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Reply to Letter to the Editor: "Addressing Selection Bias and Risk Factors in COVID-19 and CAD Research: Critical Considerations"

LETTER TO THE EDITOR
REPLY

To the Editor,

In our study, we defined severe coronary artery disease (CAD) based on real-world clinical decisions. Specifically, we considered whether a patient underwent percutaneous coronary intervention (PCI) or was referred for coronary artery bypass graft surgery. Among 1935 patients who underwent angiography, 1598 had PCI for clinically important lesions, and 339 were referred for surgery. We grouped both as severe CAD. We chose this approach because, particularly during the pandemic, only those with clearly significant coronary lesions were moved forward for intervention.[1] During the COVID-19 pandemic, hospitals across the world prioritized urgent cardiac cases and delayed elective or less severe procedures.[2,3] We agree that the pandemic changed the characteristics of patients who came in for cardiovascular procedures. Globally, elective procedures were delayed, and only more serious or urgent cases were addressed. For example, during the 2020 lockdown in England, PCI for stable angina dropped by around 66%, while emergency procedures continued.[3] This shift allowed hospitals to focus only on patients with more critical needs. Professional guidelines at the time recommended deferring non-urgent procedures.[2] In our study, patients who received angiography mostly had more severe symptoms that couldn't wait. Our data also reflect these trends: early in the pandemic, angiography numbers dropped, then increased later (2021-2022), with a larger share of severe CAD cases. This likely reflects delayed care and prioritization of serious patients, a trend also observed internationally.

As a result, only patients with serious conditions underwent angiography or intervention. Because of this shift in practice, our definition of severe CAD matches the clinical reality at the time. Using revascularization as an indicator of disease severity helped us focus on outcomes that matter most to both patients and healthcare teams.

We were unable to access vaccination records for patients who had passed away. This was due to a limitation of the national AŞILA vaccination database, which does not allow vaccination status retrieval for deceased individuals. As a result, we could only evaluate vaccine data for those who were still living. While we regret this limitation, it was beyond our control. It only affected vaccine-related analyses; infection status data from HSYS was available for all patients. We excluded these 306 deceased cases (about 16% of the total) from vaccine analysis to prevent misclassification. We clearly reported this in our article.[1] This exclusion does not represent systematic bias, as it was based solely on missing data. The conclusion—that the number of vaccine doses did not relate to increased CAD severity—remains valid and consistent across the large portion of patients with complete records.

We understand the concern about not adjusting for all cardiovascular risk factors. Our study used data from hospital records (KARMED) and national databases (HSYS and AŞILA), which didn't include all details like smoking, hypertension, or

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diabetes for every patient. However, we reported basic demographic information: for example, severe and non-severe CAD patients had similar sex distributions (around 72% male) and close median ages (64 vs. 66).[1] This suggests both groups were comparable. Though including risk factors would have strengthened the analysis, the lack of a significant relationship between COVID/vaccine status and CAD severity makes this limitation less impactful. Future studies should collect and include these variables more fully.

In summary, we stand by our methods and results. Our use of real-world clinical decisions to define disease severity was appropriate in a pandemic setting, where only the most urgent patients underwent interventions. We clearly acknowledged the data gaps, especially related to vaccination records for deceased individuals. Despite these limits, the consistency of our results across the majority of patients with full data supports the conclusions. We hope these clarifications help address the concerns raised, and thank the Editor and letter authors[4] for this important discussion.

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