Should people with chronic liver diseases be vaccinated against COVID-19?

Li-Ping Chen, Qing-Hong Zeng, Yuan-Feng Gong, Fa-Liang Liang

ORCID number: Li-Ping Chen 0000-0002-3904-6626; Qing-Hong Zeng 0000-0003-1567-6727; Yuan-Feng Gong 0000-0001-7742-6286; Fa-Liang Liang 0000-0002-8510-4997.

Author contributions: Chen LP and Liang FL designed and performed research; Zeng QH and Gong YF wrote the letter; Chen LP revised the letter.

Conflict-of-interest statement: No potential conflicts of interest and financial support for this work.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/License/s/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Abstract

Hepatic impairment in coronavirus disease 2019 (COVID-19) may derive from cholangiocyte damage in the beginning, but not from direct infection of hepatocytes. Chronic liver disease patients co-infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibited overexpression of angiotensin-converting enzyme 2 receptors and overwhelming cytokine storm. Consensus has been reached that we should encourage as many people as possible to be vaccinated in order to achieve herd immunity. SARS-CoV-2 vaccines can prevent or alleviate severe infection and cytokine storm. It is recommended that all adult patients with chronic liver diseases and liver transplant recipients should receive COVID-19 vaccines using the standard dose and schedule. Data is not yet sufficient to compare the efficacy of different types of vaccines used in chronic liver disease patients.

Key Words: Chronic liver disease; Vaccine; COVID-19; SARS-CoV-2; Hepatic impairment

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Chronic liver disease patients co-infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibited overexpression of angiotensin-converting enzyme 2 receptors and overwhelming cytokine storm. SARS-CoV-2 vaccines can prevent or alleviate severe infection, and cytokine storm. Recently, a question has been raised whether chronic liver disease patients should be vaccinated against coronavirus disease 2019 (COVID-19). The American Association for the
Coronavirus disease 2019 (COVID-19) has become a global pandemic. It poses not only a huge threat to public health, but also a major impact on economic development and regional stability. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anchors host cells by binding to angiotensin-converting enzyme 2 (ACE2). ACE2 is not simply expressed in the respiratory tract, but also in the central nervous system, heart, liver, gastrointestinal tract, kidney, and skeletal muscle. Therefore, patients with severe COVID-19 may show multiple organ dysfunction.

Due to the lack of suitable experimental models, tissue or organ tropism of the virus has not been well established. The first autopsy with COVID-19 showed moderate microvesicular steatosis and mild lobular and portal activity in the liver, indicating that the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury[1]. Chai et al[2] found that distribution of ACE2 in the liver was unique. ACE2 showed higher expression level in cholangiocytes (59.7%), compared with hepatocytes (2.6%). The ACE2 expression level in cholangiocytes was comparable to that in type 2 alveolar cells of the lungs. Further research by Fudan University using human organoids showed that liver ductal organoids were susceptible to SARS-CoV-2, and viral replication was dramatic after infection. SARS-CoV-2 infection induced cell death of host cholangiocytes and impaired bile acid transporting functions of cholangiocytes[3]. These results indicated that hepatic impairment in COVID-19 may derive from injury to liver cholangiocytes in the beginning, but not from direct target to hepatocytes. Of course, hepatocyte impairment in severe cases can also be indirectly induced by the systemic inflammatory response and abnormal metabolism. According to previous meta-analysis, abnormal serum levels of alanine transaminase, aspartate transaminase and bilirubin were reported in 15.0%, 15.0%, and 16.7% of the patients[4, 5]. However, there are few reports on the severity of hepatic impairment, clinical outcome and mortality rate in patients with different chronic liver diseases co-infected with SARS-CoV-2. Ali et al[6] summarized the remarkable impact of SARS-CoV-2 on several types of liver diseases, including non-alcoholic fatty liver disease), liver cirrhosis, hepatocellular carcinoma, and hepatitis B and C virus infection. Furthermore, they reviewed the devastating cytokine storm in COVID-19 and concluded that in a similar pattern, hepatic impairment patients co-infected with SARS-CoV-2 could exhibit overexpression of ACE2 receptors and overwhelming cytokine storm, which might worsen the hepatic impairment and increases the mortality rate.

It is widely accepted that herd immunity through vaccination is the ultimate weapon of controlling infectious diseases. Smallpox is the only human infectious disease that has been eradicated by widespread vaccination around the world. We have also eradicated poliovirus (poliomyelitis) type 2 and 3. In this point of view, countries around the world are working intensively to develop and produce SARS-CoV-2 vaccines. In June 2020, Kwok et al[7] calculated the threshold and the minimum proportion of total population required for herd immunity based on the number of new cases and the serial interval at that time. Given the mortality rate of 0.25%-3.0%, herd immunity may be difficult to achieve through natural infection. Furthermore, the threshold might be changed according to the transmissibility of variants (such as more transmissible variant B.1.617.2) and the measures taken to control the virus. So, the actual threshold in real life is still unknown, herd immunity can be observed with certainty only by retrospectively analyzing the data[8]. However, consensus has been reached that we should encourage as many people as possible to be vaccinated in order to achieve herd immunity. The estimated coverage rate must be achieved at least...
72.9% in China[9]. Moreover, a recent study also estimated the neutralization level by vaccination for 50% protection against detectable SARS-CoV-2 infection to be 20.2% of the mean convalescent level. The estimated neutralization level required for 50% protection from severe infection was significantly lower, only 3% of the mean convalescent level[10].

People with stable chronic liver disease status were included in clinical trials of mRNA BNT162b2[11] and mRNA-1273[12] vaccines and CoronaVac[13] and BBIBP-CorV[14] inactivated vaccines. Although only a small percentage of chronic liver disease patients were included, it has been proven to be safe and well tolerated. Considering the poor outcomes and high mortality rate of chronic liver disease co-infected with SARS-CoV-2, and the efficacy of vaccines against severe infection, the American Association for the Study of Liver Diseases[15] and European Association for the Study of the Liver[16] Expert Panel suggested that COVID-19 vaccines should be administered to all adult patients with chronic liver diseases and liver transplant recipients. Moreover, patients with chronic liver diseases who are receiving antiviral therapy for hepatitis B virus or hepatitis C virus should not withhold their medications while receiving the COVID-19 vaccines. Patients with hepatocellular carcinoma undergoing locoregional or systemic therapy should also be considered for vaccination without interruption of their treatment.

No large sample-size data is available on COVID-19 vaccines inoculated in immunosuppressed patients. According to the efficacy and safety of other vaccines (seasonal influenza vaccine, adjuvant subunit varicella zoster vaccine, etc.) used in solid organ transplant recipients, the immunogenicity of vaccines in these recipients is lower than in immunocompetent individuals. For patients with cancer, one dose of the BNT162b2 vaccine yielded poor efficacy. Immunogenicity increased significantly in patients with a vaccine boost at day 21 after the first dose[17]. Another novel study from Albert Einstein Cancer Center showed that comparing to solid tumors, a significantly lower rate of seroconversion was observed in patients with hematological malignancies (98% vs 85%), particularly the recipients of highly immunosuppressive therapies such as anti-CD20 therapy (70%), and stem cell transplantation (73%). Patients receiving immune checkpoint inhibitor therapy (97%) or hormonal therapies (100%) demonstrated high seroconversion after vaccination. Relatively, lower immunogenicity was observed following vaccination with the adenoviral than mRNA-based vaccines[18]. Data is not sufficient to compare the efficacy of protein subunit vaccines or other vaccine types used in liver cancer patients or candidates for liver transplantation. So, COVID-19 can be administered using the standard dose and schedule in immunosuppressed patients in order to achieve a favorable efficacy.

Even for those vaccinated, personal precautions in moderate-high risk areas should still be used, including wearing a mask, washing hands frequently, and keeping a social distance, because the effectiveness of the vaccines cannot be 100%. Some people may still be infected with SARS-CoV-2 after receiving the vaccine, but will not present with any symptoms, which is often termed as asymptomatic infection. The asymptomatic person can spread the virus to family and friends around them. Due to the emerging vaccine-resistant mutations, fight against COVID-19 pandemic is a marathon, which will last a long time.

REFERENCES

1. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]
2. Chai QX, Hu LF, Zhang Y, Han WY, Lu Z, Ke AW, Zhou J, Shi GM, Fang N, Fan J, Cai JB, Lan F. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. 2020 Preprint. Available from: bioRxiv:2020.02.03.931766 [DOI: 10.1101/2020.02.03.931766]
3. Zhao B, Ni C, Gao R, Wang Y, Yang L, Wei J, Lv T, Liang J, Zhang Q, Xu W, Xie Y, Wang X, Yuan Z, Zhang R, Lin X. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. Protein Cell 2020; 11: 771-775 [PMID: 32303993 DOI: 10.1007/s13238-020-00718-6]
4. Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, Lim JK, Falck-Ytter Y, El-Serag HB; AGA Institute. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. Gastroenterology 2020; 159; 320-334.e27 [PMID: 32407808 DOI: 10.1053/j.gastro.2020.05.001]
5. Hajifathalian K, Mahadev S, Schwartz RE, Shah S, Sampath K, Schnoll-Sussman F, Brown RS Jr,
Chen LP et al. CLD people vaccinated against COVID-19

Carr-Locke D, Cohen DE, Shararia RZ. SARS-COV-2 infection (coronavirus disease 2019) for the gastrointestinal consultant. World J Gastroenterol 2020; 26: 1546-1553 [PMID: 32127904 DOI: 10.3748/wjg.v26.i14.1546]

Ali FEM, Mohammedsaleh ZM, Ali MM, Ghogar OM. Impact of cytokine storm and systemic inflammation on liver impairment patients infected by SARS-CoV-2: Prospective therapeutic challenges. World J Gastroenterol 2021; 27: 1531-1552 [PMID: 33958841 DOI: 10.3748/wjg.v27.i15.1531]

KwoK KO, Lai F, Wei WI, Wong SYS, Tang JWT. Herd immunity - estimating the level required to halt the COVID-19 epidemics in affected countries. J Infect 2020; 80: e32-e33 [PMID: 32209383 DOI: 10.1016/j.jinf.2020.03.027]

Aschwanen C. The false promise of herd immunity for COVID-19. Nature 2020; 587: 26-28 [PMID: 30878772 DOI: 10.1038/s41586-020-02948-4]

Randolph HE, Barreiro LB. Herd Immunity: Understanding COVID-19. Immunity 2020; 52: 737-741 [PMID: 32433946 DOI: 10.1016/j.immuni.2020.04.012]

Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, Subbarao K, Kent SJ, Triccas JA, Davenport MP. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021; 27: 1205-1211 [PMID: 34002080 DOI: 10.1038/s41591-021-01377-8]

Polack FP, Thomas SJ, Kitchin N, Absalon J, Curtman A, Lockhart S, Perez JL, Perez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, French RW Jr, Hammitt LL, Tireci O, Nell H, Schaefer A, Unal S, Tresnan DB, Mather S, Dormitzer PR, Sahin U, Jansen KJ, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020; 383: 2603-2615 [PMID: 33301246 DOI: 10.1056/NEJMoa2034577]

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D. Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Broz A, Fierro C, Schwartz H, Neuziel K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Iversson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021; 384: 403-416 [PMID: 33378609 DOI: 10.1056/NEJMoA2035389]

Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, Han W, Chen Z, Tang R, Yin W, Chen X, Liu X, Jiang C, Li J, Yang M, Song Y, Wang X, Guo Q, Zha F. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021; 21: 181-192 [PMID: 33217362 DOI: 10.1016/S1473-3099(20)30843-4]

Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, Tan W, Wu G, Xu M, Lou Z, Huang W, Xu W, Huang B, Wang W, Zhang W, Li N, Xie Z, Ding L, You W, Zhao Y, Yang X, Liu Y, Wang Q, Huang L, Xu G, Luo B, Liu P, Guo W. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis 2021; 21: 39-51 [PMID: 33069281 DOI: 10.1016/S1473-3099(20)30831-8]

Fix OK, Blumberg EA, Chang KM, Chu J, Chang RT, Goecker EK, Hameed B, Kaul DR, Kulik LM, Kwok RM, McGuire BM, Mulligan DC, Price JC, Reau NS, Reddy KR, Reynolds A, Rosen HR, Ruoso MW, Schilsky ML, Verna EC, Ward JW, Fontana RJ; AASLD COVID-19 Vaccine Working Group. AASLD Expert Panel Consensus Statement: Vaccines to Prevent COVID-19 Infection in Patients with Liver Disease. Hepatology 2021; [PMID: 33577086 DOI: 10.1002/hep.31751]

Cornberg M, Buti M, Eberhardts CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatocellular cancer and liver transplant recipients. J Hepatol 2021; 74: 944-951 [PMID: 33563499 DOI: 10.1016/j.jhep.2021.01.032]

Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, Jouve ME, Blumberg EA, Chang KM, Chu J, Chung RT, Goacher EK, Hameed B, Kaul DR, Kulik LM, Kwok RM, McGuire BM, Mulligan DC, Price JC, Reau NS, Reddy KR, Reynolds A, Rosen HR, Ruoso MW, Schilsky ML, Verna EC, Ward JW, Fontana RJ; AASLD COVID-19 Vaccine Working Group. AASLD Expert Panel Consensus Statement: Vaccines to Prevent COVID-19 Infection in Patients with Liver Disease. Hepatology 2021; [PMID: 33577086 DOI: 10.1002/hep.31751]

Thakkar A, Gonzalez-Lugo JD, Goradia N, Gali R, Shapiro LC, Pradhan K, Rahman S, Kim SY, Ko B, Sica RA, Komblum N, Bachier-Rodriguez L, McCort M, Goel S, Perez-Soler R, Packer S, Sparano J, Gartrell B, Makower D, Goldstein YD, Wolgast L, Verma A, Haltos B. Seroconversion rates following COVID-19 vaccination among patients with cancer. Cancer Cell 2021; 39: 1081-1090.e2 [PMID: 34133951 DOI: 10.1016/j.ccell.2021.06.002]
