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Clinical Gastroenterology and Hepatology 2022;20:1516–1524

HEPATOLOGY

Safety and Immunogenicity of SARS-CoV-2 Vaccines in Patients With Chronic Liver Diseases (CHESS-NMCID 2101): A Multicenter Study

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BACKGROUND & AIMS: We aimed to assess the safety and immunogenicity of inactivated whole-virion severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in patients with chronic liver diseases (CLD) in this study.

METHODS: This was a prospective, multi-center, open-label study. Participants aged over 18 years with confirmed CLD and healthy volunteers were enrolled. All participants received 2 doses of

[a]Authors share co-first authorship. [b]Authors share co-senior authorship.

Abbreviations used in this paper: ACE2, angiotensin converting enzyme; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; COVID-19, coronavirus disease 2019; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2021.12.022

inactivated whole-virion SARS-CoV-2 vaccines. Adverse reactions were recorded within 14 days after any dose of SARS-CoV-2 vaccine, laboratory testing results were collected after the second dose, and serum samples of enrolled subjects were collected and tested for SARS-CoV-2 neutralizing antibodies at least 14 days after the second dose.

RESULTS: **A total of 581 participants (437 patients with CLD and 144 healthy volunteers) were enrolled from 15 sites in China. Most adverse reactions were mild and transient, and injection site pain (n = 36; 8.2%) was the most frequently reported adverse event. Three participants had grade 3 aminopherase elevation (defined as alanine aminopherase >5 upper limits of normal) after the second dose of inactivated whole-virion SARS-CoV-2 vaccination, and only 1 of them was judged as severe adverse event potentially related to SARS-CoV-2 vaccination. The positive rates of SARS-CoV-2 neutralizing antibodies were 76.8% in the noncirrhotic CLD group, 78.9% in the compensated cirrhotic group, 76.7% in the decompensated cirrhotic group ($P = .894$ among CLD subgroups), and 90.3% in healthy controls ($P = .008$ vs CLD group).**

CONCLUSION: **Inactivated whole-virion SARS-CoV-2 vaccines are safe in patients with CLD. Patients with CLD had lower immunologic response to SARS-CoV-2 vaccines than healthy population. The immunogenicity is similarly low in noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis.**

Keywords: Chronic Liver Diseases; Cirrhosis; Immunogenicity; Safety; SARS-CoV-2 Vaccines.

The ongoing coronavirus disease 2019 (COVID-19) pandemic, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to high morbidity and mortality worldwide.[1] Although physical distancing, quarantine, and isolation were effective in limiting the number of people becoming infected during the pandemic in the short term, the absence of herd immunity in the population has left them susceptible to further waves of SARS-CoV-2 infection.[2] Chronic liver disease (CLD) is of high prevalence and brings significant medical and economic burden. Global prevalence of nonalcoholic fatty liver disease (NAFLD) is estimated at 24%, whereas globally 75 million people are at risk of alcohol-associated liver disease, and 325 million people are estimated to live with viral hepatitis.[3-5] There were 6.11 million incident cases of CLD that included liver cancer and cirrhosis globally, estimated from the 2017 Global Burden of Disease study.[6] Patients with cirrhosis, especially with decompensated cirrhosis, are reported to have an increased risk of SARS-CoV-2 infection and worse outcomes.[7-9]

Vaccination is crucial for the restraining of the epidemic and lowering the overall mortality rate, and it has been proven to provide protection from SARS-CoV-2 infection and aggravation of COVID-19.[2] Various SARS-CoV-2 vaccines have been proven to induce neutralizing antibody responses and have good safety profiles in healthy adults.[10-14] However, there is not sufficient evidence about safety and immunogenicity of SARS-CoV-2 vaccines in patients with CLD. Previously, researchers have reported decreased immunogenicity of SARS-CoV-2 vaccines in patients under immunocompromised status, including kidney dialysis, using immunosuppression drugs, and organ transplantation including liver transplantation.[15-17] Our previous study has demonstrated good safety and immunogenicity of COVID-19 vaccination in patients with NAFLD.[18] Another study showed satisfactory safety but relatively lower immunogenicity in liver transplant recipients and patients with CLD; however, this single-center study had a relatively small sample size, and the results were also not compared with that of healthy controls.[19] Currently, the immunogenicity and safety data in patients with CLD are still urgently needed. This prospective, multi-center study includes patients with pre-existing CLD and assesses the safety and immunogenicity of SARS-CoV-2 vaccines in this special population.

Methods

Study Design

In this prospective, multi-center, open-label study, adult participants with pre-existing CLD and healthy volunteers were enrolled from the network of Portal Hypertension Alliance and China-National Medical Center for Infectious Diseases in China. The inclusion criteria of the CLD group included participants over 18 years old, being clinically or pathologically diagnosed with pre-existing CLD, understanding and willing to comply with the study procedures, and providing written informed consent. CLD was defined as diseases of the liver that last over 6 months, including chronic inflammation (hepatitis B, hepatitis C, NAFLD, alcoholic liver disease [ALD], autoimmune hepatitis [AIH], primary biliary cholangitis, and primary sclerosing cholangitis) with or without liver cirrhosis. The healthy control group included participants with normal serological liver function parameters and without history of any liver disease. The exclusion criteria of both groups were pregnancy, lactation, active

or known history of SARS-CoV-2 infection, known history of hepatocellular carcinoma or liver transplant, immunosuppressive or immunodeficient state including confirmed HIV infection, and history of receiving systemic immunosuppressants, systemic immunoglobulins, or immunopotentiators within 3 months prior to the day of screening.

All participants received 2 doses of inactivated whole-virion SARS-CoV-2 vaccines (600SU per dose for CoronaVac, 6.5U per dose for BBIBP-CorV and 200WU per dose for WIBP-CorV). The time interval between the first and second SARS-CoV-2 vaccine doses was 3 to 8 weeks, according to the guidance of SARS-CoV-2 vaccinations made by the National Health Commission of the People's Republic of China.[20] Basic characteristics (age, sex, body mass index), etiology of liver diseases, presence or absence of cirrhosis and compensation status, comorbidities (diabetes, hypertension, coronary artery disease, arrhythmia, and asthma), and laboratory testing results were obtained from patients' medical records. Side effects of SARS-CoV-2 vaccines were collected from paper record cards where participants were required to record the injection-site symptoms and systemic symptoms. Serum samples of enrolled subjects were taken at least 14 days after the second dose and tested for SARS-CoV-2 neutralizing antibody. Participants were divided into 3 subgroups based on their cirrhosis and compensation status, where decompensated cirrhosis was defined as cirrhosis with at least 1 episode of ascites, jaundice, hepatic encephalopathy, or variceal bleeding, or with a Child-Pugh of B or C. Abnormality in liver function was defined as any of the following parameter increased over upper limit of normal range including alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, and direct bilirubin.

Written informed consents were obtained before the enrollment. The study protocol and informed consent form were approved by the involved Ethics Committees. This study is registered at ClinicalTrials.gov, NCT04883177.

What You Need to Know

Background

Previous studies have assessed safety and immunogenicity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in the population with chronic liver diseases (CLD), but they had relatively small sample sizes, and the results were not compared with that of healthy controls.

Findings

Inactivated whole-virion SARS-CoV-2 vaccines are safe in patients with CLD. Patients with noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis all have lower immunologic response to SARS-CoV-2 vaccines than healthy population.

Implications for patient care

The data in this study supported current recommendations for people with CLD to get SARS-CoV-2 vaccination. In the future, patients with CLD might need strengthening strategies, such as a boosting dose of SARS-CoV-2 vaccination, to get better response.

Antibody Testing

A competitive binding chemiluminescence immunoassays (CLIA) SARS-CoV-2 neutralizing antibody assay (Shenzhen Mindray Bio-Medical Electronics Co, Ltd, China) was used to quantitatively detect neutralizing antibodies to SARS-CoV-2 according to the manufacturer's instructions.

In the first step, sample, sample treatment solution, and paramagnetic microparticles coated with SARS-CoV-2 antigens are added into a reaction cuvette. After incubation, SARS-CoV-2 neutralizing antibodies present in the sample will bind antigens coated on microparticles. In the second step, angiotensin converting enzyme (ACE2)-alkaline phosphatase (ALP) conjugate is added into the reaction cuvette. After incubation, the ACE2-ALP conjugate competes with the neutralizing antibody in the sample for binding sites of SARS-CoV-2 antigens. Neutralizing antibody or ACE2-ALP conjugate are bound to antigen on the microparticles, which are magnetically captured while other unbound substances are removed by washing. Then, the substrate solution is added to the reaction cuvette. It is catalyzed by ACE2-ALP conjugate in the immunocomplex retained on the microparticles. The result of chemiluminescent reaction is measured as relative light units by a photomultiplier built inside the system. The amount of neutralizing antibody present in the sample is inversely proportional to the relative light units generated during the reaction. The neutralizing antibody concentration is determined via a calibration curve, which is established on an encoded Master Calibration Curve and 3 level product calibrators.

The measuring range are 2.0 to 400.0 AU/mL, and results over 10 AU/mL was considered as evidence of immune response and below 2.0 U/mL as undetectable, according to the instruction book. We defined results over 10.0 AU/mL as positive, and results below 10.0 AU/mL as negative.

Statistical Analysis

Data is displayed as median (interquartile range [IQR]) for the continuous variables and as number of patients and percentage in each group for categorical variables. The Mann-Whitney U test was used for continuous variables, and the Pearson χ^2 test or Fisher exact test was used for categorical variables to assess the statistical significance between groups. We fitted binary logistic regression

models for univariate and multivariate analysis of factors related to the serological responses. When comparing immunogenic outcomes, we adjusted for factors that were substantially different between patients with CLD and healthy subjects, or among CLD subgroups, using logistic regression or analysis of covariance. Hypothesis testing was 2-sided, and *P* values of less than 0.05 were considered to be significant. IBM SPSS 24 (IBM Corp, Armonk, NY) and Graphpad Prism version 9.2 were used for statistical analysis.

Patient and Public Involvement Statement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Participant Characteristics

Between January 2021 and August 2021, a total of 581 participants (437 patients with CLD and 144 healthy volunteers) were enrolled from 15 medical sites in China. The demographic characteristics of participants in CLD groups are shown in Table 1, and those of the healthy control group in Supplementary Table 1. The median age was 47.0 years (IQR, 38.0-56.0 years) and 35.0 years (IQR, 28.5-41.5 years) in the CLD and healthy control groups, respectively ($P < .0001$). Among participants with CLD, 384 of 437 patients (87.8%) had chronic viral hepatitis B, whereas others had various etiologies of CLD, including nonalcoholic steatohepatitis, ALD, AIH, primary

Table 1. Baseline Characteristics of Patients With CLD

	Whole population with CLD (N = 437)	Noncirrhotic CLD (n = 284)	Compensated cirrhosis (n = 123)	Decompensated cirrhosis (n = 30)	*P* value
Age, *y*	47.0 (38.0–56.0)	43.0 (36.0–53.0)[a]	51.0 (42.0–58.3)[a]	59.0 (50.8–65.3)[a]	< .0001
Male sex	278 (63.6)	176 (62.0)	84 (68.3)	18 (60.0)	.435
BMI, *kg/m²*	23.9 (21.7–25.8)	23.8 (21.5–25.7)	24.0 (22.3–26.0)	24.2 (15.9–33.9)	.459
Overweight	191 (43.7)	120 (42.3)	56 (45.5)	15 (50.0)	.640
Etiology of CLD					
Hepatitis B	384 (87.8)	260 (91.5)	107 (87.0)	17 (56.7)[a]	< .0001
Hepatitis C	20 (4.6)	8 (2.8)	6 (4.9)	6 (20.0)[a]	< .0001
NAFLD	12 (2.7)	9 (3.2)	1 (0.8)	2 (6.7)	.999
ALD	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	.999
AIH/PBC/PSC	8 (1.8)	1 (0.4)[a]	5 (4.1)	2 (6.7)[a]	< .0001
Other	12 (2.7)	5 (1.8)	4 (3.3)	3 (10.0)	.999
Cirrhosis	153 (35.0)	–	–	–	–
Compensation, compensated	123 (80.4)	–	–	–	–
Child-Pugh classification			–	–	–
A	130/141 (85.0)	–	111/111 (100.0)	19/30 (63.3)	< .0001
B	9/141 (5.9)	–	0 (0.0)	9/30 (30.0)	
C	2/141 (1.3)	–	0 (0.0)	2/30 (6.7)	
Abnormality in liver function	272 (62.2)	164 (57.7)	84 (68.3)	24 (80.0)	.014
ALT, *U/L*	25.5 (18.0–37.2)	25.0 (18.8–42.0)	27.0 (18.0–36.0)	21.8 (15.9–33.9)	.587
AST, *U/L*	24.0 (19.5–30.7)	23.6 (19.1–29.2)	26.0 (21.0–31.6)	26.2 (18.8–36.5)	.101
GGT, *U/L*	22.0 (15.3–37.0)	20.7 (14.4–33.0)[a]	26.5 (17.8–46.3)	29.5 (19.0–40.9)[a]	< .0001
AKP, *U/L*	71.7 (57.8–89.0)	68.0 (55.0–83.6)[a]	77.8 (61.9–94.8)	90.0 (63.5–117.0)[a]	.001
TBIL, *μmol/L*	15.2 (11.5–20.1)	14.4 (10.9–18.6)[a]	17.8 (12.8–21.7)	21.9 (14.5–31.2)[a]	< .0001
DBI, *μmol/L*	3.3 (2.4–5.3)	3.0 (2.2–4.9)[a]	3.7 (2.7–6.5)	4.5 (2.9–6.8)[a]	< .0001
ALB, *g/L*	45.5 (43.0–47.9)	46.0 (43.4–47.9)[a]	45.3 (43.0–48.1)	41.0 (35.9–46.7)[a]	.002
Comorbidities	56 (12.8)	31 (9.9)[a]	24 (16.2)	14 (41.2)[a]	.001
CAD	5 (1.1)	3 (1.1)	1 (0.8)	1 (3.3)	.494
HTN	38 (8.7)	22 (7.7)	11 (8.9)	5 (16.7)	.255
DM	23 (5.3)	8 (2.8)	8 (6.5)	7 (23.3)[a]	< .0001
Arrhythmia	2 (0.5)	0 (0.0)	2 (1.6)	0 (0.0)	.999
Asthma	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	.999

Note: Data are displayed as median (interquartile range) and number (%).
AIH, Autoimmune hepatitis; AKP, alkaline phosphatase; ALB, albumin; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CLD, chronic liver diseases; DBIL, direct bilirubin; DM, diabetes mellitus; GGT, γ-glutamyl transpeptidase; HTN, hypertension; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TBIL, total bilirubin.
[a]Statistically significantly different from other subgroups.

biliary cholangitis, primary sclerosing cholangitis, etc. Overall, 153 of 437 patients (35.0%) in the CLD group were cirrhotic, 123 of 153 patients (80.4%) with cirrhosis were compensated, and 130 of 141 patients (85.0%) were classified as A in the Child-Pugh classification. In total, 272 of 437 patients (62.2%) had abnormalities in liver function parameters at baseline. As for comorbidities, hypertension (38/437; 8.7%) and diabetes (23/437; 5.3%) were the most common comorbidities in the CLD group (Table 1). Between subgroups, ages were significantly different (median, 43.0 years; IQR, 36.0-53.0 years; median, 51.0 years; IQR, 42.0-58.3 years; and 59.0 years; IQR, 50.8-65.3 years in the noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis subgroups, respectively [$P < .0001$]). The ratio of patients with abnormalities in liver function were significantly higher in the decompensated cirrhotic subgroup (164/284 [57.7%], 84/123 [68.3%], and 24/30 [80.0%] in the noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis subgroups, respectively [$P = .014$]).

Vaccine Safety

Seventy participants with CLD (16.0%) reported at least 1 adverse reaction within 14 days of either dose of SARS-CoV-2 vaccination (Table 2). There was no significant difference in adverse reactions among subgroups

Table 2. Adverse Reactions After Either Dose of SARS-CoV-2 Vaccines

	Whole population with CLD (N = 437)	Noncirrhotic CLD (n = 284)	Compensated cirrhosis (n = 123)	Decompensated cirrhosis (n = 30)
Solicited adverse reactions within 0 to 14 days				
Any	70 (16.0)	44 (15.5)	20 (16.3)	6 (20.0)
Grade 1	64 (14.6)	39 (13.7)	20 (16.3)	5 (16.7)
Grade 2	6 (1.4)	5 (1.8)	0 (0.0)	1 (3.3)
Injection site adverse reactions				
Pain	36 (8.2)	25 (8.8)	10 (8.1)	1 (3.3)
Grade 1	34 (7.8)	23 (8.1)	10 (8.1)	1 (3.3)
Grade 2	2 (0.5)	2 (0.7)	0 (0.0)	0 (0.0)
Swelling	4 (0.9)	3 (1.1)	1 (0.8)	0 (0.0)
Grade 1	4 (0.9)	3 (1.1)	1 (0.8)	0 (0.0)
Induration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	2 (0.5)	1 (0.4)	1 (0.8)	0 (0.0)
Grade 1	2 (0.5)	1 (0.4)	1 (0.8)	0 (0.0)
Pruritus	2 (0.5)	1 (0.4)	0 (0.0)	1 (3.3)
Grade 1	2 (0.5)	1 (0.4)	0 (0.0)	1 (3.3)
Systematic adverse reactions				
Fever	9 (2.1)	6 (2.1)	1 (0.8)	2 (6.7)
Grade 1	7 (1.6)	5 (1.8)	1 (0.8)	1 (3.3)
Grade 2	2 (0.5)	1 (0.4)	0 (0.0)	1 (3.3)
Cough	2 (0.5)	1 (0.4)	1 (0.8)	0 (0.0)
Grade 1	2 (0.5)	1 (0.4)	1 (0.8)	0 (0.0)
Vertigo	4 (0.9)	1 (0.4)	3 (2.4)	0 (0.0)
Grade 1	3 (0.7)	0 (0.0)	3 (2.4)	0 (0.0)
Grade 2	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Nausea	3 (0.7)	1 (0.4)	1 (0.8)	1 (3.3)
Grade 1	3 (0.7)	1 (0.4)	1 (0.8)	1 (3.3)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	3 (0.7)	2 (0.7)	0 (0.0)	1 (3.3)
Grade 1	3 (0.7)	2 (0.7)	0 (0.0)	1 (3.3)
Arthralgia	1 (0.2)	0 (0.0)	1 (0.8)	0 (0.0)
Grade 1	1 (0.2)	0 (0.0)	1 (0.8)	0 (0.0)
Fatigue	8 (1.8)	6 (2.1)	2 (1.6)	0 (0.0)
Grade 1	7 (1.6)	5 (1.8)	2 (1.6)	0 (0.0)
Grade 2	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Hypersensitivity	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Grade 1	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Data are displayed as number (%), representing the total number of participants who had adverse reactions (ie, adverse events related to vaccination).
CLD, Chronic liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(44 [15.5%], 20 [16.3%], and 6 [20.0%] in the noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis subgroups, respectively [$P = .812$]) (Table 2). Overall, the most common injection site adverse reaction was pain, which was reported in 36 of 437 cases (8.2%). The most commonly reported systematic adverse reaction was fever, which was reported in 9 of 437 cases (2.1%). Additionally, among 164 patients with available laboratory data follow-up visits, there were no cases (0.0%) in the CLD group reporting grade 2 ALT elevation (defined as 2 upper limits of normal [ULN] < ALT $\leq$ 5 ULN), 3 of 164 participants (1.8%) reported grade 3 ALT elevation (defined as ALT >5 ULN), and 4 of 164 participants (2.4%) reported grade 2 AST elevation (defined as 2 ULN < AST $\leq$ 5 ULN) after the whole schedule of SARS-CoV-2 vaccination (Supplementary Table 2). One of the 3 participants with grade 3 abnormalities was hospitalized for developing a trend of acute liver failure in the follow-up visits, and this was considered potentially related to SARS-CoV-2 vaccination, whereas the rest received related treatment and took follow-up visits as outpatients. Detailed information on the 3 participants with grade 3 ALT elevation are listed in Supplementary Table 3.

SARS-CoV-2 Vaccination Immunogenicity

The positive rate of SARS-CoV-2 neutralizing antibodies were significantly lower in participants with CLD (338/437 [77.3%] in the CLD group and 130/144 [90.3%] in the healthy control group; $P = .001$). After adjusting for age, gender, and body mass index, the difference was still statistically significant ($P = .035$). The positive rate was similar in participants with noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis (218/284 [76.8%], 97/123 [78.9%], and 23/30 [76.7%], respectively; $P = .894$) (Figure 1A). After adjusting for age, chronic hepatitis C, and diabetes, the difference was still not statistically significant ($P = .545$). The neutralizing antibody concentration were 17.7 AU/mL (IQR, 10.3-26.5 AU/mL) in the noncirrhotic CLD group, 15.9 AU/mL (IQR, 11.0-35.6 AU/mL) in the compensated cirrhotic group, 20.5 AU/mL (IQR, 10.4-36.4 AU/mL) in the decompensated cirrhotic group, and 18.8 AU/mL (IQR, 13.4-27.7 AU/mL) in the healthy control group ($P = .137$) (Figure 1B).

Factors Related to Serological Response Among Patients With Chronic Liver Diseases

Univariate and multivariate analysis of factors associated with negative serological response of SARS-CoV-2 vaccines was conducted in the CLD group (Table 3). Male gender was suggested to be an independent risk factor for negative serological response to SARS-CoV-2 vaccination (odds ratio, 1.89; 95% confidence interval, 1.12-3.90; $P = .017$) after taking age, cirrhosis, whether overweight, and compensation status into consideration.

Discussion

Previous studies had provided us with sufficient data about safety and immunogenicity of SARS-CoV-2 vaccines in healthy adults, showing a satisfactory result.[10-12] However, the immune response data in the population with CLD is still insufficient; previous studies either had a relatively small sample size or the results were not compared with that of healthy controls. Our multi-center study evaluated the safety and immunogenicity of SARS-CoV-2 vaccines in a real-world population with CLD, providing further evidence for SARS-CoV-2 vaccination in patients with CLD and those with different statuses of cirrhosis and compensation.

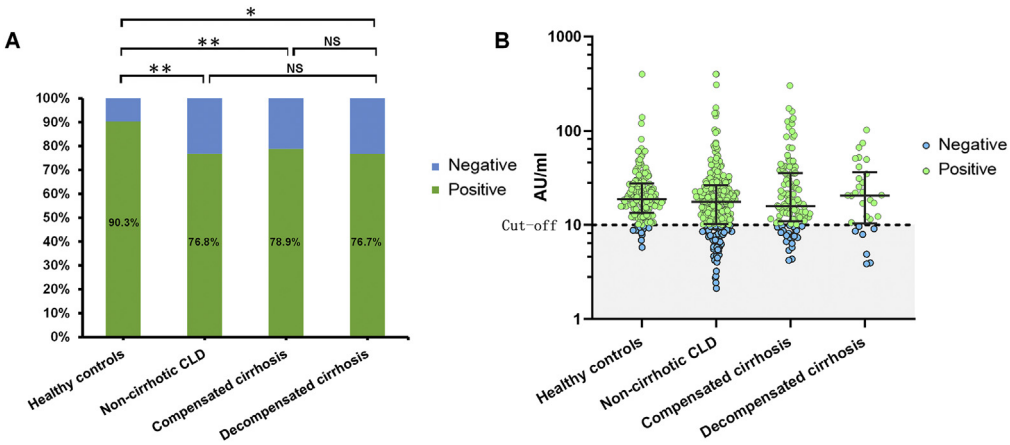

Figure 1. Serological antibody response of SARS-CoV-2 vaccines in patients with chronic liver diseases. Positive rates and concentrations of neutralizing antibodies to SARS-CoV-2 induced after the whole schedule of SARS-CoV-2 vaccination in participants with noncirrhotic CLD, compensated cirrhosis, decompensated cirrhosis, and healthy controls. Concentrations over 10.0 AU/mL were considered as positive, and concentrations below 10.0 AU/mL as negative. NS, Non-significant. *P value < .05; **P value < .01.

Table 3. Factors for Negative Serological Response to SARS-CoV-2 Vaccination in Patients With CLD

	Positive (n = 377)	Negative (n = 119)	Univariate analysis		Multivariate analysis	
			OR	*P* value	OR	*P* value
Age, *y*	46.0 (37.0–56.0)	49.0 (39.0–57.0)	–	.299	–	.161
Male sex	205 (60.7)	73 (73.7)	1.82 (1.11–3.00)	**.018**	1.86 (1.12–3.90)	**.017**
BMI, kg/m^2	23.8 (21.5–25.8)	24.3 (22.2–25.9)	–	.293		
Overweight	139 (41.1)	52 (52.5)	1.58 (1.01–2.48)	**.045**	1.47 (0.93–2.32)	.101
Etiology of CLD (viral hepatitis/ NAFLD/ALD/AIH/PBC/PSC)	–	–	–	.393		
Cirrhosis and compensation status[a]						
Noncirrhotic CLD	218 (64.5)	66 (66.7)	–	–	–	–
Compensated cirrhosis	97 (28.7)	26 (26.3)	1.00 (0.41–2.45)	.991	0.81 (0.32–2.07)	.664
Decompensated cirrhosis	23 (6.8)	7 (7.1)	1.13 (0.44–2.94)	.793	1.07 (0.41–2.82)	.894
Chronic hepatitis B						
HBeAg status, positive	67 (22.4)	26 (31.0)	1.60 (0.91–2.81)	.103		
HBV DNA status, detectable (%)	66 (22.1)	20 (23.8)	1.08 (0.60–1.95)	.801		
Under antiviral therapy	169 (56.5)	43 (51.2)	0.76 (0.32–1.82)	.542		
Different antiviral regimen	–	–	–	.694		
Abnormality in liver function at baseline	207 (61.2)	65 (65.6)	1.30 (0.79–2.14)	.300		
ALT, *U/L*	25.6 (17.9–38.2)	24.0 (18.5–37.1)	–	.649		
AST, *U/L*	24.0 (19.5–31.1)	24.0 (19.8–29.8)	–	.944		
GGT, *U/L*	22.0 (15.0–38.0)	21.0 (16.1–34.2)	–	.845		
AKP, *U/L*	69.9 (57.0–89.0)	75.0 (58.3–89.5)	–	.688		
TBIL, *μmol/L*	14.6 (11.3–19.9)	16.9 (12.9–21.9)	–	.083		
DBIL, *μmol/L*	3.2 (2.3–5.1)	3.8 (2.7–5.9)	–	.221		
ALB, *g/L*	45.6 (43.0–47.6)	45.3 (42.8–48.8)	–	.712		

Note: Data are displayed as median (interquartile range) and number (%).
AIH, Autoimmune hepatitis; AKP, alkaline phosphatase; ALB, albumin; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CLD, chronic liver diseases; DBIL, direct bilirubin; GGT, γ-glutamyl transpeptidase; HBV, hepatitis B virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TBIL, total bilirubin.
[a]OR of compensated and decompensated cirrhosis were compared with noncirrhotic CLD.

Our study indicated that the whole schedule (2 doses) of inactivated whole-virion SARS-CoV-2 vaccination is relatively safe in patients with CLD. All adverse symptoms were not severe and mostly transient, and injection site pain was the most reported symptom. As for laboratory indicator abnormalities, 3 patients had significant aminopherase elevation, all of whom had elevated aminopherase at baseline. Only 1 of them was judged as having a severe adverse event, in a patient who developed a trend of acute liver failure and had hospitalization in the follow-up. However, it was uncertain whether this severe adverse event was related to the SARS-CoV-2 vaccination, because the patient had a history of discontinuating anti-hepatitis B virus agents before SARS-CoV-2 vaccination. Overall, the safety was similarly good in patients with noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis. The result also suggested that patients with baseline liver function abnormalities may need to monitor serum indicators of liver function after SARS-CoV-2 vaccination, but the strategy of monitoring and follow-up plan need further research. As for the healthy control group, the SARS-CoV-2 inactivated vaccines used in this study had previously reported satisfactory safety results in healthy adults.[10,11] In this research, participants in the healthy control group were asked to make unsolicited reports to investigators if there was any adverse event, and no severe adverse events were reported, consistent with previous studies.

Patients with CLD had lower immunologic response to SARS-CoV-2 vaccines than healthy subjects. In the subgroup analysis, we observed similar immunologic response in the patients with noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis. These results are consistent with clinical phenomenon and previous studies, where patients with liver impairment had worse response to other vaccines such as hepatitis B virus vaccines.[21,22] Decreased responses to SARS-CoV-2 vaccination might be related to the impairment in immunity in the population with CLD.[23] CLD and fibrosis impair the synthesis of innate immunity proteins and pattern recognition receptors (although lower serum levels of these proteins are only evident in patients with advanced cirrhosis because of the large functional reserve of the liver), and also affect B lymphocytes and T

lymphocytes in both absolute counts and functions through a variety of mechanisms such as down-regulation of co-stimulation markers, loss of memory cells, and T cell exhaustion.[23-27] In the future, patients with CLD might need a boosting dose of SARS-CoV-2 vaccination to get a better response.

Our study suggested that male gender was an independent risk factor for negative serological response to SARS-CoV-2 vaccination, which is consistent with previous research about other vaccines, where male gender had been implicated in the poor vaccination responsiveness in the general population.[28-31] A number of hypotheses on the relationship between sex differences in the human immune system and mechanisms involved in the antibody response to vaccination have been made previously by scientists, such as testosterone-modulating genes involving lipid metabolism and antibody-neutralizing response, but the underlying mechanisms are still largely not understood.[32] This may further provide evidence for screening the population with higher risk of negative vaccination responsiveness and making recommendations of strengthening strategies.

The limitations of our study include a relatively small sample size of the decompensated cirrhosis subgroup and a short follow-up period. Few participants had severe impaired liver function at baseline in our study, even in the decompensated cirrhosis subgroup. Research with larger sample size and more various liver function status are required in the future. Patients receiving systemic immunosuppressants were not included in this study, which excluded a relevant number of patients with CLD, such as those patients with AIH under therapy, and this special population group also needs further investigation in the future. In addition, the population of patients with CLD in this study were typical in the East (mainly patients with chronic hepatitis B), and more patients with NAFLD or ALD need to be further observed. Moreover, we did not test for T-cell mediated response or other additional immunologic tests, which would be designed and conducted in next steps. Lastly, the findings of this study may not be extrapolated to mRNA vaccines, which can induce a stronger antibody response, and further research investigating efficacy of a variety of vaccines, regarding COVID-19 morbidity and mortality following the vaccination in patients with CLD are required in the future.

Conclusions

In conclusion, inactivated whole-virion SARS-CoV-2 vaccines are safe in patients with CLD, including patients with compensated and decompensated cirrhosis, supporting current recommendations for patients with CLD. Our findings raise a concern regarding lower immunologic response to SARS-CoV-2 vaccines in patients with CLD, and might help make recommendations of strengthening strategies in the future.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.12.022.

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Acknowledgment
The authors thank Shenzhen Mindray Bio-Medical Electronics Co., Ltd for cordially providing SARS-CoV-2 neutralizing antibody chemiluminescent immunoassay (CLIA) reagents.

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Conflicts of interest
The authors disclose no conflicts.

Supplementary Table 1. Baseline Characteristics of Healthy Controls

	Healthy controls (n = 144)
Age, *y*	35.0 (28.5–41.5)
Male sex	45 (31.3)
BMI, kg/m^2	22.6 (20.0-25.5)
Overweight	55 (38.7)

Note: Data are displayed as median (interquartile range) and number (%).
BMI, Body mass index.

Supplementary Table 2. Laboratory Abnormalities in Patients With CLD After SARS-CoV-2 Vaccination

	Whole population with CLD (n = 164)	Noncirrhotic CLD (n = 82)	Compensated cirrhosis (n = 59)	Decompensated cirrhosis (n = 23)
ALT				
Grade 1	32 (19.5)	17 (20.7)	11 (18.6)	4 (17.4)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	3 (1.8)	2 (2.4)	1 (1.7)	0 (0.0)
AST				
Grade 1	18 (11.0)	5 (6.1)	7 (11.9)	6 (26.1)
Grade 2	4 (2.4)	2 (2.4)	1 (1.7)	1 (4.3)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Data are displayed as number (%).
Note: Grade 1: 1 ULN $<$ ALT or AST $\leq$ 2 ULN; Grade 2: 2 ULN $<$ ALT or AST $\leq$ 5 ULN; Grade 3: ALT or AST $>$ 5 ULN.
ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; ULN, upper limits of normal.

Supplementary Table 3. Information on Patients With Grade 3 ALT Elevation

Basic information			
Patient ID	Sex	Age, y	BMI, kg/m^2
149	Male	31	29.3
387	Male	31	20.3
473	Male	31	24.8

Detailed information about CLD					
Patient ID	Cirrhosis and compensation	Etiology of CLD	HBeAg status	HBV-DNA status	Anti-viral drugs
149	Noncirrhotic CLD	Chronic hepatitis B	Positive	Detectable	None[a]
387	Compensated cirrhosis	Chronic hepatitis B	Positive	Detectable	TDF
473	Noncirrhotic CLD	Chronic hepatitis B	Positive	Detectable	ETV

Baseline liver function							
Patient ID	ALT, U/L	AST, U/L	GGT, U/L	AKP, U/L	TBIL, μmol/L	DBIL, μmol/L	ALB, g/L
149	167	298	131	102	54.4	31.6	38.7
387	80	75	55	40	20.5	2.3	40
473	360	112	56	81	8.4	2.2	44.7

Liver function after 2 doses of SARS-CoV-2 vaccination							
Patient ID	ALT, U/L	AST, U/L	GGT, U/L	AKP, U/L	TBIL, μmol/L	DBIL, μmol/L	ALB, g/L
149	498	192	78	108	38	10.1	44.4
387	377.5	122.7	65	45	23.8	3.6	40
473	219	120	92	89	19.4	6.2	42.1

AKP, Alkaline phosphatase; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CLD, chronic liver disease; DBIL, direct bilirubin; ETV, entecavir; HBV, hepatitis B virus; GGT, γ-glutamyl transpeptidase; TBIL, total bilirubin; TDF, tenofovir disoproxil fumarate.
[a]Patient 149 discontinued TDF against doctor's administration.