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Review Article

Efficacy of Vaccine Protection Against COVID-19 Virus Infection in Patients with Chronic Liver Diseases

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Abstract

The outbreak of coronavirus disease 2019 (COVID-19) has resulted in significant morbidity and mortality worldwide. Vaccination against coronavirus disease 2019 is a useful weapon to combat the virus. Patients with chronic liver diseases (CLDs), including compensated or decompensated liver cirrhosis and noncirrhotic diseases, have a decreased immunologic response to coronavirus disease 2019 vaccines. At the same time, they have increased mortality if infected. Current data show a reduction in mortality when patients with chronic liver diseases are vaccinated. A suboptimal vaccine response has been observed in liver transplant recipients, especially those receiving immunosuppressive therapy, so an early booster dose is recommended to achieve a better protective effect. Currently, there are no clinical data comparing the protective efficacy of different vaccines in patients with chronic liver diseases. Patient preference, availability of the vaccine in the country or area, and adverse effect profiles are factors to consider when choosing a vaccine. There have been reports of immune-mediated hepatitis after coronavirus disease 2019 vaccination, and clinicians should be aware of that potential side effect. Most patients who developed hepatitis after vaccination responded well to treatment with prednisolone, but an alternative type of vaccine should be considered for subsequent booster doses. Further prospective studies are required to investigate the duration of immunity and protection against different viral variants in patients with chronic liver diseases or liver transplant recipients, as well as the effect of heterologous vaccination.

Keywords: COVID-19; SARS-CoV-2; Chronic liver disease; Liver transplantation; Vaccine; mRNA.

Abbreviations: Ad26, adenovirus type 26; Ahr, adjusted hazard ratio; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; CLD, chronic liver diseases; COVID-19, coronavirus disease 2019; MBC, memory B-cells; NAFLD, nonalcoholic fatty liver disease; RBD, receptor-binding domain; RCT, randomized controlled trial; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This contagious virus has infected millions of people worldwide resulting in significant morbidity and mortality. Patients with chronic illnesses, including those with chronic liver disease, are more prone to severe infections or infection-related complications.[1] Moreover, patients with CLD, alcohol-associated liver disease and liver cirrhosis may have an impaired immune response to vaccination.[1] Figure 1 summarizes the mechanisms of reduced immune response in these groups of patients. There are currently four major types of COVID-19 vaccines approved by the World Health Organization (WHO), namely mRNA vaccines, adenoviral vector vaccines, inactivated vaccines and protein subunit vaccines. Studies focusing on these vaccines in patients with CLD are evolving. This review summarizes currently available data and evidence of the safety and efficacy of COVID-19 vaccines in this group of patients.

Risk and burden of COVID-19 infection in CLD patients

Chronic diseases increase the risk of mortality associated with COVID-19 infection. An international registry study of 745 patients with CLD and severe acute respiratory syndrome coronavirus 2 infection showed that the mortality rate was higher in patients with liver cirrhosis compared with those without (32% vs. 8%, $p<0.001$).[2] Factors associated with higher mortality were advanced cirrhosis, older age, and alcohol-related liver diseases. Acute hepatic decompensation occurred in 46% of patients with liver cirrhosis and half of the patients with hepatic decompensation had acute-on-chronic liver failure.

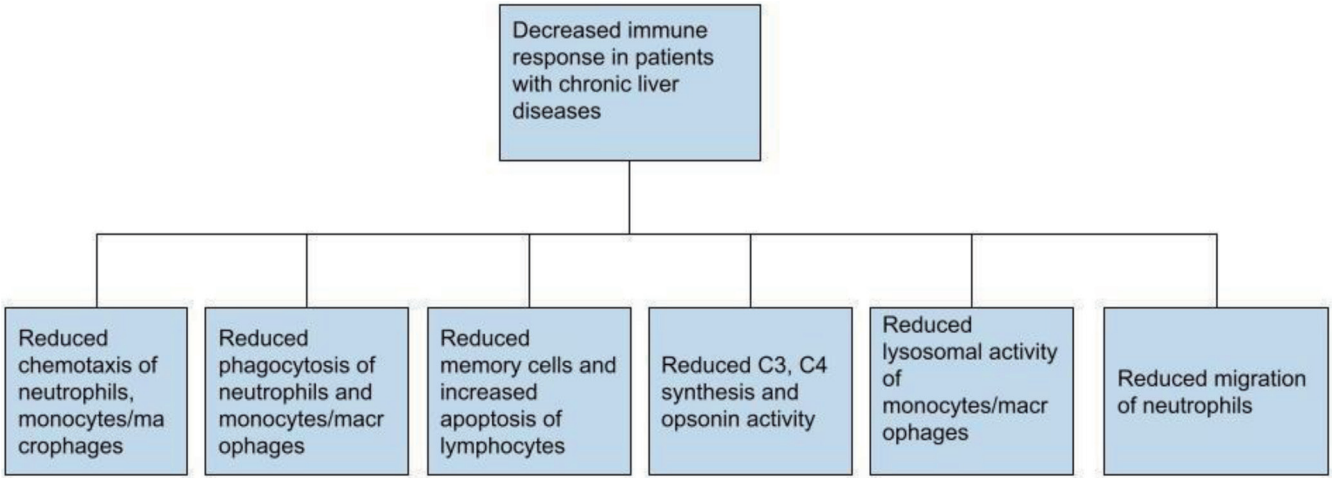

Fig. 1. Mechanisms of reduced immune response in patients with chronic liver diseases. The immune problems may be more pronounced in patients with coronavirus disease 2019 infection who have lymphopenia and reduced CD4 and CD8 T cells.

An Asian study examined the impact of COVID-19 infection in 228 patients with CLD, of whom 43 had cirrhosis and 185 did not.[3] Liver injury was progressive in 57% of patients, with a mortality rate of 43% in those with decompensated cirrhosis. Increasing bilirubin and aspartate aminotransferase (AST) levels and an aspartate aminotransferase/alanine aminotransferase (ALT) ratio >1.4 predicted mortality in cirrhosis patients.[3] In a study in the USA, Singh *et al*.[4] recruited a total of 2,780 patients with COVID-19 across 34 centers; 250 patients (9%) had pre-existing liver disease. They found that patients with pre-existing liver diseases, especially cirrhosis, were at higher risk for mortality [risk ratio (RR) 2.8; 95% confidence interval (CI), 1.9–4.0; $p<0.001$].[4] Patients with cirrhosis had a higher relative risk of mortality than those without liver disease (risk ratio 4.6; 95% confidence interval, 2.6–8.3; $p<0.001$). Previous studies have shown that a 4- to 6-fold increase in the severity of COVID-19 in patients with metabolic-dysfunction associated fatty liver (MAFLD).[5,6] The severity and mortality risk also increased in patients with higher fibrosis scores.[7] Vaccination is one of the effective methods to protect the population from COVID-19, and is of the utmost importance in high-risk subgroups such as those with CLD.

WHO-approved vaccines

mRNA vaccines

The US Food and Drug Administration and the European Medicines Agency granted an emergency approval to two mRNA vaccines against COVID-19, the Pfizer BioNTech vaccine BNT162b2 (Comirnaty) and the Moderna mRNA-1273 vaccine (Spikevax). BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA (modRNA) vaccine.[8,9] In adults 16 years of age or older, it is administered intramuscularly as two 30 μg doses in 21 days apart.[10] It provides 95% protection against COVID-19 in the immediate post-vaccination period, but a gradual decline in efficacy over time was observed.[11,12] A third booster dose of vaccine is important to maintain effectiveness over time or protect against the emergence of new variants.[13] The mRNA-1273 vaccine is also a lipid-nanoparticle-encapsulated mRNA vaccine. It is administered as two 100 μg doses intramuscularly 1 month apart, in individuals 18 years of age or older.[14,15] The vaccine efficacy was 94.1% as shown in the phase 3 randomized controlled trial (RCT, Supplementary Table 1).[16]

Effectiveness in CLD patients: There is a paucity of data from randomized controlled trials on mRNA vaccine safety and efficacy in patients with CLD and in liver transplant recipients (Table 1).[17–36] Only 0.6% subjects in the phase 3 clinical trials of the two vaccines had liver disease.[11,16] John *et al*.[17] performed a retrospective cohort study of patients with cirrhosis (n=20,037) who received at least one dose of an mRNA vaccine at the Veterans Health Administration in the USA, and compared outcomes with a propensity score-matched unvaccinated control group.[17] In the 28 days after the first dose of mRNA vaccine, there was no significant reduction in COVID-19 infection, indicating weakened early protection in patients with cirrhosis, but there was a 64.8% reduction in the risk from ≥28 days after the first dose. The vaccine-associated reduction in COVID-19 infections after the first dose was lower among patients with decompensated (50.3%) than with compensated cirrhosis (66.8%). In the 7 days after receiving a second dose of mRNA vaccine, there was a 78.6% reduction in COVID-19 infections and 100% reduction in COVID-19-related hospitalization or death in cirrhosis patients (Table 1).[17]

Because the protection from COVID-19 infection was lower in patients with cirrhosis than in healthy individuals in randomized controlled trials, post-vaccination breakthrough infection is expected. However, while infection cannot be completely avoided, vaccination in cirrhosis patients is still beneficial. A retrospective cohort study compared the outcome of COVID-19 infection in cirrhosis patients, 254 of whom had been vaccinated and 508 of whom were unvaccinated.[18] There was a reduction in the risk of overall mortality [adjusted hazard ratio (aHR) 0.21; 95% CI: 0.10–0.42; $p<0.0001$] and COVID-19-related death (adjusted hazard ratio 0.23; 95% CI: 0.10–0.53; $p=0.001$) within 60 days in vaccinated patients.[18] The decrease in mortality was seen in cirrhosis patients after full (adjusted hazard ratio 0.22; 95% CI: 0.08–0.63; $p=0.005$) or partial (aHR 0.19; 95% CI: 0.07–0.54; $p=0.002$) vaccination.[18] The significant reduction in COVID-19-related death was seen in patients with compensated cirrhosis (aHR 0.16; 95% CI: 0.06–0.46; $p=0.0001$) but not those with decompensated cirrhosis (aHR 0.51; 95% CI: 0.14–1.88; $p=0.31$).[18]

Although decompensated cirrhosis is a risk factors for

Table 1. Studies reporting the safety and efficacy of COVID-19 vaccines in patients with chronic liver disease or liver transplantation

Study and year [REF]	Study type	Vaccine used	Type of liver disease (*n*)	Median age, years	Efficacy data	Safety data
John *et al*. 2021[17]	Retrospective cohort comparing vaccinated and unvaccinated patients with cirrhosis	BNT162b2 or mRNA-1273	Cirrhosis (40,074)	69.1	COVID-19 infections occurring ≥28 days after the first dose of vaccine were reduced by 64.8% in vaccinated vs. unvaccinated patients overall, by 50.3% in those with decompensated cirrhosis and by 66.8% in those with compensated cirrhosis. 7 days after the second dose of vaccine, three patients in vaccine group compared to 14 patients in control group developed COVID-19 infection, corresponding to a 78.6% reduction in COVID-19 infections. No vaccinated patient with cirrhosis was hospitalized or died from COVID-19 (100% protection).	NR
John *et al*. 2022[18]	Retrospective cohort comparing outcomes of COVID-19 infection in vaccinated vs. unvaccinated patients with cirrhosis	BNT162b2, mRNA-1273, or Ad.26.COV2.S	Cirrhosis (762)	63.8 post-vaccination; 64.2 unvaccinated	Vaccination was associated with a reduced overall risk of death within 60 days (aHR 0.21; 95% CI 0.10–0.42; $p<0.0001$), of COVID-19-related death (aHR 0.23; 95% CI 0.10–0.53; $p=0.001$), and of mechanical ventilation within 60 days (aHR 0.33; 95% CI 0.11–0.96; $p=0.04$) but did not reduce risk of hospitalization (aHR 0.88; 95% CI 0.66–1.18; $p=0.41$). In patients with decompensated cirrhosis, vaccination was associated with a reduction in risk of death (aHR 0.27; 95% CI 0.08–0.90; $p=0.03$) but not COVID-19-related death	NR
Bakasis *et al*. 2022[19]	Prospective cohort comparing patients with CLD and age- and gender-matched controls	BNT162b2 or mRNA-1273	HBV (30), NAFLD (16), AIH (14), PBC (12), alcoholic liver disease (6), PSC (4), HCV (2), other (3)	67	S IgG seroconversion rate: cirrhosis: 37/38 (97.4%); CLD without cirrhosis: 43/49 (87.8%); controls: 40/40 (100%). Adequate neutralizing activity: cirrhosis: 35/38 (92.1%); CLD without cirrhosis: 43/49 (87.8%); controls: 40/40 (100%)	Common AEs: pain at the injection site (40.2%), fatigue (14.2%), low-grade fever (9.5%) and headache (8%), with no statistically significant difference between CLD patients and controls. No cirrhotic patients showed post-vaccination liver-related AEs

(continued)

Table 1. *(continued)*

Study and year [REF]	Study type	Vaccine used	Type of liver disease (*n*)	Median age, years	Efficacy data	Safety data
Thuluvath *et al*. 2021[20]	Prospective cohort study comparing LT recipients, patients with cirrhosis, and patients with CLD but no cirrhosis	BNT162b2, mRNA-1273, or Ad.26.COV2.S	NAFLD (84), HBV/HCV (63), AIH/PBC/PSC (61), alcoholic liver disease (32), other (32)	63 (mean)	S IgG 4 weeks after 2 doses were: undetectable (<0.40 U/mL) in 11/62 LT recipients, 3/79 patients with cirrhosis and 4/92 patients with noncirrhotic CLD; suboptimal (0.40–250 U/mL) in 15/62 LT recipients (median titer 17.6, range 0.47–212 U/mL), 15/79 patients with cirrhosis (median titer 41.3, range 0.49–221 U/L), and 19/92 patients with noncirrhotic CLD (median titer 95.5, range 4.9–234 U/L)	None of the patients had serious AEs. Common AEs after first dose were local pain at the injection site (53%) and fatigue (16%); and after second dose were local pain at the injection site (49%), fatigue (23%), fever (8%), chills (6%), headache (7%) and myalgia (6%)
Ruether *et al*. 2022[21]	Prospective observational study examining immunological response in patients with cirrhosis (*n*=48), LT recipients (*n*=138) and healthy controls (*n*=52)	BNT162b2, mRNA-1273, or AZD1222	Alcoholic liver disease (51), AIH (51), viral liver disease (20), cryptogenic (18), NAFLD (11), other (35)	LT: 55; Cirrhosis: 53.8; Control: 50.9	Anti-S trimer seroconversion rate: LT recipients: 63.0%; cirrhosis: 97.9%; control: 100%. Anti-S RBD seroconversion rate: LT recipients: 73.9%; cirrhosis: 100%; control: 100%. T-cell response rate: LT recipients 36.6%: cirrhosis: 65.4%; control: 100%. 28% of LT recipients had neither a humoral nor a T-cell response after second vaccination	Common AEs included pain/swelling, fever, fatigue, headache, myalgia, and arthralgia, which did not differ between groups
Shafrir *et al*. 2022[22]	Retrospective study examining the relationship between liver fibrosis and immunological response	BNT162b2	NAFLD	56.7 (mean)	The proportion of people with a strong vaccine response (S IgG >200 AU/mL) was significantly lower in those with high fibrosis ranges (elastography threshold >6 kPa)	NR
Huang *et al*. 2022[25]	Prospective cohort study comparing immunological response in LT candidates and recipients	BNT162b2 or mRNA-1273	NR	61 (LT candidates); 62 (LT recipients)	Anti-SARS-CoV-2 total Ig response. LT candidates (*n*=76): after first dose: 77.3%; after second dose: 100%. LT recipients (*n*=274): after first dose: 24.2%; after second dose: 51.2%. S IgG response. LT candidates (*n*=76): after first dose: 68%; after second dose: 100%. LT recipients (*n*=274): after first dose: 19.5%; after second dose: 42.5%	NR
Toniutto *et al*. 2022[26]	Prospective cohort study comparing immunological response in LT recipients (*n*=143) and healthy controls (*n*=58)	BNT162b2	NR	67.7	Positive anti-S RBD response in LT recipients: 3 weeks after first dose: 22.1%; 1 month after second dose: 66.4%; 4 months after second dose: 77%; → median titer 32 U/mL; 6 months after second dose: 78.8%. Positive anti-S RBD response in controls:4 months after second dose: 100%; → median titer 852 U/mL	No severe AEs or significant liver test abnormalities. Systemic symptoms such as fever, asthenia, or myalgia, were reported in 12/58 (20.6%) controls and 7/143 (4.9%) LT patients (p<0.001)

(continued)

Table 1. *(continued)*

Study and year [REF]	Study type	Vaccine used	Type of liver disease (*n*)	Median age, years	Efficacy data	Safety data
Strauss *et al*. 2021[23]	Prospective observational cohort study examining immunological response	BNT162b2 or mRNA-1273	LT recipients	64	Detectable anti-S1 or anti-S RBD IgG was seen in 34% (95% CI 27–42%) of patients after first dose (at a median of 21 days [IQR 109–25 days]), and in 81% (95% CI 74–87%) after second dose (at a median of 30 days [IQR, 28–31 days])	NR
Rabinowich *et al*. 2021[24]	Prospective cohort comparing immunological response in LT recipients (*n*=80) and healthy controls (*n*=25)	BNT162b2 or mRNA-1273	HCV (26), NAFLD (16), HBV (13), AIH/PBC/PSC (16), Other (8)	LT recipients: 60.1; Control: 52.7	S IgG was detected in all controls but in only 38/80 (47.5%) LT recipients; A lower mean S IgG titer was found in LT recipients compared with controls (95.41±92.4 vs. 200.5±65.1 AU/mL; $p<0.001$)	No major AEs occurred in any participant; Systemic symptoms after second dose of vaccine occurred in significantly fewer LT recipients compared with controls (25% vs. 85.7% respectively, $p<0.001$)
Davidov *et al*. 2022[27]	Prospective cohort study comparing immunological response in LT recipients (*n*=76) and age-mat c hed immunocompetent controls (*n*=174)	BNT162b2	HCV (19), NAFLD (13), PSC (11), HBV (7), PBC (3), other (23)	LT recipients: 64	Positive antibody response was documented 55/76 (72.4%) LT recipients compared with 164/174 (94.3%) controls (OR 6.26; 95% CI 2.8–14.1; $p<0.0001$), measured at a median 35 days after second vaccine dose. Mean (95% CI) titer of IgG antibodies was 2.1 (1.6–2.6) in LT recipients vs. 4.6 (4.1–5.1) in controls ($p<0.0001$), and of neutralizing antibodies was 150 (96–234) in LT recipients vs. 429 (350–528) in controls ($p<0.001$)	No transplant rejection or allergic reactions at a mean follow-up of 30 days following the second dose; Local AEs developed in 30.3% after first vaccine dose and 19.7% after second dose
Herrera *et al*. 2021[28]	Prospective cohort study examining immunological response in transplant recipients	mRNA-1273	LT recipients (58)	61.5	22/58 LT recipients (37.9%) had IgM or IgG antibodies against S protein after first dose of vaccine and 41 (71%) after second dose; After second dose of vaccine, 50/58 (86%) showed positive cellular response in the IFN-γ assay	Common AEs were pain (80%), fatigue (15%), swelling (12%) and low-grade fever (7%); No rejection, and no significant changes in ALT or increase in HLA antibodies from baseline
Fernández-Ruiz *et al*. 2021[29]	Prospective cohort study examining immunological response in solid organ transplant recipients (*n*=44)	mRNA-1273	LT recipients (14)	52.4 (mean, in the entire cohort)	Cell-mediated immunity (IFN-γ assay) in 10/13 LT recipients and serum neutralizing activity in 5/13 at 2 weeks after completion of 2 doses	No serious AEs and no graft rejection; ≥1 unsolicited AE reported by 12 recipients (27.3%): pain at the injection site (*n*=6), headache (*n*=3), fatigue (*n*=2), fever (*n*=1), tachycardia (*n*=1), and nausea (*n*=1)

(continued)

Table 1. *(continued)*

Study and year [REF]	Study type	Vaccine used	Type of liver disease (*n*)	Median age, years	Efficacy data	Safety data
Rahav *et al*. 2021[30]	Prospective cohort study examining immunological response in immunocompromised patients (*n*=1,002) and immunocompetent controls (*n*=272)	BNT162b2	LT recipients (36)	NR	Positive anti-RBD-IgG after second dose of vaccine 25/36 LT recipients (69.4%); anti-RBD-IgG geometric mean titer 2.14 (95% CI 1.46–3.14) and neutralizing antibody geometric mean titer 264.6 (95% CI: 121.8–574.9)	In all solid organ transplant recipients, 26.7% reported local AEs and 24% reported systemic AEs after second dose of vaccine
Nazaruk *et al*. 2021[31]	Retrospective cohort examining immunological response in kidney transplant and LT recipients	BNT162b2	LT recipients (55)	58.4 (mean)	In LT recipients, anti-S1 antibody response in 63% after first dose and 88.9% after second dose	NR
Boyarsky *et al*. 2021[32]	Prospective cohort examining immunological response in kidney transplant and LT recipients	BNT162b2 or mRNA-1273	LT recipients (129)	NR	In LT recipients, 26/129 (20%) were nonresponders, 41/129 (32%) had an anti-S1 or anti-S RBD response after first and second vaccine doses and 62/129 (32%) had a response after the second dose but not the first	NR
Ai *et al*. 2022[33]	Prospective cohort study examining the immunological response and safety in patients with CLD (*n*=437) and healthy volunteers (*n*=144)	BBIBP or WIBP	CHB (384), CHC (20), NAFLD (12), AIH/PBC/PSC (8), alcoholic liver disease (1), other (12)	47	SARS-CoV-2 neutralizing antibody (>10 AU/mL) positivity was seen in 338/437 patients with CLD (77.3%), 120/153 patients with cirrhotic CLD (78.4%), 218/284 with noncirrhotic CLD (76.8%), and 13/144 controls (90.3%)	Common AEs were pain at the injection site (8.2%), fatigue (1.8%), low-grade fever (2.1%); 3/164 participants with follow-up laboratory data (1.8%) had grade 3 ALT elevation and 4/164 (2.4%) had grade 2 AST elevation
He *et al*. 2022[34]	Prospective cohort study examining the immunological response and safety in patients with CHB (*n*=362) and healthy controls (*n*=87)	BBIBP	CHB (362)	CHB: 45; Control: 44	Seropositivity rates of SARS-CoV-2 antibodies 3 months after full-course of vaccination were: S IgG in 63/66 CHB patients (95.5%) and 30/32 controls (93.8%); RBD-specific IgG in 65/66 CHB patients (98.5%) and 31/32 controls (96.9%); RBD-ACE 2 blocking antibody in 29/66 CHB patients (43.9%) and 9/32 controls (28.1%)	Common AEs included pain at the injection site (5.8%), fatigue (4.7%), dizziness (1.9%)

(continued)

Table 1. *(continued)*

Study and year [REF]	Study type	Vaccine used	Type of liver disease (*n*)	Median age, years	Efficacy data	Safety data
Xiang *et al.* 2021[35]	Prospective observational study examining the immunological response and safety in CHB patients who were unvaccinated (*n*=81) or had received 1 (*n*=54) or 3 (*n*=149) vaccine doses	BBIBP	CHB (248)	41	In patients who completed the two doses of the vaccination regimen (*n*=149), seropositivity for anti-S-RBD-IgG was 87.25% and for neutralizing antibodies 74.5%	Common AEs were pain at the injection site (25.5%), fatigue (1.3%), drowsiness (2.0%)
Wang *et al.* 2021[36]	Prospective observational study examining the immunological response and safety in patients with NAFLD	BBIBP	NAFLD (381)	39	Neutralizing antibodies against SARS-CoV-2 were detected in 364/381 (95.5%) patients; median neutralizing antibody titer was 32 (IQR 8–64)	Common AEs were injection site pain (18.4%), muscle pain (5.5%), headache (5.2%), and fatigue (4.7%)

ACE, angiotensin converting enzyme; AE, adverse event; aHR, adjusted hazard ratio; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CI, confidence interval; CLD, chronic liver disease; HBV, hepatitis B; HCV, hepatitis C; HLA, human leukocyte antigen; IFN-γ, Interferon gamma; IgG, Immunoglobulin G; IQR, interquartile range; LT, liver transplant; NAFLD, nonalcoholic fatty liver disease; NR, not reported; OR, odds ratio; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RBD, receptor-binding domain; S IgG, anti-SARS-CoV-2 S-spike immunoglobulin G, S1 subunit 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

lower vaccine response,[37] multiple studies substantiate an antibody response after mRNA vaccine in that group of patients. In a prospective cohort study of 87 patients with CLD, including 38 (43.7%) with cirrhosis and 30 (34.5%) under immunosuppressive treatment, seroconversion rates were 97.4% in cirrhotic patients, 87.8% in noncirrhotic patients and 100% in controls, based on levels of anti- severe acute respiratory syndrome coronavirus 2 S-spike immunoglobulin G (S IgG) antibodies.[19] Adequate neutralizing activity was detected in 92.1%, 87.8% and 100% of patients with cirrhosis, without cirrhosis, and controls, respectively.[19] Immunosuppressive therapy was associated with lower anti-SARS-CoV-2 antibody titers [coefficient±standard error (SE) −2.716±0.634; $p<0.001$] and neutralizing activity (coefficient±SE −24.379±4.582; $p<0.001$).[19] In a study by Thuluvath *et al*.,[20] in which more than 90% of the included patients received mRNA vaccine, poor antibody responses were seen in 61% of liver transplant recipients and 24% of those with CLD. However, after adjusting for other variables, liver cirrhosis was not associated with poor antibody responses. Among the suboptimal responders, higher median antibody titers were observed in patients with CLD compared with liver transplant recipients.[20] Similar results were demonstrated in a study by Ruether *et al*.,[21] in which patients with liver cirrhosis and controls had comparable vaccine-specific humoral immune responses and T-cell responses after vaccination.[21] All these findings support the use of mRNA vaccine in patients with CLD including those with cirrhosis.

Shafrir *et al*.[22] analyzed the correlation between the degree of liver fibrosis, using a fibrosis-4 score, in which age, aspartate aminotransferase, alanine aminotransferase, and platelet count are included[38] and serum S IgG titers in 511 employees at a medical center. The higher the fibrosis-4 score, the lower the serum S IgG titers ($p=0.004$).[22] The association was further confirmed by FibroScan in another 76 patients with nonalcoholic fatty liver disease (NAFLD) who received an mRNA vaccine. Among patients with results in the high fibrosis range on transient elastography, a lower proportion achieved a strong vaccine response in terms of antibody titer compared with patients who had low fibrosis scores.[22]

Efficacy in liver transplant recipients: A suboptimal response to mRNA vaccines in liver transplant recipients has been consistently demonstrated in various studies, although it is difficult to compare results because of different methods/parameters used to measure antibody response and the different assay sensitivities.[39] A number of studies suggest that only about half of the liver transplant recipients who received a COVID-19 mRNA vaccine developed an immune response. Strauss *et al*.[23] described the antibody response in 161 liver transplant recipients, 53% of whom had received BNT162b2 and 47% mRNA-1273. Around one-third of the patients had an antibody response after the first dose of mRNA vaccine, 47% responded after the second dose, and 19% were non-responders. Risk factors for a diminished vaccine response included vaccination within 6 years from transplant or vaccination with BNT162b2 compared with mRNA-1273.[23] In the study by Ruether *et al*.,[21] almost half of the liver transplant recipients had suboptimal humoral responses and more than one-quarter were potentially immunologically unprotected even after the second vaccination. Another prospective cohort study including 80 liver transplant recipients found that around half the liver transplant recipients were seronegative, and in transplant recipient who had a response, the antibody titer was lower than in control group (mean 95.41±92.4 vs. 200.5±65.1 AU/mL, $p<0.001$).[24] In a study by Huang *et al*.,[25] 68% of liver transplant candidates developed reactive S IgG responses after a single dose of mRNA vaccine and

100% responded after two doses, compared with only 19.5% and 42.5%, respectively, of liver transplant recipients.[25] Multivariable logistic regression found that transplant candidates had a 14 times higher likelihood of having a positive immune response to a single dose of mRNA vaccine compared with transplant recipients (odds ratio 14.6; 95% CI: 2.19–98.11; p=0.02).[25] Other studies reported a higher rate of response to mRNA vaccines against COVID-19, with at least 70% of liver transplant recipients responding. A positive anti-severe acute respiratory syndrome coronavirus 2 S-receptor-binding domain antibody (anti-S-RBD) response was seen in 77% of liver transplant recipients compared with 100% of controls at 4 months after the second dose of BNT162b2 in a prospective cohort by Toniutto *et al*.[26] However, the transplant recipients had a significantly lower median S-receptor-binding domain antibody titers (32 U/mL vs. 852 U/mL; p<0.0001).[26] Davidov *et al*.[27] reported a 72% response rate to the BNT162b2 mRNA vaccine in 76 liver transplant recipients. Vaccination in the first year after transplant and hypogammaglobulinemia were independent risk factors for a poor response to the mRNA vaccines.[28] The high response rate reported by Davidov *et al*.[27] may have been related to the relatively long median time from transplant of 7 years and a low immunosuppressive burden.[27]

It should be noted that there is discordance between vaccine-induced cell-mediated and neutralizing humoral immunities in transplant recipients.[29] For example, around 19% of seronegative patients exhibited detectable cell-mediated immunity in a study by Fernández-Ruiz *et al*.[29] The reason is not clear, but immunosuppressant drugs are known to have differential effects on T-cell subsets, including the CD4 subsets involved in the generation of long-lived plasma cells. Therefore, it is possible that some transplant recipients have sufficient T-cell populations to mount a cytotoxic cell-mediated response to the COVID-19 vaccine, but not sufficient to generate detectable levels of antibody.[29]

Liver transplant recipients appear to have a better vaccine response compared with people with transplants of other solid organs.[28–30] For example, a prospective cohort study recruited 1,002 immunocompromised patients, including 36 with liver, 111 with kidney, and 80 with heart transplants.[30] The proportions of transplant recipients achieving an effective anti-receptor-binding domain antibody response and neutralizing antibodies 2–4 weeks after the second vaccine dose were 69.4%, 45% and 18.8%, respectively.[30] An unexpectedly high BNT162b2 vaccine efficacy (88.9%) was found in patients who had received a liver transplant compared with a kidney transplant (57.1%).[31] That may be related to renal function, as a decreased estimated glomerular filtration rate (eGFR) is a negative predictor of vaccination response.[21,24,26] In addition, the fact that the liver is an immunologically privileged organ, and liver transplant recipients usually require less immunosuppressive therapy than recipients of other solid organ transplants, might also explain the better response to vaccination.[31]

The type of immunosuppressive therapy has an important impact on vaccine efficacy in liver transplant recipients. In the studies described above, the use of mycophenolate mofetil, particularly high daily doses, or antimetabolites, was associated with poor vaccine response.[23,24,26,28] A higher proportion of organ transplant recipients using antimetabolites are nonresponders.[32] A lower antibody response was also seen in patients on combination immunosuppression compared with calcineurin inhibitor monotherapy.[27] Use of high-dose prednisone in the previous 12 months and triple immunosuppressant therapy were significant predictors of impaired serologic response to mRNA vaccines in liver transplant recipients.[24] The tacrolimus dose at vaccination was negatively correlated with the increase in anti-S1 Ab titer after completion of the second vaccine dose in patients who had undergone liver transplantation.[31]

Safety and tolerability: An interim analysis of surveillance of 6.2 million unselected individuals who had received a total of 11,845,128 doses of mRNA vaccines showed no significant concern regarding serious outcomes like arterial or venous thromboembolism, Bell palsy, Guillain-Barré syndrome, myocarditis/pericarditis, or thrombosis with thrombocytopenia syndrome.[40] The occurrence of adverse events was reported to be higher with mRNA-1273 than with BNT162b2, but mRNA-1273 is less temperature sensitive and therefore easier to transport and store.[41]

There have been reports of liver injury with no other clear precipitants following COVID-19 vaccination.[42,43] A multicenter case series of 16 patients who presented with liver injury after mRNA vaccine reported that all 10 patients with liver biopsies had portal inflammation and five had a significant plasma cell component. Those ten patients were treated with prednisone.[44] This raises the concern that COVID-19 vaccines may cause immune-mediated hepatitis or drug-induced liver injury (Table 2).[42–59] Molecular mimicry and bystander activation have been suggested as potential mechanisms for autoimmunity.[60,61] Upregulation of proinflammatory signals, especially the type I interferon response caused by mRNA binding to Toll-like receptors may also trigger autoimmune hepatitis (AIH).[56,62] In patients with autoimmune hepatitis, re-exposure to the vaccine may trigger fulminant hepatitis.[54] Therefore, physicians should vigilantly manage patients who present with liver injury and recent vaccination and consider another class of vaccine for subsequent booster doses.

Adenoviral Vector Vaccines

AZD1222: The AstraZeneca ChAdOx1 nCoV-19 vaccine (AZD1222, Covishield or Vaxzevria) is an adenoviral vector vaccine that consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1 that contains the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene.[63] A phase 3 randomized controlled trial recruited 32,451 participants ≥18 years of age and randomized them in a 2:1 ratio to receive AstraZeneca ChAdOx1 nCoV-19 vaccine (n=21,635) or placebo (n=10,816).[64] The two doses of AstraZeneca ChAdOx1 nCoV-19 vaccine, each containing 5×10^{10} viral particles, were administered 4 weeks apart. The percentage of individuals with liver diseases was 1.5% in each group, but the types of liver diseases were not reported. The overall efficacy of preventing symptomatic illness 15 days or more after the second dose was 74%. The estimated vaccine efficacy against COVID-related hospitalization was 94.2%.[64] A third dose of vaccine, either of the same class or a different class, boosted neutralizing antibody, and T-cell responses.[65,66] The vaccine was safe, with low incidences of serious (0.5%) and medically attended adverse events.[64] However, there were safety concerns of the thrombotic risk associated with the vaccine.[67] A pathogenic PF4-dependent syndrome that occurred after the administration of the vaccine and was unrelated to the use of heparin was identified.[68] The mechanism mimicked autoimmune heparin-induced thrombocytopenia.[69] Treatment included intravenous immune globulin and a nonheparin anticoagulant.[70] Clinicians should pay special attention to vaccine recipients with thrombotic risk factors. Another concern are reports of autoimmune hepatitis in people after receiving AZD1222. Most patients who developed vaccine-related hepatitis responded well to treatment with prednisolone.[57,58] However, one patient had a poor response to prednisolone and courses of plasma exchange

Table 2. Case reports or case series of liver injury following SARS-CoV-2 vaccination

Study	Age	Sex	Type of vaccine	Time to presentation	Drug history	Autoimmune disease	Antibodies	IgG (g/L)	ALT level at diagnosis (U/L)	Liver biopsy	Treatment	Outcome
mRNA vaccine												
Alqarni *et al*. 2021[42]	14	F	BNT162b2	3 days after second dose	Nil	Nil	Negative	Nil	4,500	Nil	NAC, lactulose, vitamin K, and empirical antibiotic	LFT gradually improved by the seventh day
Dumortier J 2022 [43]	46	M	BNT162b2	12 days after first dose	Aspirin, tacrolimus and MMF (post liver transplant)	Nil	Negative	Nil	287	Nil	Nil	Normalization of ALT, AST and ALP in 1 month
Shroff *et al*. 2021 [44]	25–74	M: 6; F: 10	BNT162b2 (*n*=12); mRNA-1273 (*n*=4)	5–46 days after first dose, with 12 patients presenting after second dose	Antibiotic: 2; NSAID: 2; Paracetamol: 2	AIH: 4	ANA: 5; ASMA: 4	Elevated in one patient	96 to >5,000	Performed in 10 patients: Portal inflammation: 10; Plasma cell infiltration: 5; Cholestasis and bile duct reaction: 1	7 patients treated with steroid	All patients were either recovering or fully recovered
Lodato *et al*. 2021[45]	43	F	BNT162b2	2 days after second dose	Ginkgo-biloba >100 days before admission	Nil	Negative	NA	171	Moderate portal inflammatory infiltrate and interface hepatitis in the portal tract with biliary injury and mild ductular proliferation; Spotty necrosis, lymphocytes along the sinusoid, focal moderate steatosis, and intranuclear glycogen inclusions in the lobule; Immunostaining with cH7-Ab showed mild ductular proliferation and diffuse immunoreactivity in hepatocytes zone 1–2	Methyl-prednisolone 1 mg/kg/day	LFT completely normalized in 8 weeks

(continued)

Table 2. *(continued)*

Study	Age	Sex	Type of vaccine	Time to presentation	Drug history	Autoimmune disease	Antibodies	IgG (g/L)	ALT level at diagnosis (U/L)	Liver biopsy	Treatment	Outcome
Bril *et al*. 2021[46]	35	F	BNT162b2	13 days after first dose	Labetalol	Nil	ANA; Anti-dsDNA	10.81 (not elevated)	2,001	Pan-lobular hepatitis; Intense lymphoplasmacytic infiltrate effacing the interface with rosette formation; Primarily lymphocytic inflammation with plasma cells and eosinophils; Scattered hepatocyte necrosis	Prednisolone 20mg daily	Normalization of LFT in around 2 months
Avci *et al*. 2021 [47]	61	F	BNT162b2	1 month after first dose	Valsartan and levothyroxine	Hashimoto's thyroiditis	ANA; ASMA	42.6↑	455	Narrow sinusoids and lymphocyte infiltration; Severe portal and periportal lymphocyte infiltration; Periseptal interface hepatitis, spotty necrosis, and limiting plate disorder; Mild fibrosis	Prednisolone 40mg daily, then azathioprine added, and steroid dose tapered	Improved to mildly elevated transaminase and bilirubin on day 35
Palla *et al*. 2022[48]	40	F	BNT162b2	1 month after second dose	Nil	Nil	ANA	24↑	4 x ULN	Active hepatitis with significant interface necroinflammation and severe lobular inflammatory infiltration composed predominantly of lymphocytes with an admixture of plasma cells; Portal/periportal fibrosis was evident as well as fibrous septa with occasional bridging	Prednisolone 40mg daily	LFT normalized 1 week after start of treatment

(continued)

Table 2. *(continued)*

Study	Age	Sex	Type of vaccine	Time to presentation	Drug history	Autoimmune disease	Antibodies	IgG (g/L)	ALT level at diagnosis (U/L)	Liver biopsy	Treatment	Outcome
Rocco *et al*. 2021[49]	80	F	BNT162b2	1 week after second dose	Levothyroxine, pravastatin, and aspirin	Hashimoto's thyroiditis	ANA	35↑	1,186	Interface hepatitis with a moderate degree of lymphoplasmacytic infiltrate and multiple confluent foci of lobular necrosis with Councilman bodies	Prednisolone 1 mg/kg/day	Progressive improvement in LFT in 2 months
Garrido *et al*. 2021[50]	65	F	mRNA-1273	2 weeks after first dose	Pegylated interferon, aspirin, sertraline, and esomeprazole	Nil	ANA	20↑	1,092	Marked expansion of the portal tracts due to dense inflammatory infiltrate, with aggregates of plasma cells; severe interface hepatitis and multiple confluent foci of lobular necrosis	Prednisolone 60mg daily	Quick improvement of LFT and normalization of IgG levels after start of prednisolone
Vuille-Lessard *et al*. 2021[51]	76	F	mRNA-1273	2–3 days after first dose	Levothyroxine, midodrine, and zolpidem	Hashimoto's thyroiditis	ANA; ASMA; Anti-actin antibody; ANCA	39.4↑	579	Chronic markedly active hepatitis with interface hepatitis, plasma cells, feathery degeneration, and pseudorosettes	Prednisolone 40mg daily; Azathioprine was added 14 days later	LFT completely normalized in 4 weeks after treatment
Ghielmetti *et al*. 2021[52]	63	M	mRNA-1273	7 days after first dose	Metformin, aspirin, and rosuvastatin	Nil	ANA; Anti-parietal cell antibody	19.96↑	1,038	Intense lymphoplasmacytic infiltrate with scattered eosinophils, interface hepatitis, and centrilobular necrosis	Prednisolone 40mg daily	Improvement in LFT 2 weeks after treatment

(continued)

Table 2. *(continued)*

Study	Age	Sex	Type of vaccine	Time to presentation	Drug history	Autoimmune disease	Antibodies	IgG (g/L)	ALT level at diagnosis (U/L)	Liver biopsy	Treatment	Outcome
Tan *et al*. 2021[53]	56	F	mRNA-1273	6 weeks after first dose	Rosuvastatin	Nil	ANA; ASMA	32.6↑	1,701	Portal inflammation with interface hepatitis, conspicuous lobular inflammation with the presence of plasma cell aggregates, rosette formation, and apoptotic hepatocytes; A few eosinophils were identified; Early young fibrosis	Budesonide	Rapid clinical and biochemical improvement after start of steroid
Zin Tun *et al*. 2022[54]	47	M	mRNA-1273	3 days after first dose	Nil	Nil	ANA	25.1↑	1,048	Widespread areas of bridging necrosis, marked interface hepatitis, lymphoplasmatic inflammation including eosinophils, ballooned hepatocytes, multinucleated giant cells, and emperipolesis; Minimal fibrosis	Prednisolone 40mg daily	PT normalized within 2 weeks
McShane *et al*. 2021[55]	71	F	mRNA-1273	4 days after first dose	Paracetamol 2 g within 24 h after vaccination	Nil	ASMA	21.77↑	1,067	Marked polymorphous inflammatory cell infiltrate of plasma cells, lymphocytes, eosinophils, neutrophils, and PASD-positive ceroid laden macrophages; Interface hepatitis with portal-portal and portal-central bridging necrosis	Prednisolone 40mg daily	LFT continued to improve on a tapering course of prednisolone

(continued)

Table 2. *(continued)*

Study	Age	Sex	Type of vaccine	Time to presentation	Drug history	Autoimmune disease	Antibodies	IgG (g/L)	ALT level at diagnosis (U/L)	Liver biopsy	Treatment	Outcome
Londoño *et al*. 2021[56]	41	F	mRNA-1273	7 days after second dose	Hormonal replacement therapy	Nil	ANA; ASMA; Anti-SLA; Anti-liver cytosol	20.8↑	1,312	Marked expansion of the portal tracts with a dense inflammatory infiltrate composed of lymphocytes and plasma cells, severe interface hepatitis, and lobular inflammation with disperse necroinflammatory foci, apoptotic bodies, and hepatocyte ballooning; No signs of parenchymal or perisinusoidal fibrosis	Prednisolone 1 mg/kg	Rapid normalization of LFT after start of prednisolone
Adenoviral vector vaccine												
Clayton-Chubb *et al*. 2021[57]	36	M	AZD1222	26 days after first dose	Olmesartan, paracetamol, ibuprofen	Nil	ANA	12.8 (not elevated)	1,774	Significant interface hepatitis with a mixed, predominantly lymphocytic, inflammatory cell infiltrate without significant fibrosis	Prednisolone 60mg daily	LFT improvement with gradual tapering of steroid
Rela *et al*. 2021 [58]	38	F	AZD1222	20 days after first dose	Levothyroxine	Hypothyroidism	ANA	16.5↑	1,025	Multiacinar hepatic necrosis and diffuse portal/ periportal neo-cholangiolar proliferation; Inflammation comprising of lymphocytes, plasma cells, and rare eosinophils were noted; Sinusoidal pigment laden histiocytes and central venulitis were noted, and suggestive of AIH	Prednisolone 30mg daily	LFT normalization with gradual tapering of steroid

(continued)

Table 2. *(continued)*

Study	Age	Sex	Type of vaccine	Time to presentation	Drug history	Autoimmune disease	Antibodies	IgG (g/L)	ALT level at diagnosis (U/L)	Liver biopsy	Treatment	Outcome
	62	M	AZD1222	16 days after first dose	Nil	Nil	Negative	Nil	1,094	Porto-central bridging necrosis; Portal/periportal neocholangiolar proliferation and mild to moderate inflammation comprising of lymphocytes along with plasma cells, eosinophils, and polymorphs; Focal rosetting and emperipolesis; Patchy hepatocanalicular bilirubinostasis and central venulitis; Mild portal fibrosis (Ishak stage 2/6)	Prednisolone 30mg daily; 5 cycles of therapeutic plasma exchange	Poor response to treatment; patient died 3 weeks after admission
Inactivated virus vaccine												
Ghorbani *et al*. 2022[59]	62	M	Sinopharm	3 days after second dose	Metformin, glibenclamide and losartan	Nil	Nil	Nil	722	Severe infiltration of lymphocytes, eosinophils, and neutrophils in portal tract (score: 3/4) and lobules (score: 4/4) accompanied by interface hepatitis (score: 4/4) and feathery change. Foci of ductular reaction; Final grading and staging, according to Ishak modified hepatitis activity index, were 11/18 and 1/6, respectively	Ursodeoxycholic acid	Liver enzymes gradually improved

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; Anti-dsDNA, anti-double stranded DNA; anti-SLA, anti-soluble liver antigen; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; IgG, Immunoglobulin G; LFT, liver function test; MMF, mycophenolate mofetil; NAC, N-acetylcysteine; NSAID, nonsteroidal anti-inflammatory drug; PASD, periodic acid–Schiff with diastase digestion; PT, prothrombin time; ULN, upper limit of normal.

and died 3 weeks after admission (Table 2).[58]

Ad26.COV2.S: The Ad26.COV2.S vaccine (Jcovden, Johnson & Johnson). Is an adenoviral vector vaccine consisting of a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector encoding a full-length and membrane-bound SARS-CoV-2 spike protein in a prefusion-stabilized conformation.[71,72] The key phase 3 study included 39,321 participants randomized in a 1:1 ratio to receive a single dose of Ad26.COV2.S or placebo.[73] Patients with liver diseases comprised 0.5% of the populations in each arm of the study. There were 66 cases of moderate-to-severe critical COVID-19 in the vaccine group and 193 cases in the placebo group, yielding a vaccine efficacy of 66.1% (adjusted 95% CI, 55.0–74.8%). To date, there are no published data reporting on the safety and efficacy of AZD1222 or Ad26.COV 2.S vaccines in liver transplant recipients or patients with CLD. Further research is needed.

Inactivated virus vaccines

Two inactivated COVID-19 vaccines have been approved and are used in some countries. They are CoronaVac developed by Sinovac Life Sciences and the Sinopharm vaccine. Inactivated vaccines can induce a wide range of cellular and humoral responses, but their disadvantages include limited immunogenicity, which requires adjuvants to enhance the immune response, the need to handle large quantities of live virus, and the integrity of antigens or epitopes that must be verified.[74] Tanriover *et al.*[75] conducted a phase 3 study on CoronaVac using two doses of 3 μg inactivated SARS-CoV-2 virion in a 0.5 mL aqueous suspension administered 14 days apart. The estimated efficacy of the vaccine was 83.5%. The results of other RCTs on inactivated vaccines are shown in Supplementary Table 1.[76–78]

Emerging evidence shows that a booster dose is needed for people who have received two doses of inactivated vaccine.[79–83] A recent study showed that the initial neutralizing antibody response to two doses of CoronaVac declined to near or below the lower limit of seropositivity after 6 months.[84] A third dose of CoronaVac (3 μg) given 8 months after the second dose resulted in a strong, immunogenic boost.[84]

Efficacy and safety in patients with CLD or liver transplants: The use of inactivated vaccine and its antibody response have been studied in patients with CLD or liver transplant recipients. The largest was conducted by Ai *et al*.[33] and included 581 participants, 437 with CLD, and 144 healthy volunteers from 15 sites in China.[33] CLD included liver diseases of more than 6 months duration, including chronic inflammation from conditions like hepatitis B, hepatitis C, NAFLD, alcoholic liver disease, autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis, with or without liver cirrhosis. Two doses of inactivated whole virion SARS-CoV-2 vaccine were given to all participants 3 to 8 weeks apart. Serum samples were taken 14 days or more after the second dose and tested for SARS-CoV-2 neutralizing antibody. The positive rates of neutralizing antibodies were 76.8% in the group with noncirrhotic CLD, 78.9% in the group with compensated cirrhosis, 76.7% in the group with decompensated cirrhosis, and 90.3% in healthy controls. The immunogenicity rates were similar across different CLD groups (p=0.894) but were significantly lower than in the healthy population (p=0.008).[33] Most adverse reactions were mild and transient. Injection site pain was the most commonly reported adverse event, with an incidence of 8.2%.[33] Comparable safety was shown in patients with noncirrhotic CLD, compensated cirrhosis, and decompensated cirrhosis. Three participants had grade 3 aminotransferase elevations, defined as an alanine aminotransferase level >5 times the upper limit of normal after the second dose of vaccine. In one of those participants, it was regarded as a severe adverse event potentially related to the vaccination. The patient had discontinued antiviral agents against hepatitis B before SARS-CoV-2 vaccination. Therefore, it was uncertain whether the severe adverse event was related to the vaccination or to hepatitis B reactivation after discontinuation of antiviral treatment.[33]

Several studies have investigated the efficacy of inactivated SARS-CoV-2 vaccines in hepatitis B patients. He *et al*.[34] conducted a study in 362 chronic hepatitis B (CHB) patients and 87 healthy controls who received two doses of inactivated vaccine at an interval of at least 21 days. Researchers analyzed the antibody profiles of the anti-spike IgG, anti-RBD IgG, and RBD-angiotensin-converting enzyme 2 (RBD-ACE2) blocking antibody at 1, 2, and 3 months, as well as levels of SARS-CoV-2 specific B cells. chronic hepatitis B patients had lower titers of the three antibodies than healthy controls at 1 month, but seropositivity rates of the three antibodies were similar in chronic hepatitis B patients and healthy controls at 2 and 3 months. Patients who were positive for hepatitis e-antigen (HBeAg) had higher titers of all three antibodies at 3 months (all p<0.05) and a slower decline in antibody titers compared with healthy controls.[34] Atypical memory B-cells (MBCs) are a subset short-lived activated cells that ate plasma cell (PC) precoursors.[85] The percentage of Atypical memory B-cells is usually increased in patients with chronic diseases.[86] The number of RBD+ memory B-cells was higher in HBeAg-positive CHB patients than in controls at 3 months. It was proposed that the higher frequency of RBD+ atypical MBCs in HBeAg-positive CHB patients would lead to a higher frequency of plasma cells, which might then result in higher antibody titers.[85]

A study by Xiang *et al*.[35] recruited 284 CHB participants, of whom 81 were unvaccinated, 54 who had received the first dose of vaccine and 149 who had received two doses of vaccine. The seropositivity rates for anti-S-RBD-IgG and neutralizing antibody was 87.25% and 74.5%, respectively for participants with two doses of inactivated vaccines.[35] In addition, the study showed that the hepatitis B patients receiving nucleos(t)ide analog therapy had a significantly higher neutralizing antibody titer than those who had not (p<0.05).[35] The reason is not clear, but it was proposed that long-term antiviral therapy for hepatitis B inhibited viral replication and led to the recovery of the impaired immune system by restoring the function of circulating T cells, natural killer cells, or dendritic cells. The effects would be more prominent in patients receiving nucleotide analogs that induce the production of interferon-α3.[87,88] It is therefore recommended to continue administration of nucleos(t)ide analogs during vaccination to avoid negatively impacting CHB treatment.

Wang *et al*.[36] conducted a multicenter study in 381 patients with nonalcoholic fatty liver disease and without a history of SARS-CoV-2 infection who were being treated at 11 designated centers in China. All nonalcoholic fatty liver disease patients were given with two doses of inactivated vaccine. Levels of neutralizing antibody against SARS-CoV-2 were measured at least 14 days after the full vaccination course. Antibodies were detected in 364 (95.5%) patients. The median neutralizing antibody titer was 32 (interquartile range 8–64), and the median period between the completion of vaccination and neutralizing antibody detection was 39.0 days (interquartile range 35–50 days).[36] Inactivated vaccines have shown their efficacy in patients with different types of CLD. The adverse effects were mild and self-limiting and there were few reports of vaccine-induced hepatitis in patients with CLD after receiving this type of vaccine.[59]

Protein subunit vaccines

The Novavax NVX-CoV2373 vaccine (Nuvaxovid, Covovax) is a recombinant SARS-CoV-2 nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant.[89] The two vaccine components trigger both B- and T-cell immunity to the SARS-CoV-2 S protein, and the full-length S protein has common epitopes that could protect against variants.[90] It is given intramuscularly as two 5 μg doses, 21 days apart.[91] A phase 3 randomized trial included 15,187 participants (14,039 of whom were included in the per-protocol analysis). Vaccine efficacy against both B.1.1.7 (alpha) and non-B.1.1.7 variants was 89.7% (95% CI: 80.2–94.6%).[92] Similar levels of protection were shown in another phase 3 trial including 29,949 adults in the USA and Mexico, with B.1.1.7 the most sequenced viral strain.[93] The vaccine efficacy of NVX-CoV2373 against any variant was 92.6% (95% CI: 83.6–96.7%), but lower protection, a vaccine efficacy of 49.4%. was found against B.1.351 variants.[94] The efficacy of NVX-Cov2373 may be affected by coexisting illnesses with a higher number needed to treat to prevent COVID-19 infection in individuals with comorbidities.[95] In patients living with stable HIV-1 infection, viral load of <1,000 copies/mL, and on stable antiretroviral therapy for ≥8 weeks, the humoral immune response to NVX-CoV2373 was attenuated compared with HIV-negative vaccine recipients.[96] HIV-positive participants were more likely to have underlying comorbidities (36.1% vs. 22.2%) and hepatitis B surface antigen positivity (7.0% vs. 1.0%) compared with HIV-negative vaccinees.[96] In the phase 3 studies by Heath *et al*.[92] and Dunkle *et al*.,[93] more than 40% of the participants had coexisting illnesses but the percentages of patients with CLD were not reported. At the time of writing, there are no studies reporting the safety or efficacy of NVX-Cov2373 in liver transplant recipients or patients with CLD. Future research is needed to guide immunization decisions in those patients. Most of the reported solicited local and systemic adverse events after receiving NVX-Cov2373 were mild to moderate and transient. Common solicited systemic adverse events included headache, myalgia, fatigue, and fever. There were no episodes of anaphylaxis, Guillain Barré syndrome, vaccine-induced immune thrombotic thrombocytopenia, or an increased risk of myocarditis or pericarditis, although the follow-up period in the phase 3 studies was relatively short.[93,94]

Conclusion

COVID-19 vaccination in cirrhosis patients reduced overall mortality, and they should be vaccinated unless there are contraindications. Liver transplant recipients may benefit from an early third booster dose to achieve a better protective effect. Currently, there are more data supporting the use of mRNA vaccines compared with other COVID-19 vaccines in patients with CLD. Recent evidence also shows that the mRNA vaccines and ChAdOx1 nCoV-19 vaccine are useful against new strains such as the omicron variants.[97,98] Clinicians should remain cautious about the potential for vaccine-induced immune-mediated hepatitis or drug-induced liver injury. More research is needed on the duration of immunity, need for booster doses, effects of heterologous vaccination, and protection against novel variants in patients with CLD or liver transplant recipients.

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Conflict of interest

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Author contributions

Study concept and design (CKC, MFL), acquisition of data (CKC, KWT, AWH, RH, MFL), analysis and interpretation of data (CKC, KWT, AWH, RH, MFL, SHW), drafting of the manuscript (CKC, MFL), critical revision of the manuscript for important intellectual content (CKC, SHW, MFL). All authors have made a significant contribution to this study and have approved the final manuscript.

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