Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

data or a fixed treatment duration imposed by a health care policy. Because the long-term safety of the current first-line Nuc agents is well established,[8] severe clinical adverse events and deaths from elective cessation of such therapy generally should be avoided whenever possible.

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Conflicts of interest
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Most current article

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Poor Response to Inactivated SARS-CoV-2 Vaccine in Patients With Chronic Liver Disease

Dear Editor:

We read with great interest the article by Jingwen Ai et al[1] recently published in *Clinical Gastroenterology and Hepatology*, showing that patients with chronic liver diseases (CLD) had lower immunologic response to SARS-CoV-2 vaccines than healthy populations. This multicenter study is the first to evaluate the safety and immunogenicity of SARS-CoV-2 vaccine in the real-world population with CLD, and its results were important and timely for guiding clinical practice during the current COVID-19 pandemic. More importantly, this study supported that patients with CLD, especially cirrhosis, are those we should pay much more attention to following vaccination. However, some aspects need further discussion.

First, the range of the time interval from the second dose to serum collection was not reported. A recent study proved that the SARS-CoV-2 IgG seropositivity declined over time since vaccination for Sinovac's inactivated CoronaVac vaccine recipients. The IgG positivity reached a peak of 77.4% during Week 3 and decreased to 47.3% during Week 16 after the second dose.[2] Therefore, we suggested that the authors should analyze the correlation between blood collection time points with antibody titer. The results will be very important to understand the decline pattern of antibody titers after SARS-CoV-2 vaccine, and valuable for determining the time of the third vaccination dose for patients with CLD.

Second, patients with cirrhosis are considered immunocompromised and usually have poor response to vaccination, which has been demonstrated in several studies regarding vaccines of influenza, hepatitis A, and hepatitis B.[3-5] The underlying mechanism is that cirrhosis impairs the T-cell activation and synthesis of innate immunity proteins and pattern recognition receptor.[6,7] However, the current study showed that the neutralizing antibody concentration was 20.5 (10.4–36.4) AU/mL in the decompensated cirrhotic group, which was higher than those in the healthy control subject group 18.8 (13.4–27.7) AU/mL. It will be interesting and informative to know the reasons for these unexpected differences.

Third, the authors also included participants with autoimmune diseases, such as autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, in the study. The immune response after vaccination among patients with CLD with autoimmune diseases may be different from those without autoimmune diseases. Previous study had demonstrated that the level of neutralizing antibodies in patients with systemic autoimmune rheumatic disorders was lower than

that in the healthy control subjects and not related to ongoing treatments.[8] Therefore, we suggested that the patients with autoimmune disease should be analyzed separately.

Finally, a total of 3 participants reported grade 3 alanine aminotransferase elevation and 1 of them was hospitalized. We noticed that these 3 patients had elevated alanine aminotransferase level before vaccination. So, whether patients with abnormal alanine aminotransferase should postpone the COVID-19 vaccination needs further investigation.

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Reply. We would like to thank Cao et al[1] for their constructive comments on our recent publication.[2] We would like to provide some clarifications and explanations on their comments.

First, Cao et al[1] 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, because antibody titers decline over time.[3] We limited this time interval within 14–90 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 ($P = .78$). 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 patients with chronic liver disease (CLD) 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 control subjects (76.7% vs 90.3%; $P < .05$).

Third, our study enrolled a subset of patients with CLD with autoimmune liver disease but excluded patients receiving systemic immunosuppressive therapy, to reduce the effect of immunosuppressive drugs on final antibody outcomes.[3,4] When comparing immunogenic outcomes, we adjusted for different etiologies. In the future, we will continue to expand the large-scale autoimmune liver disease cohort, especially patients with autoimmune liver disease under immunosuppressive treatment for further analysis.

Finally, our study concluded that inactivated vaccines were safe for patients with CLD. In our study, only 3 patients had grade 3 abnormal liver function after vaccination, and they had different degrees of elevated transaminases before vaccination, and 1 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. Because of the limited number of patients with abnormal liver function postvaccination 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.[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.[2,8] Nonetheless, because of that the population of patients with CLD mainly had chronic hepatitis B in our