99)	.024	0.98 (0.97-0.99)	.034	0.98 (0.97-0.99)	.013
COVID-19 disease*	1.10 (0-78-1.55)	.585	1.00 (0.74-1.35)	.992	1.04 (0.81-1.33)	.777
COVID-19 vaccine**	0.58 (0.31-1.08)	.084	0.66 (0.36-1.23)	.191	0.73 (0.39-1.34)	.302

*COVID-19 disease: Not having had the disease was taken as the reference.
**COVID-19 vaccination: Not being vaccinated was taken as the reference.

individuals in the Ministry of Health system, the unknown interval between vaccination and death, and the lack of information on the cause of death may have led to an underestimation of the association between vaccination and CAD development. These are among the limitations mentioned in the study. Due to its retrospective design, the severity and duration of COVID-19 illness, complications during the disease course, and hospitalization status are unknown. Therefore, the study could only temporally examine the relationship between COVID-19 infection and CAD development based on the time elapsed after infection.

With this research, the authors aimed to investigate the relationship between COVID-19 infection, COVID-19 vaccination, and the development of CAD. However, it is well known that among observational study types in the evidence pyramid, cohort studies are the least prone to bias.[5] Therefore, while the authors aimed to investigate this relationship in a broad population in Türkiye, the evidence level of the study remains lower than that of cohort studies due to its design and inherent biases. Cohort studies are recommended for future research.

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