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COVID-19 Vaccination in Liver Transplant Recipients in View of Evidence-Based Policymaking

Dear Editors:

We read with great interest the study by John et al.[1] The authors conducted a retrospective cohort analysis using a large database of veterans in the United States to capture liver transplant (LT) recipients, and found that full COVID-19 mRNA vaccine (2 doses) was associated with a lower incidence of COVID-19 infection, symptomatic COVID-19, and COVID-19–related death in LT recipients.

This is a well conducted study for which the authors should be congratulated. The study is especially valuable in the context of the lack of clinical trials in this population. Any intervention that shows a positive impact on LT recipients is informative and welcome. However, because one of the most vigorously debated topics in this arena is the appropriateness of mandating vaccination against COVID-19 for transplant recipients/candidates,[2,3] caution should be exercised when interpreting the associations identified in observational studies as support for or against mandating vaccinations.

The authors used a large national transplant cohort with nearly 2000 recipients from the Veterans Outcomes and Costs Associated with Liver Disease (VOCAL) study. Well designed inverse probability treatment weighting (IPTW) methods were applied to adjust for the imbalance between those who were and were not vaccinated. However, as the authors themselves pointed out, this type of weighting can only consider variables recorded in the database. Significant residual confounding likely remains, including those unmeasured factors related to psychosocial characteristics. Although many variables, particularly those related to social determinants of health and other psychosocial characteristics, may not have been captured in the administrative data, it was unclear why geographic factors and additional comorbidities such as diabetes mellitus, etiology of original liver disease such as alcoholic and nonalcoholic fatty liver disease, and viral hepatitis were not included. Many, if not most, of those variables were likely available in the VOCAL cohort. If the space allowed, the distribution of the propensity scores would also have been of interest because multiple variables' values were distributed unevenly between vaccine-exposed and -unexposed patients. One good example that addressed those viewpoints is the study by Ioannou et al.[4] that estimated the real-world effectiveness of the COVID-19 vaccine among persons receiving care in the VA health care system overall; in that observational study, they used a sophisticated "target trial" approach for identifying and controlling for biases, and confounding emulated several key features of a randomized trial.

Furthermore, acknowledging that this was a brief research letter with limited space, important details related to the statistical methods were lacking, especially as they relate to the following 3 points. (1) How they handled outcomes: The authors reported 3 different analyses: time to positive PCR test, time to symptomatic disease, and time to COVID-19–related death. However, whether and how they considered each as competing risks was not apparent. (2) How vaccination status was defined: The authors set different "time zeros" for the fully vaccinated and control subjects. An alternative would be to designate time zero as when vaccines first become available for both groups and treat vaccination status as a time-dependent covariate, which also might allow certain patients (eg, the partially vaccinated) to be incorporated in the analysis more effectively. And (3) how the IPTW and Cox proportional hazard regression were modeled: It was unclear whether the authors applied Cox proportional hazard regression to the pseudo-population generated through IPTW, adjusting for variables that were believed to be associated with outcomes, including race (which, interestingly, was not used for IPTW). Alternatively, they might have attempted a doubly robust procedure[5,6]; however, the robustness of that procedure would likely be limited owing to significant unobserved confounding.

Finally, as noted by authors, in addition to confounding, the possibility of selection bias cannot be ignored in observational studies. To address potential concerns about residual confounding and biases, a sensitivity analysis would be one way to evaluate the robustness of their estimates.[7,8]

Vaccination against COVID-19 is an urgent public health topic that needs prompt data analysis to benefit society. This also applies to liver transplant candidates and recipients. Amid pressures to institute policies mandating vaccinations even before being waitlisted, it is crucial to estimate the robust causal effect of the vaccinations to inform evidence-based policies; we should recognize that such a mandate could unnecessarily and unreasonably prevent patients with end-stage liver disease from receiving life-saving liver transplants.

In summary, vaccination against COVID-19 may significantly reduce COVID-19 incidence, disease severity, and mortality in liver transplant recipients. However, if robust causal inference is not well established, results should be interpreted with caution before implementing vaccine mandate policies in this population.

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Conflicts of interest
The authors disclose no conflicts.

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Reply. We thank Drs Tanaka and Vander Weg for their interest in our research exploring COVID-19 vaccination in liver transplant recipients.[1] They discuss several excellent points and clarifications on the methodology, and we appreciate the opportunity to respond.

We chose not to adjust for the etiology of the liver disease that led to transplantation. The most common indication for liver transplantation in the VA during the study period were alcohol and chronic hepatitis C–related cirrhosis, both of which are uncommon causes of significant liver disease after transplantation.[2,3] Therefore, we thought that unlike studies of participants with cirrhosis, the condition that led to cirrhosis was not a potential confounder in a study of transplant recipients.[4] The variables we chose to adjust for in our multivariable analysis included those that were used in early studies published on the topic.[5,6] However, we agree that diabetes mellitus, race/ethnicity, and geographic location within the US are important risk factors for COVID-19.[7] We therefore repeated our analysis by controlling for the suggested variables, including location within the US (northeast, southeast, midwest, south, northwest, and southwest), race/ethnicity, and diabetes mellitus, in estimating the propensity scores. We also controlled for diabetes mellitus and race in the Cox hazard model. Our revised analysis shows that the observed associations are similar to those from the original analysis, with full COVID-19 vaccination being associated with a significant reduction in COVID-19 (adjusted hazard ratio [aHR] 0.33, 95% confidence interval [CI] 0.23–0.49; $P < 0.0001$), symptomatic COVID-19 (aHR 0.32, 95% CI 0.19°0.55; $P < 0.0001$), and COVID-19 related death (aHR 0.11, 95% CI 0.03–0.37; $P = 0.0001$).

Regarding outcomes, we reported the time to a positive PCR test, time to symptomatic COVID-19, and the time to COVID-19–related death. By definition, participants with a positive SARS-CoV-2 PCR test (defined as COVID-19) are either symptomatic or asymptomatic, and COVID-19–related death occurs only after being infected with COVID-19. Therefore, we do not consider these as competing events.

We did set different "time zeros" for the fully vaccinated and control subjects to match for the time of exposure to COVID-19. We agree that an alternative would be to designate time zero as when vaccines first become available for both groups and treat vaccination status as a time-dependent covariate. However, the number of partially vaccinated participants in our study sample was low, and evaluating the effect of partial vaccination was outside the aims of the study.

We confirm that we applied Cox proportional hazard regression to the pseudo-population generated through IPTW, as adjusted for variables that were thought to be associated with outcomes. As Tanaka and Vander Weg pointed out, we did not attempt a doubly robust procedure owing to the possibility of significant unobserved confounding.

We agree on the importance of addressing confounding and selection bias in observational studies. Propensity score weighting and matching are widely accepted to account for observed characteristics in observational studies.[8,9] In our study, we tried to control for observed covariates that might confound the relation between COVID-19 vaccination and outcomes. Sensitivity analysis is a great tool to evaluate the size of confounding and bias of some potential confounders that were not observed, and we performed an analysis to estimate the E-value as suggested.

Our results estimated the aHR of COVID-19 infection at 0.36 (95% CI 0.26–0.51). The E-value for this was 5.0, with the upper confidence limit of 3.33, meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association at least as large as 5.0 with both COVID-19 infection and vaccination. Similarly, the E-values and the upper confidence limits were large: respectively, 4.19 and 2.45 for symptomatic COVID-19 and 14.87 and 4.85 for COVID-19–related death. Compared with the observed risk factors (ranges from 0.93 to 1.29), the unmeasured confounding would need to have a much stronger effect to explain away the reported vaccination association.

We think that the observed variables we used cover most potential confounders. Although, factors such as psychosocial factors, political beliefs, and vaccine hesitancy related to these beliefs may represent unmeasured confounding, it is unlikely that these confounders would significantly change the associations observed, based on the calculated E-values.