



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Safety and immunogenicity of COVID-19 vaccination in patients with non-alcoholic fatty liver disease (CHESS2101): A multicenter study

Jitao Wang^{1,2,3,#}, Zhiyun Hou^{2,#}, Jianxin Liu^{4,#}, Ye Gu^{5,#}, Yunhong Wu^{6,#}, Zhenhui Chen^{7,#}, Jiansong Ji^{8,#}, Shiqi Diao^{9,#}, Yuanwang Qiu¹⁰, Shengqiang Zou¹¹, Aiguo Zhang², Nina Zhang², Fengxian Wang⁴, Xue Li⁴, Yan Wang⁵, Xing Liu⁵, Cheng Lv⁵, Shubo Chen³, Dengxiang Liu³, Xiaolin Ji³, Chao Liu⁶, Tao Ren⁶, Jingwei Sun⁷, Zhongwei Zhao⁸, Fazong Wu⁸, Fenxiang Li⁹, Ruixu Wang⁹, Yan Yan¹⁰, Shiliang Zhang¹⁰, Guohong Ge¹¹, Jiangbo Shao¹¹, Shiyong Yang¹², Chuan Liu¹, Yifei Huang¹, Dan Xu¹, Xiaoguo Li¹, Jingwen Ai¹³, Qing He¹⁴, Ming-Hua Zheng¹⁵, Liting Zhang¹², Qing Xie¹⁶, Don C. Rockey¹⁷, Jonathan A. Fallowfield¹⁸, Wenhong Zhang^{13,*}, Xiaolong Qi^{1,*}

¹CHESS Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China; ²CHESS-COVID-19 Group, Jincheng People's Hospital, Jincheng, China; ³CHESS-COVID-19 Group, Xingtai People's Hospital, Xingtai, China; ⁴CHESS-COVID-19 Group, Jinzhou Central Hospital, Jinzhou, China; ⁵CHESS-COVID-19 Group, The Sixth People's Hospital of Shenyang City, Shenyang, China; ⁶CHESS-COVID-19 Group, Hospital of Chengde Office, People's Government of Tibet Autonomous Region, Chengde, China; ⁷CHESS-COVID-19 Group, Baoding People's Hospital, Baoding, China; ⁸CHESS-COVID-19 Group, Lishui Central Hospital, Lishui, China; ⁹CHESS-COVID-19 Group, The Third People's Hospital of Linfen City, Linfen, China; ¹⁰CHESS-COVID-19 Group, The Fifth People's Hospital of Wuxi, Affiliated Hospital of Jiangnan University, Wuxi, China; ¹¹CHESS-COVID-19 Group, The Third People's Hospital of Zhenjiang City, Zhenjiang, China; ¹²Department of Hepatology, The First Hospital of Lanzhou University, Lanzhou, China; ¹³Department of Infectious Disease, Huashan Hospital affiliated to Fudan University, Shanghai, China; ¹⁴National Clinical Research Center for Infectious Diseases, The Third People's Hospital of Shenzhen, Shenzhen, China; ¹⁵NAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; ¹⁶Department of Infectious Disease, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ¹⁷Digestive Disease Research Center, Medical University South Carolina, Charleston, South Carolina, USA; ¹⁸Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK

See Editorial, pages 265–266

Background & Aims: The development of COVID-19 vaccines has progressed with encouraging safety and efficacy data. Concerns have been raised about SARS-CoV-2 vaccine responses in the large population of patients with non-alcoholic fatty liver disease (NAFLD). The study aimed to explore the safety and immunogenicity of COVID-19 vaccination in NAFLD.

Methods: This multicenter study included patients with NAFLD without a history of SARS-CoV-2 infection. All patients were vaccinated with 2 doses of inactivated vaccine against SARS-CoV-2. The primary safety outcome was the incidence of adverse reactions within 7 days after each injection and overall incidence of adverse reactions within 28 days, and the primary immunogenicity outcome was neutralizing antibody response at least 14 days after the whole-course vaccination.

Results: A total of 381 patients with pre-existing NAFLD were included from 11 designated centers in China. The median age was

39.0 years (IQR 33.0–48.0 years) and 179 (47.0%) were male. The median BMI was 26.1 kg/m² (IQR 23.8–28.1 kg/m²). The number of adverse reactions within 7 days after each injection and adverse reactions within 28 days totaled 95 (24.9%) and 112 (29.4%), respectively. The most common adverse reactions were injection site pain in 70 (18.4%), followed by muscle pain in 21 (5.5%), and headache in 20 (5.2%). All adverse reactions were mild and self-limiting, and no grade 3 adverse reactions were recorded. Notably, neutralizing antibodies against SARS-CoV-2 were detected in 364 (95.5%) patients with NAFLD. The median neutralizing antibody titer was 32 (IQR 8–64), and the neutralizing antibody titers were maintained.

Conclusions: The inactivated COVID-19 vaccine appears to be safe with good immunogenicity in patients with NAFLD.

Lay summary: The development of vaccines against coronavirus disease 2019 (COVID-19) has progressed rapidly, with encouraging safety and efficacy data. This study now shows that the inactivated COVID-19 vaccine appears to be safe with good immunogenicity in the large population of patients with non-alcoholic fatty liver disease.

© 2021 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Received 8 April 2021; received in revised form 18 April 2021; accepted 20 April 2021; available online 24 April 2021

* Corresponding authors. Addresses: CHESS Center, Institute of Portal Hypertension, The First Hospital of Lanzhou University, Lanzhou, China; Tel.: 86-18588602600. (X. Qi), or Department of Infectious Disease, Huashan Hospital affiliated to Fudan University, Shanghai, China (W. Zhang).

E-mail addresses: qixiaolong@vip.163.com (X. Qi), zhangwenhong@fudan.edu.cn (W. Zhang).

Co-first authors

<https://doi.org/10.1016/j.jhep.2021.04.026>



ELSEVIER

recent article by Cornberg *et al.*,¹ in which they summarized the data on vaccine safety, immunogenicity, and efficacy in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. The development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines has progressed at an unprecedented rate with encouraging safety and efficacy data emerging from clinical trials.^{3–5} Despite the large number of clinical trials of COVID-19 vaccines, only a few participants with pre-existing liver diseases were included.^{1,6} Concerns have been raised recently about SARS-CoV-2 vaccine responses in the large population of patients with non-alcoholic fatty liver disease (NAFLD),^{1,6,7} who may be uniquely susceptible to COVID-19 infection and disease progression.^{8–10} The study aimed to explore the safety and immunogenicity of COVID-19 vaccination in patients with NAFLD in a large Chinese cohort.

Patients and methods

This multicenter study included patients with NAFLD without a history of SARS-CoV-2 infection, from 11 designated centers in the network of Chinese Portal Hypertension Alliance (CHESS) between 4 October 2020 and 26 February 2021, with a final follow-up on March 18, 2021. NAFLD was diagnosed by liver biopsy and/or clinical findings. All patients were vaccinated with 2 doses (0.5 ml/dose) of inactivated vaccine against SARS-CoV-2 (Beijing Institute of Biological Products Co., Ltd.). Blood samples were collected at least 14 days after the whole-course vaccination. Neutralizing antibodies were detected by magnetic particle chemiluminescence immunoassay using SARS-CoV-2 neutralizing antibody detection kit (Beijing Hotgen Biotech Co., Ltd.). The primary safety outcome was the incidence of adverse reactions within 7 days after each injection and the overall incidence of adverse reactions within 28 days, and the primary immunogenicity outcome was neutralizing antibody response at least 14 days after the whole-course vaccination. Continuous variables were presented as median (IQR), and categorical variables were presented as n (%). The study was approved by the ethics committees of participating centers.

Results

A total of 381 patients with pre-existing NAFLD were included in the analysis. The median age was 39.0 years (IQR 33.0–48.0 years) and 179 (47.0%) were male. The median BMI was 26.1 kg/m² (IQR 23.8–28.1 kg/m²). Of these, 348 (91.3%) patients were of Han ethnicity. Comorbidities other than NAFLD were present in 53 (13.9%) patients, consisting of 42 (11.0%) hypertension, 14 (3.7%) diabetes, 4 (1.0%) arrhythmia and 1 (0.3%) asthma. Baseline characteristics are summarized in Table 1.

The number of adverse reactions within 7 days after each injection and adverse reactions within 28 days totaled 95 (24.9%) and 112 (29.4%) of patients, respectively. The most common adverse reactions were 70 (18.4%) injection site pain, followed by 21 (5.5%) muscle pain, 20 (5.2%) headache, and 18 (4.7%) fatigue. All adverse reactions were mild and self-limiting, and no grade 3 adverse reactions were recorded. The median interval between the completion of whole-course vaccination and the detection of neutralizing antibodies was 39.0 days (IQR, 35.0–50.0 days). Notably, neutralizing antibodies against SARS-CoV-2 were detected in 364 (95.5%) patients with NAFLD. The median neutralizing antibody titer was 32 (IQR 8–64). The adverse reactions and immunogenicity outcomes of COVID-19 vaccination in patients with NAFLD are shown in Table 2. According to the locally weighted scatterplot smoothing, the neutralizing

Table 1. Baseline characteristics of study cohort.

Characteristics	Patients (n = 381)
Age, median (IQR), years	39.0 (33.0–48.0)
Age groups, years	
18–29, n (%)	50 (13.1)
30–44, n (%)	203 (53.3)
45–59, n (%)	128 (33.6)
Sex	
Female, n (%)	202 (53.0)
Male, n (%)	179 (47.0)
Body mass index, median (IQR), kg/m ²	26.1 (23.8–28.1)
Ethnicity	
Han ethnicity, n (%)	348 (91.3)
Manchu ethnicity, n (%)	19 (5.0)
Hui ethnicity, n (%)	4 (1.0)
Mongolian ethnicity, n (%)	4 (1.0)
Other, n (%)	6 (1.6)
Any comorbidity, n (%)	53 (13.9)
Hypertension, n (%)	42 (11.0)
Diabetes, n (%)	14 (3.7)
Arrhythmia, n (%)	4 (1.0)
Asthma, n (%)	1 (0.3)
Other, n (%)	3 (0.8)

Table 2. Safety and immunogenicity of COVID-19 vaccination in patients with NAFLD.

Characteristics	Patients (n = 381)
Total reactions within 7 days after each injection	
Any, n (%)	95 (24.9)
Grade 3, n (%)	0 (0)
Injection site adverse reactions	
Pain, n (%)	70 (18.4)
Induration, n (%)	7 (1.8)
Redness, n (%)	5 (1.3)
Swelling, n (%)	5 (1.3)
Itch, n (%)	3 (0.8)
Systemic adverse reactions	
Muscle pain, n (%)	21 (5.5)
Headache, n (%)	20 (5.2)
Fatigue, n (%)	18 (4.7)
Fever, n (%)	8 (2.1)
Nausea, n (%)	7 (1.8)
Oropharyngeal pain, n (%)	5 (1.3)
Joint pain, n (%)	3 (0.8)
Cough, n (%)	2 (0.5)
Rhinorrhea, n (%)	2 (0.5)
Diarrhea, n (%)	2 (0.5)
Chill, n (%)	2 (0.5)
Vomiting, n (%)	1 (0.3)
Hypersensitivity, n (%)	1 (0.3)
Syncope, n (%)	1 (0.3)
Appetite impaired, n (%)	1 (0.3)
Dyspnea, n (%)	1 (0)
Pruritus, n (%)	0 (0)
Total adverse reactions within 28 days	
Any, n (%)	112 (29.4)
Grade 3, n (%)	0 (0)
Antibody responses after whole-course vaccination	
Neutralizing antibody titer, median (IQR)	32 (8–64)
Seroconversion of neutralizing antibodies, n (%)	364 (95.5)

antibody titers were maintained over the time since whole-course vaccination (Fig. 1).

Discussion

This multicenter study showed that COVID-19 vaccination appeared to be safe and effective in patients with NAFLD. There

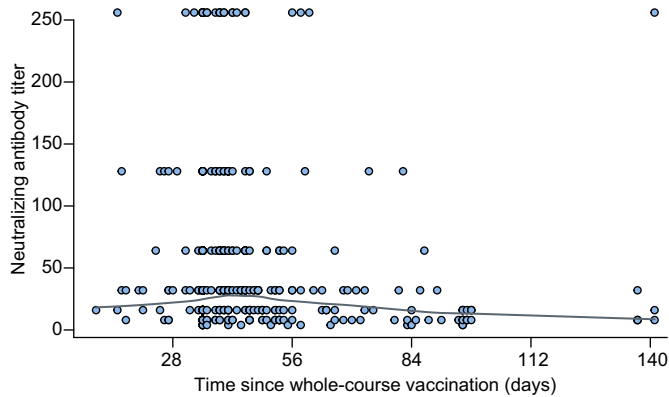


Fig. 1. Correlation between the time since whole-course vaccination and the neutralizing antibody titer. General trend line is shown in black and was calculated using the locally weighted scatterplot smoothing algorithm.

were no serious adverse reactions and neutralizing antibody responses appeared to be robust in patients with NAFLD who completed vaccination. Although the results of large-scale phase III trials have been released for a variety of COVID-19 vaccines, data on patients with pre-existing liver diseases are extremely limited, consisting of 0.6% (217) of 37,706 participants in the BNT162b2 mRNA COVID-19 vaccine trial and 0.6% (196) of 30,351 participants in the mRNA-1273 COVID-19 vaccine trial.^{4,5} Similar to the general population, side effects related to the COVID-19 vaccine in patients with NAFLD were mild and self-limiting, and no serious adverse events were reported. Compared to participants in the phase II trial of the same COVID-19 vaccine used in our study,³ patients with NAFLD showed a comparable neutralizing antibody seropositivity rate after the whole-course vaccination (95.5% vs. 97.6%, respectively). More importantly, our study showed that the titers of neutralizing antibodies in patients with NAFLD persisted over time. However, our study has several limitations. First, there was a lack of baseline information on histopathological grade/stage of NAFLD, liver function and neutralizing antibodies considering the retrospective nature of the study. Second, although the inactivated vaccine produced neutralizing antibody responses in the majority of patients with NAFLD, whether this could protect patients with NAFLD from SARS-CoV-2 infection remains unknown. A larger prospective follow-up study for robust evidence of efficacy (*i.e.*, protection against severe disease and death) is needed. In conclusion, the inactivated COVID-19 vaccine appears to be safe with good immunogenicity in patients with NAFLD.

Abbreviations

COVID-19, coronavirus disease 2019; NAFLD, non-alcoholic fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Financial support

Don C. Rockey was supported by the NIH: P30DK123703. Other authors received no financial support to produce this manuscript.

Conflicts of interest

The authors have declared no conflict of interest related to the study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Concept and design: Xiaolong Qi, Jitao Wang. *Acquisition, analysis, or interpretation of data:* Zhiyun Hou, Jianxin Liu, Ye Gu, Yunhong Wu, Zhenhuai Chen, Shiqi Diao, Yuanwang Qiu, Jiansong Ji, Aiguo Zhang, Nina Zhang, Fengxian Wang, Xue Li, Yan Wang, Xing Liu, Cheng Lv, Shubo Chen, Dengxiang Liu, Xiaolin Ji, Chao Liu, Tao Ren, Jingwei Sun, Fenxiang Li, Ruixu Wang, Yan Yan, Shiliang Zhang, Zhongwei Zhao, Fazong Wu, Shengqiang Zou, Guohong Ge, Jiangbo Shao, Shiyang Yang, Chuan Liu, Yifei Huang, Dan Xu, Xiaoguo Li, Jingwen Ai, Qing He, Ming-Hua Zheng, Liting Zhang, Qing Xie, Jonathan A. Fallowfield. *Drafting of the manuscript:* Jitao Wang. *Critical revision of the manuscript for important intellectual content:* Xiaolong Qi, Wenhong Zhang, Don C. Rockey, Jonathan A. Fallowfield. *Statistical analysis:* Jitao Wang. *Administrative, technical, or material support:* Zhiyun Hou, Jianxin Liu, Ye Gu, Yunhong Wu, Zhenhuai Chen, Jiansong Ji, Liting Zhang, Shiqi Diao, Yuanwang Qiu, Shengqiang Zou. *Supervision:* Xiaolong Qi.

Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.04.026>.

References

- Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. *J Hepatol* 2021. <https://doi.org/10.1016/j.jhep.2021.01.032>.
- Qi X, Liu Y, Wang J, Fallowfield JA, Wang J, Li X, et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. *Gut* 2021;70:433–436. <https://doi.org/10.1136/gutjnl-2020-321666>.
- Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes. *JAMA* 2020;324:951. <https://doi.org/10.1001/jama.2020.15543>.
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020;383:2603–2615. <https://doi.org/10.1056/nejmoa2034577>.
- Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403–416. <https://doi.org/10.1056/nejmoa2035389>.
- Marjot T, Webb GJ, Barritt AS, Ginès P, Lohse AW, Moon AM, et al. SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question. *Lancet Gastroenterol Hepatol* 2021. [https://doi.org/10.1016/S2468-1253\(21\)00008-X](https://doi.org/10.1016/S2468-1253(21)00008-X).
- Fix OK, Blumberg EA, Chang K, Chu J, Chung RT, Goacher EK, et al. AASLD expert panel consensus statement: vaccines to prevent COVID-19 infection in patients with liver disease. *Hepatology* 2021. <https://doi.org/10.1002/hep.31751>.
- Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. *J Hepatol* 2020;73:451–453. <https://doi.org/10.1016/j.jhep.2020.03.044>.
- Zhou YJ, Zheng KI, Wang XB, Yan HD, Sun QF, Pan KH, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. *J Hepatol* 2020;73:719–721. <https://doi.org/10.1016/j.jhep.2020.04.027>.
- Meijnikman AS, Bruin S, Groen AK, Nieuwdorp M, Herrema H. Increased expression of key SARS-CoV-2 entry points in multiple tissues in individuals with NAFLD. *J Hepatol* 2021;74:748–749. <https://doi.org/10.1016/j.jhep.2020.12.007>.