

Safety and immunogenicity of COVID-19 vaccination in patients with hepatocellular carcinoma (CHESS-NMCID 2101): A multicenter prospective study

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Abstract

Data on safety and immunogenicity of coronavirus disease 2019 (COVID-19) vaccinations in hepatocellular carcinoma (HCC) patients are limited. In this multicenter prospective study, HCC patients received two doses of inactivated whole-virion COVID-19 vaccines. The safety and neutralizing antibody were monitored. Totally, 74 patients were enrolled from 10 centers in China, and 37 (50.0%), 25 (33.8%), and 12 (16.2%) received the CoronaVac, BBIBP-CorV, and WIBP-CorV, respectively. The vaccines were well tolerated, where pain at the

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injection site (6.8% [5/74]) and anorexia (2.7% [2/74]) were the most frequent local and systemic adverse events. The median level of neutralizing antibody was 13.5 (interquartile range [IQR]: 6.9–23.2) AU/ml at 45 (IQR: 19–72) days after the second dose of vaccinations, and 60.8% (45/74) of patients had positive neutralizing antibody. Additionally, lower γ -glutamyl transpeptidase level was related to positive neutralizing antibody (odds ratio = 1.022 [1.003–1.049], $p = 0.049$). In conclusion, this study found that inactivated COVID-19 vaccinations are safe and the immunogenicity is acceptable or hyporesponsive in patients with HCC. Given that the potential benefits may outweigh the risks and the continuing emergences of novel severe acute respiratory syndrome coronavirus 2 variants, we suggest HCC patients to be vaccinated against COVID-19. Future validation studies are warranted.

KEYWORDS

coronavirus disease 2019, hepatocellular carcinoma, immunogenicity, inactivated vaccine, safety

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide and the second most common cause of cancer-related death.¹ Meanwhile, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in millions of fatalities worldwide.² Notably, patients with hepatobiliary malignancies appear to be at elevated risk of SARS-CoV-2 infections, which in turn translates into elevated mortality.^{3–5} Therefore, it is particularly important to properly deal with these two aspects at the same time in a real-life setting, especially in the prevention of SARS-CoV-2 infection.

COVID-19 vaccination is an important measure to prevent SARS-CoV-2 infection.^{3,4} However, stringent inclusion criteria of COVID-19 vaccination studies did not include individuals with HCC specifically.^{6–14} Additionally, patients with HCC may have immunosuppression that is associated with licensed vaccine hyporesponsiveness.^{3,4} Therefore, data on safety and immunogenicity/efficacy/effectiveness of COVID-19 vaccinations in HCC patients are limited and largely unknown. This study intended to answer some aspects of this knowledge gap to some extent.

2 | METHODS

2.1 | Study design and participants

In this multicenter prospective study, adult participants with HCC were enrolled from the network of Portal Hypertension Alliance in China (CHESS) and the National Medical Center for Infectious

Diseases (NMCID) in China. All participants received two doses of inactivated SARS-CoV-2 vaccines (CoronaVac, BBIBP-CorV, or WIBP-CorV). The time interval between the first and second SARS-CoV-2 vaccine doses was 3–8 weeks, according to the guidance of the SARS-CoV-2 vaccination enacted by the National Health Commission of China. The exclusion criteria mainly contained an active or known history of SARS-CoV-2 infection, liver transplantation, and human immunodeficiency virus infection.

2.2 | Safety assessment

The primary safety outcome is the adverse events of participants injected with inactivated SARS-CoV-2 vaccines within 14 days of either dose of vaccination. All the related adverse effects after vaccinations were collected by using the predesigned form where investigators and participants were required to record the injection site and systemic reactions.

2.3 | Immunogenicity evaluation

The primary effectiveness outcome is the immunogenicity of inactivated COVID-19 vaccines. Serum samples of enrolled participants were taken at least 14 days after the second dose of vaccination to quantitatively detect neutralizing antibodies to SARS-CoV-2 by using the SARS-CoV-2 neutralizing antibody (chemiluminescence immunoassay) assay (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) according to the manufacturer's instructions.¹⁵ The measuring ranges are 2.0–400.0 AU/ml.

Results above 10AU/ml were considered as an evidence of an immune response and results below 2.0AU/ml as undetectable, according to the instruction book. We defined results above 10.0AU/ml as positive and results below 10.0AU/ml as negative.

2.4 | Statistical analysis

Continuous variables are summarized as the medians and interquartile ranges (IQRs). The percentage of patients in each category was calculated for categorical variables. The percentages were compared between the two groups using the χ^2 test. We fitted binary logistic regression models for univariate and multivariate analysis of factors related to the serological responses. In the multivariate analysis, we adjusted for the factors that were substantially different in the univariate analysis ($p < 0.1$). A two-sided $p < 0.05$ was considered significant. The analyses were performed using SPSS software 25.0 for Windows (SPSS Inc.).

2.5 | Ethical concerns

Written informed consents were obtained from all the participants before enrollment. The study protocol and informed consent form were approved by the involved Ethics Committees and the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975, as revised in 1983. This study is registered at ClinicalTrials.gov (NCT04883177).

3 | RESULTS

3.1 | Participants' characteristics

In total, 74 participants were included from 10 centers in China between January 2021 and December 2021 (Table 1). Notably, hepatitis B virus infection accounted for 93.2% (69/74) of etiology. Hypertension is the most common comorbidity (16.7% [12/74]). Liver function parameters were generally normal or stable (Table 1). A total of 61 (82.4%) patients had the Child-Pugh score of A level, and 37 (50.0%), 25 (33.8%), and 12 (16.2%) received the CoronaVac, BBIBP-CorV, and WIBP-CorV, respectively (Table 1). Other baseline characteristics are presented in Table 1.

3.2 | COVID-19 vaccination safety

The inactivated COVID-19 vaccinations were generally well tolerated. A total of 12.2% (9/74) of patients reported at least one adverse reaction (Table 2). The most common local and systemic adverse reactions were pain (6.8% [5/74]) and anorexia (2.7% [2/74]),

TABLE 1 Baseline characteristics of HCC patients

Parameters	Patients (n = 74)
Age (years)	57.0 (51.3–64.8)
Sex, male	60 (81.1)
Body mass index	23.7 (22.2–25.4)
Overweight	27 (36.5)
Etiology	
Hepatitis B virus	69 (93.2)
Hepatitis C virus	1 (1.4)
Alcoholic hepatitis	5 (7.1)
Nonalcoholic fatty liver disease	0 (0)
Autoimmune hepatitis	0 (0)
Others	4 (5.4)
Chronic hepatitis B	
Hepatitis B e antigen positive	13 (17.8)
Hepatitis B virus DNA detectable	20 (27.4)
Antiviral therapy	61 (82.4)
Comorbidities	
Hypertension	12 (16.7)
Diabetes	3 (4.1)
Arrhythmia	1 (1.4)
Asthma	0 (0)
Coronary artery disease	1 (1.4)
Liver function	
Alanine aminotransferase (U/L)	24.0 (18.0–38.0)
Aspartate aminotransferase (U/L)	28.0 (22.0–39.0)
Albumin (g/L)	45.0 (40.9–48.8)
Total bilirubin (μ mol/L)	19.9 (15.0–27.5)
Direct bilirubin (μ mol/L)	5.6 (3.3–7.7)
γ -Glutamyl transpeptidase (U/L)	30.0 (18.0–72.0)
Alkaline phosphatase (U/L)	79 (65.0–108.0)
Child-Pugh score	
A	61 (82.4)
B + C	13 (17.6)
Number of tumors	
Single	56 (75.7)
Multiple (≥ 2)	18 (24.3)
Tumor diameter per capita (cm)	3.1 (1.9–5.4)
COVID-19 vaccine type	
CoronaVac	37 (50.0)
BBIBP-CorV	25 (33.8)
WIBP-CorV	12 (16.2)

Note: Data are presented as median (interquartile range) or n (%). Abbreviations: COVID-19, coronavirus disease 2019; HCC, hepatocellular carcinoma.

TABLE 2 Safety of inactivated COVID-19 vaccination in HCC patients

Parameters	Patients (n = 74)	Neutralizing antibody		p Value
		Positive (n = 45)	Negative (n = 29)	
Total reactions after each injection				
Any	9 (12.2)	6 (13.3)	3 (10.3)	0.984
Grade 3	0 (0)	0 (0)	0 (0)	-
Injection site adverse reactions				
Any	6 (8.1)	4 (8.9)	2 (6.9)	1.000
Pain	5 (6.8)	4 (8.9)	1 (3.4)	0.663
Erythema	1 (1.4)	0 (0)	1 (3.4)	0.392
Systemic adverse reactions				
Any	5 (6.8)	4 (8.9)	1 (3.4)	0.663
Anorexia	2 (2.7)	1 (2.2)	1 (3.4)	1.000
Swelling	2 (2.7)	1 (2.2)	1 (3.4)	1.000
Fever	1 (1.4)	1 (2.2)	0 (0)	1.000
Vertigo	1 (1.4)	1 (2.2)	0 (0)	1.000
Fatigue	1 (1.4)	1 (2.2)	0 (0)	1.000
Cough	1 (1.4)	1 (2.2)	0 (0)	1.000
Nausea	1 (1.4)	1 (2.2)	0 (0)	1.000
Sleepy	1 (1.4)	1 (2.2)	0 (0)	1.000
Unformed stool	1 (1.4)	1 (2.2)	0 (0)	1.000

Note: Data are presented as n (%).

Abbreviations: COVID-19, coronavirus disease 2019; HCC, hepatocellular carcinoma.

respectively. Notably, all the local and systemic adverse reactions can be resolved spontaneously. Additionally, no significant differences in the adverse events were observed between the neutralizing antibody positive and negative subgroups (all $p > 0.05$; Table 2).

3.3 | COVID-19 vaccination immunogenicity

Totally, the median level of SARS-CoV-2 neutralizing antibody was 13.5 (interquartile range [IQR]: 6.9–23.2) AU/ml at 45 (IQR: 19–72) days after the second dose of vaccinations, and 60.8% (45/74) of patients had positive neutralizing antibody (Table 3). Meanwhile, it was found that patients with Child-Pugh score of A levels are associated with a higher positive rate of neutralizing antibodies. Additionally, during the 45 (19–72) days of full postvaccination follow-up, no one was infected with the SARS-CoV-2.

TABLE 3 Immunogenicity of inactivated COVID-19 vaccination in HCC patients

Parameters	Patients (n = 74)
Neutralizing antibody testing timepoint (days)	45.0 (19.0–72.0)
Neutralizing antibody level (AU/ml)	13.5 (6.9–23.2)
Neutralizing antibody positive rate	45 (60.8)
Neutralizing antibody level in positive patients (AU/ml)	19.3 (15.0–38.3)
Neutralizing antibody level in negative patients (AU/ml)	6.3 (4.4–7.7)

Note: Data are presented as median (interquartile range) or n (%).

Abbreviations: COVID-19, coronavirus disease 2019; HCC, hepatocellular carcinoma.

3.4 | Factors associated with vaccination responses

The univariate and multivariate analysis of factors that are potentially associated with the serological response of COVID-19 vaccines were conducted in all patients (Table 4). In univariate analysis, overweight, hepatitis B e antigen-positive status, γ -glutamyl transpeptidase level, and Child-Pugh score levels were identified as the potential affecting factors of serological response to COVID-19 vaccinations. However, in multivariate analysis, only a lower γ -glutamyl transpeptidase level was suggested to be the independent affecting factor for positive serological response to COVID-19 vaccination after taking into consideration all the potential factors derived from the univariate model (odds ratio = 1.022 [1.003–1.049], $p = 0.049$; Table 4).

4 | DISCUSSION

Given that advanced liver disease and COVID-19 can lead to death separately, the probability of death is significantly increased if advanced liver disease overlapped with SARS-CoV-2 infection.⁵ Therefore, in early 2021, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) were concerned with the issue of COVID-19 vaccination for special populations with chronic liver diseases (CLDs), and both the AASLD and EASL indicated that vaccination against SARS-CoV-2 administered as early as possible in patients with CLDs is an important protective measure.^{3,4}

HCC is one of the most advanced CLDs; to date, few data concerning the safety and efficacy/effectiveness/immunogenicity of COVID-19 vaccination in HCC patients are available worldwide. In this study, we found that the inactivated COVID-19 vaccinations are safe and 60.8% (45/74) of HCC patients produced positive levels of SARS-CoV-2 neutralizing antibody. Notably, this SARS-CoV-2 neutralizing antibody positive rate (60.8%) in HCC patients is significantly lower than that of 90.3% (130/144), 76.8% (218/284), and 78.9%

TABLE 4 Factors associated with positive neutralizing antibody to COVID-19 vaccinations in HCC patients

Parameters	Neutralizing antibody status		p Value	Univariable analysis		p Value	Multivariable analysis	
	Positive (n = 45)	Negative (n = 29)		OR (95% CI)	OR (95% CI)		OR (95% CI)	p Value
Age (year)	58.0 (53.0–65.0)	56.0 (47.0–63.0)	0.508	0.983 (0.938–1.028)		0.464		
Sex, male	36 (80.0)	24 (82.8)	0.767	1.2 (0.367–4.31)		0.768		
Body mass index	24.0 (22.2–25.6)	23.4 (22.3–24.8)	0.727	0.968 (0.807–1.154)		0.718		
Overweight	20 (44.4)	7 (24.1)	0.076	0.398 (0.134–1.085)		0.081	0.367 (0.085–1.375)	0.15
Etiology								
Hepatitis B virus	42 (93.3)	27 (93.1)	0.969	0.964 (0.15–7.681)		0.969		
Hepatitis C virus	0 (0)	1 (3.4)	0.392	-		0.991		
Alcoholic hepatitis	4 (8.9)	1 (3.4)	0.663	0.375 (0.019–2.713)		0.392		
Others	4 (8.9)	0 (0)	0.261	-		0.989		
Chronic hepatitis B								
Hepatitis B e antigen positive	5 (11.1)	8 (27.6)	0.069	3.022 (0.88–11.314)		0.084	0.946 (0.13–5.641)	0.95
HBV DNA detectable	9 (20.0)	11 (37.9)	0.090	2.377 (0.837–6.943)		0.106		
Antiviral therapy	37 (82.2)	24 (82.8)	0.953	1.038 (0.308–3.783)		0.953		
Comorbidities								
Hypertension	8 (17.8)	4 (13.8)	0.896	0.75 (0.183–2.666)		0.666		
Diabetes	3 (6.7)	0 (0)	0.415	-		0.991		
Arrhythmia	1 (2.2)	0 (0)	1.000	-		0.992		
Coronary artery disease	1 (2.2)	0 (0)	1.000	-		0.992		
Liver function								
Alanine aminotransferase (U/L)	23.0 (17.0–27.9)	36.0 (21.5–56.2)	0.017	1.016 (1.001–1.044)		0.145		
Aspartate aminotransferase (U/L)	26.0 (22.0–31.0)	31.5 (22.5–57.2)	0.055	1.012 (1–1.03)		0.114		
Albumin (g/L)	45.6 (41.9–48.7)	44.0 (37.8–48.7)	0.291	0.939 (0.855–1.024)		0.166		
Total bilirubin (μmol/L)	19.9 (14.2–25.0)	21.4 (15.0–30.7)	0.347	1.023 (0.999–1.06)		0.125		
Direct bilirubin (μmol/L)	5.1 (3.6–7.6)	5.6 (3.2–9.4)	0.668	1.057 (1.002–1.159)		0.138		
γ-Glutamyl transpeptidase (U/L)	23.0 (16.5–39.8)	48.0 (22.0–120.0)	0.009	1.014 (1.004–1.028)		0.017	1.022 (1.003–1.049)	0.049
Alkaline phosphatase (U/L)	69.5 (59.5–84.5)	87.0 (73.0–115.0)	0.007	1.011 (0.999–1.028)		0.124		

(Continues)

TABLE 4 (Continued)

Parameters	Neutralizing antibody status		p Value	Univariable analysis		Multivariable analysis	
	Positive (n = 45)	Negative (n = 29)		OR (95% CI)	p Value	OR (95% CI)	p Value
Child-Pugh, n (%)							
A	41 (91.1)	20 (69.0)	0.026	3.403 (0.907–14.469)	4.083 (0.314–116.45)	0.076	0.32
B + C	4 (8.9)	9 (31.0)					
Number of tumors							
Single	35 (77.8)	21 (72.4)	0.600	1.57 (0.776–3.324)		0.217	
Multiple (≥2)	10 (22.2)	8 (27.6)					
Tumor diameter per capita	2.9 (1.8–5.3)	4.1 (3.0–6.6)	0.097	1.069 (0.933–1.231)		0.329	

Note: Data are presented as median (interquartile range) or n (%).

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; HCC, hepatocellular carcinoma; OR, odds ratio.

(97/123) in healthy populations, noncirrhotic CLD patients, and compensated cirrhosis patients presented in our previous study ($p < 0.001$, $p = 0.006$, and $p = 0.006$, respectively, non-head-to-head comparisons).¹⁵ Additionally, in our previous study,¹⁵ the neutralizing antibody concentration was 18.8 (13.4–27.7) AU/ml in the healthy control group, 17.7 (10.3–26.5) AU/ml in the noncirrhotic CLD group, and 15.9 (11.0–35.6) AU/ml in the compensated cirrhotic group, which are significantly higher than the 13.5 (6.9–23.2) AU/ml in our current study (all $p < 0.001$), although it is not the head-to-head comparisons. Interestingly, the lower γ -glutamyl transpeptidase level was found to be associated with a positive serological response to COVID-19 vaccination (Table 4), which indicated that favorable liver function parameters may increase the positive serological response.

The current study has limitations. First and apparently, the sample size is small. In the current study, only 74 HCC cases from as many as 10 centers in China taken one whole year (January 2021 and December 2021) were available; where there is a high incidence of HCC, the difficulty of enrollment may be the key reason of why the safety and response data are limited in HCC patients vaccinated with COVID-19 vaccines. There are two reasons for the enrollment difficulty; first of all, the HCC patients worry that their HCC conditions will get worse because of the COVID-19 vaccinations; additionally, the HCC patients are relatively old, and it is common for elderly people to worry about adverse reactions or poor outcomes after COVID-19 vaccination in China, and because the lower vaccination rate among elderly people, the Chinese government decided to continue implementing “ZERO COVID-19” policy to protect the elderly population until high vaccination rate among the elderly population. Second, we did not have real-world effectiveness against COVID-19 due to the “ZERO COVID-19” policy implemented for more than 2 years in China, and just because only a few COVID-19 cases were existing in China, the vaccinated populations have an extremely low probability to be exposed to the source of infection. In other words, we did not know whether these neutralizing antibody levels could protect HCC patients from infection and critical conditions or not. Despite these limitations, this study provides insight into the initial safety and the immunogenicity of COVID-19 vaccination in HCC patients.

In conclusion, this study found that inactivated COVID-19 vaccinations are safe and the immunogenicity is acceptable or hyporesponsive in patients with HCC. Given that the potential benefits may outweigh the risks and the continuing emergence of novel SARS-CoV-2 variants, we suggest that HCC patients be vaccinated against COVID-19. However, future validation studies are warranted.

AUTHORS CONTRIBUTIONS

Concept and design: Xiaolong Qi, Qing-Lei Zeng, and Wenhong Zhang. *Acquisition of data:* Jitao Wang, Qiran Zhang, Jingwen Ai, Chuan Liu, Qianqian Li, Ye Gu, Jiaojian Lv, Yifei Huang, Yanna Liu, Dan Xu, Shubo Chen, Dengxiang Liu, Jinlong Li, Huiling Xiang, Jing Liang, Li Bian, Zhen Zhang, Luxiang Liu, Xuying Zhang, Wei Qin, Xiaodong Wang, Zhiyun Hou, Nina Zhang, Aiguo Zhang, Hongmei Zu, Yun Wang, Zhaolan Yan, Xiufang Du, Aifang Hou, Jiansong Ji,

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article.

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