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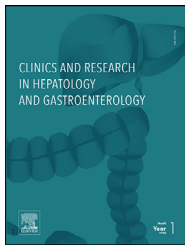

LETTER TO THE EDITOR

Long-term antibody response to inactivated SARS-CoV-2 vaccination in patients with chronic liver disease: A multicenter study

KEYWORDS
Chronic liver disease;
SARS-CoV-2;
Vaccine;
Antibody response

Summary Patients with chronic liver disease (CLD) are at a greater risk of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. This study investigated the antibody response to inactivated SARS-CoV-2 vaccination in a long-term prospective cohort of CLD patients. The seropositivity rates and antibody concentrations of anti-SARS-CoV-2 NAbs were similar among patients with different severity of CLD 6 months after the third vaccination. In addition, older CLD patients appeared to have lower antibody responses. These data might be helpful to inform vaccine decisions for patients with chronic liver disease.

Introduction

Patients with chronic liver disease (CLD) are at a greater risk of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection, resulting in an increased risk of morbidity and mortality following infection [1,2]. SARS-CoV-2 vaccination is the mainstay of effective ways to protect individuals from SARS-CoV-2 infection and decrease the overall mortality rate [3]. CLD patients have multiple mechanisms of immune dysfunction which might lead to a lower short-term antibody response to the SARS-CoV-2 vaccine [3], and antibody levels gradually decrease over time after receipt of SARS-CoV-2 vaccines [4]. However, the long-term antibody response induced by the inactivated SARS-CoV-2 vaccine in CLD patients has not yet been investigated, and the understanding of the sustainability of SARS-CoV-2 vaccines in CLD patients is urgently needed. In the current work, we aimed to investigate the antibody response to inactivated SARS-CoV-2 vaccination in a long-term prospective cohort of CLD patients.

Abbreviation: CLD, chronic liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Non-ACLD, nonadvanced CLD; CACLD, compensated advanced CLD; DACLD, decompensated advanced CLD; NAb, neutralizing antibody; S/CO, signal-to-cutoff ratio; IQR, interquartile range.

Materials and methods

In this prospective multicenter study, patients with chronic liver disease and healthy controls were enrolled from Shandong Provincial Hospital, Heze Municipal Hospital, and Qilu Hospital of Shandong University. Demographic and clinical data were collected from the electronic medical record. All participants received the initial two doses of inactivated SARS-CoV-2 vaccines (CoronaVac or BBIBP-CorV) between June 2021 to September 2021. The third dose of inactivated SARS-CoV-2 vaccine was administered 196 days (interquartile range [IQR], 188—211 days) after the second dose. Participants who were pregnant, less than 18 years old, with malignant tumors or other major diseases, with previous COVID-19 infection, and with a history of receiving systemic immunosuppressants or systemic immunoglobulins were excluded. The participants were monitored for SARS-CoV-2 infection by polymerase chain reaction. According to Fibrosis-4 score and previous history or current history of hepatic decompensation, patients with different severity of CLD were divided into three groups: nonadvanced CLD (non-ACLD), compensated advanced CLD (CACLD), or decompensated advanced CLD (DACLD) [5]. Serum SARS-CoV-2 neutralizing antibody (NAb) and anti-spike IgG antibody were measured at 6 months (±30 days) after the third dose of vaccination using chemiluminescence immunoassay (Maccura

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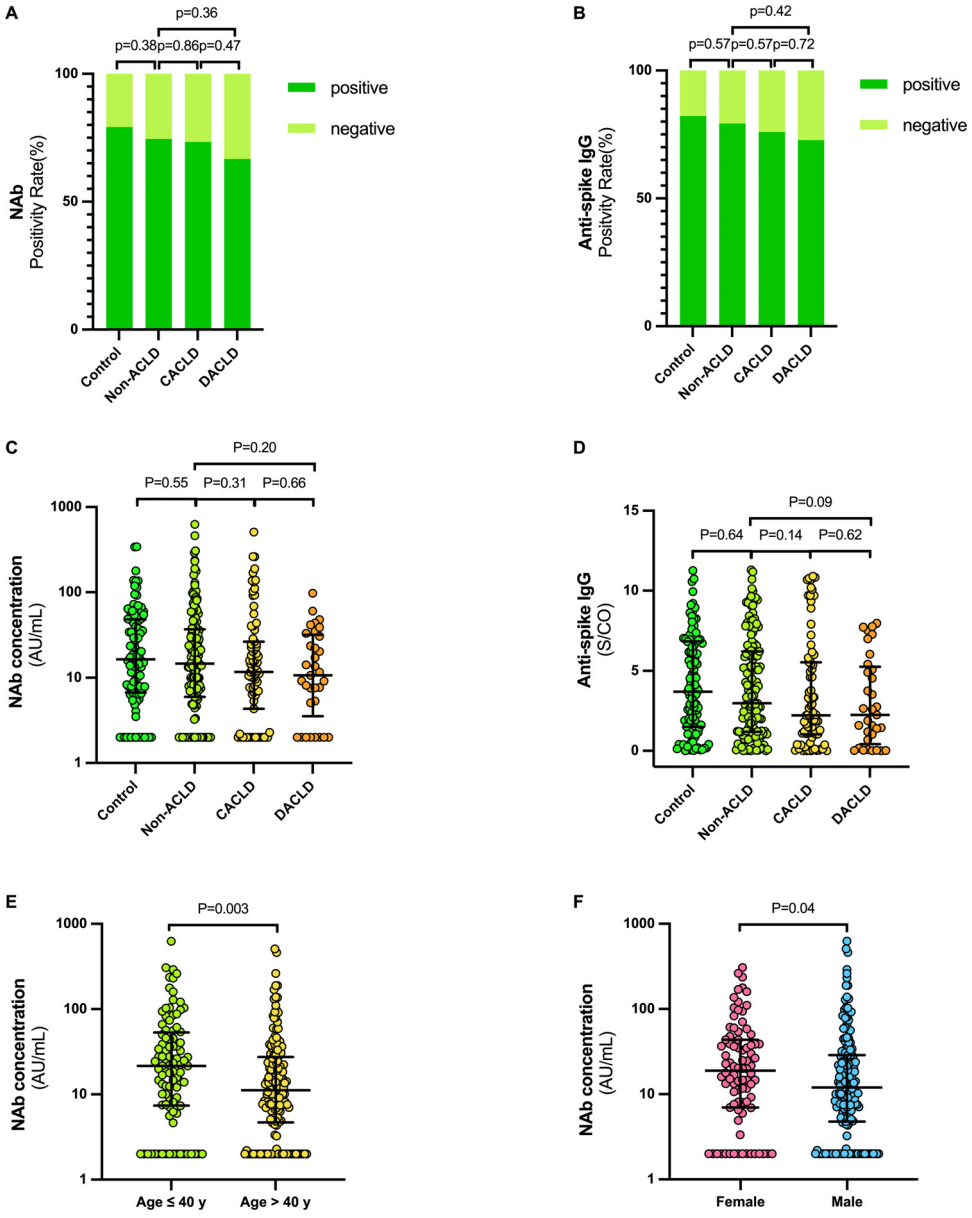

Fig. 1 Long-term antibody response to the inactivated SARS-CoV-2 vaccine. (**A, B**) Seropositive rates of NAb and anti-spike IgG among patients with different severity of CLD and healthy controls. (**C, D**) NAb concentrations and anti-spike IgG levels among patients with different severity of CLD and healthy controls. (**E, F**) Subgroup analyses of NAb concentrations in CLD patients. Circles indicate individual antibody responses. NAb concentrations above 6.00 AU/mL and anti-spike IgG levels above 1.00 S/CO ratio were considered positive.
CACLD, compensated advanced CLD; CLD, chronic liver disease; DACLD, decompensated advanced CLD; NAb, neutralizing antibody; Non-ACLD, nonadvanced CLD.

Biotechnology Co., Ltd., China). NAb concentrations above 6.00 AU/mL and anti-spike IgG levels above 1.00 S/CO were considered positive. The study was approved by the ethics committees of the participating centers and all patients provided written informed consent before the study procedures.

Results

Between June 2021 to September 2021, four hundred and twenty-one participants were recruited. During the follow-up period, 46 individuals were lost to follow-up and 8 individuals died (3 died of hepatic failure, 2 died of cardiovascular causes, 1 died of variceal bleeding, 1 died of peritonitis, and 1 died of multisystem organ failure). No participant tested positive for SARS-CoV-2 infection by polymerase chain reaction during the follow-up period. The remaining 261 CLD patients and 106 healthy controls were included in this study (**Supplementary Table 1**). In CLD patients, 149 (57.1%) had non-ACLD, 79 (30.3%) had CACLD and 33 (12.6%) had DACLD. These CLD patients included 175 men (67.0%) and 86 women (33.0%). The most common etiology of CLD was hepatitis B virus infection (67.8%), followed by non-alcoholic fatty liver disease (16.9%). The time from

the second SARS-CoV-2 vaccination to blood collection was 384.0 days (IQR, 369.5−392.0 days). The time from the third SARS-CoV-2 vaccination to blood collection was comparable among patients with different severity of CLD and healthy controls (p = 0.731).

The seropositive rates of NAb were 79.2% (84 of 106) in healthy control group, 74.5% (111 of 149) in non-ACLD group, 73.4% (58 of 79) in CACLD group, and 66.7% (22 of 33) in DACLD group, respectively, with no significant difference (p = 0.50) (Fig. 1A). The seropositive rates of anti-spike IgG were 82.1% (87 of 106) in healthy control group, 79.2% (118 of 149) in non-ACLD group, 75.9% (60 of 79) in CACLD group, and 72.7% (24 of 33) in DACLD group, respectively, also with no significant difference (p = 0.61) (Fig. 1B). After adjusting for age and BMI, the differences remained non-significant (both $p > 0.05$).

The NAb concentrations were 16.44 AU/mL (IQR, 6.72−48.04 AU/mL) in healthy control group, 14.69 AU/mL (IQR, 5.98−36.97 AU/mL) in non-ACLD group, 11.74 AU/mL (IQR, 4.32−26.51 AU/mL) in CACLD group, and 10.68 AU/mL (IQR, 3.54−31.93 AU/mL) in DACLD group, respectively (Fig. 1C). The anti-spike IgG levels were 3.70 S/CO (IQR, 1.50−6.84) in healthy control group, 2.99 S/CO (IQR, 1.19−6.22) in non-ACLD group, 2.22 S/CO (IQR, 1.03−5.53) in CACLD group, and 2.24 S/CO (IQR, 0.43−5.26) in DACLD group, respectively (Fig. 1D). Neither the NAb concentrations nor the anti-spike IgG levels were significantly different among the four groups (p = 0.25 and p = 0.11, respectively).

In subgroup analyses, older CLD patients (age > 40 years) appeared to have a lower level of NAb concentration as compared to younger patients (11.17 AU/mL [IQR, 4.70−27.47 AU/mL] vs. 21.54 AU/mL [IQR, 7.39−53.14 AU/mL], p = 0.003) (Fig. 1E). Male CLD patients showed a lower level of NAb concentration than female patients (11.96 AU/mL [4.77−28.71 AU/mL] vs. 18.85 AU/mL [IQR, 6.97−43.50 AU/mL], p = 0.04) (Fig. 1F).

Univariate and multivariate logistic regression analyses were performed to select risk factors associated with NAb negativity in CLD patients. After taking the time from the third vaccination to measurement into consideration, age (OR, 1.03; 95% CI, 1.00−1.05; p = 0.025) was identified as an independent risk factor for NAb negativity, while the severity of CLD was not a risk factor (**Supplementary Table 2**). Similar results were also observed for anti-spike IgG negativity in CLD patients (**Supplementary Table 3**).

Discussion

This is the first study assessing the long-term antibody response in CLD patients after three doses of inactivated SARS-CoV-2 vaccination. We found that there was no notable difference in antibody response 6 months after the completion of inactivated SARS-CoV-2 vaccination among patients with different severity of CLD and healthy controls. Yet, a previous study has demonstrated that CLD patients had lower antibody response to SARS-CoV-2 vaccination than healthy controls shortly after the second vaccine dose [3]. A similar phenomenon was observed in multiple sclerosis patients treated with cladribine tablets [6]. The possible explanation might be that the third vaccine dose may overcome the negative effect of immune dysfunction in CLD patients [7,8].

This study has several limitations. First, the sample size in our study may not be large enough. Larger cohort of CLD patients with different etiologies need to be further observed. Second, we had no access to data on antibodies for each month, so the dynamic changes in antibodies could not be monitored. Third, we had no data on the vaccine efficacy for preventing laboratory-confirmed COVID-19 in CLD patients. We will continue to investigate the SARS-CoV-2 vaccine efficacy in these patients.

In conclusion, long-term antibody response to inactivated SARS-CoV-2 vaccination was similar among patients with different severity of CLD and healthy controls. These data might be helpful to inform vaccine decisions for patients with chronic liver disease, especially for patients with hepatitis B.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2023.102150.

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