RE: Poor response to inactivated SARS-CoV-2 vaccine in patients with chronic liver disease

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TITLE PAGE

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Conflicts of interest
The authors have declared no conflict of interest related to the study.
To the Editors,

We would like to thank Cao and colleagues for their constructive comments\(^1\) on our recent publication\(^2\). We would like to provide some clarifications and explanations on their comments.

First, Cao et al. highlight the time interval from the second dose of SARS-CoV-2 vaccine to serum collection may affect antibody titers. We agree that it is important to accurately assess the time interval between completed vaccination and serum collection, as antibody titers decline over time.\(^3\) We limited this time interval within 14 to 90 days when conducting the multicenter study, but the data regarding the time interval were partially missing in our study because some patients were unable to determine their exact vaccination date. However, among patients who have these data available, we further analyzed the time interval from the second dose of vaccination to serum collection. The overall time interval from the second dose to serum collection was 29.0 (range, 19.0-39.0) days, and there was no significant difference between subgroups (\(P = 0.78\)). We will continue our follow up of patients and hope to provide more valuable information for this question in the future. At the same time, we are initiating another study that will examine the effect of the third homologous booster vaccination using inactivated vaccines (ClinicalTrials.gov ID: NCT05204602) to answer the questions regarding dynamic changes of antibodies after vaccination in CLD patients and the efficacy and safety of booster vaccination in this special population.

Second, our study showed that the absolute titer of neutralizing antibodies in the decompensated cirrhosis group was slightly higher than that in the healthy control group, but there was no statistical difference. However, we were limited by relatively small sample size of the decompensated cirrhosis subgroup. More importantly, the proportion of neutralizing antibody positive (defined as absolute titer value >10 AU/mL) in patients with decompensated cirrhosis was significantly lower than that in healthy controls (76.7% vs. 90.3%, \(P < 0.05\)).
Thirdly, our study enrolled a subset of CLD patients with autoimmune liver disease (ALD) but excluded patients receiving systemic immunosuppressive therapy, to reduce the effect of immunosuppressive drugs on final antibody outcomes.\textsuperscript{3,4} When comparing immunogenic outcomes, we adjusted for different etiologies. In the future, we will continue to expand the large-scale ALD cohort, especially ALD patients under immunosuppressive treatment for further analysis.

Finally, our study concluded that inactivated vaccines were safe for CLD patients. In our study, only three patients had grade 3 abnormal liver function after vaccination, and they had different degrees of elevated transaminases before vaccination, and one patient with later hospitalization had a history of discontinuing anti-hepatitis B virus agents before SARS-CoV-2 vaccination. The long-term follow-up of these patients showed that they had no persistent deterioration of liver function. Due to the limited number of patients with abnormal liver function post vaccination in our study, we think the topic of whether patients with abnormal transaminases need to postpone SARS-CoV-2 vaccination should be more cautiously evaluated using larger real-world cohorts.

Importantly, recent studies have confirmed that pre-existing liver diseases are associated with disease progression, intensive care, and high mortality in patients with COVID-19.\textsuperscript{5-7} Our studies seem to be the first to evaluate the safety and immunogenicity of inactivated whole-virion SARS-CoV-2 vaccines in patients with CLD.\textsuperscript{2,8} Nonetheless, due to that the population of CLD patients mainly had chronic hepatitis B in our study, further large-scale studies are warranted to validate our findings in populations with other etiologies of liver disease.
References: